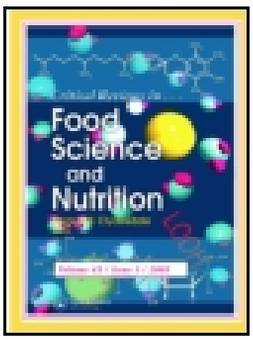

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REVIEW

Novel insights in the relationship of gut microbiota and coronary artery diseases

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ABSTRACT

Atherosclerosis is a chronic, progressive, inflammatory disease in the vasculature and is common in both coronary and peripheral arteries. Human beings harbor a complex and dynamic population of microorganisms defined as the microbiota. Importantly, alterations in the bacterial composition (dysbiosis) and the metabolic compounds produced by these bacteria have been associated with the pathogenesis of many inflammatory diseases and infections. There is also a close relationship between intestinal microbiota and cardiovascular diseases. The aim of this review was to analyze how changes in the gut microbiota and their metabolites might affect coronary artery diseases. The most representative groups of bacteria that make up the intestinal microbiota are altered in coronary artery disease patients, resulting in a decrease in *Bacteroidetes* and an increase in *Firmicutes*. In relation to metabolites, trimethylamine-N-oxide plays an important role in atherosclerosis and may act as a cardiovascular risk predictor. In addition, the use of probiotics, prebiotics, diet modulation, and fecal transplantation, which may represent alternative treatments for these diseases, is thoroughly discussed. Finally, the role of lipid-lowering treatments is also analyzed as they may affect and alter the gut microbiota and, conversely, gut microbiota diversity could be associated with resistance or sensitivity to these treatments.

KEYWORDS

Atherosclerosis; cardiovascular diseases; intestinal microbiota; probiotics; statins; trimethylamine-N-oxide

Introduction

The human microbiota can be defined as the population of microorganisms present in the different ecosystems of our body (intestinal tract, mouth, vagina, skin, etc.), whereas the genes they encode are known as the microbiome. The microbiome is essential for gut epithelial health, energy homeostasis, immunologic activity, metabolism, and neurodevelopment (Barko et al. 2018). It is estimated that the number of human cells is 3.0×10^{13} and the number of bacterial cells in the body is 3.8×10^{13}, thus showing a bacteria/human cell ratio of 1.3:1 (Sender, Fuchs, and Milo 2016). These bacteria include between 500 and 1000 different species. The most abundant species are members of the phyla *Bacteroidetes* and *Firmicutes*, and they play an important role in the regulation of metabolic functions and maintenance of immune homeostasis (Zatorski and Fichna 2014). The human endogenous gut microbiota is essential for health maintenance, and an aberrant gut microbiota has been shown to be associated with diseases, including inflammatory bowel disease, asthma, obesity, metabolic syndrome, cardiovascular diseases (CVDs), immune conditions, and neurodevelopmental conditions such as autism spectrum disorder (Carding et al. 2015; DeGruttola et al. 2016; Larroya-Garcia, Navas-Carrillo, and Orenes-Piñero 2019). Compositional and functional alterations of the microbiota are known as dysbiosis.

The composition of the microbiota is dynamic and changes in response to a variety of factors, including birth method (vaginal or cesarean), breastfeeding, diet, stress, environment, medical interventions, and disease states (Barko et al. 2018). Thus, our future microbiome depends on multiple variables from the moment we are born.

CVDs represent a group of disorders involving the heart and blood vessels (WHO 2020a), and many of them have atherosclerosis as a base. Atherosclerosis is a chronic, progressive inflammatory disease in the vasculature and is common in both coronary and peripheral arteries (Sigvant et al. 2019). CVDs are the leading cause of death worldwide. In 2016, 17.9 million people died owing to CVDs, representing 31% of global deaths, and 85% of these individuals died due to heart attack and stroke (WHO 2020a). It is estimated that, by 2030, almost 23.6 million people will die from CVDs, primarily due to coronary artery disease (CAD) or peripheral artery disease (PAD) (WHO 2020b). CAD is a pathological process characterized by atherosclerotic plaque accumulation in the epicardial arteries, whether obstructive or non-obstructive (Knuuti et al. 2020). Peripheral artery disease (PAD) is a common circulatory problem in which

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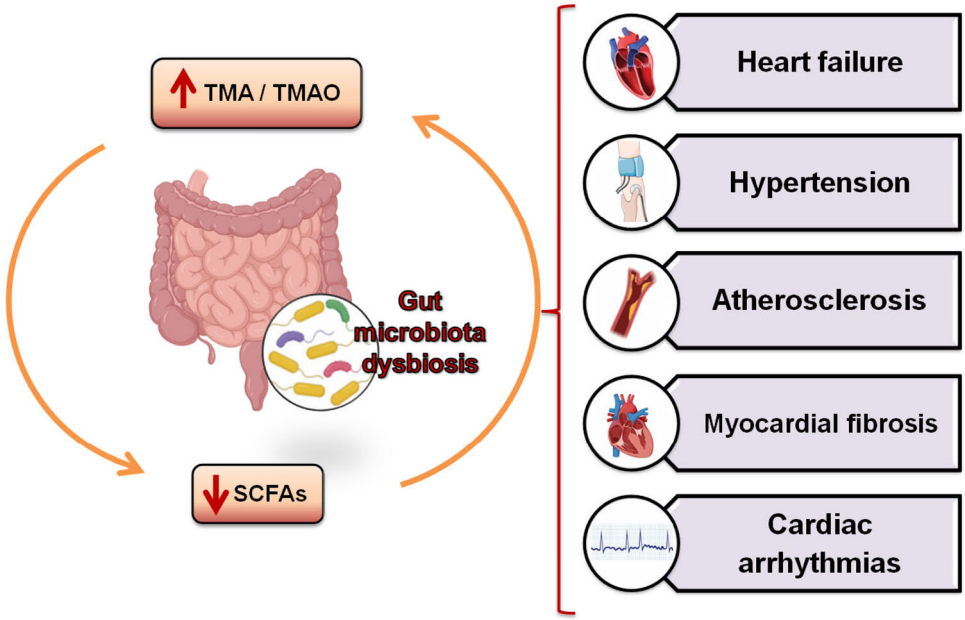

Figure 1. Relationship between microbiota and cardiovascular diseases. Dysbiosis of gut microbiota leads to altered levels of TMAO and SCFAs which are associated with cardiovascular diseases.

narrowed arteries reduce blood flow to the legs, stomach, arms, and head. PAD encompasses all arterial diseases other than those of the coronary arteries and the aorta (Aboyans et al. 2018).

