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REVIEW

Gut microbiome and its meta-omics perspectives: profound implications for cardiovascular diseases

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ABSTRACT

Cardiovascular diseases (CVDs) still remain the leading concern of global health, accounting for approximately 17.9 million deaths in 2016. The pathogenetic mechanisms of CVDs are multifactorial and incompletely understood. Recent evidence has shown that alterations in the gut microbiome and its associated metabolites may influence the pathogenesis and progression of CVDs such as atherosclerosis, heart failure, hypertension, and arrhythmia, yet the underlying links are not fully elucidated. Owing to the progress in next-generation sequencing techniques and computational strategies, researchers now are available to explore the emerging links to the genomes, transcriptomes, proteomes, and metabolomes in parallel meta-omics approaches, presenting a panoramic vista of culture-independent microbial investigation. This review aims to outline the characteristics of meta-omics pipelines and provide a brief overview of current applications in CVDs studies which can be practical for addressing crucial knowledge gaps in this field, as well as to shed its light on cardiovascular risk biomarkers and therapeutic intervention in the near future.

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Introduction

Cardiovascular diseases (CVDs) remain the leading cause of mortality and morbidity worldwide. It was estimated that 17.9 million people died from CVDs in 2016, representing approximately 30% of all global deaths.[1] Despite adherence to recommended therapies including high-dose statins and modification of lifestyle risk factors, curative effect is individual and varied, as well as significant residual risks remain.[2,3] Additionally, although genetic predisposition contributes to the pathogenesis of CVDs, genetic variation could only explain 20% of the risk in disease progression.[4] Together, these observations suggest that the multiple mechanisms that participate in the pathophysiology of CVDs are incompletely understood, convincing data from biochemical, bioinformatical, epidemiological, and clinical studies will enhance our feasibility in CVDs prophylactic managements.

Within the last decade, research regarding the function and composition of the human gut microbiome has come to be a strong evolutionary force. The human gastrointestinal tract is populated by trillions of microorganisms including bacteria, viruses, fungi, and protozoa, which along with their genome, are collectively referred as the gut microbiome.[5] The gut microbiome is a complex community that interacts with host dynamic functions such as processing nutrients and modulation of the immune system which are essential to homeostasis maintenance.[6] An alteration in gut microbial composition and linked activity is known as gut dysbiosis,[7] and in-depth characterization of the human microbiome by meta-omics analysis spurred a paradigm shift in human health and disease without the need for culturing.[8] It has been demonstrated that microbial communities may be associated with the pathogenesis of several human diseases including obesity,[9,10] inflammatory bowel disease,[11,12] cancer,[13,14] and rheumatic disease;[15,16] moreover, increasing evidence has shown that changes in the gut microbiome and its associated metabolites may influence the pathogenesis and progression of CVDs such as atherosclerosis, heart failure, hypertension, and arrhythmia.[17,18] However, the underlying mechanistic links are multifactorial and yet to be determined.

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The purpose of this review is to provide a brief overview of recent progress in our understanding of gut microbiome in the development of CVDs and to outline meta-omics approaches that can be practical for addressing crucial knowledge gaps in this field. Together, this body of work supports the notion that the gut microbiome may shed its light on cardiovascular risk biomarkers and therapeutic intervention in the near future.

Gut meta-omics algorithms and current applications in CVDs

While isolating and culturing each individual microorganism is an intractable task, our capability to accurate characterization and quantification these microbial communities and perceive their impact on human biology from the collective nucleotide contents contained in a stool sample has been transformed by progress in technology, particularly next-generation sequencing (NGS) techniques and computational strategies. These advances have opened up a panoramic vista of untangling the emerging links to mapping the genomes, transcriptomes, proteomes, and metabolomes in parallel, presenting an exciting future field of investigation, especially considering the reality that gut microorganisms play a key role in plasticity and adaptation to environmental change and physiological stress. Here we summarized a set of pipelines for properly performing meta-omics studies (Figure 1), which can provide information from different layers of the biosystem.

Metagenomics: revealing the diversity and function of the human gut microbiome

The composition of human-associated microbial communities has been well assessed by means of culture-independent sequencing technologies, for example by sequencing the 16S ribosomal ribonucleic acid (rRNA) genes to yield phylogenetic or taxonomic profiles on account of its applicability in prokaryotes and availability of considerable reference database, giving insight into non-cultivated microorganisms.[19] The amplicon-based (marker gene) technologies are limited in their phylogenetic ranges;[20] for example, 16S primarily targets in bacteria, whereas 18S in eukaryotes, and internal transcribed spacer (ITS) typically in fungi. Besides, these technologies also suffer from biases from copy-number variations,[21] amplification inefficacy,[22] and inconsistent characterization.[23,24] More recently, genome-wide sequencing approaches, such as metagenomics, have further expanded the popularity and effectiveness for studying the microbiome. Metagenomics is the method of generating millions of short reads (mostly performed using Illumina platforms or Roche 454 pyrosequencing) that randomly sampled from all microbial genomes present in a defined environment or ecosystem, including viral and eukaryotic DNA. Based on adequate sequencing depth (the number of sequencing reads per sample), the taxonomic resolution to species or strain level by aligning reads to annotation reference genomes, and the assembly of whole microbial genomes from the overlapped DNA sequence reads (contigs) are possible.[25,26] The complete genome of dominantly abundant microbes can also be reconstructed,[27,28] providing a more comprehensive view of their biological potential. Adding a higher level of refinement, metagenomic operational taxonomic units (mOTUs) are clustered as groups of covariance single-copy marker genes, providing a powerful approach to classify and quantify known and currently unknown microorganisms at species-level resolution.[29] Additionally, microbial growth rates can be extrapolated from the metagenomic sequencing read coverage, revealing the rates at which bacteria undergo DNA replication in each sample, which could provide insights into pathology.[21]

