Review

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The gut–heart axis: a review of gut microbiota, dysbiosis, and cardiovascular disease development

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Background: Cardiovascular diseases (CVDs) are a major cause of morbidity and mortality worldwide and there are strong links existing between gut health and cardiovascular health. Gut microbial diversity determines gut health. Dysbiosis, described as altered gut microbiota, causes bacterial translocations and abnormal gut byproducts resulting in systemic inflammation.
Objective: To review the current literature on the relationships between gut microbiota, dysbiosis, and CVD development, and explore therapeutic methods to prevent dysbiosis and support cardiovascular health.
Summary: Dysbiosis increases levels of pro-inflammatory substances while reducing those of anti-inflammatory substances. This accumulative inflammatory effect negatively modulates the immune system and promotes vascular dysfunction and atherosclerosis. High *Firmicutes* to *Bacteroidetes* ratios, high trimethylamine-n-oxide to short-chain fatty acid ratios, high indole sulfate levels, low cardiac output, and polypharmacy are all associated with worse cardiovascular outcomes. Supplementation with prebiotics and probiotics potentially alleviates some CVD risk. Blood and stool samples may be used in clinical practice to quantify and qualify gut bacterial ratios and byproducts, assess patients' risk for adverse cardiovascular outcomes, and track their gut health progress. Further research is required to set population-based cutoffs for normal and abnormal gut microbiota and byproduct ratios.

Keywords: atherosclerosis and dysbiosis, dysbiosis, gut–heart axis, gut microbiota, polypharmacy and dysbiosis

Introduction

Gut health is linked to cardiovascular health. This association is of grave importance given that cardiovascular disease (CVD) remains the leading worldwide cause of morbidity and mortality. According to a 2024 statistics report by the American Heart Association, there are 19.05 million cardiovascular-related deaths worldwide every year. The United States alone accounts for 697 000 of these deaths annually. The most common CVDs contributing to these deaths are myocardial ischemia, heart failure (HF), and coronary artery disease (CAD). Apart from CVD mortality, up to 48% of U.S. adults suffer from one or more CVDs. This high morbidity can be attributed to multiple cardiovascular risk factors that are common among the U.S. population. Risk factors include diabetes mellitus, chronic kidney disease, high body mass index, and hyperlipidemia[1].

HIGHLIGHTS

- Gut microbial composition is influenced by diet, medications, and genetic factors. Alterations result in a leaky gut and subsequent proinflammatory responses that promote atherosclerosis.
- Butyrate suppresses histone deacetylase reducing cardiovascular risk. Mediterranean diets, curcumin, green tea, and resveratrol enhance butyrate synthesis.
- Trimethylamine N- oxide is a potential biomarker for cardiovascular risk. Elevated levels are associated with an increased risk of all-cause mortality and cardiovascular events.
- Supplementing with prebiotics, probiotics, and berberine and addressing the underlying causes of dysbiosis enhances cardiovascular health.

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During infancy, the gut microbiota formulates and continues to grow[2]. There are over 10 trillion microorganisms in the human gut, including bacteria, archaea, viruses, protozoa, and fungi species[3]. Gut microbiota breaks down food into specific metabolites that increase the risk of CVD[4]. The gut microbiota is fundamentally composed of *Bacteroidetes, Firmicutes, Proteobacteria, Actinobacteria*, and *Verrucomicrobia. Bacteroidetes* and *Firmicutes* account for nearly 90% of the microbial population. These species support hemostasis of the intestinal epithelial barrier, provide nutrients, help digest indigestible nutrients, govern innate immunity, and protect against infections[5]. Gut microbiotas maintain the integrity of the intestinal epithelial barrier by repairing tight junctions, augmenting the mucin gene, and blocking pathogenic bacteria from binding to intestinal epithelial cells[6]. Dysbiosis refers to an imbalance in the microbial composition of the gut[7], that is triggered by dietary and environmental changes, as well as intestinal infections that promote inflammation and metabolic disorders, which lead to CVD development[8]. Dysbiosis disrupts the intestinal epithelial barrier, an integral part of intestinal absorption, leading to increased permeability of gut metabolites that correlate with myocardial dysfunction[9]. Specific gut microbiota, such as *Escherichia coli, Klebsiella pneumonia*, and *Streptococcus viridians*, are associated with HF[10]. The resulting intestinal wall edema from HF is linked to CVD evolution[11]. Gut bacterial translocation has also been identified in patients with atrial fibrillation and is linked to serious adverse cardiac events[12]. Further, short-chain fatty acids (SCFAs), metabolites generated from the microbial fermentation of complex carbohydrates in the colon, are considerably less abundant in patients with CAD[13].

Gut microbiota-derived products interact with cardiovascular phenotypes via molecular pathways and host receptors[11]. Gut microbiota also affects bioactivation, a process by which biologically active molecules, like enzymes, attain the ability to perform their functions[14,15]. Metabolites like bile acid and trimethylamine (TMA), and hormones including leptin, can assault host systems both directly and indirectly[16-18]. Recent systematic review publications have outlined the gut microbiome's impact on atherosclerosis and CVD, underscoring the role of metabolites like trimethylamine-n-oxide (TMAO) and SCFAs[19]. However, some inconsistencies in the evidence remain[20]. This review comprehensively highlights the current knowledge of gut microbiota and dysbiosis and their effects on cardiovascular health and disease development. It also addresses therapeutic avenues for preventing and improving dysbiosis, which are especially pertinent for clinical practitioners.

Review

Dysbiosis and cardiovascular disease

A disrupted or compromised intestinal barrier integrity, also called leaky gut, impairs baseline immune functions, causing diseases, including CVD[21]. A leaky gut causes movement or displacement of gut microbiota-derived components, such as lipopolysaccharides (LPSs) from the intestines to the circulation. LPSs are glycolipid components of the gram-negative bacteria cell envelope. Microbiota translocation elevates serum levels of toxins and LPSs, which are thought to induce the production of pro-inflammatory cytokines leading to inflammation[22]. This causes suboptimal cardiovascular function and triggers atherosclerosis[23]. LPSs initiate pro-inflammatory pathways that promote leukocyte infiltration into atherosclerotic lesions. This multifaceted process depends on intricate protein–protein interactions involving LPS-binding protein (LBP), toll-like receptor-4, cluster of differentiation 14, and protein MD-2. LBP, a liver-derived glycoprotein, plays a pivotal role as the first LPS binder. This suggests its potential as a reliable biomarker of innate immune activation in atherosclerosis[24-27]. A study of 247 men undergoing elective coronary angiography noted a significant positive correlation between serum LBP levels and the severity of CAD, highlighting its potential utility as a CAD biomarker[28].

The link between gut microbiota composition and atherosclerotic plaque development is backed by recent investigations reporting the presence of bacterial DNA, mainly LPS deposition, within atherosclerotic lesions. Two studies identified an elevated *Firmicutes* to *Bacteroidetes* ratio (F/B ratio) in patients with CAD or high intima-media thickness values. The F/B ratio could be therefore considered a marker for subclinical atherosclerosis. This finding was also observed in obese individuals[29-31]. Despite the presence of *Firmicutes* and *Proteobacteria* in atherosclerotic lesions, consensus regarding the criticality of the gut microbiota in atherosclerosis severity remains elusive. One study reported significant differences in gut microbiota between patients with stable and unstable plaques. Another study, however, observed no major dissimilarities in bacterial DNA content or composition between these plaque types[32,33]. Bacterial DNA activates macrophages via Toll-like receptors, immunity system receptors that recognize pathogens, potentially influencing plaque stability[34,35]. A multi-omics study reported an abundance of *Acidaminococcus, Christensenella*, and *Lactobacillus* genera in patients with CAD compared to healthy patients. Although *Acidaminococcus* is considered normal flora, it has often been associated with inflammatory diseases and positively correlates with pro-inflammatory dietary patterns. This suggests its potential role as an inflammatory biomarker in patients with atherosclerosis[36].