Dysbiosis has been associated with many CVDs, but in many cases, it remains unclear whether dysbiosis is a cause or consequence of the disease. Changes in the composition of the gut microbiota have been linked to pathologies such as atherosclerosis, hypertension, heart failure, obesity, and type 2 diabetes mellitus (DM) (Aron-Wisnewsky and Clement 2016; Mozaffarian et al. 2016; Tang, Kitai, and Hazen 2017; Yoshida, Yamashita, and Hirata 2018). In addition to alterations in the gut microbiota composition, the metabolic potential of the gut microbiota has been identified as a contributing factor in the development of diseases such as atherosclerosis (Tang et al. 2013).

Thus, the aim of this review was to comprehensively analyze how changes in the gut microbiota and in their metabolites affect CVDs, especially CADs (Figure 1).

Materials and methods

The data published in this review were identified by means of search and selection in the following databases: PubMed, Google Scholar, Elsevier, and Scielo. The search was conducted in two steps. First, a quest was made using the keywords "gut microbiota" and "cardiovascular diseases." Second, the role of the microbiota in different diseases was assessed separately, adding it to a second selection: "atherosclerosis," "acute coronary syndrome," "acute myocardial infarction," "coronary artery disease," "prebiotics," "probiotic," "statins," and "fecal microbiota transplantation" In addition, the bibliography of each selected article was reviewed to include other relevant articles.

Pathophysiology of CAD

CAD presents a complex pathophysiology. The pathophysiologic mechanisms begin with the process of atherosclerosis. Atherosclerosis develops and progresses for a long time before the acute event. It is described as a low-grade inflammatory state of the intima of medium-sized arteries and has a predilection for the proximal segments of the major coronary arteries, often at arterial bifurcation points that alter flow in the artery (Ambrose and Singh 2015). The acute phase of CAD (acute atherothrombotic event caused by plaque rupture or erosion) is accompanied by an imbalance between thrombotic and fibrinolytic components having a focal effect on the artery and distal myocardial reperfusion (Ko et al. 2006).

Plaque disruption exposes subendothelial collagen, which results in the activation of platelets and the coagulation cascade, leading to thrombus formation (Makki, Brennan, and Girotra 2015). Activation of adherent platelets promotes the release of thromboxane A2 and adenosine diphosphate, which in turn may activate neighboring platelets via the sensitive receptors P2Y and tissue plasminogen activator located on the platelet surface. Platelet activation induces conformational changes in the surface integrin glycoprotein IIb/IIIa, leading to fibrinogen and vWF binding that bridges the platelets and results in platelet aggregation. Simultaneously, platelets increase the expression of anionic phospholipids on their surface and promote the coagulation cascade through assembly of coagulation factor complexes. Complementary to platelet activation and aggregation, plaque disruption exposes the tissue factor expressed by lipid-laden macrophages and smooth muscle cells found in the core of the disrupted plaque, which results in the activation of the components of the coagulation system, such as thrombin (Navas-Carrillo et al. 2017). Thrombin converts fibrinogen to fibrin, leading to the formation of platelet-rich thrombi at