Gut microbial communities can be recognized not only as independent groups of microbes, but as collections of biochemical functions affecting the host physiology. Remarkably, the bioinformatics analysis of metagenomics sequences, so-called annotation, enables researchers to profile major metabolic pathways and functional modules carried by an entire community that of clinical interest at the gene level.[30] Biological interpretation of genome sequences is computationally annotated and evaluated by homology using reference databases such as COG,[31] KEGG,[32] or eggNOG.[33] Alternatively, raw sequence reads can be directly utilized to generate functional profiles (using pipelines such as EBI metagenomics[34] and HUMAnN[30]

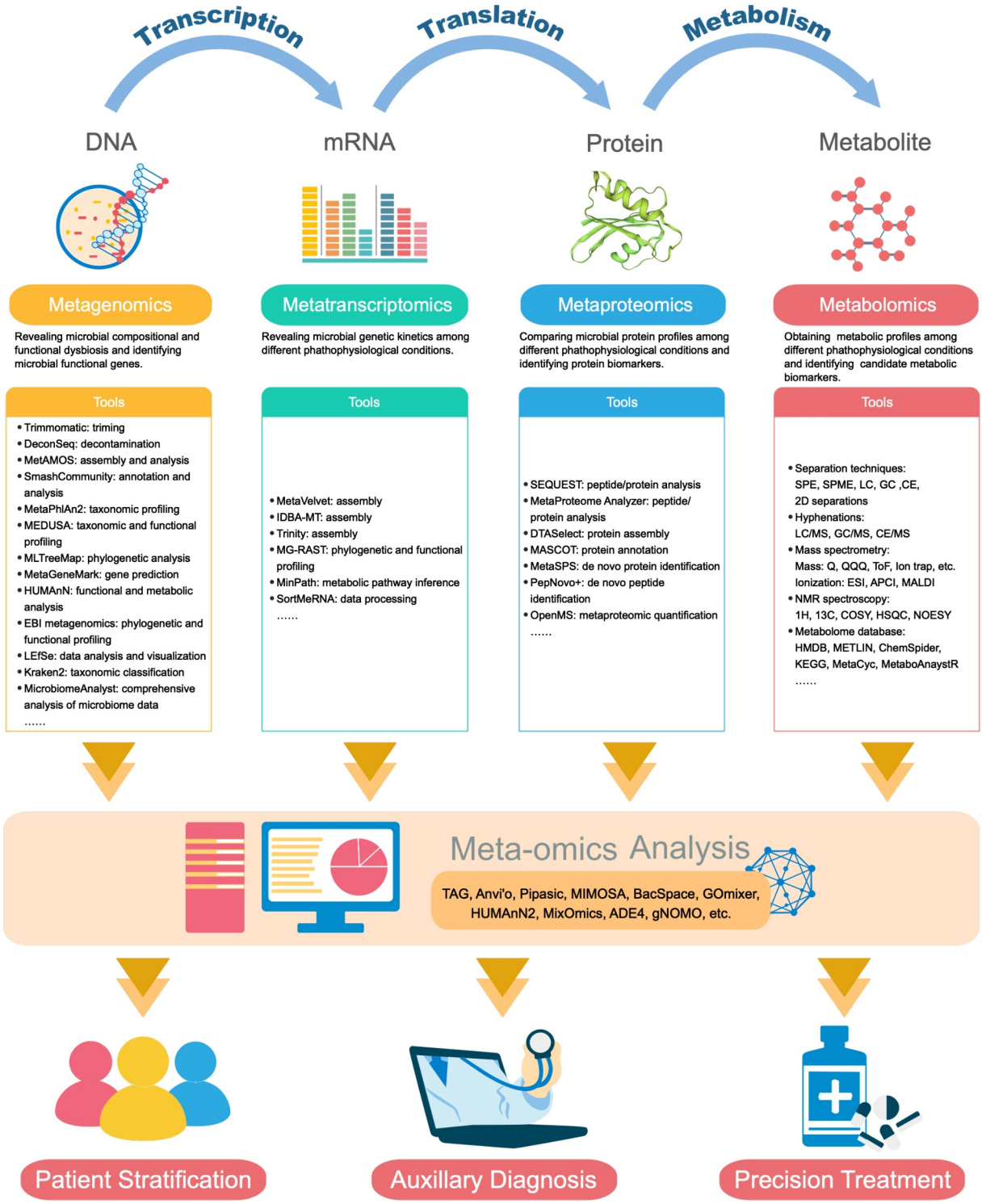

Figure 1. Meta-omics algorithm for investigating the host–microbiome interactions. Each omics provides information in the different layers of eco-systems. In the tools box, we collect the current computational pipelines for omics analysis. The detailed introductions and instructions are available on its official websites or the reference in National Center for Biotechnology Information (NCBI) database. SPE = solid phase extraction; SPME = solid phase microextraction; LC = liquid chromatography; GC = gas chromatography; CE = capillary electrophoresis; 2D = LC&GC, LC&CE, GC&CE; MS = mass spectrometry; Q = quadrupole; QQQ = triple quadrupole; ToF = time-of-flight; ESI = electrospray ionization; APCI = atmospheric pressure chemical ionization; MALDI = matrix-assisted laser desorption/ionization; NMR = nuclear magnetic resonance; COSY = correlation spectroscopy; HSQC = heteronuclear single quantum coherence; NOESY = nuclear Overhauser effect spectroscopy.