Certain factors such as nucleotide-binding domain, leucine-rich-containing family, Pyrin domain-containing-3 (NLRP3) inflammasome, adequate intestinal perfusion, and anti-inflammatory modulators maintain intestinal epithelium stability and are protective against dysbiosis. NLRP3 inflammasome is an intracellular sensor for innate immunity. Showcasing this fact was a study that reported colons of NLRP3-deficient mice being more heavily colonized with bacteria than mice with normal NLRP-3 expression[37]. In patients with HF, abnormally low cardiac output leads to low gastrointestinal perfusion, which induces intestinal ischemia and edema. These vascular changes alter intestinal morphology and function, gut microbiota composition, and cause elevated levels of circulating endotoxins which accelerate the systemic inflammatory response[8]. Invariably, a myriad of evidence links inflammation to an amplified CVD risk[38,39]. A randomized, double-blind trial, the Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS), compared Canakinumab to placebo in over 10,000 patients with a history of myocardial infarction. Canakinumab is an antibody against interleukin-1β, a strong pro-inflammatory cytokine. Compared to the placebo arm, Canakinumab administration caused a 15% reduction in cardiovascular accident risk, independent of lipid levels[40].

Microbiota-derived gut metabolites and cardiovascular disease

Bile acids

Bile acids have a bidirectional relationship with gut microbiota. Their functions are strongly linked to bacterial metabolism. They alter gut microbiota composition and cause bacterial overgrowth syndromes through dynamic antimicrobial and immune properties[41]. An example is abnormal bile acid levels linked to insulin resistance in type 2 diabetes mellitus[42,43]. A randomized, open-label, two-arm, multicenter clinical trial evaluating patients' responses to diabetic treatments noted vast differences in the bile acid profiles between treatment responders and non-responders. The concentration of certain bile acids like ursodeoxycholic acid was higher in therapy responders versus non-responders. It concluded that treatment outcomes for anti-diabetic treatments like Acarbose were dependent on gut microbiota composition pre-treatment. Those with a higher *Bacteroides* abundance responded better to Acarbose treatment than patients with *Prevotella* abundance[44]. Measuring bile acid levels can potentially assist in evaluating the effects of gut microbiota on cardiometabolic diseases[43]. Farsenoid X receptor is vital in bile acid homeostasis and is thought to contribute to bile acids' anti-inflammatory effects[34]. Another bile acid receptor that reduces inflammation is Gpbar1 (TGR5). It regulates energy and glucose utilization and protects against LPS-induced inflammation and atherosclerosis[45].

Short chain fatty acids

The main SCFAs are acetate, propionate, and butyrate. Butyrate triggers colonic regulatory T cells and exerts regional anti-inflammatory actions in the intestinal mucosa. Gut microbial alterations influencing butyrate formation also affect inflammatory pathways[46]. Multiple studies note that SCFA producers, specifically butyrate producers, are remarkably less abundant in patients with CAD[13] A study looking at the gut microbiota of 169 patients with symptomatic CAD observed a reduction in *Roseburia* and *Eubacterium* species, both SCFA-forming bacteria[47]. This reduction was also noted in other studies that displayed a relationship between dysbiosis and hypertension. In hypertensive rats, a significant decrease in butyrate and acetate was observed, as well as an abundance of lactate-producing bacteria. In addition, oral minocycline improved dysbiosis and hypertension. Reduced blood pressure was also noted in animal subjects supplemented with SCFAs, suggesting a preventative role of SCFAs against hypertension[48,49]. SCFAs protect against hypertension by lowering plasma lipid levels. SCFAs inhibit cholesterol synthesis or redirect it to the liver. Therefore, they are suggested as protective elements against CAD development[50]. In humans, butyrate specifically helps lower diastolic blood pressure. A randomized, double-blind trial studying the effect of butyrate on 60 patients with type 2 diabetes mellitus noted a statistically significant ($P < 0.05$) reduction in diastolic blood pressure in treatment groups. The abundance of *Akkermansia muciniphila,* a bacteria known for its anti-inflammatory effects, was also increased in treated individuals[51]. Butyrate modulates blood pressure through vasorelaxation and activation of a SCFA sensor, the G protein-coupled receptor 41[52,53].

Bacteroidetes produce acetate and propionate, and *Firmicutes* produce butyrate[54]. This information is the basis for the F/B ratio, which helps assess patients' metabolic gut configuration. A normal F/B ratio is 2:1. Higher F/B ratios have been noted in obese individuals[55]. In obese patients, the higher F/B ratio is associated with cardiovascular pathologies. In the elderly, a decrease in *Bacteroidetes* and an increase in *Firmicutes* has been related to the development of atherosclerosis[48,56-58]. Patients with elevated blood pressure display systemic inflammation that can be linked to dysbiosis[59]. This is backed by data from multiple studies on hypertensive models that have demonstrated a higher F/B ratio in affected hosts[46,48,60].

Indoxyl sulfate

Indoxyl sulfate (IS) is a protein-bound uremic toxin produced from tryptophan. Tryptophan is an amino acid consumed in the diet and metabolized by the gut microbiota to indole. Indole is then oxidized in the liver to form IS, which is excreted in the urine[61]. IS activates the aryl hydrocarbon receptor, a transcription factor that regulates gene expression of cytochrome P450 enzymes. Cytochrome P450 enzymes typically metabolize both endogenous metabolites and xenobiotics[62]. Various studies have concluded that IS causes endothelial dysfunction through aryl hydrocarbon receptor activation[61-64]. As such, IS promotes thrombosis, atherosclerosis, and arteriosclerosis. Thrombosis is caused by platelet and tissue factor activation. While atherosclerosis is caused by leukocyte adhesion and endothelial dysfunction, IS promotes arteriosclerosis via pro-oxidative effects that contribute to vascular calcification and vascular smooth muscle cell proliferation[64]. High levels of IS have been noted in individuals with chronic kidney disease and dysbiosis, and are correlated with elevated cardiovascular risk[63]. A prospective study followed 147 pre-dialysis chronic kidney disease patients over 3 years. It aimed to explore the association between IS levels and major adverse cardiovascular events (MACEs). MACEs occurred in 32% of patients. IS levels were higher in patients with MACEs (2.36 mg/100 mL) than those without MACEs (1.21 mg/100 mL). Being female, of older age, with hypertension or diabetes mellitus were factors associated with high IS and MACEs[65]. The association between IS and accelerated CVD in chronic kidney disease can be combated by developing novel therapies that lower gut derived IS[66].

Trimethylamine-N-oxide

Individuals with CVD tend to have elevated TMAO levels. TMA is produced by choline and carnitine-consuming gut bacteria. These are predominantly *Firmicutes, Proteobacteria*, and *Actinobacteria*[67]. In subjects with high TMAO levels, *Firmicutes* bacteria appear significantly more prevalent than *Bacteroidetes* bacteria. *Clostridiales* genera of the *Firmicutes phylum*, including, *Clostridiaceae, Lachnospiraceae*, and *Veillonellaceae* are especially abundant[68]. Betaine, L-carnitine, phosphatidylcholine, lecithin, and choline are among the dietary

Table 1

Various foods containing the dietary components involved in TMAO production. Created using MS word.