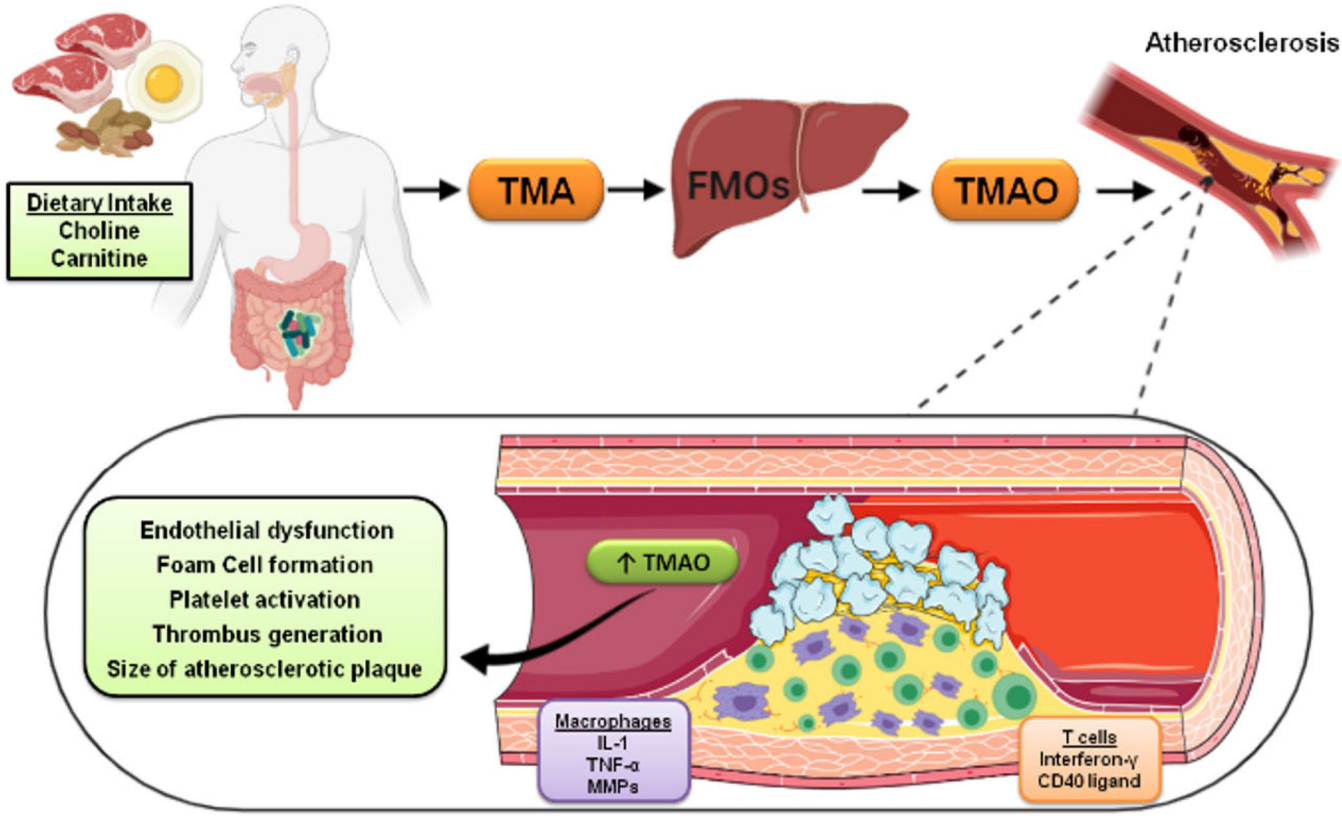

Figure 2. Schematic representation of an atherosclerotic clot rupture in a coronary and role of TMAO in the pathological process: TMAO upregulates the expression of cluster of differentiation 36 (CD36) and scavenger receptors A1 (SR-A1) which are important for the foam formation. TMAO also promotes macrophage migration and increases the expression of TNF-α and interleukin-6 (IL-6). TMAO downregulates the expression of interleukin-10 (IL-10), which protect endothelium cells, and reduces nitric oxide (NO). Furthermore, TMAO damages the self-repairing capacity of injured endothelial cells. TMAO improves platelet hyperreactivity and platelet adhesion. FMOS: Flavin-containing monooxygenases.

the vascular injury site (Coughlin 2000). Simultaneously, certain anatomic characteristics of the atherosclerotic plaque (it is a thin fibrous cap characterized by a large lipid core populated by numerous inflammatory cells, abundant production of matrix metalloproteinases, and a relative lack of smooth muscle cells) help it to rupture (Figure 2) (Makki, Brennan, and Girotra 2015).

Additionally, macrophages, T lymphocytes, and mast cells are present and activated at the sites of plaque rupture. Their biological activity appears to induce the dysregulation of extracellular matrix (ECM) metabolism and, consequently, plaque destabilization (Figure 2). Thus, activated T cells secrete interferon-ɤ and CD40 ligands. Macrophages secrete pro-inflammatory cytokines such as interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α) and a wide range of matrix metalloproteinases (MMPs) (Navas-Carrillo et al. 2017).

A bioactive gut microbiota-derived metabolite, trimethylamine-N-oxide (TMAO), is known to be involved and plays an important role in the pathological process of atherosclerosis, which makes the atherosclerotic plaque more vulnerable to rupture. These processes include endothelial dysfunction, platelet activation, and thrombus generation (Zhu, Li, and Jiang 2020) (Figure 2).

Gut microbiota and CAD

On comparing gut microbiota profiles among CAD patients with stable angina pectoris and old myocardial infarction, controls with coronary risk factors, and healthy volunteers, a classification was developed: *Prevotella*, *Bacteroides*, Lactobacillales (including *Lactobacillus*, *Streptococcus*, and *Enterococcus*), *Bifidobacterium*, *Clostridium* IV, *Clostridium* XIVa, *Clostridium* IX, *Clostridium* XI, and *Clostridium* XVIII (Emoto et al. 2016). Interestingly, the order Lactobacillales (one of the main components of the human gut microbiota belonging to the phylum Firmicutes) was increased in the CAD group; thus, it could be positively associated with CAD (Emoto et al. 2016). In contrast, the prevalence of the phylum Bacteroidetes (*Bacteroides* + *Prevotella* genera) decreased in the CAD group, thus showing an inverse association with CAD. For this reason, the Firmicutes/Bacteroidetes ratio increased in the CAD group (Emoto et al. 2016; Yamashita et al. 2016).

These previous observations are in accordance with the results reported by Cui et al., where the phylum Bacteroidetes was the most representative phylum in CAD patients (56.12% in total) (Cui et al. 2017; Yoshida et al. 2018). Upon checking the diversity, it was observed that the α-diversity was different between CAD patients and healthy controls: the bacterial communities in the patients had greater genera richness than those in the healthy controls. Therefore, the authors concluded that increased gut flora diversity might be related to CAD (Cui et al. 2017).

Analysis of the gut microbiota composition and CAD severity revealed that the gut microbiota changed significantly with CAD severity. On studying a "cross-comparison

scheme," it was confirmed that the structural characteristics of the gut microbiota were altered: a co-abundance network in which 274 operational taxonomic units (OTUs) were shared by at least 20% of the samples and clustered into 24 CAGs (co-abundance groups) was constructed. The presence of CAG17 (containing several gram-negative bacteria such as *Veillonella*, *Haemophilus*, and *Klebsiella*) increased with CAD severity, and CAG9, CAG19, and CAG23, which are composed of Ruminococcaceae, were also significantly enriched in patients with severe disease, whereas CAGs containing Lachnospiraceae were significantly reduced with CAD severity (Liu et al. 2019).

A recent study carried out on an MI rat model suggested that the abundance of the gut microbiota, especially the Synergistetes and Spirochetes phyla; Lachnospiraceae, Syntrophomonadaceae, Lactobacillaceae, and Bifidobacteriaceae families; and *Tissierella*, *Soehngenia*, and *Clostridium* genera, was significantly associated with acute MI (Wu, Li, et al. 2017).

The sequencing of the gut metagenome in patients with symptomatic atherosclerosis showed that patients had an increase in the number of the genus *Collinsella*, whereas the controls had an increase in the abundance of *Eubacterium* and *Roseburia* (Karlsson et al. 2012). In addition, it was found that the composition of the gut microbiota from 218 individuals with CAD deviated from that in healthy individuals via an increase in the abundance of Enterobacteriaceae (*Escherichia coli*, *Klebsiella* spp., *Enterobacter aerogenes*) and *Streptococcus* spp. (Jie et al. 2017). Recently, two bacterial species (*Bacteroides vulgatus* and *Bacteroides dorei*) have been shown to be effective in preventing atherosclerosis (Yoshida et al. 2018). Human fecal 16S ribosomal RNA gene sequencing revealed a significantly lower abundance of *Bacteroides vulgatus* and *Bacteroides dorei* in patients with CAD (Yoshida et al. 2018), and these results are in accordance with previous reports showing a lower abundance of the genus *Bacteroides* in patients with atherosclerosis (Emoto et al. 2016; Karlsson et al. 2012). The protective role of these two species of the genus *Bacteroides* against atherosclerosis was also observed in atherosclerosis-prone mice deficient in apolipoprotein E. Oral gavage with live *Bacteroides vulgatus* and *Bacteroides dorei* five times per week for 10 weeks attenuated atherosclerotic lesion formation, showing significantly reduced lesion size in the aortic root without significant differences in body weight, cholesterol levels, or glucose levels. Furthermore, immunohistochemical staining followed by morphometric analysis of atherosclerotic lesions in the aortic sinus revealed a marked reduction in macrophage and CD4+ T-cell accumulation. Subsequently, the mRNA expression of several proatherogenic immune cell markers and chemokines/chemokine receptors decreased in mice gavaged with live *Bacteroides* sp. (Yoshida et al. 2018).