or by mapping them to higher-quality catalogs of reference genes in the human gut microbiome).[35] It is important to emphasize that gene-scale functional profiling is still in its infancy; it provides permissive links between the microbial organismal compositions and metabolic potential, not the metabolic activity per se. However, these profiles are appropriate as inputs into more sophisticated metabolic activity networks and molecular mechanisms, allowing us to obtain more comprehensive information from annotated genomes, and making this integration more biologically meaningful.[36]

The application of metagenomics has massive potentiality in revealing the interactions and mechanisms between the gut microbiome and diseases. However, it also has limitations and requires improvements. First, as metagenomics requires a much higher average genome size than 16S rDNA sequence analysis,[37] the involved costs and time are relatively far greater. Second, quality control protocols include human DNA contamination removing are essential to obtain high coverage required for metagenomics.[38] Third, different DNA extraction kits, as well as laboratory sampling and storage protocols, also have biases on the assessment of microbial configuration.[39] Comparing data across studies applying different bacterial DNA extraction methodologies is challenging.[40] Fourth, a proportion of data cannot be assigned due to the insufficient reference databases, particularly a lack of matches for eukaryotes and viruses, which impacts the extraction of organismal and functional information.[41] Thus, future advances in the study of the human gut microbiome using metagenomics are promising and more efforts are urgently needed.

Metatranscriptomics, metaproteomics and metabolomics: enormous complements to characterize microbial communities

Metagenomics provides us with an unprecedented tool that can be used to access the genetic potential and metabolic features of the microorganisms that exist in our biosphere. However, the abundances of metagenomically prevalent pathways inferred by the pipelines describe only the enzymes encoded by one or more microbial genomes, and the relationships to gene expression, protein abundance, and metabolite concentration may not be straightforward. With the rapidly growing area of metatranscriptomics,[42] metaproteomics,[43] and metabolomics,[44] experimental, computational, and conceptual connections between the meta-omics have started to put forward a better understanding of the dynamic gut ecosystem.

A metatranscriptomic assay routinely involves reverse transcription and cDNA sequencing of high-quality and sufficient amounts of RNA isolated from a microbiome sample. Such measurements of gene expression at the community level yield important information regarding gene expression patterns induced/repressed under specific conditions.[45] Additionally, identifying genomes with active transcription can inherently discriminate metabolically active microbes from dormant or dead microbes and extracellular DNA.[46] However, due to the ubiquitous presence of RNases in host-derived samples, it is also challenging to handle the laborious and complex procedures including sample collection, storage, and preparation when performing metatranscriptomic analysis.[47] In contrast with metagenomics and metatranscriptomics, metaproteomics can not only identify and quantify the expressed proteins present in a sample by the development of higher resolution mass spectrometers and quantitative proteomics techniques, but link the proteins to closely related species/strains of microorganisms via reference databases and the bioinformatic tools, which should in principle provide superior insight into taxon-specific functional activities and metabolic pathways, since not all transcripts are subsequently translated into proteins.[48] Metaproteomics is not yet a mature area and can suffer from a variety of drawbacks including insufficient universal guidelines and protocols for performing metaproteomic experiments and interpreting metaproteomic results.[49] In addition to the microbiome's functional activity, a further goal of microbiome research is to measure the levels and flux of metabolites. Metabolomics is uniquely suited to capture these functional host–microbe interactions via mass spectroscopy (MS), nuclear magnetic resonance (NMR), or other analytical methods. Metabolomics research strategies can be conducted in a targeted or non-targeted

manner. Targeted metabolomics can accurately quantify a set of known metabolites, while non-targeted methods can cover as many metabolites as possible.[50,51] In fact, many gut metabolites may be of microbial origin or microbially modified,[52] typically result in a mutualistic relationship between microbe and host, highlighting the necessity to correlate specific microbes or genetic components with the specific molecules that, in turn, mediate human health phenotypes. Metabolomics shares similar weaknesses of incomplete databases, and remains intricate to distinguish host- and microbiome-origin metabolites and link the metabolites to specific taxa.[53]

Despite these challenges, the future potential for multi-omics data integration represents also opportunities. Multi-omics approaches provide additional insights beyond the capacity of single omics studies, illuminating gene regulation and correlating the presence of microbes with metabolites. Correlation analysis and multivariate statistical methods are the most straightforward and commonly used methods for statistically studying the interconnected relationships,[54,55] as well as identifying the key features in multi-omics data integration,[56] so that the functional phenotype of gut microorganisms can be inferred. The development of computational methods that complement experimental approaches will likely revolutionize our ability to integrate and interpret multi-omics data and help the research transition into the mechanism.[57] Within this context, multi-omics analysis of microbiome with efficiency and quality will become a sufficiently powerful tool to elucidate the ecologic roles of the human gut microbiome.

Sequencing measurements revealed altered gut microbial composition associated with CVDs

Epidemiological studies have revealed a series of associations between alterations in the organismal composition of the gut microbiome and cardiovascular traits. In Table 1, we summarize recent findings from clinical cohorts showing associations between gut microbes and CVDs in humans. From these studies, a discovery pipeline for identifying common and distinctive microbial players in CVDs emerges.