Dietary components	Dietary foods
Choline	Beef, eggs, soybeans, chicken, fish, potatoes, wheat germ, kidney beans, quinoa, and diary.
Phosphatidylcholine	Eggs, peanuts, dairy, and chicken.
Betaine	Beets, spinach, quinoa, wheat, oats, brown rice, and barley.
L-carnitine	Fish, red meat, and dairy.

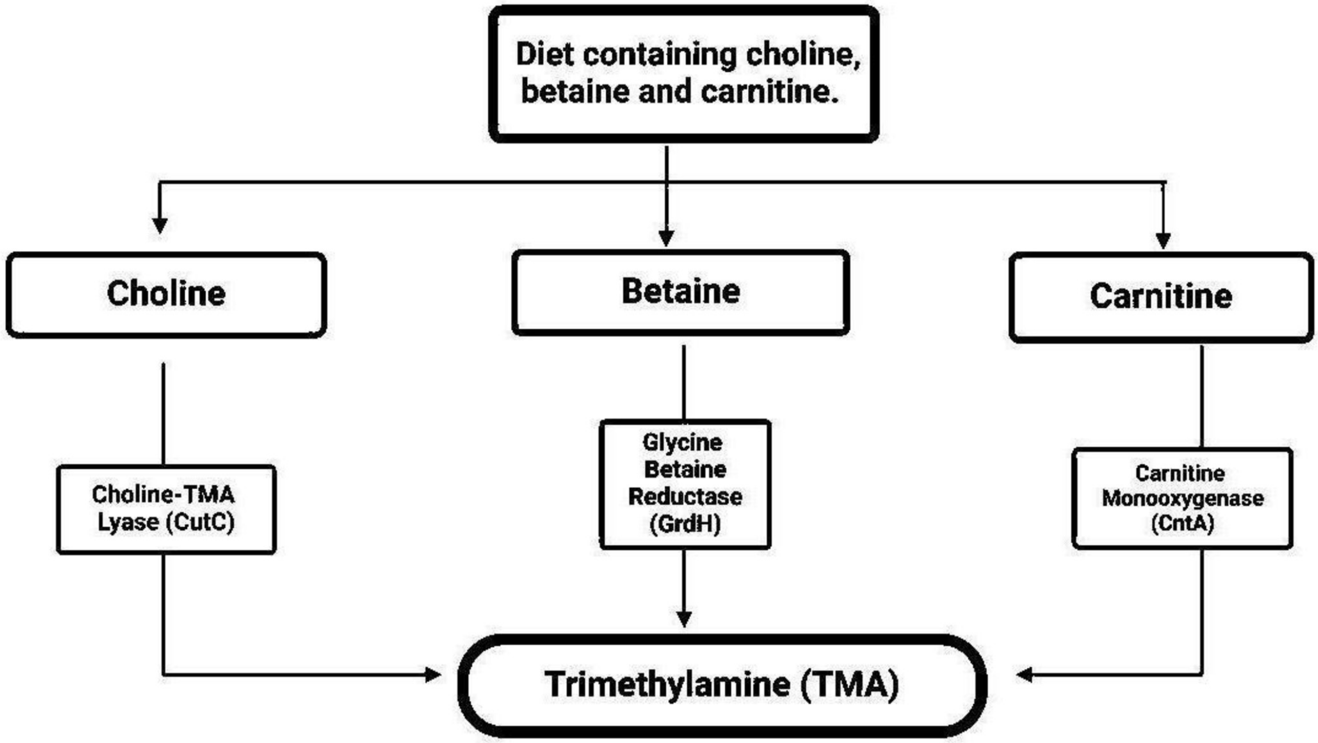

Figure 1. Pathways involved in the production of TMA. Created using BioRender.

components contributing to TMA production, as shown in Table 1[69-73]. TMA is the precursor of TMAO. In a human dietary intervention study, different protein sources, red meat versus white meat versus non-meat, were investigated for their effects on TMAO levels. Subjects who consumed approximately 8 oz of red meat daily for 4 weeks had substantially higher levels of TMAO than any of the other subjects[74].

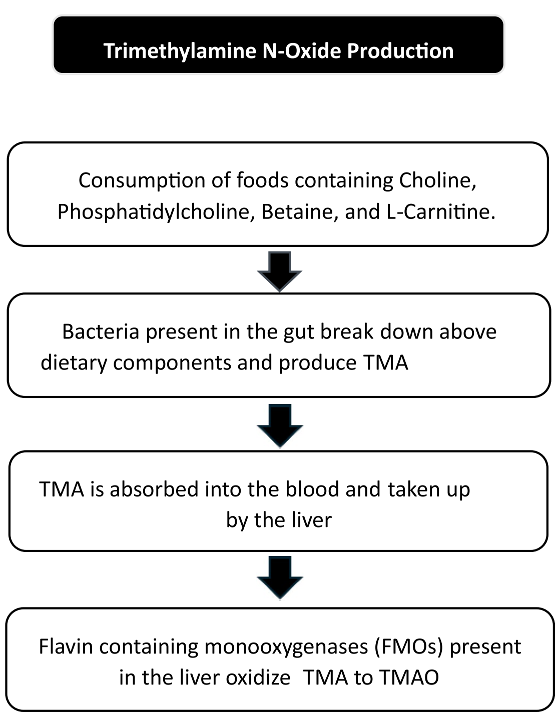

Figure 2. TMAO production in the gut. Created using MS Word.

Gut microbes degrade the dietary components described in Table 1 into TMA. Several recognized pathways produce bacterial TMA, including choline-TMA lyase, carnitine monooxygenase, and glycine betaine reductase, as shown in Fig. 1 [75]. The main pathway, however, is that of choline and carnitine. Choline is anaerobically metabolized to TMA via a radical-containing glycyl enzyme. Carnitine, on the other hand, is aerobically metabolized to TMA via the enzyme carnitine monooxygenase[68,75]. TMA is subsequently oxidized to produce TMAO in the liver via flavin-containing monooxygenases, as depicted in Fig. 2[16,76-80]. Afterward, TMAO is primarily excreted by the kidneys. This is one of the reasons patients with chronic kidney disease have high levels of TMAO and are more susceptible to accelerated atherosclerosis[81]. Since TMA is the precursor for TMAO, knowledge of the various pathways that produce TMA is necessary for atherosclerosis risk reduction. It paves the way for proper dietary recommendations and targeted pharmaceutical developments that block or reduce TMAO production.