Furthermore, studies analyzing fecal lipopolysaccharide (LPS) levels in patients with CAD found that these levels were significantly higher and negatively correlated with the abundance of *Bacteroides vulgatus* and *Bacteroides dorei* compared with those in patients without CAD (Yoshida et al. 2018). This finding suggests that the abundance of *Bacteroides vulgatus* and *Bacteroides dorei* has a direct impact on microbial LPS synthesis in the human gut, thus improving the enteric environment, providing the gut bacteria with good living conditions, and having a beneficial effect on bacterial LPS production.

CAD is often associated with other comorbidities. Thus, the prevalence of type 2 DM in patients with CAD has been reported to be 50% in many countries, and DM patients have a 2- to 4-fold greater risk of developing atherosclerotic CAD than non-DM patients (Aronson and Edelman 2016; Holscher, Bode, and Bugger 2016; Sanchez-Alcoholado et al. 2017). It was observed that diversity and gut microbial composition were different between DM-CAD patients and non-DM-CAD patients. Bacterial communities in DM patients with CAD had lower taxa richness than those in the non-DM group, and the presence of DM in patients with CAD was related to a decrease in the phylum Bacteroidetes and an increase in the phyla Firmicutes and Proteobacteria. In addition, DM-CAD patients had more opportunistic pathogens such as *Enterobacteriaceae*, *Megasphaera*, *Streptococcus*, *Dialister*, and *Desulfovibrio* and lower beneficial bacteria, including Bacteroides (*Bacteroides fragilis*), Faecalibacterium (*Faecalibacterium prausnitzii*), and *Prevotella* (Sanchez-Alcoholado et al. 2017) (Table 1).

Gut microbiota metabolites and CAD

It has been observed that the gut microbiota changes significantly with CAD, but these changes do not occur only at the microorganism level. Upon analyzing the metabolites, it was shown that metabolites such as phosphatidylethanolamine, phosphatidylcholine, phosphatidylserine, and sphingolipids were negatively correlated with atherosclerosis severity, and myocardial markers, taurine, and hypotaurine metabolic module were also negatively associated with CAD severity (Liu et al. 2019). In addition, several molecules important for cardiovascular health (folate, butyrate, propionate, trimethylamine (TMA), and pyruvate-formate lyase) were altered in atherosclerotic patients (Jie et al. 2017).

TMAO and short-chain fatty acids (SCFAs) are well-studied metabolites. TMA is a metabolite produced by the gut microbiota from dietary phosphatidylcholine (lecithin), choline, or L-carnitine, which can be found mainly in red meat, meat products, eggs, and shellfish. TMA is absorbed and enters the portal circulation and is then converted into TMAO by FMO3 in the liver (Peng et al. 2018) (Figure 2). The positive correlation of TMAO with the prediction of cardiovascular risk has been demonstrated, even after the adjustment of traditional risk factors (Peng et al. 2018; Tang et al. 2013). Indeed, TMAO may act as a cardiovascular risk predictor that correlates with atherosclerosis (Randrianarisoa et al. 2016). One study including patients with stable CAD who underwent cardiac angiography showed that elevated TMAO levels, after adjusting for high-sensitivity C-reactive protein and estimated glomerular filtration rate, were associated with increased 5-year mortality up to ≈2-fold (Senthong, Wang, Li, et al. 2016). More recently, increased TMAO was significantly associated with mortality and MI at 2 years following hospitalization for acute MI (Suzuki et al.

Table 1. Studies demostrating gut microbiota changes in patients with CAD.

Microbiota changes	Study population	Analysis	References
Collinsella ↑ *Eubacterium* ↓ *Roseburia* ↓ patients with symptomatic atherosclerosis	12 patients with symptomatic atherosclerosis and 13 age- and sex-matched healthy controls	Metagenome	Karlsson et al. (2012)
Lactobacillales ↑ Bacteroidetes (*Bacteroides* + *Prevotella*)↓ Firmicutes/Bacteroidetes ratio ↑ in CAD patients	39 CAD patients, 30 age- and sex-matched no-CAD controls (Ctrls) with coronary risk factors, and 50 healthy volunteers (HVs) without coronary risk factors.	Terminal restriction fragment length polymorphism	Emoto et al. (2016)
Enterobacteriaceae (*Escherichia coli, Klebsiella* spp, *Enterobacter aerogenes*), *Streptococcus* spp, *Lactobacillus salivarius, Solobacterium moorei, Ruminococcus gnavus, Eggerthella lenta*↑ *Roseburia intestinalis, Provetella copri*↓in CAD patients	218 individuals with CAD and 187 healthy controls.	Metagenome	Jie et al. (2017)
α diversity higher in CAD patients vs healthy controls. Bacteroidetes (the highest abundance of reads in CAD patients) ↓(class Bacteroidia ↓); Firmicutes ↑(class Clostridia ↑); Proteobacteria ↓ Fusobacteria ↑ in CAD	29 CAD in-hospital patients and 35 healthy volunteers as controls	High-throughput sequencing	Cui et al. (2017)
Bacteroidetes (*Bacteroides fragilis, Prevotella*), ↓ Firmicutes and Proteobacteria (*Megasphaera*, *Streptococcus*, *Dialister*, *Enterobacteriaceae*, *Desulfovibrio*)↑ *Faecalibacterium prausnitzii*) ↓ in diabetes-CAD patients	16 coronary CAD-DM2 patients, and 16 age, sex, and BMI matched CAD patients without DM2 (CAD-NDM2	Sequencing in a GS Junior 454 platform followed by bioinformatic analysis (QIIMEand PICRUSt)	Sanchez-Alcoholado et al. (2017)
Bacteroides vulgatus and *Bacteroides dorei* prevent atherosclerosis	30 CAD patients and 30 controls without CAD with coronary risk factors	16S ribosomal RNA gene sequencing	Yoshida et al. (2018)
Roseburia, Klebsiella, Clostridium IV and *Ruminococcaceae* change at different stages of CAD. Distinguish stable coronary artery disease from acute coronary syndrome accurately.	161 CAD patients and 40 healthy controls	Multi-omic analyses (sequencing of the V3-V4 regions of the 16S rRNA gene and metabolomics)	Liu et al. (2019)

CAD, coronary artery disease; DM 2, type 2 diabetes mellitus.

