ŚWIĄTKO, Mateusz, SOSNOWSKI, Paweł, RYBAK, Joanna, GRZEBYK, Marcin, TOKARSKA, Anna, ARNISTA, Aleksandra, GAWROŃSKA, Katarzyna, WASZCZUK, Agnieszka, KOŁODZIEJCZYK, Aleksandra and ŁAPIŃSKI, Piotr. The role of the gut microbiome in cardiovascular disease. Journal of Education, Health and Sport. 2025;82:60447. eISSN 2391-8306.
https://doi.org/10.12775/JEHS.2025.82.60447
https://apcz.umk.pl/JEHS/article/view/60447

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).
The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 21.04.2025. Revised: 25.04.2025. Accepted: 18.06.2025. Published: 19.06.2025.

The role of the gut microbiome in cardiovascular disease

Corresponding Author:

Mateusz Świątko

District Hospital in Sochaczew, Batalionów Chłopskich 3/7, 96-500 Sochaczew, Poland
mateusz.swiatko@gmail.com https://orcid.org/0009-0003-0467-1290

Paweł Sosnowski

Central Clinical Hosipital, Banacha 1A, 02-087, Warsaw, Poland
pawelsosno@gmail.com https://orcid.org/0009-0008-0097-3669

Joanna Rybak

Father Jerzy Popiełuszko „Bielański" Hospital, Independent Public Health Care Institution in Warsaw, Cegłowska 80, 01-809, Warsaw, Poland
asia.rybak307@gmail.com https://orcid.org/0009-0005-3815-4149

Marcin Grzebyk

Organmedica, gen. Augusta Emila Fieldorfa „Nila" 10 lok. 317 03-984 Warsaw, Poland
marcin.grzebyk@gmail.com https://orcid.org/0000-0002-7647-1226

Anna Tokarska

Central Clinical Hospital, Banacha 1A, 02-097 Warsaw, Poland aniatokarska.98@gmail.com
https://orcid.org/0009-0003-8601-4269

Aleksandra Arnista

Military Institute of Medicine-National Research Institute, Szaserów 128, 04-141 Warsaw, Poland

aleksandra.arnista0605@gmail.com
https://orcid.org/0009-0000-1274-1373

Katarzyna Gawrońska

Specialized Provincial Hospital in Ciechanów, Powstańców Wielkopolskich 2, 06-400 Ciechanów, Poland
gawronskakatarzyna1@gmail.com
https://orcid.org/0009-0004-7378-1626

Agnieszka Waszczuk

The Provincial Specialist Hospital in Biała Podlaska, Terebelska 57-65, 21-500, Biała Podlaska, Poland waszczukaga@gmail.com
https://orcid.org/0009-0009-9201-1391

Aleksandra Kołodziejczyk

District Hospital in Grójec, 05-600 Piotra Skargi 10, Grójec, Poland aleksandra.kolodziejczyk19@gmail.com https://orcid.org/0009-0001-3955-724X

Piotr Łapiński

Central Clinical Hospital, Banacha 1A, 02-097 Warsaw, Poland piotr.konstanty13@gmail.com https://orcid.org/0009-0005-5740-3016

Abstract

In recent years, the gut microbiome has gained increasing recognition as a crucial modulator of physiological homeostasis, including cardiovascular function. Numerous studies indicate that disruptions in the composition and activity of intestinal microbiota—referred to as dysbiosis—may significantly contribute to the onset and progression of cardiovascular diseases, including atherosclerosis, hypertension, heart failure, and arrhythmias. Particular attention has been paid to microbial metabolites such as trimethylamine-N-oxide (TMAO), short-chain fatty acids (SCFAs), and lipopolysaccharides (LPS), which exert significant effects on inflammatory, immunological, and metabolic pathways.

The aim of this review was to synthesize current evidence regarding the association between the gut microbiota and the pathogenesis of cardiovascular disorders, emphasizing potential molecular mechanisms and therapeutic opportunities arising from microbiome modulation. Additionally, environmental, dietary, and pharmacological factors influencing microbiota composition and their implications for cardiovascular risk were discussed.

Accumulated evidence suggests the gut microbiome could serve both as a biomarker of cardiovascular risk and as a potential therapeutic target within personalized medicine frameworks. However, further clinical research is required to precisely define its role in the pathogenesis and treatment of cardiovascular diseases.

Keywords
gut microbiota, cardiovascular disease, TMAO, SCFA, LPS, dysbiosis

Objectives

The objective of this paper was to provide a comprehensive overview of the current state of knowledge regarding the role of gut microbiota in the pathogenesis of cardiovascular diseases. The emphasis was placed on exploring potential biological mechanisms through which intestinal microorganisms and their metabolites—such as trimethylamine N-oxide (TMAO), short-chain fatty acids (SCFA), and lipopolysaccharides (LPS)—influence cardiovascular system function. Particular attention was given to the relationships between intestinal dysbiosis and the development of atherosclerosis, arterial hypertension, heart failure, and arrhythmias. Additionally, the paper aimed to assess the impact of environmental factors, lifestyle choices, and therapeutic interventions on the composition and function of the microbiome.

Methodology

This study is a narrative review based on a comprehensive analysis of the scientific literature concerning the relationship between gut microbiota and cardiovascular diseases. The literature search was conducted using reputable databases, including PubMed, Google Scholar, and ScienceDirect.