Elevated TMAO concentrations have been linked to a 62% and 23% greater risk of all-cause mortality and cardiovascular events, respectively[76]. Some studies observed that a TMAO cut-off value of >6 μM amplified the possibility of unfavorable cardiac events[7]. A meta-analysis study that examined over 25,000 subjects concluded that for every 10-μmol/L accretion of TMAO, there was a subsequent 7.6% increase in all-cause mortality[82]. These elevated cardiovascular risks with increased TMAO levels are linked to accelerated atherosclerosis. TMAO stimulates calcium release from the rough endoplasmic reticulum, which induces platelet hyperactivity, modulates lipid metabolism, and promotes endothelial dysfunction. TMAO also stimulates cholesterol influx, reduces cholesterol efflux, and inhibits the bile acid pathway, leading to platelet hyperactivity and subsequent plaque formation[81,83,84] . In CAD patients with elevated TMAO, non-culprit plaques exhibit characteristics of vulnerability. These include reduced fibrous cap thickness, increased prevalence of thin-cap fibroatheroma, and increased microvascularization. Mice fed a high-choline diet demonstrate an increased tendency for intraplaque hemorrhage without significant alterations in the plaque composition or atherosclerotic burden[85,86]. Supplementing healthy human subjects with choline results in elevated levels of TMAO and enhanced platelet responsiveness and aggregation[87]. Apart from impacting platelet function, recent studies have demonstrated that TMAO triggers the expression of tissue factor, the initiator of extrinsic clotting, in in vitro endothelial cells[88]. In patients with higher levels of TMAO, such as those with type 2 diabetes mellitus, vascular tissue factor accelerates both thrombosis and vascular inflammation[89-92]. TMAO also causes foam cell formation by activating a protein folding molecule called heat shock protein 60. TMAO-induces other receptors, such as class A1 scavenger receptors and cluster of differentiation 36 in macrophages that can also stimulate heat shock protein 60[93-96]. In addition to promoting atherosclerosis, TMAO has been linked to hypertension, peripheral artery disease, coronary heart disease, myocardial infarction, and HF[83]. TMAO causes hypertension by stimulating nuclear factor kappa B (NF-κB), a protein transcription factor, and inflammasomes. Both raise endothelin-1 levels and decrease nitric oxide levels triggering endothelial dysfunction. TMAO also increases serum C-reactive protein and LPS endotoxin levels. Over time, these effects combined cause uncontrolled hypertension, increased vascular stiffness, and worsening cardiac output, ultimately resulting in HF[97-99].

A recent study divided patients with peripheral artery disease into two groups, critical limb ischemia (CLI) and intermittent claudication (IC). Two observations were noted, the first was that CLI patients had greater levels of TMAO than IC patients, and the second was that TMAO levels >2.26 μmol/L were associated with increased adverse cardiovascular events[83]. Another study examined the relationship between TMAO levels and MACEs in HF patients. Elevated TMAO levels were associated with MACEs. This association was indicated by a relative risk of 1.39 with a *P*-value of <0.0001[98]. A study by the American Heart Association used optical coherence tomography to evaluate plaque status in patients with ST-segment elevation myocardial infarction (STEMI). Patients with plaque rupture had significantly higher TMAO concentrations than those with plaque erosion. The TMAO cutoff value discriminating between plaque rupture and erosion in this study was 1.95 μmol/L[100]. Furthermore, a large prospective cohort study concluded that TMAO plasma levels were correlated with the occurrence of arterial thrombotic events in patients undergoing elective coronary angiography[87]. The SYNTAX score, a measure of atherosclerotic burden, can be used in CAD patients, those with stable angina or STEMI, to assess correlations between TMAO levels and disease severity[100,101]. The mechanisms of atherosclerosis development induced by TMAO are illustrated in Fig. 3.

TMAO is also associated with HF. A large cohort study on patients with acute and chronic HF demonstrated that increased TMAO levels were predictive of long-term mortality risk[102,103]. In another observation, HF patients with higher TMAO levels had 1.18-to-1.79-fold higher mortality and heart transplant rates than those with HF and lower TMAO levels[104]. These observations are likely due to TMAO playing a role in cardiac hypertrophy and fibrosis[105]. Metagenomics studies examining the gut microbial composition of patients with HF also reported that alterations in the gut microbiome led to higher levels of TMAO and lower levels of SCFAs. These changes prognosticate the development of inflammation, which considerably increases the risk of adverse cardiovascular outcomes. This illustrates a clear correlation between a high TMAO-to-SCFA ratio and CVD. Further research is required to figure out a golden ratio that would indicate a definitive increase or decrease in CVD risk[13]. Despite the presence of some inconsistent reports about the relationship between TMAO levels and CVD risk, diverse meta-analyses examining numerous cohorts from various continents established the presence of a profound relationship between elevated TMAO levels and CVD risk and mortality[76,82,106].

In summary, choline and carnitine-consuming bacteria form TMA which is converted to TMAO. Individuals with elevated TMAO exhibit an abundance of *Firmicutes, Proteobacteria, Actinobacteria, Clostridiaceae, Lachnospiraceae*, and *Veillonellaceae*. TMAO's most prominent cardiovascular complication is atherosclerosis. TMAO stimulates calcium release from the rough endoplasmic reticulum, modulates lipid and bile acid metabolism, triggers the expression of tissue factors, and induces heat shock protein 60. These effects combined lead to accelerated platelet activity, thrombosis, vascular inflammation, endothelial dysfunction, and foam cell formation. TMAO also weakens pre-existing plaques, predisposing CAD patients to plaque rupture and hemorrhage. Elevated TMAO levels are linked to a greater risk of adverse cardiovascular events in cardiac and noncardiac patients, and an incremental relationship exists between TMAO levels and adverse cardiovascular outcomes. Therefore, it could be considered a hazard biomarker for CVD risk and MACEs. However, a strict TMAO cut-off value is yet to be established.

Factors influencing the genetics and epigenetics of the gut–heart axis

Host genetic factors contribute to the variability of the gut microbiota[107]. Studies demonstrate a strong correlation between genetic loci and gut microbiota modifications[108]. A genome-wide analysis showed that the long-chain triglyceride locus encoding the enzyme lactase influenced the abundance of *Bifidobacterium*. This indicates that dairy intake can modulate gut microbiota genes. In addition, a variant of the MED13L allele associated with *Enterococcus faecalis* was linked to colorectal cancer development[109]. Studies also highlight the abundance of *Enterobacteriales* species in patients with major depressive disorder[110]. Intriguingly, certain blood types and ABO polymorphisms are highly linked to gut dysbiosis, CVDs, stomach cancers, insulin resistance, diabetes mellitus, asthma, and memory loss[111]. Epigenetic modifications are emerging as key targets for recomposing the gut microbiota. They present potential therapeutic options for not only CVD but also cancer. One of the most implicated epigenetic changes in this context is