2017). Later, TMAO levels were independently associated with a higher risk of a combined vascular endpoint, including MI, recurrent stroke, and cardiovascular death, at 1-year follow-up (Haghikia et al. 2018). Currently, some mechanisms for the pro-atherosclerotic role of TMAO have been proposed. In one of them, cholesterol levels are clearly implicated as TMAO can inhibit reverse cholesterol transport by reducing cholesterol 7α-hydroxylase (Cyp7α1), the rate-limiting enzyme of bile acid synthesis. Furthermore, TMAO may also upregulate the expression of macrophage scavenger receptors SRA and CD36, resulting in the deposition of cholesterol in macrophages and the generation of foam cells (Koeth et al. 2013).

In addition, TMAO has been correlated with the incidence of thin-cap fibroatheroma in a study in which 90 patients with 180 non-culprit plaques were analyzed (Liu et al. 2018). It was observed that patients with high TMAO concentrations exhibited a significantly higher presence of thin-cap fibroatheroma and microvessels and thinner fibrous cap thickness. The levels of TMAO were significantly and inversely correlated with fibrous cap thickness and significantly correlated with the presence of thin-cap fibroatheroma in non-culprit lesions, with good specificity and sensitivity. According to these findings, it is possible to hypothesize that TMAO could exert proatherogenic effects by promoting the formation of microvessels within a plaque (Liu et al. 2018).

Moreover, it has been shown that TMAO, p-cresyl sulfate, p-cresyl glucuronide, and phenylacetylglutamine play important roles in atherosclerosis. Patients with unexplained atherosclerosis who did not have any traditional risk factors but still had high levels of plaque burden had significantly higher blood levels of these metabolites that were produced by the intestinal bacteria. This study noted that these differences could not be explained by diet or kidney function, pointing to a difference in the make-up of the intestinal bacteria (Bogiatzi et al. 2018). By studying the association between TMAO levels and PAD severity and prognosis, TMAO levels were found to be associated with disease severity and CV mortality. Moreover, TMAO levels predicted long-term adverse event risk and incremental prognostic value in patients with PAD (Roncal et al. 2019; Senthong, Wang, Fan, et al. 2016) (Table 2).

SCFAs are metabolites of the gut microbiota and the major end products of dietary fiber metabolism (Sonnenburg and Backhed 2016). They are carboxylic acids, including acetate, propionate, and butyrate, that are produced in the gastrointestinal tract and can enter the bloodstream primarily via the portal vein (Koh et al. 2016). SCFAs have been found to be beneficial for blood pressure control (Gomez-Arango et al. 2016; Peng et al. 2018; Pluznick 2014; Yang et al. 2015). Conversely, other products of dietary fiber metabolism are branched-chain fatty acids (BFAs), including isobutyrate, methyl butyrate, and isovalerate. Depending on the composition of the microbiota, source of the substrate, and intestinal transit time, the production of these fatty acids is different. It has been observed that higher levels of BFAs are associated with opportunistic intestinal bacteria, whereas higher levels of SCFAs are associated with commensal microbiota (Koh et al. 2016). Clinical trials have confirmed that the gut microbiota

Table 2. Impact of TMAO and SCFAs levels on cardiovascular diseases.

Metabolite	Study population	Results	References
TMAO	220 Caucasians from Southern Germany who participated in the Tübingen Lifestyle Intervention Program.	TMAO levels predict cardiovascular disease and are associated with carotid intima-media thickness (cIMT)	Randrianarisoa et al. (2016)
	2235 patients with stable CAD	TMAO levels pose a higher long-term mortality risk among patients with stable CAD managed with optimal medical treatment	Senthong, Wang, Li, et al. (2016)
	935 patients with PAD who underwent elective angiography for cardiac evaluation at a tertiary care hospital.	Elevated TMAO levels are associated with increased mortality risk. Similar prognostic values for elevated TMAO are present for subjects with carotid artery, non–carotid artery, or lower extremity PAD.	Senthong, Wang, Fan, et al. (2016)
	1079 acute myocardial infarction patients	TMAO is associated with combined mortality and myocardial infarction at 2 years following the hospitalization for acute myocardial infarction	Suzuki et al. (2017)
	16 coronary CAD-DM2 patients and 16 age, sex, and BMI matched CAD patients without DM2 (CAD-NDM2)	Patients with diabetes and CAD have significantly higher levels of TMAO	Sanchez-Alcoholado et al. (2017)
	180 non-culprit plaques from 90 patients with CAD and with stable angina	TMAO levels are correlated with the incidence of thin-cap fibroatheroma	Liu et al. (2018)
	Two prospective cohorts of patients with first-ever ischemic stroke (total n: 686)	Relation between TMAO levels and the risk of subsequent cardiovascular events in patients with recent prior ischemic stroke	Haghikia et al. (2018)
	262 symptomatic PAD patients categorized in intermittent claudication (n = 147) and critical limb ischemia (n = 115)	TMAO levels increase in critical limb ischemia compared to intermittent claudication C. Patients with elevated TMAO exhibit a higher risk of cardiovascular death.	Roncal et al. (2019)
SCFAs	218 individuals with CAD and 187 healthy controls.	The potential for the synthesis of the anti-inflammatory short-chain fatty acid butyrate was lower in CAD patients. One module involved in propionate synthesis was less abundant in CAD patients compared with controls and no significant changes were observed for pathways involved in the acetate synthesis.	Jie et al. (2017)

BMI, body mass index; CAD, coronary artery disease; DM2, type 2 diabetes mellitus; PAD, peripheral artery disease; SCFA, short-chain fatty acid; TMAO, trimethylamine-N-oxide.

metabolize dietary fiber, thus producing SCFAs. A metagenomic study showed that patients with atherosclerotic CVD presented lower synthesis of butyrate and propionate than healthy individuals, whereas acetate synthesis was not altered (Jie et al. 2017) (Table 2).