Current evidence mainly shows the associations between gut microbiome configurations and susceptibility to CVDs, while the discrepant results of these studies are obvious due to the various factors that contribute to gut microbiome composition (e.g., subjects toward a region-specific genetic background and dietary habits; different sequencing strategies, etc.). A beneficial spin-off from these massive sequencing projects has been their deposition into online accessible databases, which has enabled researchers to leverage and reuse these data to create reference databases and conduct further studies. Importantly, several studies have also taken advantage of machine learning algorithms to either differentiate between health and different disease states or identify microbe-related features that predict clinical outcomes,[67,70,88] which would lend a hand to push the frontiers of translational microbiome research. Given that CAD like other common complex disorders develops over time and involves both genetics and environmental risk factors, full mechanistic insight will allow the generation of reliable prediction models based on coordinated sets of microbial data at multiple time points, especially when acute clinical outcomes (e.g., stable CAD vs. myocardial infarction) need to be modeled.[89]

Nevertheless, the ability to extract precise insights of the interplay between the gut microbiome and CVDs from published research has so far been restricted due to lack of appropriate data in large enough cohorts, as well as flexibility, effectiveness, and robustness of data integration. As the gut microbiome is multiplex, dynamic, and spatially structured, as well as the fact that biological processes do not operate separately but manifest conjointly as molecular cascades and interact across multidimensional omics domains to affect CVDs etiology, it is progressively recognized that specialize in any explicit form of information solely provides limited knowledge into the underlying molecular mechanisms and CVDs phenotypes. Considering the great promise such studies hold for the treatment and prevention for CVDs, it is expected that parallel measurements on multi-omics will be rapidly collected during the next couple of years, and novel methods with standard pipelines for efficient data integration, modeling, visualization, and interpretation will be urgently

Table 1. Altered Gut Microbiome Composition Associated with CVDs in humans.

First Author, Year	Study Population and Disease Status	Microbial measurements	Main Findings	Reference
Atherosclerosis				
Koren et al., 2011	15 patients with atherosclerosis and 15 matched controls from Sweden	16S rRNA	Gut microbes from *Erysipelotrichaceae* and *Lachnospiraceae* families positively correlated with LDL-C and TC levels.	58
Karlsson et al., 2012	12 patients with symptomatic atherosclerotic plaques and 13 matched controls from Sweden	Metagenomic data utilization and analysis (MEDUSA)	Genus *Collinsella* was enriched in patients whereas genera *Eubacterium* and *Roseburia* were enriched in control subjects.	59
Yin et al., 2015	141 large-artery atherosclerotic ischemic stroke and transient ischemic attack patients and 97 asymptomatic controls from China	16S rRNA	Higher levels of opportunistic pathogens including *Enterobacter*, *Megasphaera*, *Oscillibacter*, and *Desulfovibrio*, and fewer commensal or beneficial microbes from genera *Bacteroides*, *Prevotella*, and *Faecalibacterium* were observed in the patients.	60
Feng et al., 2016	59 CHD patients and 43 healthy controls from China	Metagenomic sequencing	*Clostridium sp. HGF2*, *Streptococcus sp. M334* and *M143* were enriched in CHD patients.	61
Emoto et al., 2016	39 CAD patients, 30 matched controls with coronary risk factors and 50 healthy volunteers from Japan	Terminal restriction fragment length polymorphism (T-RFLP).	The order *Lactobacillales* was significant increased, while genera *Bacteroides* and *Prevotella* were significantly decreased in CAD patients.	62
Jie et al., 2017	218 participants with atherosclerotic cardiovascular disease and 187 healthy controls from China	Metagenomic sequencing	Species including *Escherichia coli*, *Klebsiella spp.*, *Enterobacter aerogenes*, *Streptococcus spp.*, *Lactobacillus salivarius*, *Solobacterium moorei*, *Atopobium parvulum*, *Ruminococcus gnavus*, and *Eggerthella lenta* were enriched in ACVD patients, while *Roseburia intestinalis*, *Faecalibacterium cf. prausnitzii*, *Bacteroides spp.*, *Prevotella copri*, and *Alistipes shahii* were relatively depleted in ACVD patients.	63
Gózd-Barszczewska et al., 2017	20 participants with central obesity, 15 participants with atherosclerosis, and 5 healthy controls from Poland	16S rRNA	Subjects with improper levels of TC were enriched in *Prevotella* and decreased level of *Clostridium*.	64
Yoshida et al., 2018	30 patients with CAD and 30 controls from Japan	16S rRNA	Lower abundances of *Bacteroides vulgatus* and *Bacteroides dorei* and higher abundances of *Faecalibacterium prausnitzii* and *Prevotella copri* in patients with CAD.	65
Zhu et al., 2018	70 CAD patients and 90 healthy controls from China	16S rRNA	*Escherichia Shigella* and *Enterococcus* were significant enriched while *Faecalibacterium*, *Subdoligranulum*, *Roseburia*, and *Eubacterium rectale* were significant depleted in the CAD group.	66
Liu et al., 2019	161 CAD patients and 40 healthy controls from China	16S rRNA	Microbes including *Klebsiella*, *Streptococcus*, *Haemophilus*, and *Granulicatella* were significantly enriched in CAD patients.	67
Hypertension and arterial stiffness				
Yang et al., 2015	7 patients with hypertension and 10 controls	16S rRNA	Lower richness and diversity of gut microbiota was observed in hypertension patients.	68
Gomez-Arango et al., 2016	205 participants at 16-week gestation from Australia	16S rRNA	The gut microbiota including the *Odoribacteraceae* and *Clostridiaceae* families, *Christensenellaceae* family, the *Blautia* genus, and the *Odoribacter* genus were negatively associated with systolic blood pressure.	69
Li et al., 2017	56 participants with pre-hypertension, 99 participants with primary hypertension, and 41 healthy controls from China	Metagenomic sequencing	Genera *Prevotella* and *Klebsiella* were overrepresented in individuals with pre-hypertension or hypertension, whereas *Faecalibacterium*, *Oscillibacter*, *Roseburia*, *Bifidobacterium*, *Coprococcus*, and *Butyrivibrio* were enriched in healthy controls.	70
Yan et al., 2017	60 patients with primary hypertension and 60 matched controls from China	Metagenomic sequencing	Genera including *Klebsiella*, *Clostridium*, *Streptococcus*, *Parabacteroides*, *Eggerthella*, and *Salmonella* were enriched while *Faecalibacterium*, *Roseburia*, and *Synergistetes* were decreased in hypertensive patients compared to control group.	71
Kim et al., 2018	22 patients with hypertension and 18 controls	Metagenomic sequencing	*Ruminococcus torques*, *Eubacterium siraeum*, and *Alistipes finegoldii* were positively correlated with hypertension, while *Bacteroides thetaiotaomicron* and *Eubacterium rectale* were inversely correlated with hypertension.	72