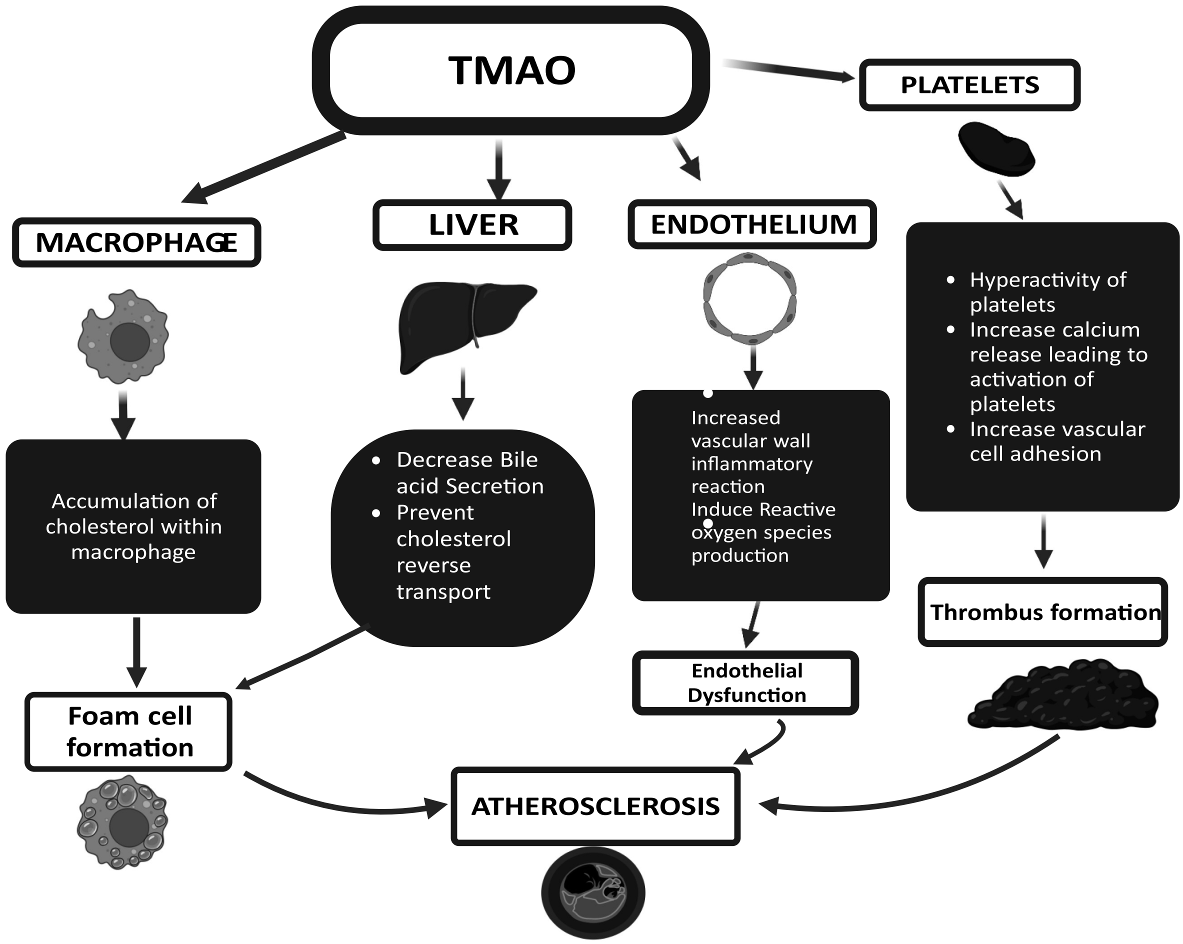

Figure 3. Mechanisms of atherosclerosis development due to TMAO. Created using Bio Render.

histone acetylation modification, which is mediated by histone acetyltransferase (HAT) and histone deacetylase (HDAC)[112]. In animal models, butyrate inhibits HDAC 1 activity in the heart, effectively attenuating cardiac dysfunction and fibrosis[113-115].

Mediterranean diets are abundant in nutrient-dense foods and xenobiotic compounds and have been regularly recommended to combat CVD[116]. Xenobiotic compounds are antioxidant and anti-inflammatory. They also modulate histone acetylation[117]. For example, curcumin, the main bioactive element in turmeric, has been shown to suppress HDAC 1 and reduce HAT activity by inhibiting acetyltransferase p300, an epigenetic controller known to promote cardiac hypertrophy and fibrosis, as well as atherosclerosis and myocardial infarction[113,118]. Curcumin supplementation in mice resulted in an increase in *Alistipes* and *Bacteroides* and a reduction in *Prevotella* species[119]. Consistent with this, a double-blind randomized pilot study concluded that curcumin supplementation in humans leads to increased *Clostridium xylanolyticum, Kluyvera intermedia, Collinsella aerofaciens*, and *Raoultella electrica*, and reduced *Coprococcus catus*[120]. Curcumin metabolism also increases SCFA synthesis in hypertensive patients[121].

Additional examples that illustrate an intimate connection between the microbiome, epigenome, phytochemicals, and CVD are resveratrol and the flavonoid epigallocatechin-3-gallate. Resveratrol is found in grapes and peanuts and regulates pro-inflammatory pathways implicated with HDACs in the heart. Resveratrol also induces sirtuin 1 and NAD+-dependent class III HDAC activation, reduces cardiomyocyte apoptosis, alters gut microbial composition, and increases SCFA production. Therefore, it protects the heart through a microbiome-epigenome-dependent mechanism[117,122,123]. In contrast to Resveratrol, epigallocatechin-3-gallate, found in green tea, attenuates HDAC 1 expression in mice. This leads to increased acetylation of the sarcoplasmic/endoplasmic reticulum Ca2 + ATPase 2a (SERCA2a) promoter, and elevated cardiac troponin I expression, a critical protein involved in cardiac contractility and relaxation[124,125]. Epigallocatechin-3-gallate is also considered anti-obesogenic and leads to increased expression of DNA methyltransferase 1, an enzyme critical for maintaining genomic stability[126,127].

Gut dysbiosis and congenital heart disease

Maternal gut dysbiosis has emerged as an environmental factor contributing to the pathogenesis of congenital heart disease (CHD). A case–control study recruited 196 mothers, 101 of which had CHD infants, while the rest had normal infants. Stool and plasma samples were analyzed to determine the links between maternal gut microbiota and the risk of CHD in infants. Results showed differences in both metabolic profiles and bacterial genera between the groups. 219 bacteria species were found in different abundances between the two groups. Overall microbial diversity was decreased in mothers with CHD infants. Specifically, *Bifidobacteria* and *Lactobacillus* were significantly reduced. *Bifidobacteria* and *Lactobacillus* have been linked to folate production which might explain the increased risk for CHD[128]. Interestingly, newborns with CHD display altered gut microbiota characteristics. Newborns with CHD have long-lasting hypoxemia and aberrant gut perfusion. This predisposes them to gut dysbiosis and intestinal barrier dysfunction that result in other inflammatory and metabolic conditions[129]. Implicated molecules and pathways include the vascular endothelial growth factor signaling pathway, cytokine–cytokine receptor interaction, and the NF-κB signaling pathway. The NF-κB signaling pathway is integral to intestinal homeostasis, inflammation, immunity, cell proliferation, differentiation, and survival. A study comparing the gut microbiota of 12 children with Tetralogy of Fallot to that of nine healthy controls. Researchers noted drastic dysbiosis in the Tetralogy of Fallot patients. Dysbiosis was marked by reduced microbial adaptability, synthesis, and metabolism. As well as, impaired gut functionality, including elevated oxidative, inflammatory, and immune responses. 14 microbiota genera were identified as biomarkers distinguishing Tetralogy of Fallot patients from healthy controls, including *Faecalibacterium, Akkermansia*, and *Subdoligranulum*. The most abundant bacteria in the Tetralogy of Fallot patients were *Firmicutes* (47.33%), *Proteobacteria* (24.44%), and *Bacteroidetes* (17.90%), compared to *Proteobacteria* (36.05%), *Firmicutes* (34.67%), and *Actinobacteria* (14.30%) in the control group[130].