As previously discussed, the presence of type 2 DM in patients with CAD might be related to gut microbiota changes, and it has also been observed that patients with diabetes and CAD have significantly higher levels of plasma zonulin, TMAO, and IL-1B and significantly lower levels of IL-10 and FOXP3 mRNA expression than non-diabetic patients with CAD. Linking these metabolites and bacterial presence in these patients, the increase in Enterobacteriaceae and the decrease in *Faecalibacterium prausnitzii* was significantly associated with an increase in serum TMAO levels, whereas the decrease in the abundance of *Bacteroides fragilis* was associated with a reduction in FOXP3 mRNA expression, which was implicated in the development and function of Treg cells and was considered to have an atheroprotective role (Sanchez-Alcoholado et al. 2017).

Microbiota modulation and CVDs

The manipulation of the gut microbiota presents new opportunities to treat diseases. Currently, diet modulation is the major therapeutic tool utilized in clinical practice for the treatment of metabolic diseases. Interestingly, additional approaches to modify the gut microbiome include prebiotics, probiotics, and fecal transplants, which could be the new alternatives for the treatment of CVDs.

Diet modulation

The modulation of the diet is one of the simplest and easiest ways to modify the microbiome (Wu et al. 2011). The Mediterranean diet, rich in vegetables, fruits, grains, and legumes and low in red meats and processed carbohydrates, is beneficial in the prevention of CVDs because of the presence of antioxidants, nitrate, and fiber as well as low saturated/trans fatty acids, sodium, and phosphate (Eckel et al. 2014; Ros et al. 2014). The Western diet, which is high in saturated fat, is known to increase CVD risk by decreasing gut microbiota diversity and commensal bacteria such as *Bifidobacterium* spp. This reduction is correlated with impairments in vascular function (Battson et al. 2018).

In the PREDIMED study (prevention with Mediterranean diet), the largest primary prevention trial conducted in Spain involving individuals with high cardiovascular risk without CVD, the incidence of major cardiovascular events over a period of 5 years was lower among those assigned to an energy-unrestricted Mediterranean diet supplemented with extra-virgin olive oil or nuts than among those assigned to a reduced-fat diet (Estruch et al. 2018). The effect of nutrient compounds and adherence to the Mediterranean diet on the gut microbiome of healthy adults was also studied, and it was found that specific nutritional components and dietary patterns influenced gut microbiota composition, diversity, and activity (Garcia-Mantrana et al. 2018). It was also observed that a higher ratio of Firmicutes/Bacteroidetes was related to lower adherence to the Mediterranean diet, and a greater presence of Bacteroidetes was associated with lower animal protein intake. High

consumption of animal protein, saturated fats, and sugars affected gut microbiota diversity. A significantly higher presence of Christensenellaceae was found in individuals with greater adherence to the Mediterranean diet than in individuals with lower adherence, whereas a better adherence to the Mediterranean diet was associated with significantly higher levels of total SCFA (Garcia-Mantrana et al. 2018). These results indicate that diet, health status, and microbiota may be interrelated.

On studying the association between metabolites from the choline pathway (TMAO, betaine, choline, phosphocholine, and a-glycerophosphocholine) and risk of incident CVD and the potential modifying effect of Mediterranean diet interventions, a metabolite score combining plasma metabolites from the choline pathway was found to be associated with an increased risk of CVD in a Mediterranean population at high cardiovascular risk (Guasch-Ferre et al. 2017). An higher risk of CVD events was observed in participants who had a higher choline score and were assigned to the control group than in those with a lower score and assigned to the Mediterranean diet intervention groups. Participants with a higher betaine/choline ratio and assigned to the Mediterranean diet intervention group had a lower risk of CVD than those with a lower ratio and in the control group. However, the p values for the interaction between the continuous choline score, betaine/choline ratio, and intervention group (Mediterranean diet versus control group) and CVD were non-significant (Guasch-Ferre et al. 2017). Thus, adherence to a Mediterranean diet and a reduction in the intake of animal products might improve metabolite profiles and, consequently, the risk of CVD. However, further studies are needed to confirm this. Moreover, when the association between the levels of TMAO and adherence to Mediterranean diet was evaluated, it was found that men who presented with higher levels of TMAO and lower adherence to Mediterranean diet were consuming less plant protein and ω6 polyunsaturated fatty acids than women. The lowest levels of TMAO were predicted by a score of adherence of $\leq$9 in women and $\leq$10 in men (Barrea et al. 2019).

There is clear evidence that a polyphenol-rich diet (polyphenols are present in apples, grapes, berries, citrus, tea, and coffee, among others) contributes to the prevention of several disorders, including CVD and DM (Ahmad et al. 2018; Jumar and Schmieder 2016; Pang et al. 2016). For example, black tea increases flow-mediated dilatation of the brachial artery and lowers heart rate (Ahmad et al. 2018). Moreover, consumption of green tea is associated with favorable outcomes with respect to the risk of cardiovascular and ischemic diseases (Pang et al. 2016), and cocoa flavanol has been shown to lower systolic and diastolic blood pressure (Jumar and Schmieder 2016). In addition, extra-virgin olive oil and red wine are the main sources of fat and alcohol in the traditional Mediterranean diet, and they contain several bioactive polyphenols. The anti-atherogenic properties and cardioprotective action of olive oil have been attributed to its high content of oleic acid and bioactive polyphenols (Guasch-Ferre et al. 2014; Guo et al. 2016).

Probiotics

Probiotics are living organisms that carry out beneficial functions in the body (Sanders 2008). They help to maintain the integrity of the intestinal lining, maintain pH, regulate immunity, and control inflammation, thus diminishing the levels of LPS, blocking the spread and invasion of pathogens, facilitating the absorption of food, and improving the bioavailability of nutrients such as the A, C, K, and B group vitamins (Larroya-Garcia, Navas-Carrillo, and Orenes-Piñero 2019).

The most important probiotic strains are *Bifidobacterium* spp., *Lactobacillus* spp., and *Bacteroides fragilis* (Larroya-Garcia, Navas-Carrillo, and Orenes-Piñero 2019). Several studies have shown that probiotics may be able to decrease blood cholesterol levels and blood pressure, thus decreasing the risk of severe heart problems. It has been observed that *Lactobacillus* probiotics, particularly *Lactobacillus plantarum* and *Lactobacillus reuteri*, significantly reduced both total cholesterol and LDL-cholesterol levels (Wu, Zhang, et al. 2017).