(*Continued*)

Table 1. (Continued).

First Author, Year	Study Population and Disease Status	Microbial measurements	Main Findings	Reference
Menni et al., 2018	617 middle-aged women from the TwinsUK cohort	16S rRNA	Gut microbiome diversity is inversely correlated with arterial stiffness in women.	[73]
Sun et al., 2019	529 participants of the biracial (African- and European-American) Coronary Artery Risk Development in Young Adults (CARDIA) study	16S rRNA	Positive associations were observed between hypertension and genera *Anaerovorax*, *Clostridium IV*, *Oscillibacter*, and *Sporobacter*.	[74]
Huart et al., 2019	38 patients with hypertension, 7 participants with pre-hypertension, and 9 healthy controls	16S rRNA	*Clostridium sensu stricto 1* was positively whereas *Ruminococcaceae_ge_DQ807686* and *Clostridiales_ge_16S_OTU1343* were negatively correlated with BP levels.	[75]
Verhaar et al., 2020	4672 subjects articipating in the HEalthy Life In an Urban Setting (HELIUS) study	16S rRNA	Subjects with low BP had higher abundance of *Roseburia* spp., *Roseburia hominis*, and *Ruminococcaceae spp*.	[76]
Heart failure				
Sandek et al., 2007	22 patients with CHF and 22 controls from Germany	Fluorescence in-situ hybridization (FISH)	Increased detection frequency of *Bacteroides*, *Prevotella*, *Eubacterium rectale*, and *Faecalibacterium prausnitzii* in CHF patients.	[77]
Sandek et al., 2014	65 patients with CHF and 25 controls from Germany	FISH	Increased anaerobic juxtamucosal bacteria was positively associated with decreased intestinal blood flow in CHF patients.	[78]
Pasini et al., 2016	30 patients with stable CHF in NYHA class I–II, 30 patients with moderate to severe CHF NYHA class III–IV, and 20 matched healthy controls from Italy	Using traditional culture techniques to measure bacteria and Candida species	CHF population had massive quantities of pathogenic bacteria such as *Campylobacter*, *Shigella*, *Salmonella*, *Yersinia enterocolitica*, and *Candida* species; Patients with more severe disease had a significantly increased development rate of *Candida*, *Campylobacter*, and *Shigella* species in stools as compared with patients with mild CHF.	[79]
Luedde et al., 2017	20 patients with HF with reduced ejection fraction due to ischemic or dilated cardiomyopathy and 20 matched controls from Germany	16S rRNA	Patients with HF had significant decreases in abundances of *Coriobacteriaceae*, *Erysipelotrichaceae*, and *Ruminococcaceae* at the family level, and decreases in abundances of *Blautia*, *Collinsella*, *unclassified Erysipelotrichaceae*, and *unclassified Ruminococcaceae* at the genus level compared to controls.	[80]
Kamo et al., 2017	12 NYHA class II–IV HF patients and 12 matched healthy controls; 12 patients with HF aged <60 years and 10 patients with HF aged ≥60 years from Japan	16S rRNA	Patients with HF were less abundant in *Clostridium* and *Dorea* at the genus level, as well as *Eubacterium rectale* and *Dorea longicatena* at the species level; Older HF patients had depletion of *Faecalibacterium* and enrichment of *Lactobacillus* at the genus level compared with younger HF patients	[81]
Kummen et al., 2018	84 stable HF with reduced ejection fraction patients (NYHA class II–IV) and 266 population-based controls from Norway	16S rRNA	Increased abundances of genera *Prevotella*, *Hungatella*, and *Succinclasticum* in HF patients; Decreased abundances of genera *Anaerostipes*, *Blautia*, *Coprococcus*, *Fusicatenibacter*, *Lachnospiraceae FCS020*, *NCS2004*, and *ND3007*, *Pseudobutyrivibrio*, and *Eubacterium hallii* group.	[82]
Cui et al., 2018	53 chronic HF patients (NYHA class II–IV) and 41 controls from China	Metagenomic sequencing	The network showed the differential enrichments of bacteria such as *Ruminococcus gnavus*, *Streptococcus sp.* and *Veillonella sp.*in CHF patients, by contrast, *Faecalibacterium prausnitzii, Oscillibacter sp.* and *Sutterella wadsworthensis* in controls.	[83]
Arrhythmia				
Zuo et al., 2020	50 nonvalvular AF patients and 50 matched controls from China	Metagenomic sequencing	Similar gut microbiome diversity was observed between paroxysmal AF and persistent AF; Genera including *Bacteroides*, *Prevotella*, and *Faecalibacterium*, and species including *Faecalibacterium prausnitzii*, *Prevotella copri*, and *Bacteroides vulgatus* exhibited similar abundance in paroxysmal AF and persistent AF but were remarkably distinct from controls.	[84]
Metabolic risk factors				
Fu et al., 2015	893 samples from the LifeLines-DEEP population cohort in Netherlands	16S rRNA	Gut microbiome can explain a strong association with variations in BMI and blood lipid levels independent of host age, sex and genetics.	[85]

(*Continued*)

Table 1. (Continued).