Priority was given to publications from the past decade (2013–2023); however, selected earlier sources were also included when they offered foundational insights or significant scientific value relevant to the discussed topic.

The selection of articles was guided by thematic relevance, methodological rigor, and scientific credibility. Special emphasis was placed on clinical studies, experimental models,

and review articles describing the impact of gut-derived microbial metabolites—such as trimethylamine-N-oxide (TMAO), short-chain fatty acids (SCFAs), and lipopolysaccharides (LPS)—on pathophysiological processes associated with cardiovascular conditions. This methodological approach aimed to provide an integrative synthesis of current knowledge regarding the role of gut microbiota in the development and progression of cardiovascular diseases, with particular attention to molecular mechanisms and emerging therapeutic opportunities arising from microbiome modulation.

Keywords:

- gut microbiota
- cardiovascular diseases
- TMAO
- SCFA
- LPS
- dysbiosis

1. Introduction

Cardiovascular diseases (CVD) comprise a broad spectrum of disorders affecting both the heart and circulatory system. Among these, notable conditions include hypertension, impaired coronary blood flow leading to ischemic heart disease, cerebrovascular disorders associated with abnormal cerebral perfusion, and peripheral artery diseases. Additionally, this category encompasses heart failure, rheumatic diseases involving cardiac structures, congenital cardiovascular malformations, and cardiomyopathies of diverse etiologies [1].Globally, a significant rise in both morbidity and mortality due to cardiovascular diseases has been observed. The number of recorded cases increased by approximately 77%, from 31.3 million in 1990 to over 55.4 million in 2019, whereas mortality in the same period rose by nearly 54%, reaching 18.56 million deaths annually [2]. In recent years, considerable attention has been directed toward the gut microbiota as a possible factor influencing the progression of cardiovascular diseases (CVD) and related metabolic disorders. Advances in sequencing technologies have facilitated detailed characterization of intestinal microbiota and their associations with the pathogenesis of cardiovascular conditions [3]. Multiple epidemiological

studies have reported significant differences in the composition of gut microbiota between healthy individuals and those exhibiting elevated risk for developing cardiometabolic disorders [4][5][6].

In patients diagnosed with chronic heart failure (HF), a significant reduction in blood flow through intestinal vasculature has been documented. Reduced intestinal tissue perfusion promotes excessive bacterial overgrowth within the submucosal layer, simultaneously exacerbating mucosal inflammatory responses. This process contributes to the emergence of gastrointestinal symptoms and may amplify systemic inflammation, accelerating myocardial deterioration. Consequently, disturbances in intestinal microcirculation can substantially affect the progression of advanced HF stages, deteriorating the overall clinical status of affected patients [7]. Microbiological analyses of fecal samples from heart failure patients revealed an elevated prevalence of potentially pathogenic microorganisms, including Candida, Campylobacter, Shigella, and Yersinia. The occurrence of these microorganisms was directly correlated with the clinical severity of heart failure [8].

An imbalance in gut microbiota composition, known scientifically as dysbiosis, may result from diverse factors including improper dietary habits, exposure to harmful environmental agents, and gastrointestinal infections. These alterations lead to enhanced intestinal barrier permeability, potentially triggering chronic inflammatory conditions [9][10]. Findings from numerous studies, particularly those involving animal models, indicate that gut microbiota plays a crucial role in regulating physiological processes of the host organism. Emerging evidence suggests that alterations in microbiota composition may be associated with the pathogenesis of metabolic disorders, including cardiovascular diseases (CVD) [11].

2. Gut Microbiome – Basic Information

• 2.1 Composition and functions of the gut microbiome

Colonization of the gastrointestinal tract by microorganisms commences immediately after birth and encompasses a diverse array of microbial taxa, including bacteria, viruses, fungi, and archaea. This process is characterized by dynamic shifts, ultimately leading to the establishment of a relatively mature and stable microbial community structure within the first few years of life, typically reaching functional stability around the age of three [10]. The human gut microbiota comprises a complex community of microorganisms, with bacteria

constituting the predominant component. Among them, Firmicutes represent the most abundant phylum, followed by Bacteroidetes as the second major group. In addition to these dominant taxa, less numerous but functionally significant bacterial populations—such as those belonging to the phyla Verrucomicrobia, Actinobacteria, and Proteobacteria—also contribute critically to maintaining the functional equilibrium of the intestinal ecosystem [12]. Moreover, gut microorganisms serve as a source of bioactive compounds, including essential amino acids and vitamins such as vitamin K, thiamine, folic acid, biotin, riboflavin, and pantothenic acid. Their presence is also critical for the proper maturation and functional development of the host immune system [13].

• 2.2 Factors influencing the composition of the microbiome (antibiotics, lifestyle)

Intestinal dysbiosis, defined as an alteration in the quantitative and qualitative composition of gut microorganisms alongside disruption of their functional activity, arises from a multitude of factors. These include chronic intestinal inflammation, exposure to cold, psychological stress, excessive antibiotic use, and other environmental stimuli [14].