The metabolism and immunological development of newborns with CHD are significantly affected by dysbiosis. Compared to healthy controls, neonates with critical CHD show increased amounts of *Proteobacteria*, a phylum that contributes to inflammation, decreased amounts of *Bacteroides*, and altered SCFAs and bile acid metabolism. In addition, *Enterococcus* overgrowth is linked to the reduction of probiotic-associated metabolites, especially aromatic lactic acids, lactic acid products, and B vitamins, suggesting an active underlying inflammatory response[129]. Further solidifying the relationship between dysbiosis and CHD is a cohort study on the effects of HF on gut microbiota in newborns with CHD. This study looked at 50 infants, 28 had CHD and HF, and the rest were healthy. *Firmicutes, Actinobacteria, Proteobacteria*, and *Bacteroidetes* were ample in CHD and HF infants, while the control group was rich in *Firmicutes, Proteobacteria, Actinobacteria*, and *Bacteroidetes*. Furthermore, the study noted a higher proportion of pathologic to desirable bacteria in the diseased infants. Specifically, the abundance of *Enterococcus, Shigella,* and *Subdoligranulum* was very high, whereas *Bifidobacterium, Blautia*, and *Bacteroides* were very low[131]. Table 2 summarizes the differences in gut health and bacterial abundance between healthy individuals and those with CHD.

Another connection between CHD and dysbiosis is the increased risk of necrotizing enterocolitis, a potentially fatal intestinal disease. CHD is one of the most common risk factors for necrotizing enterocolitis. Reduced cardiac output and shock in HF are linked to the underlying pathophysiology of necrotizing enterocolitis[2]. Hypoxia from reduced cardiac output results in intestinal inflammation and damaged gut barrier. Neutrophil-induced oxidative stress in inflammation disrupts inter-endothelial junctions. This facilitates the migration of inflammatory cells, bacteria, and bacterial products through the endothelium barrier causing mucosal damage and impaired mucosal immunity. A vicious cycle is created, where reduced gut perfusion from CHD leads to inflammation and secondary vasoconstriction This subsequently exacerbates gut hypoperfusion[132]. This cycle is illustrated in Fig. 4. CHD and dysbiosis associations offer preventive and therapeutic prospects for newborns with CHD and those predisposed to necrotizing enterocolitis without the presence of CHD, like preterm infants. Prompt medical and surgical intervention to optimize cardiac output along with prebiotics and probiotics supplementation would lower the risk of gastrointestinal inflammation and infection. This could ultimately reduce infant mortality rates from gastrointestinal infections.

Drug-induced dysbiosis

Drug-induced dysbiosis describes the general change or imbalance in intestinal microbiota composition or diversity induced by chronic or acute drug intake[133]. Current literature shows that out of the 1000 marketed cardiovascular drugs tested so far, approximately 24% inhibit at least one bacterial strain in the gut[134] Drugs can alter the intestinal microenvironment, microbial metabolism, and bacterial growth. Thereby affecting gut microbial composition and function[135]. We focused on the

Table 2

Comparison between healthy individuals and those with congenital heart disease. Created using MS Word.

Feature	Healthy individuals	Individuals CHD
Gut function	• Normal gut function; intact gut barrier • Modulates the immune system and protects against infections	• Impaired gut function; altered gut barrier • Disturbed immune system functions
Metabolic profile	• Normal SCFA and bile acid metabolism	• Altered SCFA and bile acid metabolism
Microbial diversity	• Normal to high microbial diversity • Balanced populations of beneficial bacteria	• Reduced diversity in infants and mothers of diseased infants • Increased presence of pathogenic bacteria and decreased beneficial bacteria
Bacterial abundance	• *Proteobacteria, Firmicutes, Actinobacteria* and *Bacteroidetes*	• *Firmicutes, Proteobacteria*, and *Bacteroidetes* in Tetralogy of Fallot patients • *Enterococcus, Shigella,* and *Subdoligranulum*

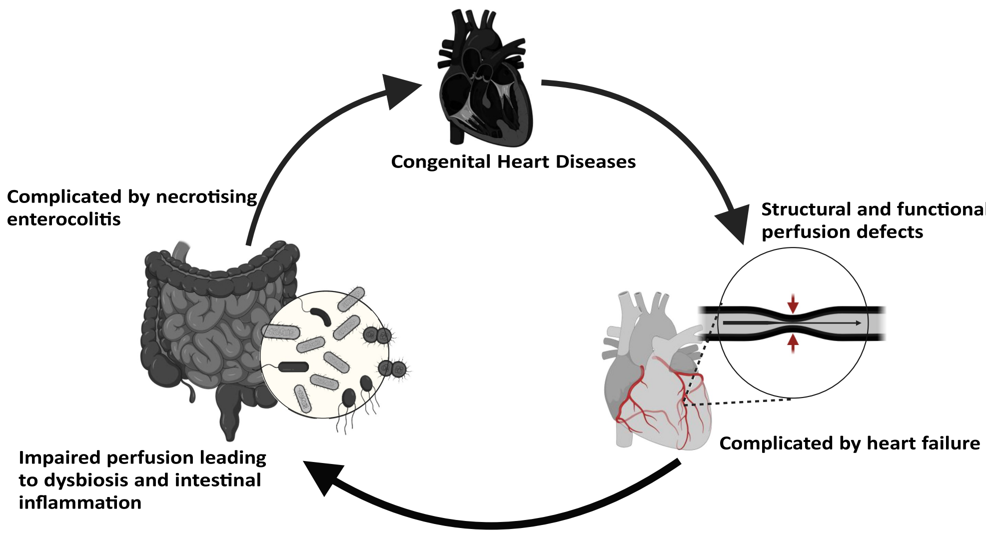

Figure 4. The relationship between CHD and Gut Microbiota. Created using BioRender.

pattern of dysbiosis caused by the most prescribed cardiovascular drugs[136]. Table 3 summarizes the relationship between various drugs and gut microbiota.

Antiplatelets and anticoagulants

Aspirin

The antiplatelet effects of aspirin may be attenuated in patients with high TMAO levels. This suggests TMAO's role in platelet reactivity and "aspirin resistance." Baby aspirin can cause dysbiosis and halt TMAO-mediated platelet hyper-responsiveness[11,137]. Aspirin mainly causes alterations in four bacterial taxonomic gut species: *Prevotella, Bacteroides*, family *Ruminococaceae*, and *Barnesiella* species[137]. *Prevotella* has been associated with better glucose metabolism and reported abundant in individuals who consume a plant-rich diet[138]. *Prevotella* also appeared to exacerbate intestinal inflammation in rats, decrease SCFA levels, mainly acetate, and alter intestinal IL-18 levels[139]. Further, a randomized controlled trial studying patients on 325 mg of aspirin observed improving levels of *Akkermisia*, a beneficial bacterium[140] . Conversely, *Ruminococaceae*, a bacteria linked to antibiotic-associated diarrhea was also increased in aspirin users. Both diarrhea and antibiotics were independent risk factors for intestinal dysbiosis[141-143]. Another study assessing the gut microbiota of patients on dual antiplatelet therapy, including aspirin and clopidogrel observed that the microbiota of subjects on dual antiplatelet therapy was abundant in *Streptococcaceae* and *Lactobacillaceae*, and deficient in *Acidaminococcaceae* and *Erysipelotrichaceae*[144]

Ticagrelor

Ticagrelor is an oral, reversible P2Y12 antagonist. It is currently recommended as the standard of care for patients with acute coronary syndrome. It reduces infarct size, and improves cardiac function and coronary blood flow, amongst other benefits[145]. Gut microbiota appears to influence the body's response to ticagrelor. A study examining 155 patients with poor ticagrelor response post-percutaneous coronary intervention noted varying gut microbiota composition between subjects. The participants were divided into a high platelet reactivity group and

Table 3

Summary of the relationship between various drugs and gut microbiota. Created using MS Word.