First Author, Year	Study Population and Disease Status	Microbial measurements	Main Findings	Reference
Kelly et al., 2016	55 high and 57 low CVD risk participants from America	16S rRNA	Genera *Prevotella 2*, *Prevotella 7*, *Tyzzerella* and *Tyzzerella 4* were associated with high CVD risk profile, whereas genera *Alloprevotella* and *Catenibacterium* were associated with low CVD risk profile.	[86]
Rothschild et al.	1046 healthy individuals from Israel	16S rRNA and Metagenomic sequencing	Microbiome predominantly shaped by non-genetic factors and explain over 20% of the variance in HDL, fasting glucose, and BMI.	[87]

CAD = coronary artery disease; CHD = coronary heart disease; HF = heart failure; NYHA = New York Heart Association; AF = atrial fibrillation.

needed to efficiently cope with this multi-dimensional data,[90] and transform into practicable precision medicine tools.

Gut-heart axis: the interplay between the microbiome and dietary-derived metabolites affects the pathogenesis of CVDs

The gut microbiome is known to aid in the harvest of nutrients from diet, with about half of the total genome of the gut microbiome being related to the metabolism of central carbon and amino acid as well as the biosynthesis of secondary metabolites.[91] Dietary components that are unutilized by the host can serve as growth nutrient substrates for the gut microbes, which in turn generate myriad molecules, many of which impact the host physiology,[92] functioning as an endocrine organ.[93] Through the development of metabolomics techniques and efforts in a series of experiments, there is increasing evidence that some of these metabolites contribute to CVDs pathology (Figure 2).

The microbe-dependent metabolite trimethylamine-N-oxide (TMAO)

TMAO was firstly reported by Wang et al. in a landmark paper, which has become the most compelling evidence of a causative link between the gut microbiome, oral intake of nutrient precursors, and CAD risk.[94] The conversion of TMAO in humans has been shown to arise via a multistep, metaorganismal, and microbe-dependent pathway commencing with the dietary precursors including choline,[94] phosphatidylcholine,[94,95] carnitine,[18] betaine,[94] γ-butyrobetaine (γ-BB),[96] and trimethyllysine (TML),[97] which are most abundant in foods found in a western diet, including red meat, egg yolks, milk, and other animal products with high levels of saturated or unsaturated fat.[98,99] Gut microbial metabolism of these precursors begins with specific microbial trimethylamine (TMA) lyases encoded by genes including choline-TMA lyase system (*CutC/D*) and the carnitine Rieske-type oxygenase/reductase system (*CntA/B* and *YeaW/X*), which humans do not possess, to generate TMA.[100] After absorption, the TMA produced is then transported to liver via the portal vein and readily oxidized by host hepatic FMOs (flavin-containing monooxygenases; mainly FMO3) into TMAO.[94]

A role for TMAO in atherosclerosis has been implied in most, but not all, mechanistic and animal model studies.[18,94,101–103] TMAO can enhance cholesterol accumulation in macrophages by significantly increasing the mRNA and surface protein levels of CD36 receptor and scavenger receptor A1 (SR-A1), as well as the formation of macrophage-derived foam cells,[94] which are markers of atherosclerotic plaques.[104] Cholesterol 7alpha-hydroxylase (Cyp7a1) is one of the major enzymes in bile acid synthesis. TMAO can reduce Cyp7a1 expression, inhibit cholesterol transport, cause cholesterol accumulation and form cell formation, and ultimately result in atheromatous plaque formation.[18] Research evidence further suggests that feeding TMAO or either carnitine or choline to mice also inhibits in vivo cholesterol efflux in macrophages.[18] Moreover, another mechanism by which TMAO may increase the risk of cardiovascular events is mediated via platelet reactivity and thrombosis potential.[105–108] TMAO alters platelet intracellular Ca^{2+} signaling, heightening its responsiveness to submaximal stimulus-dependent activation (e.g., thrombin, ADP, collagen).[106] Inflammasome activation and vascular

inflammation are critically involved in the progression of atherosclerosis and thrombotic complications.[109–111] Seldin et al. reported that acute injection of physiological levels of TMAO in mice induced vascular inflammation, including activation of mitogen-activated protein kinase (MAPK) and nuclear factor-kappa B (NF-κB) signaling pathways, upregulating the levels of cyclooxygenase 2 (COX2), IL-6, and intercellular adhesion molecule 1 (ICAM1), leading to subsequent leukocytes recruitment.[109] Similarly, investigations by Chen et al. have suggested TMAO can also promote the release of inflammatory cytokines IL-18 and IL-1β via priming and activation of the NLRP3 (nucleotide binding oligomerization domain–like receptor family pyrin domain-containing-3) inflammasome in vitro and in vivo through SIRT3-SOD2-mtROS (sirtuin-3-superoxide dismutase 2-mitochondrial reactive oxygen species) pathway to induce vascular inflammation.[110]