A meta-analysis combining results from 32 studies found a significant beneficial cholesterol-reducing effect associated with probiotic supplements. It was observed that these supplements, especially specific strains of *Lactobacillus acidophilus*, *Bifidobacterium lactis*, and *Lactobacillus plantarum*, significantly reduced serum total cholesterol (Wang, Guo, et al. 2018). However, a randomized double-blind controlled trial comparing placebo to *Lactobacillus acidophilus* plus *Bifidobacterium bifidum* administration in patients with hypercholesterolemia showed that a combination of these probiotics decreased serum total cholesterol, LDL-cholesterol, and HDL-cholesterol levels in hypercholesterolemic patients (Rerksuppaphol and Rerksuppaphol 2015).

Lactobacillus paracasei TD3 has been found to decrease cholesterol and triglycerides in rats (Dehkohneh, Jafari, and Fahimi 2019). Furthermore, the levels of aspartate aminotransferase and alanine aminotransferase hepatic enzymes were significantly decreased in the probiotic group. The administration of the *Lactobacillus paracasei* TD3 strain prevented the accumulation of fats in the liver and had inhibitory effects on adipogenesis (Dehkohneh, Jafari, and Fahimi 2019). In another study in rats, the administration of *Saccharomyces cerevisiae* ARDMC1 produced a significant reduction in serum total cholesterol, LDL-cholesterol, and triglycerides at the end of 42 days (Saikia et al. 2018).

High blood pressure is another risk factor for heart disease, and certain probiotics can significantly reduce blood pressure. It was found that taking *Lactobacillus plantarum* for 6 weeks significantly reduced blood pressure and could be useful as a protective agent in the primary prevention of atherosclerosis in smokers (Naruszewicz et al. 2002). More recently, a meta-analysis based on the results of nine clinical trials found that the consumption of probiotics reduced blood pressure, overall, in patients with elevated basal blood pressure. This analysis also showed that several species of probiotics used together provided enhanced effects and that the duration of the intervention must be 8 weeks or more (Khalesi et al. 2014).

Prebiotics

Prebiotics are nondigestible products that play an important role in health. They stimulate the development and activity of beneficial bacteria. They are generally carbohydrates: nondigestible oligosaccharides or polysaccharides (inulin), fructooligosaccharides (FOS), galactofructose, galactooligosaccharides (GOS), and xiloligosaccharides (Larroya-Garcia, Navas-Carrillo, and Orenes-Piñero 2019; Marchesi et al. 2016). The majority of identified prebiotics are naturally occurring in the human diet, and the presence of prebiotics in the diet might lead to numerous health benefits, including the reduction of cholesterol levels. A study involving 12 patients revealed that inulin (longer-chain prebiotics) significantly reduced serum triglycerides and serum LDL-cholesterol and increased serum HDL-cholesterol levels (Causey et al. 2000). Other prebiotics such as oligodextrans, lactose, resistant starches and their derivatives, lactoferrin-derived peptides, and N-acetylchitooligosaccharides have also been identified to maintain hypocholesterolemic effects in people with type 2 DM (Gibson et al. 2004; Yoo and Kim 2016). In addition, an inulin/FOS mixture (10 g/day) stimulated *Bifidobacterium* spp. growth (Ramirez-Farias et al. 2008). β-glucan is another prebiotic with a clear influence on lowering cholesterol levels and maintaining blood glucose homeostasis. The administration of β-glucan to 26 healthy volunteers for 2 months demonstrated a significant decrease in LDL-cholesterol and total cholesterol levels as well as an improvement in endothelial function in healthy individuals, thus providing cardioprotective effects, mainly through beneficial SCFA production via the gut microbiome (Cosola et al. 2017).

Besides the lipid-lowering effect, prebiotics also reduce obesity, one of the most important risk factors for CVDs. On analyzing 48 healthy adults with a BMI >25, a reduction in body weight of 1.03 ± 0.43 kg with oligofructose supplementation was observed, whereas the control group experienced an increase in body weight. Moreover, glucose levels decreased in the oligofructose group and increased in the control group, and oligofructose was well tolerated.

Fecal microbiota transplantation

Fecal microbiota transplantation is a therapeutic intervention designed to displace intestinal pathogens by introducing fecal contents from healthy donors into the gastrointestinal tract of patients. The most effective and well-studied indication for fecal microbiota transplantation is *Clostridium difficile* infection (Vindigni and Surawicz 2017).

Fecal microbiome transplantation needs to be regulated before being offered as a suitable treatment option. This intervention is currently limited due to associated risks, including possible transfer of endotoxins or infectious agents. In this direction, in a study performed in mice, it was observed that atherosclerosis susceptibility might be transmitted via the transplantation of the gut microbiota (Gregory et al. 2015). An atherosclerosis-prone and high TMAO-producing mouse strain, C57BL/6J and an atherosclerosis-resistant and low TMAO-producing mouse strain, NZW/LacJ were selected as donors for fecal microbial transplantation into apolipoprotein E-null mice in which resident intestinal microbes were first suppressed with antibiotics. Mice receiving C57BL/6J fecal microbes demonstrated a choline diet-dependent enhancement in the atherosclerotic plaque burden compared with the recipients of NZW/LacJ microbes. Using microbial DNA analyses, it was observed that specific microbial taxa correlated with plasma TMAO levels in donors and recipients and with the atherosclerotic lesion area in recipients (Gregory et al. 2015). Another study in mice showed the potential use of fecal microbiota transplantation in hypertension. When the feces of hypertensive patients were transferred into germ-free mice, the blood pressure of the recipient mice increased in comparison with that of the germ-free recipients of the healthy donor microbiome (Li et al. 2017).

In a recent trial, the impact of fecal microbiota transplantation on vascular inflammation was analyzed. In a small randomized double-blind pilot trial, TMAO production and vascular inflammation were evaluated using computed tomography scans of the abdominal aorta in 20 obese male patients with cardiometabolic syndrome who received either allogeneic fecal microbiota transplantation from a vegan donor or autologous fecal microbiota transplantation. As expected, at baseline, the fecal microbiota composition differed significantly between the vegans and metabolic syndrome patients. In addition, after vegan-donor fecal microbiota transplantation, the intestinal microbiota composition in the metabolic syndrome patients changed toward a vegan profile in some of the patients, though the authors could not detect significant changes in TMAO metabolism (Smits et al. 2018)

These results suggest the important role of the gut microbiota in CVDs, but data to support the role of fecal microbiota transplantation in humans is limited.