Drug category	Drug example	Relationship with gut microbiota
Antiplatelets	Aspirin	• Alters 4 bacterial taxonomic gut species: *Prevotella, Bacteroides, Ruminococaceae,* and *Barnesiella* species • Reduces short-chain fatty acid levels and increases intestinal inflammation • Increases levels of Akkermansia, a beneficial bacterium. • Increases *Ruminococaceae*, linked to antibiotic-associated diarrhea
	Ticagrelor	• High platelet reactivity is associated with 17 bacterial species, including *Bacillus, Methylbacterium, Staphylococcus, Acinetobacter,* and *Brevibacterium* • Anti-bacterial against *Clostridium difficile*
Anticoagulants	Warfarin	• Reduces in warfarin response is associated with increased *Escherichia* and *Shigella* • Decreases *Ruminococcus*, an anti-inflammation species. • Increases *Escherichia, Shigella*, and *Streptococcus*, which increase bleeding risk
Antihypertensives	Losartan	• Restores hypertension-induced gut dysbiosis
	Metoprolol Succinate	• Increases hippuric, hydroxy hippuric, and methyluric acid in the gut

a control group, those with normal platelet reactivity. Gut microbial diversity was higher in the high platelet reactivity group compared to the normal platelet reactivity group. 17 species of bacteria were found to be more abundant in the high platelet reactivity group, including *Bacillus, Methylbacterium, Staphylococcus, Acinetobacter,* and *Brevibacterium*[146]. High platelet reactivity is a risk factor for stent thrombosis, worse acute coronary syndrome outcomes, and myocardial infarction in patients with a history of invasive treatments[147]. An in vitro experimental study evaluating ticagrelor's activity against Clostridium *difficile* bacteria demonstrated anti-bacterial growth and anti-biofilm abilities. 20–40 µg/mL of ticagrelor was reported as the minimum inhibitory concentration against *C. difficile*[148].

Oral anticoagulants

In a prospective observational study, 200 patients undergoing heart valve replacement were investigated for the effect of gut microbiota on their response to warfarin. Patients were categorized according to their sensitivity to warfarin into low and high responders. Enterococcus levels were elevated in patients with higher warfarin response, while *Escherichia* and *Shigella* were elevated in patients with a reduced response. Warfarin's effectiveness is affected by Vitamin K, and an abundance of *Escherichia* and *Shigella* appears to influence the biosynthesis of vitamin K[149]. Another study on atrial fibrillation patients receiving warfarin versus atrial fibrillation patients not receiving warfarin versus healthy controls. Warfarin intake increased *Escherichia, Shigella*, and *Streptococcus*, all of which increased bleeding risk. Warfarin also reduced *Ruminococcus. Ruminococcus* displayed a favorable correlation with the neutrophil-to-lymphocyte ratio, an inflammatory marker, and an unfavorable correlation with the CHA_2DS_2-VASc scoring system for atrial fibrillation. These results imply both protective and inflammatory roles of warfarin on gut microbiota[150]. Heparin also appears to modulate gut microbiota. Oral administration of heparin in mice reduced the biodiversity of gut microbiota. Relative abundances of *Alistipes, Parasutterella*, and *Akkermansia* were observed, whereas *Ruminiclostridium* and *Bacteroides* decreased[151].

Antihypertensives

Multiple trials have explored the role of gut microbiota in antihypertensive drug absorption, efficacy, and pharmacokinetics. Still, only a few have clearly explained the changes in the gut microbial composition caused by individual antihypertensive classes[152]. Commonly used antihypertensives that affect gut microbial composition are losartan, captopril, enalapril, benazepril, and metoprolol[134]. Studies on hypertensive rodents observed that losartan, an angiotensin receptor blocker, increased colon integrity and intestinal sympathetic tone. This restored hypertension-induced gut dysbiosis. However, hydralazine, a nitric oxide-mediated vasodilator did not demonstrate this effect. Moreover, captopril, an angiotensin-converting enzyme inhibitor, showed an impact on gut microbial composition and permeability that persisted even after it was discontinued[153]. Elevated levels of gut metabolites, namely, hippuric, hydroxy hippuric, and methyluric acids were observed in a metabolomics data analysis on the effects of metoprolol succinate. Metoprolol is a beta-1 adrenergic antagonist used in the management of various common cardiac conditions. The underlying mechanism for this observation is unclear, but increased urinary excretion of all three metabolites was noted with chronic metoprolol therapy[154,155].

Polypharmacy and dysbiosis

The term "polypharmacy" has been synonymously used with "inappropriate medication usage" or "prescription without indication." The current acceptable definition of polypharmacy is the usage of 5 or more drugs. Polypharmacy can lead to unwarranted drug–drug interactions in which cardiovascular drugs are commonly known to be involved[156]. In long-term rodent studies, non-antibiotic polypharmacy resulted in a relevant decrease in *Bifidobacteriaceae, Lactobacillaceae, Clostridiacea*, and *Turicibacteraceae*, and an increase in *Desulfovibrionaceae, Lachnospiraceae*, and *Prevotellaceae*[157]. *Bifidobacteriaceae* form up to 80% of the gut microbiota during infancy and childhood. It gradually decreases to compromise approximately 4% of the adult gut, and further decreases upon aging[158,159]. *Bifidobacteriaceae* possess both anti-inflammatory and antioxidant functions[160,161]. They are linked to the reduction of multiple cardiovascular threats, such as obesity, dyslipidemia, and type 2 diabetes mellitus[162]. A clear-cut reduction in this species is observed with CVD and the use of multiple cardiovascular medications[159]. Other drugs that decrease *Bifidobacterium* levels include antibiotics, proton pump inhibitors, and laxatives[162]. Physicians must be acquainted with the harmful inflammatory gut effects associated with polypharmacy, and use caution when prescribing multiple drugs simultaneously, especially in the elderly or those with known CVD. It is also pertinent for practitioners to adapt strategies to preserve gut balance, including prebiotics and probiotics. Patient education in the form of regular check-ins and drug counseling also plays a role in reducing polypharmacy.

Therapeutic approaches to prevent dysbiosis

Diet

Dietary fibers, oligosaccharides, polysaccharides, and stubborn starches maintain the balance of gut microbiota, thereby regulating plasma glucose and lipid levels. One study found that a 3-month supplementation with oligofructose significantly improved weight management and insulin resistance[163] . In randomized controlled trials, Mediterranean diets rich in fruits and vegetables reduced the incidence of HF by 70%[164]. Consuming a Mediterranean diet was also linked to lower TMAO levels in both males and females[165]. Moreover, in a 5-week randomized trial comparing two groups of diets, 200 g versus 500 g of unprocessed lean red meat per week. TMAO levels in the group consuming 200 g of red meat per week had reduced TMAO levels compared to the group consuming 500 g of red meat per week[166].