Several epidemiological studies showed the prognostic value of plasma levels of TMAO that predicted future cardiovascular events including myocardial infarction, stroke, and all-cause mortality.[18,95,104,112,113] In addition, elevated levels of plasma TML, alone, or together with TMAO, have been shown to be associated with both near- and long-term major adverse cardiac events after acute coronary syndrome, independent of troponin T levels,[114] and circulating levels of γ-BB and its precursor TML may also act as cardiovascular risk markers in patients with carotid artery atherosclerosis.[115] Furthermore, several independent studies reported that TMAO may be a strong

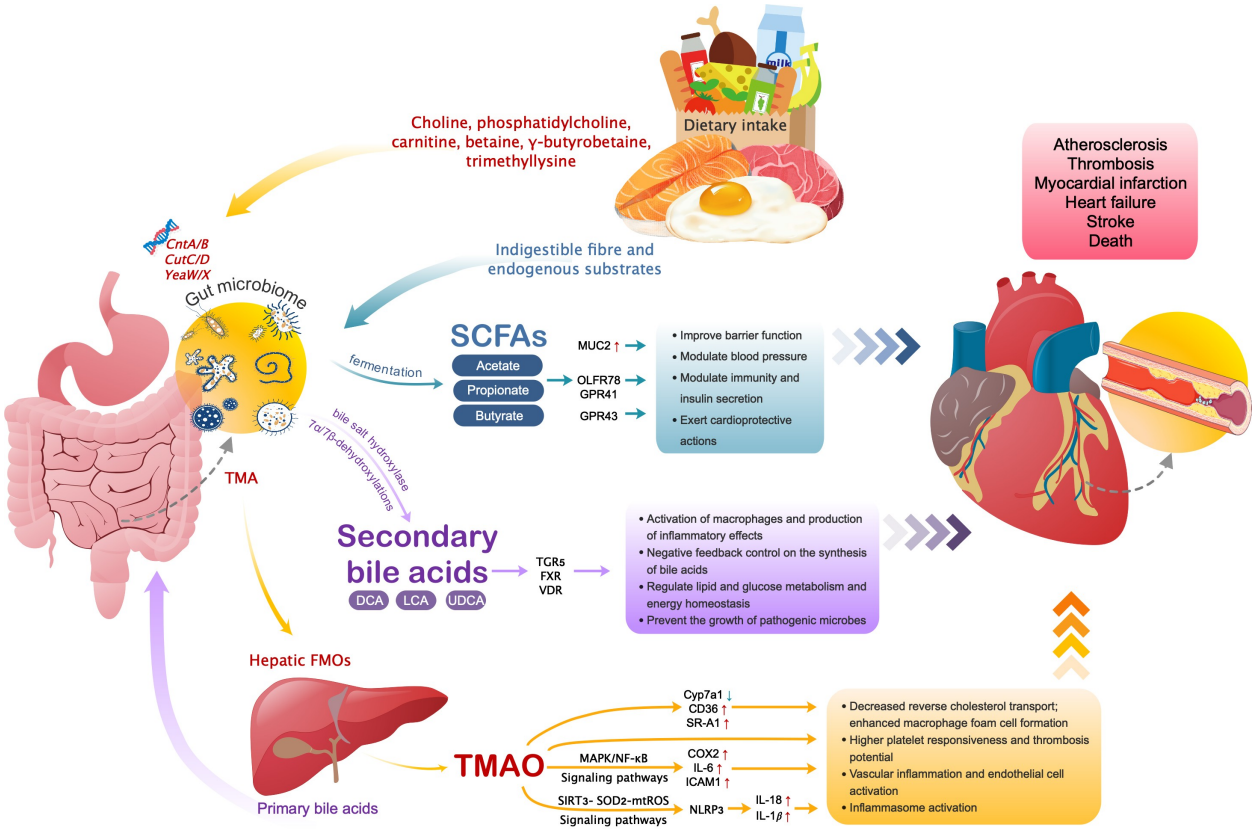

Figure 2. Downstream effects of microbe-derived metabolites and their roles in CVDs. SCFA = short chain fatty acids; MUC2 = mucin 2; OLFR78 = olfactory receptor 78; GPR41 = G-protein–coupled receptors 41; GPR43 = G-protein–coupled receptors 43; DCA = deoxycholic acid; UDCA = ursodeoxycholic acid; LCA = lithocholic acid; TGR5 = takeda G-protein–coupled receptor 5; FXR = farnesoid X receptor; VDR = vitamin D receptor; *CutC/D* = choline-TMA lyase system; *CntA/B* and *YeaW/X* = carnitine Rieske-type oxygenase/reductase system; TMA = trimethylamine; FMOs = flavin-containing monooxygenases; TMAO = trimethylamine-N-oxide; MAPK/NF-κB = mitogen-activated protein kinase and nuclear factor-kappa B; SIRT3-SOD2-mtROS = sirtuin-3-superoxide dismutase 2-mitochondrial reactive oxygen species; Cyp7a1 = Cholesterol 7alpha-hydroxylase; CD36 = cluster of differentiation 36; SR-A1 = scavenger receptor A1; COX2 = cyclooxygenase 2; IL = interleukin; ICAM1 = intercellular adhesion molecule 1; NLRP3 = nucleotide binding oligomerization domain–like receptor family pyrin domain-containing-3.

predictor of clinical outcomes in patients with HF.[116–118] A meta-analysis of eight studies also demonstrated that higher circulating TMAO concentration was positively associated with hypertension prevalence, which was dose-dependent.[119] Hence, with these inspiring results, although gut microbiome analyses are not yet ready for clinical use, there is a need to include TMAO and its precursors in future studies to delineate the mechanistic pathways involved in CVDs and explore potential therapeutic targets.