2.2.1 Antibiotic

The administration of antibiotic therapy disrupts the microbial homeostasis of the gut, leading to an increase in the concentration of endogenously derived free sialic acid [15]. This compound serves as an accessible metabolic substrate for opportunistic pathogenic microorganisms, such as *Salmonella typhimurium* and *Clostridioides difficile*, thereby facilitating their enhanced colonization and expansion within the host environment [15]. Ciprofloxacin, despite its limited activity against classical anaerobic constituents of the gut microbiota, exerts a substantial impact on its taxonomic structure. Administration of this fluoroquinolone has been associated with a marked reduction in the abundance of nearly onethird of the identifiable taxonomic units within the intestinal microbiome [16]. Exposure to antibiotics during early life exerts profound and long-lasting effects on the development of the gut microbiome. Early modulation of microbial composition constitutes a significant predisposing factor for the onset of excessive body weight and metabolic disturbances later in life [17].

2.2.2 lifestyle

Psychophysiological stress has been associated with increased intestinal barrier permeability, potentially facilitating the translocation of bacterial components and the activation of

inflammatory responses [18]. Regular physical activity is associated with a reduction in inflammatory markers, thereby fostering an intestinal environment conducive to the proliferation of beneficial microbial taxa [19]. Interestingly, statistical analyses have demonstrated that cohabitation with companion animals—particularly dogs—is associated with observable alterations in the structure and diversity of the host microbiome [20].

- ***3.*** **Microbiota Metabolism Products and Their Impact on the Cardiovascular System**

Current scientific evidence increasingly supports the hypothesis that metabolites produced by the gut microbiota exert a significant influence on the development of cardiovascular diseases. Among the key bioactive compounds implicated in this process are short-chain fatty acids (SCFAs), trimethylamine (TMA), trimethylamine N-oxide (TMAO), and bacterial lipopolysaccharides (LPS) [21].

3.1 Trimethylamine and its oxide (TMAO)

Trimethylamine N-oxide (TMAO) is produced through a hepatic metabolic process involving the oxidation of trimethylamine (TMA). TMA itself is generated in the intestinal lumen as a result of microbial metabolic activity, wherein dietary substrates such as choline, betaine, and L-carnitine are enzymatically converted [22]. Following nutrient intake, dietary compounds such as choline, phosphatidylcholine (PC), carnitine, and γ-butyrobetaine serve as metabolic substrates for the gut-resident microbiota. Within these microorganisms, trimethylamine (TMA) lyase enzymes—specifically the enzymatic complexes CutC/D, CntA/B, and YeaW/X—catalyze the bioconversion of these substrates into TMA. The generated TMA subsequently enters the portal circulation and is transported to the host liver, where it undergoes further metabolic oxidation [23]. The metabolism of trimethylamine (TMA) is primarily mediated by enzymes belonging to the flavin-containing monooxygenase (FMO) family, particularly FMO1 and FMO3. Both enzymes catalyze the oxidation of TMA to trimethylamine N-oxide (TMAO); however, the enzymatic activity of FMO3 is approximately tenfold greater than that of FMO1. This suggests that FMO3 represents the predominant metabolic pathway responsible for TMAO generation in the human body [24].Studies indicate that the accumulation of trimethylamine N-oxide (TMAO) in the organism exhibits significant sex-related differences, with higher concentrations observed in females compared to males. However, this disparity is not primarily attributed to increased microbial production of the

precursor trimethylamine (TMA) in females, but rather to enhanced activity of flavin-containing monooxygenase (FMO) enzymes—particularly the FMO3 isoform. This observation aligns with previous findings demonstrating elevated FMO3 expression in female subjects. These results suggest that FMO3 enzymatic activity is a key determinant underlying sex-specific differences in systemic TMAO levels [25].

Dietary composition exerts a significant influence on TMAO production. The principal nutritional precursors of this metabolite—L-carnitine and choline—are predominantly derived from animal-based foods, particularly red meat, processed meat products, eggs, and seafood. Betaine, another substrate involved in TMAO biosynthesis, is found primarily in plant-based foods. Variability in dietary intake of these compounds modulates gut microbial activity and may consequently determine systemic TMAO levels—a metabolite implicated in the risk of developing cardiovascular diseases [26] [27]. This study demonstrated a significant association between choline intake and elevated TMAO levels, which in turn correlated with an increased susceptibility to prothrombotic events [28].Chronic consumption of red meat has been shown to selectively elevate TMAO levels derived from L-carnitine, without significantly affecting TMAO production from choline. Additionally, regular intake of red meat was found to reduce renal excretion of TMAO. Upon cessation of red meat consumption, plasma TMAO concentrations decreased significantly within approximately four weeks, indicating the potential reversibility of diet-induced metabolic alterations. These findings suggest a link between red meat intake and cardiovascular risk mediated by gut microbiota-dependent mechanisms [29].

TMAO has been shown to upregulate the expression of the CD36 receptor via activation of the MAPK/JNK signaling pathway, thereby promoting lipid accumulation in macrophages and the formation of foam cells—critical contributors to the development of atherosclerotic lesions [30]. Evidence suggests that elevated serum concentrations of trimethylamine Noxide (TMAO) are significantly correlated with increased carotid intima-media thickness (cIMT), a well-established marker of atherosclerotic progression that reflects the combined thickness of the intimal and medial layers of the carotid artery [31]. Furthermore, another study demonstrated that elevated TMAO concentrations are significantly associated with the severity of atherosclerotic lesions within the coronary arteries and may serve as a prognostic indicator of increased long-term mortality risk in patients with chronic kidney disease [32].