Prebiotics and Probiotics

In the last decade, the administration of exogenous live prokaryotic microbes, also called probiotics, to maintain gut health has gained popularity. When administered in adequate quantities, they confer tangible health benefits[167]. Prebiotics, non-digestible food fibers, also positively affect the gut bacteria. Administration of antibiotics and prebiotics in animals resulted in decreased microbial configuration associated with insulin resistance, improved insulin sensitivity, increased intestinal permeability, decreased metabolic endotoxemia, and suppressed inflammation[168]. However, ill-defined antimicrobial approaches can lead to undesirable side effects. Probiotics with less optimum safety records can potentially increase the chance of probiotic translocation into the systemic circulation[169]. Prebiotics can also promote the growth of beneficial gut bacteria and reduce TMAO levels. Prebiotics decrease the ability of bacteria to transform dietary precursors into TMA. For example, mice fed resveratrol, remodeled gut microbiota, decreased TMA production, and accelerated bile acid synthesis[170,171]. Phytochemical Allicin (garlic) also reduced TMAO formation in mice. A study exploring the effect of Berberine recruited 21 patients with atherosclerosis. One group was put on oral Berberine 0.5 g twice daily for 4 months, while the other group received rosuvastatin plus aspirin, clopidogrel, or ticagrelor. A 38% and 37% TMA decrease was noted in feces and plasma, respectively. In addition, TMAO decreased in feces and plasma, by 29% and 35%, respectively. The Plaque score was also reduced by 3.2% in the berberine group, while it increased by 1.9% in the other group[172].

Probiotic strains such as *Lactobacillus* and *Bifidobacterium* improve lipid metabolism, lower TMAO levels, and reduce systemic inflammation[173]. In a 4-week double-blinded randomized controlled trial, 40 young healthy males were stratified into a probiotic and a control group. 78.9% of the probiotic-consuming group showed a decrease in TMAO levels, compared to only 45% in the control group. An abundance of *Faecalibacterium prausnitzii* and *Prevotella* in the probiotic group was also observed[174]. In another randomized trial, the administration of *Saccharomyces boulardii*, a probiotic, decreased inflammatory markers and improved cardiovascular function in patients with HF[175]. Additionally, an 18-weeklong double-blind study in 2019 explored the effect of probiotic strains on bile acids levels in obese individuals. It concluded that the probiotics *Bacillus subtilis* and *Bacillus lactis* caused a 691 and 380 nmol/L change from baseline, respectively. Subtle changes in total cholesterol were also seen with *B. subtilis* and *B. lactis*, noted as 2.5% and 2.1% reductions from baseline, respectively[176].

Research around the full impact of prebiotics, probiotics, and combinations of both called "synbiotics" on health is still evolving. A recent review of probiotics and their efficacy in adults noted the limited indications for their current use in clinical practice[177]. Another recent comprehensive review emphasized the role of prebiotics in the gut–brain axis, highlighting that prebiotics also affect mental health[178]. The exact mechanisms by which prebiotics, probiotics, and synbiotics affect gut microbiota, immune regulation, metabolic diseases, and genomics and metabolomics are particularly being explored. There are currently 3 active studies on prebiotics and 14 on probiotics in the United States[179,180].

TMA lyase inhibitors

TMA lyase inhibitors inhibit the conversion of TMA to TMAO, reducing TMAO levels. Research is underway to validate the efficacy of these inhibitors. Two TMA lyase inhibitors have been explored in animal models. These are fluoromethylcholine and iodomethylcholine. Both drugs significantly reduced systemic TMAO levels and reversed TMAO-induced platelet hyperactivity and thrombus formation. In mice, 3,3-dimethyl-1-butanol, a TMA lyase inhibitor naturally found in purely cold-pressed olives, also reduced circulating TMAO concentrations[181].

Table 4

Summary of therapeutic approaches for dysbiosis. Created using MS Word.

Therapy approaches
1. **Mediterranean diet:** fruits, vegetables, unprocessed lean meat
2. **Prebiotics:** garlic, berberine
3. **Probiotics:** *Lactobacillus, Bifidobacterium, Bacillus subtilis, Bacillus lactis, Saccharomyces boulardii*
4. **TMA lyase inhibitors:** fluoromethylcholine, Iodomethylcholine, cold-pressed olives
5. **Fecal transplant**

MicroRNAs

MicroRNAs play a regulatory role in TMAO production. MicroRNAs influence the expression of genes regulating TMA metabolism. They also affect vascular dysfunction and the production of gut metabolites. Understanding miRNA-mediated processes provides insight into limiting TMAO production and improving cardiovascular health. In LPS-treated human endothelial tissue, probiotics, such as *Lactobacillus*, increase anti-apoptotic microRNA-21 and decrease pro-inflammatory microRNA-155[182]. Future research efforts to identify probiotic strains that modify miRNAs and correlate with genes for TMA lyase are essential to better address cardiovascular dysfunction[183].

Fecal transplant

Fecal microbiota transplantation describes the implantation of donor fecal solution into a recipient's intestinal tract. It aims to restore normal functional gut microflora[184]. Fecal transplant donors are usually healthy and are selected based on the lack of prior disease history i.e. without family history, autoimmune, metabolic, or malignant disease. The donor fecal solution is prepped and administered to the recipient via a nasogastric tube, colonoscopy, or retention enema[185]. In animal models, fecal transplantation improved myocarditis[186]. Multiple studies with heterogeneous patient populations have reported various obstacles, including low-cost effectiveness, requiring repeated fecal transfers, and poor patient compliance. The possibility of transferring a donor's endotoxins and immune rejection by the recipient are also ongoing concerns that limit the use of fecal in humans[80,187]. A summary of the therapeutic avenues for dysbiosis is mentioned in Table 4.

Conclusions

A multitude of factors establish the gut microbiota, the most important of which are age, diet, drugs, and disease. Alterations in the gut microbiota cause dysbiosis. The resultant bacterial translocations and systemic inflammation ultimately increase CVD risk. Dysbiosis also impedes drug metabolism and effectiveness. Patients with multiple CVD risk factors or cardiovascular co-morbidities or suffer from suboptimal cardiovascular drug responses could benefit from prebiotic and prebiotic supplementation, as well as anti-inflammatory therapies. Future large-scale, long-term, prospective, and retrospective human studies should be geared toward addressing the major factors causing dysbiosis in healthy and diseased individuals. More diet-based studies conducted on young and healthy individuals will better quantify and deepen our knowledge of the interlinks between gut health and CVD prevention. In addition, exploring the effects of prebiotics and probiotic bacterial strains on gene modulation is pertinent to help individualize supplementation regimens. The safety and cost concerns for promising therapies like fecal transplants must be addressed to broaden their clinical application.

Ethical approval

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Consent

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Author's contribution

A.O.A. and N.S.P.D. contributed to article conceptualization, outline formation, data acquisition, manuscript drafting, and write-up. They both contributed equally to the manuscript and should be considered first co-authors. N.S. contributed to data acquisition, interpretation of literature findings, draft compilation, and manuscript write-up. A.G. contributed to data acquisition, and manuscript write-up, and ensured questions related to the accuracy or integrity of references were resolved. J.T. and K. S. contributed to data acquisition, interpretation of literature findings, and manuscript write-up. E.A. contributed to data acquisition, manuscript write-up, and reference list compilation. K.R., S.B, V.G., M.L., and A.M. contributed to data acquisition and manuscript write-up. N.A. supervised draft compilation, critically proofread the paper, conducted draft revisions, and finalized the draft for submission. All authors contributed to the paper's critical review and final approval.

Conflict of interest

All the authors declare to have no conflicts of interest relevant to this study.

Research registration unique identifying number (UIN)

Not applicable.

Guarantor

All authors take full accountability for this article.

Provenance and peer review

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Data availability statement

Data sharing is not applicable to this article.

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