Lipid lowering treatments and gut microbiome

Statins have been used for 30 years to prevent CAD and stroke and often represent the first lipid-lowering therapy (Oesterle, Laufs, and Liao 2017). Statins belong to a class of cholesterol-lowering pharmaceutical agents and are known for their ability to inhibit 3-hydroxy-3-methylglutaryl-CoA reductase, an enzyme involved in the rate-limiting step of cholesterol biosynthesis. This treatment exerts pleiotropic effects on a variety of pathways (Oesterle, Laufs, and Liao 2017; Orenes-Piñero et al. 2011). Statins decrease cholesterol biosynthesis and decrease serum LDL-cholesterol and triglyceride levels (Hiro et al. 2009; LIPID Study Group 1998; Sever et al. 2003). To date, several studies analyzing the association between statins and the gut microbiota have been carried out, and these studies showed that statins and the gut microbiota are related in two ways: statin treatment affects and alters the gut microbiota and gut microbiota diversity is associated with resistance or sensitivity to statins.

A study on rats demonstrated alterations in the gut microbiota associated with hypercholesterolemia and modifications under atorvastatin treatment (Khan et al. 2018). Importantly, the atorvastatin-treated high-fat diet (HFD) group showed a relative increase in biodiversity compared to the HFD control group. In addition, atorvastatin promoted the relative abundance of Proteobacteria in the HFD group and decreased Firmicutes abundance compared

to the HFD group. Overall, the bacterial community composition was altered, and the diversity of the gut microbiota increased with atorvastatin treatment in the HFD group (Khan et al. 2018). In another study, it was found that atorvastatin and rosuvastatin significantly altered the gut microbiota upon HFD administration in aged obese mice. *Bacteroides*, *Butyricimonas*, and *Mucispirillum* were significantly increased by statins and were associated with hyperglycemia and hyperlipidemia. Furthermore, the downregulation of IL-1β and the upregulation of TGFβ1 by statins were significantly correlated with the abundance of these bacteria (Kim et al. 2019). In another study, the effect of rosuvastatin on total and LDL-cholesterol was affected by the intestinal microbiota. It was found that dysbiosis reduced the efficacy of rosuvastatin in rats. However, after recovering eubiosis, the effect of rosuvastatin on lipid reduction returned to normal levels (Wang, Wang, et al. 2018). Using a murine model and three different treatments (pravastatin, atorvastatin, or no treatment), it was observed that statin therapy led to a profound remodeling of the gut microbiota and metabolic alterations in mice. Six significantly different OTUs were obtained between the treatment groups and the pravastatin groups and 13 OTUs between the no-treatment group and the atorvastatin group. When both statin-treated groups were compared, only two OTUs were significantly different (Caparrós-Martín et al. 2017). Statin therapy was characterized by a marked reduction in the abundance of many gram-positive OTUs (i.e., the constituents of the *Clostridium* clusters XIVa and IV). Members of both clusters are spore formers and synthesize butyric acid as the end product of carbohydrate fermentation. In agreement with the observed taxonomic profiles, statin treatment resulted in a dramatic reduction in the production of butyric acid. The levels of acetic, propionic, and valeric acids remained unaltered in both statin-treated and control groups (Caparrós-Martín et al. 2017). In this study, it was also observed that when the statin therapies were combined with an HFD, the gut microbial composition and metabolites of the gut microbiota did not significantly differ from the microbiota and metabolites resulting from a normal diet and statin treatment (Caparrós-Martín et al. 2017).

Similarly, a study involving 202 hyperlipidemic Chinese patients showed that gut microbiota diversity was associated with resistance or sensitivity to atorvastatin (Sun, Li, and Zhou 2018). Patients with higher microbiota diversity were more sensitive to atorvastatin treatment, thus showing significantly lower levels of total and LDL-cholesterol.

Another hypocholesterolemic treatment is ezetimibe. This compound is a noncompetitive inhibitor of the Niemann-Pick C1-like 1 (NPC1L1) transporter that mediates cholesterol absorption in the apical brush border membrane of jejunum enterocytes (Altmann et al. 2004). A study on mice investigated the potential impact of simvastatin and ezetimibe, administrated separately or in combination, on gut microbiota modulation. This study showed that ezetimibe significantly affected the composition of the gut microbiota, leading to a significant decrease in *Lactobacillus* spp. Importantly, it has been suggested that members of genus *Lactobacillus* play an important role in cholesterol metabolism (Catry et al. 2015).

Conclusions and future perspectives

The advent of genomic, sequencing, and metabolomic techniques has assisted in obtaining an understanding of the interaction between the microbiome and CVDs. In this review, a number of studies were found to support the notion that the gut microbiome mediates many of the beneficial and detrimental effects of the diet on CVDs. Furthermore, the metabolites relevant to CVDs such as TMAO and novel potential therapeutic opportunities such as the use of probiotics, prebiotics, and fecal transplantation, which could be appropriate treatment options for CVDs, have been analyzed. Thus, the gut microbiota may represent a new target for the therapeutic manipulation, treatment, and prevention of complex cardiometabolic diseases through the regulation of the immune system.

The microorganisms that are present in our bodies and some of their metabolites are well known; however, how they interact among themselves and with us is still unknown. It is crucial to focus on which microbial genes are being expressed in CVDs and the secreted bioactive compounds that exert effects on the host's immune system. Although the identification of the microbial population in our body shows the bidirectional interactions occurring in the intestine and the cardiovascular system, it will be necessary to decipher the meaning of all of this information in terms of health or illness and to investigate the complex interaction of gene-microbiota. In this context, there is a clear interest in the interaction between microbiota and CAD, demonstrated by the fact that several clinical trials are currently being performed around the world. Indeed, a number of clinical trials are currently ongoing, analyzing, for example, the impact of different diets (including the Mediterranean diet) and the microbiota in CAD patients, identifying the microbiota as a predictor of cardiac risk, studying the effects of gut microbiota dysbiosis on the immune response after open heart surgery; or highlighting the microbiota as a target for precision medicine in atherosclerosis, among others.

Abbreviations

ACS	acute coronary syndrome
BFA	branched-chain fatty acid
CAD	coronary artery disease
CVD	cardiovascular disease
DM	diabetes mellitus
FOS	fructooligosaccharides
GOS	galactooligosaccharides
HFD	high-fat diet
MI	myocardial infarction
PAD	peripheral artery disease
SCAD	stable coronary artery disease
SCFA	short-chain fatty acid
TMA	trimethylamine
TMAO	trimethylamine-N-oxide

Disclosure of interests

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