In a prospective analysis involving a cohort of patients hospitalized due to ST-elevation myocardial infarction (STEMI) or unstable angina, a significant association was identified between elevated trimethylamine N-oxide (TMAO) levels and the occurrence of acute

coronary syndrome [33]. Similar conclusions were reached by researchers in another independent study [34]. Interestingly, TMAO concentration demonstrated significant prognostic value in predicting both mortality risk and the occurrence of cardiovascular events in patients with suspected functionally significant coronary artery disease [35].

Elevated TMAO levels were also found to correlate with an increased risk of cardiovascular mortality in patients with established coronary artery disease [36]. Current evidence suggests that the molecular mechanisms through which TMAO contributes to the development of cardiovascular diseases have not yet been fully elucidated and warrant further investigation.

Gut microbiota play a critical role in enhancing platelet activation and increasing thrombotic risk through the production of the metabolite TMAO [37]. The authors of the study under discussion proposed that therapeutic strategies aimed at reducing the synthesis or activity of trimethylamine N-oxide (TMAO) could represent a novel approach to mitigating thrombotic risk [38].

3.2 Short-chain fatty acids (SCFA)

The gut microbiota plays a pivotal role in human gastrointestinal physiology, participating in a wide array of metabolic and immunological processes. Through the production of specific enzymes, it facilitates the degradation of commonly occurring polysaccharides, including glycosaminoglycans, leading to the generation of short-chain fatty acids (SCFAs) [13].

These compounds primarily serve as an energy source for intestinal epithelial cells while simultaneously modulating local immune responses. Through the production of specific signaling molecules, the gut microbiota supports mucosal regeneration and stimulates intestinal angiogenesis. Consequently, SCFAs and other bacterial metabolites exert beneficial effects on the integrity of the intestinal barrier, ensuring its proper function and providing protection against the development of potential pathological conditions [14].

Short-chain fatty acids (SCFAs) are primarily represented by acetate, propionate, and butyrate, although this group also includes less abundant metabolites such as formate and lactate. Reduced concentrations of SCFAs have been observed in patients diagnosed with atherosclerotic vascular disease as well as in individuals with arterial hypertension, suggesting a potential link between SCFA deficiency and the pathogenesis of cardiovascular disorders [40].

SCFAs play a significant role in the regulation of blood pressure through their interaction with the Olfr78 and GPR41 receptors [41]. Experimental studies indicate that mice with a

knockout of the gene encoding the Olfr78 receptor exhibit reduced arterial blood pressure [42]. Conversely, deletion of the gene encoding the GPR41 receptor in mice results in elevated arterial blood pressure [43]. In another noteworthy study, it was demonstrated that fecal transplantation from hypertensive patients into normotensive, germ-free mice resulted in the transfer and subsequent manifestation of elevated blood pressure in the recipient animals, indicating a potential causal role of gut microbiota in the development of hypertension [44].

3.3 Lipopolysaccharide (LPS)

Bacterial lipopolysaccharide (LPS) is a fundamental structural component of the outer membrane of Gram-negative bacteria [45]. Bacterial lipopolysaccharide (LPS) exerts a broad spectrum of detrimental effects on gastrointestinal function. It initiates inflammatory responses within the intestinal tract and compromises the integrity of the gut barrier by disrupting tight junction (TJ) intercellular structures. Moreover, LPS induces oxidative stress in intestinal epithelial cells, leading to mitochondrial dysfunction and the activation of mitophagy, thereby further impairing the functional state of the intestinal barrier [46]. Lipopolysaccharide (LPS) may influence the stability of atherosclerotic plaques within arterial walls through both direct and indirect mechanisms, potentially contributing to their destabilization [47], [48], [49]. Studies have indicated that the occurrence of cardiovascular events following myocardial infarction may be attributable to the translocation of gut microbial products—such as lipopolysaccharide (LPS) and D-lactate—into the systemic circulation [50].

4. **Probiotics and prebiotics**

Probiotics are live microorganisms that, when administered to the host in appropriate quantities, exert beneficial effects on health and physiological functioning [51]. Prebiotics are selectively fermented dietary components that can modulate both the composition and metabolic activity of the gut microbiota, leading to beneficial physiological effects that support the health and homeostasis of the host organism [52]. Research indicates that microorganisms classified as probiotics may exert beneficial effects on the host's nonspecific immune response, primarily through the activation of natural killer (NK) cells and macrophages, as well as the stimulation of cytokine secretion. Moreover, scientific evidence

suggests that probiotics possess antiproliferative, pro-apoptotic, and antioxidant properties [53].

The conducted study demonstrated that a twelve-week supplementation with probiotic formulations in patients with diabetes and ischemic heart disease led to improvements in glycemic control parameters, an increase in high-density lipoprotein (HDL) cholesterol levels, and a favorable reduction in the total cholesterol to HDL ratio. Additionally, a decrease in inflammatory biomarkers and oxidative stress was observed, suggesting a multifaceted therapeutic effect of the administered probiotics [54]. In an experimental rat model of hypercholesterolemia, prebiotic supplementation was shown to reduce total serum cholesterol levels, thereby indicating the potential hypolipidemic properties of prebiotics [55]. Conversely, a human study demonstrated that regular consumption of yogurts enriched with synbiotic components exerts cardioprotective effects in individuals with elevated blood cholesterol levels, contributing to a reduced risk of cardiovascular disease development within this population [56].

5. **Fecal Microbiota Transplantation (FMT)**

This procedure involves the collection and appropriate preparation of fecal material obtained either from a healthy donor or from the patient themselves, in the case of autologous fecal microbiota transplantation (FMT), with the autologous material being collected prior to the onset of disease and associated dysbiosis. The processed material is then introduced into the gastrointestinal tract of the affected individual with the aim of restoring the normal composition of the gut microbiome [57]. Experimental studies have demonstrated that transplantation of cecal microbiota from inbred mouse strains with high susceptibility to atherosclerosis, as compared to microbiota from resistant strains, resulted in an increased severity of diet-induced atherosclerotic lesions in response to a choline-rich diet. This effect was associated with elevated serum TMAO levels, highlighting the critical role of gut microbiota composition in the pathogenesis of atherosclerosis [58]. Despite growing interest in fecal microbiota transplantation (FMT) as a therapeutic strategy, its broader application remains limited due to potential safety concerns. Major risks include the possible transmission of endotoxins and pathogenic microorganisms, which may lead to the emergence of new gastrointestinal disorders and other adverse reactions in the recipient [59].

6. Conclusions

The accumulated body of evidence underscores the multifaceted involvement of intestinal microbiota in the complex pathophysiological landscape of cardiovascular diseases. Observations derived from both preclinical and clinical research converge on the hypothesis that disturbances in microbial composition—particularly those influencing the generation of key metabolites such as TMAO, SCFAs, and LPS—contribute to alterations in immunoinflammatory tone, vascular homeostasis, and systemic metabolic equilibrium.

Notably, trimethylamine-N-oxide (TMAO) has emerged as a metabolite of particular relevance, displaying proatherogenic and prothrombotic properties with prognostic implications in diverse cardiovascular cohorts. Conversely, short-chain fatty acids exhibit a spectrum of beneficial actions, including maintenance of epithelial integrity and blood pressure modulation, suggesting their therapeutic potential in cardiovascular risk reduction.

In this context, dysbiosis—whether instigated by dietary habits, pharmacological interventions, or environmental stressors—may serve not only as a marker of systemic perturbation but also as a modifiable determinant of disease progression. Interventions targeting microbial modulation, including probiotics, prebiotics, synbiotics, and fecal microbiota transplantation, remain promising yet insufficiently validated tools that warrant rigorous clinical appraisal.

Taken together, the intestinal microbiome should be regarded as an active regulatory interface with neuroimmune and endocrine capacities, intricately linked to cardiovascular health. Its inclusion in the paradigm of precision medicine holds the promise of novel diagnostic and therapeutic avenues, contingent upon future investigations delineating causative relationships, mechanistic pathways, and strain-specific functions within hostmicrobiome dynamics.

Disclosure

Author's contribution

Conceptualization: M. Świątko, P.Sosnowski; methodology: Marcin Grzebyk, A. Tokarska; software: A. Arnista, J. Rybak; check: A. Waszczuk, A. Kołodziejczyk, M. Grzebyk; formal analysis: P. Sosnowski, A. Arnista; investigation: M. Świątko, K. Gawrońska; resources: P.

Łapiński, A. Tokarska; data curation: J. Rybak, A. Kołodziejczyk; writing-rough preparation: A. Waszczuk, P. Łapiński; writing –review and editing: M. Świątko, P. Sosnowski; visualization: M. Grzebyk, A. Arnista; supervision: J. Rybak, A. Kołodziejczyk ; project administration: M. Świątko
All authors have read and agreed with the published version of the manuscript.

Financing statement

This research received no external funding.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement Not applicable.

Data Availability Statement

Not applicable.

Conflict of interest

The authors deny any conflict of interest

References

[1] E. Sanchez-Rodriguez *et al.*, 'The gut microbiota and its implication in the development of atherosclerosis and related cardiovascular diseases', Mar. 01, 2020, *MDPI AG*. doi: 10.3390/nu12030605.

[2] Y. Li, G. Cao, W. Jing, J. Liu, and M. Liu, 'Global trends and regional differences in incidence and mortality of cardiovascular disease, 1990−2019: findings from 2019 global burden of disease study', *Eur J Prev Cardiol*, vol. 30, no. 3, pp. 276–286, Feb. 2023, doi: 10.1093/eurjpc/zwac285.

[3] W. H. W. Tang, T. Kitai, and S. L. Hazen, 'Gut Microbiota in Cardiovascular Health and Disease', *Circ Res*, vol. 120, no. 7, pp. 1183–1196, Mar. 2017, doi:

10.1161/CIRCRESAHA.117.309715.

[4] J. Qin *et al.*, 'A metagenome-wide association study of gut microbiota in type 2 diabetes', *Nature*, vol. 490, no. 7418, pp. 55–60, Oct. 2012, doi: 10.1038/nature11450.

[5] E. Le Chatelier *et al.*, 'Richness of human gut microbiome correlates with metabolic markers', *Nature*, vol. 500, no. 7464, pp. 541–546, Aug. 2013, doi: 10.1038/nature12506.

[6] F. H. Karlsson *et al.*, 'Symptomatic atherosclerosis is associated with an altered gut metagenome', *Nat Commun*, vol. 3, 2012, doi: 10.1038/ncomms2266.

[7] A. Sandek *et al.*, 'Intestinal Blood Flow in Patients With Chronic Heart Failure A Link With Bacterial Growth, Gastrointestinal Symptoms, and Cachexia', 2014. doi: 10.1016/j.jacc.2014.06.1179.

[8] E. Pasini *et al.*, 'Pathogenic Gut Flora in Patients With Chronic Heart Failure', 2016. doi: 10.1016/j.jchf.2015.10.009.

[9] A. Luqman *et al.*, 'Role of the intestinal microbiome and its therapeutic intervention in cardiovascular disorder', *Front Immunol*, vol. 15, Jan. 2024, doi: 10.3389/fimmu.2024.1321395.

[10] A. M. Carías Domínguez, D. de Jesús Rosa Salazar, J. P. Stefanolo, M. C. Cruz Serrano, I. C. Casas, and J. R. Zuluaga Peña, 'Intestinal Dysbiosis: Exploring Definition,

Associated Symptoms, and Perspectives for a Comprehensive Understanding — a Scoping Review', Feb. 01, 2024, *Springer*. doi: 10.1007/s12602-024-10353-w.

[11] B. K. Perler, E. S. Friedman, and G. D. Wu, 'The Role of the Gut Microbiota in the Relationship Between Diet and Human Health', *Annual Review of Physiology Downloaded from www.annualreviews.org. Guest*, 2025, doi: 10.1146/annurevphysiol-031522.

[12] G. P. Donaldson, S. M. Lee, and S. K. Mazmanian, 'Gut biogeography of the bacterial microbiota', Dec. 16, 2015, *Nature Publishing Group*. doi: 10.1038/nrmicro3552.

[13] F. Di Vincenzo, A. Del Gaudio, V. Petito, L. R. Lopetuso, and F. Scaldaferri, 'Gut microbiota, intestinal permeability, and systemic inflammation: a narrative review', Mar. 01, 2024, *Springer Science and Business Media Deutschland GmbH*. doi: 10.1007/s11739-023-03374-w.

[14] X. Chen *et al.*, 'Gut microbiota and microbiota-derived metabolites in cardiovascular diseases', Oct. 05, 2023, *Lippincott Williams and Wilkins*. doi: 10.1097/CM9.0000000000002206.

[15] K. M. Ng *et al.*, 'Microbiota-liberated host sugars facilitate post-antibiotic expansion of enteric pathogens', *Nature*, vol. 502, no. 7469, pp. 96–99, 2013, doi: 10.1038/nature12503.

[16] S. M. Huse, L. Dethlefsen, J. A. Huber, D. M. Welch, D. A. Relman, and M. L. Sogin, 'Exploring microbial diversity and taxonomy using SSU rRNA hypervariable tag sequencing', *PLoS Genet*, vol. 4, no. 11, Nov. 2008, doi: 10.1371/journal.pgen.1000255.

[17] L. Trasande, J. Blustein, M. Liu, E. Corwin, L. M. Cox, and M. J. Blaser, 'Infant antibiotic exposures and early-life body mass', *Int J Obes*, vol. 37, no. 1, pp. 16–23, Jan. 2013, doi: 10.1038/ijo.2012.132.

[18] J. P. Karl *et al.*, 'Changes in intestinal microbiota composition and metabolism coincide with increased intestinal permeability in young adults under prolonged physiological stress', *American Journal of Physiology-Gastrointestinal and Liver Physiology*, vol. 312, no. 6, pp. G559–G571, Jun. 2017, doi: 10.1152/ajpgi.00066.2017.

[19] M. D. Cook *et al.*, 'Exercise and gut immune function: evidence of alterations in colon immune cell homeostasis and microbiome characteristics with exercise training', *Immunol Cell Biol*, vol. 94, no. 2, pp. 158–163, Feb. 2016, doi: 10.1038/icb.2015.108.

[20] S. J. Song *et al.*, 'Cohabiting family members share microbiota with one another and with their dogs', *Elife*, vol. 2013, no. 2, Apr. 2013, doi: 10.7554/eLife.00458.

[21] J. Zhu, J. Lyu, R. Zhao, G. Liu, and S. Wang, 'Gut macrobiotic and its metabolic pathways modulate cardiovascular disease', 2023, *Frontiers Media SA*. doi: 10.3389/fmicb.2023.1272479.

[22] M. Canyelles, C. Borràs, N. Rotllan, M. Tondo, J. C. Escolà-Gil, and F. Blanco-Vaca, 'Gut Microbiota-Derived TMAO: A Causal Factor Promoting Atherosclerotic Cardiovascular Disease?', Feb. 01, 2023, *MDPI*. doi: 10.3390/ijms24031940.

[23] J. M. Brown and S. L. Hazen, 'Microbial modulation of cardiovascular disease', Feb. 12, 2018, *Nature Publishing Group*. doi: 10.1038/nrmicro.2017.149.

[24] B. J. Bennett *et al.*, 'Trimethylamine-N-Oxide, a metabolite associated with atherosclerosis, exhibits complex genetic and dietary regulation', *Cell Metab*, vol. 17, no. 1, pp. 49–60, Jan. 2013, doi: 10.1016/j.cmet.2012.12.011.

[25] K. A. Romano, E. I. Vivas, D. Amador-Noguez, and F. E. Rey, 'Intestinal microbiota composition modulates choline bioavailability from diet and accumulation of the proatherogenic metabolite trimethylamine-N-oxide', *mBio*, vol. 6, no. 2, Mar. 2015, doi: 10.1128/mBio.02481-14.

[26] M. H. Janeiro, M. J. Ramírez, F. I. Milagro, J. A. Martínez, and M. Solas, 'Implication of trimethylamine n-oxide (TMAO) in disease: Potential biomarker or new therapeutic target', Oct. 01, 2018, *MDPI AG*. doi: 10.3390/nu10101398.

[27] D. Mafra *et al.*, 'Red meat intake in chronic kidney disease patients: Two sides of the coin', *Nutrition*, vol. 46, pp. 26–32, Feb. 2018, doi: 10.1016/j.nut.2017.08.015.

[28] W. Zhu, Z. Wang, W. H. W. Tang, and S. L. Hazen, 'Gut microbe-generated trimethylamine N-oxide from dietary choline is prothrombotic in subjects', Apr. 25, 2017, *Lippincott Williams and Wilkins*. doi: 10.1161/CIRCULATIONAHA.116.025338.

[29] N. B. B. S. L. X. S. L. S. C. X. J. R. A. K. L. L. Y. W. H. W. T. R. M. K. and S. L. H. A. Zeneng Wang, 'Impact of chronic dietary red meat, white meat, or non-meat protein on trimethylamine N-oxide metabolism and renal excretion in healthy men and women', Feb. 14, 2019, *Oxford University Press*. doi: 10.1093/eurheartj/ehy905.

[30] J. Geng *et al.*, 'Trimethylamine N-oxide promotes atherosclerosis via CD36-dependent MAPK/JNK pathway', *Biomedicine & Pharmacotherapy*, vol. 97, pp. 941–947, Jan. 2018, doi: 10.1016/j.biopha.2017.11.016.

[31] E. Randrianarisoa *et al.*, 'Relationship of serum trimethylamine N-oxide (TMAO) levels with early atherosclerosis in humans', *Sci Rep*, vol. 6, May 2016, doi: 10.1038/srep26745.

[32] J. R. Stubbs *et al.*, 'Serum Trimethylamine-N-Oxide is Elevated in CKD and Correlates with Coronary Atherosclerosis Burden', *Journal of the American Society of Nephrology*, vol. 27, no. 1, pp. 305–313, Jan. 2016, doi: 10.1681/ASN.2014111063.

[33] J. Gao *et al.*, 'Gut microbial taxa as potential predictive biomarkers for acute coronary syndrome and post-STEMI cardiovascular events', *Sci Rep*, vol. 10, no. 1, Dec. 2020, doi: 10.1038/s41598-020-59235-5.

[34] G. G. Schiattarella *et al.*, 'Gut microbe-generated metabolite trimethylamine-N-oxide as cardiovascular risk biomarker: a systematic review and dose-response metaanalysis', *Eur Heart J*, vol. 38, no. 39, pp. 2948–2956, Oct. 2017, doi: 10.1093/eurheartj/ehx342.

[35] M. Amrein *et al.*, 'Gut microbiota-dependent metabolite trimethylamine N-oxide (TMAO) and cardiovascular risk in patients with suspected functionally relevant coronary artery disease (fCAD)', *Clinical Research in Cardiology*, vol. 111, no. 6, pp. 692–704, Jun. 2022, doi: 10.1007/s00392-022-01992-6.

[36] C. Roncal *et al.*, 'Trimethylamine-N-Oxide (TMAO) Predicts Cardiovascular Mortality in Peripheral Artery Disease', *Sci Rep*, vol. 9, no. 1, Dec. 2019, doi: 10.1038/s41598-01952082-z.

[37] W. Zhu *et al.*, 'Gut Microbial Metabolite TMAO Enhances Platelet Hyperreactivity and Thrombosis Risk', *Cell*, vol. 165, no. 1, pp. 111–124, Mar. 2016, doi: 10.1016/j.cell.2016.02.011.

[38] A. B. Roberts *et al.*, 'Development of a gut microbe–targeted nonlethal therapeutic to inhibit thrombosis potential', *Nat Med*, vol. 24, no. 9, pp. 1407–1417, Sep. 2018, doi: 10.1038/s41591-018-0128-1.

[39] D. J. Morrison and T. Preston, 'Formation of short chain fatty acids by the gut microbiota and their impact on human metabolism', May 03, 2016, *Taylor and Francis Inc.* doi: 10.1080/19490976.2015.1134082.

[40] V. Gerdes, M. Gueimonde, L. Pajunen, M. Nieuwdorp, and K. Laitinen, 'How strong is the evidence that gut microbiota composition can be influenced by lifestyle interventions in a cardio-protective way?', *Atherosclerosis*, vol. 311, pp. 124–142, Oct. 2020, doi: 10.1016/j.atherosclerosis.2020.08.028.

[41] Y. Wu, H. Xu, X. Tu, and Z. Gao, 'The Role of Short-Chain Fatty Acids of Gut Microbiota Origin in Hypertension', Sep. 28, 2021, *Frontiers Media S.A.* doi: 10.3389/fmicb.2021.730809.

[42] J. L. Pluznick *et al.*, 'Olfactory receptor responding to gut microbiotaderived signals plays a role in renin secretion and blood pressure regulation', *Proc Natl Acad Sci U S A*, vol. 110, no. 11, pp. 4410–4415, Mar. 2013, doi: 10.1073/pnas.1215927110.

[43] N. Natarajan *et al.*, 'Microbial short chain fatty acid metabolites lower blood pressure via endothelial G protein-coupled receptor 41', *Physiol Genomics*, vol. 48, pp. 826–834, 2016, doi: 10.1152/physiolgenomics.00089.2016.-Short.

[44] J. Li *et al.*, 'Gut microbiota dysbiosis contributes to the development of hypertension', *Microbiome*, vol. 5, no. 1, 2017, doi: 10.1186/s40168-016-0222-x.

[45] R. F. Maldonado, I. Sá-Correia, and M. A. Valvano, 'Lipopolysaccharide modification in gram-negative bacteria during chronic infection', Jul. 01, 2016, *Oxford University Press*. doi: 10.1093/femsre/fuw007.

[46] S. Cao *et al.*, 'LPS challenge increased intestinal permeability, disrupted mitochondrial function and triggered mitophagy of piglets', *Innate Immun*, vol. 24, no. 4, pp. 221–230, May 2018, doi: 10.1177/1753425918769372.

[47] S. Nooti *et al.*, 'Oxidized Low-density Lipoproteins and Lipopolysaccharides Augment Carotid Artery Plaque Vulnerability in Hypercholesterolemic Microswine', *Cardiol Cardiovasc Med*, vol. 07, no. 04, 2023, doi: 10.26502/fccm.92920338.

[48] J. E. Jaw *et al.*, 'Lung exposure to lipopolysaccharide causes atherosclerotic plaque destabilisation', *European Respiratory Journal*, vol. 48, no. 1, pp. 205–215, Jul. 2016, doi: 10.1183/13993003.00972-2015.

[49] M. Ni *et al.*, 'Atherosclerotic plaque disruption induced by stress and lipopolysaccharide in apolipoprotein E knockout mice', *American Journal of Physiology-Heart and Circulatory Physiology*, vol. 296, no. 5, pp. H1598–H1606, May 2009, doi: 10.1152/ajpheart.01202.2008.

[50] X. Zhou *et al.*, 'Gut-dependent microbial translocation induces inflammation and cardiovascular events after ST-elevation myocardial infarction', *Microbiome*, vol. 6, no. 1, p. 66, Apr. 2018, doi: 10.1186/s40168-018-0441-4.

[51] J. Gerritsen, H. Smidt, G. T. Rijkers, and W. M. De Vos, 'Intestinal microbiota in human health and disease: The impact of probiotics', Aug. 2011. doi: 10.1007/s12263-0110229-7.

[52] D. M. Linares, P. Ross, and C. Stanton, 'Beneficial Microbes: The pharmacy in the gut', Jan. 02, 2016, *Taylor and Francis Inc.* doi: 10.1080/21655979.2015.1126015.

[53] A. Nowak, A. Paliwoda, and J. Błasiak, 'Anti-proliferative, pro-apoptotic and antioxidative activity of *Lactobacillus* and *Bifidobacterium* strains: A review of mechanisms and therapeutic perspectives', *Crit Rev Food Sci Nutr*, vol. 59, no. 21, pp. 3456–3467, Nov. 2019, doi: 10.1080/10408398.2018.1494539.

[54] F. Raygan *et al.*, 'The effects of probiotic supplementation on metabolic status in type 2 diabetic patients with coronary heart disease IRCT2017082733941N5 IRCT', *Diabetol Metab Syndr*, vol. 10, no. 1, Jun. 2018, doi: 10.1186/s13098-018-0353-2.

[55] J. A. Parnell and R. A. Reimer, ‘Effect of prebiotic fibre supplementation on hepatic gene expression and serum lipids: A dose-response study in JCR:LA-cp rats’, *British Journal of Nutrition*, vol. 103, no. 11, pp. 1577–1584, Jun. 2010, doi: 10.1017/S0007114509993539.

[56] V. Mofid, A. Izadi, S. Y. Mojtahedi, and L. Khedmat, ‘Therapeutic and Nutritional Effects of Synbiotic Yogurts in Children and Adults: a Clinical Review’, *Probiotics Antimicrob Proteins*, vol. 12, no. 3, pp. 851–859, Sep. 2020, doi: 10.1007/s12602-01909594-x.

[57] A. Leshem, N. Horesh, and E. Elinav, ‘Fecal microbial transplantation and its potential application in cardiometabolic syndrome’, 2019, *Frontiers Media S.A.* doi: 10.3389/fimmu.2019.01341.

[58] J. C. Gregory *et al.*, ‘Transmission of atherosclerosis susceptibility with gut microbial transplantation’, *Journal of Biological Chemistry*, vol. 290, no. 9, pp. 5647–5660, Feb. 2015, doi: 10.1074/jbc.M114.618249.

[59] L. M. De Leon, J. B. Watson, and C. R. Kelly, ‘Transient Flare of Ulcerative Colitis After Fecal Microbiota Transplantation for Recurrent Clostridium difficile Infection’, *Clinical Gastroenterology and Hepatology*, vol. 11, no. 8, pp. 1036–1038, Aug. 2013, doi: 10.1016/j.cgh.2013.04.045.