Bile Acids (BAs) serve as modulators of host metabolism

BAs are amphipathic molecules that are composed of a diverse array of structurally specific categories.[120] Primary BAs are initially synthesized from cholesterol in the host liver and stored in the gall bladder, then secreted into the intestinal (duodenum) lumen upon ingestion of a meal to assist the emulsification of fats and oils for digestion and absorption of lipid-soluble dietary nutrients.[121] Most of the primary BAs are actively absorbed and recycled back to the liver, while a small fraction escapes this enterohepatic circulation and enters the colon, where they are deconjugated into secondary BAs via bacterial bile salt hydrolase (BSH) activity identified in the bacterial genera including *Bacteroides, Bifidobacterium, Lactobacillus, Clostridium*, and *Listeria*,[121–123] as well as 7α/7β-dehydroxylations found only in anaerobic gut microbes,[124] providing microbes with a way in which to reduce the toxicity of bile acids.[125]

The most well-discussed secondary BAs include deoxycholic acid (DCA), ursodeoxycholic acid (UDCA), and lithocholic acid (LCA), many of which have pleiotropic and hormonal functions through interaction with a variety of host receptors including farnesoid X receptor (FXR), specific G-protein–coupled receptors (GPCRs) like takeda G-protein–coupled receptor 5 (TGR5), and vitamin D receptor (VDR).[122,126,127] Activation of FXR and TGR5 regulates BAs synthesis, conjugation, transport, and detoxification, as well as glucose, lipid, and energy homeostasis.[128,129] BAs also play an important role in regulating the gut microbiome structure by controlling gut bacteria overgrowth and maintaining intestinal barrier function via FXR signaling.[130] When bound to the TGR5 receptor, secondary BAs cause macrophage activation and subsequent production of inflammatory cytokines.[131] Additionally, studies have shown that BAs may control inflammation and fibrosis, maintain vascular integrity, and control aging and circadian rhythms.[132] These observations demonstrate the systematic regulatory role of BAs, providing a biochemical bridge for the gut microbiome to influence a range of host metabolic processes.

Perturbations to the dynamic interactions among dietary intake, gut microbiome, and specific BAs may thus contribute to cardiometabolic phenotypes and CVDs susceptibly. For example, altered BAs concentrations in plasma are correlated with insulin resistance in patients with type 2 diabetes mellitus,[133,134] and increased relative abundances of *Lactobacillus* and *Bifidobacterium* in the gut may contribute to metabolic improvements via modulation of BAs signaling pathways when applying Acarbose treatments.[135] A recent cross-sectional study found an increased ratio of secondary to primary BAs in patients with chronic heart failure, which was associated with reduced overall survival in univariate analysis.[136] Microbial dysbiosis can lead to decreased BSH activity and impaired cholesterol elimination, thus, promoting atherosclerosis,[137] while a randomized placebo-controlled clinical trial showed that treatment with *Lactobacillus reuteri*, a bacteria with elevated BSH activity, significantly reduced low-density lipoprotein cholesterol (LDL-C) levels.[138] A better understanding of how perturbation in candidate BAs profiles is mechanistically linked to these processes of disease status or responses to therapy may enhance our views of CVDs pathogenesis in the future.

Altered gut microbiome with reduced capacity for short chain fatty acids (SCFAs) production

The human gut microbiome is capable of fermenting carbohydrates in the form of dietary non-digestible fibers, leading to the production of SCFAs, mainly butyrate, propionate, and acetate.[139] SCFAs act as main energy source for colonocytes and play an important role in maintaining gut mucosal integrity by facilitating the tight junction assembly.[140] Gut dysbiosis can

bring a reduction in SCFAs production, causing increased mucosal permeability and leakage of lipopolysaccharide (LPS) and other pro-inflammatory bacterial products such as circulating endotoxins into the systemic circulation, as well as allowing bacterial translocation.[139]

A previous study has reported that SCFAs could stimulate MUC2 mucin expression in intestinal epithelial cells by regulating prostaglandins production, thus may improve barrier function.[141] Other mechanistic studies provided numerous lines of evidence show that SCFAs may serve as microbial mediators that contribute to the vasomotor tone and blood pressure via the olfactory receptor 78 (Olfr78) and G-protein–coupled receptors (GPRs) including GPR41 (also known as free fatty acid receptor 3, FFAR3) and GPR43 (also known as FFAR2).[142–145] Olfr78 is expressed in renal artery branches and the juxtaglomerular afferent arteriole, mediates renin secretion so that modulate vascular resistance, contributing to hypertension.[143] By contrast, GPR41 and GPR43, which are expressed within the vasculature, can exert vasodilator action.[142,144] In addition, SCFAs can activate GPR41 or GPR43 leading to consequent production of chemokines and cytokines, which are necessary for adequate recruitment of leukocytes and activation of effector T lymphocytes during immune responses.[146] SCFAs also play a key role in glucose homeostasis by promoting the release of glucagon-like peptide-1 (GLP-1) via the activation of GPR43, resulting in increased insulin, decreased glucagon secretion, and suppressed appetite.[147,148] Importantly, multiple studies demonstrate that GLP-1 can exert robust cardioprotective actions including attenuation of ischemic cardiac injury, preservation of ventricular function, as well as improved survival,[149–151] which holds great perspectives to favorably modify outcomes in patients with CVDs.

More recently, propionate has been shown to exert cardioprotective effects via attenuating adverse ventricular remodeling, atherosclerotic lesion area, and cardiovascular inflammation in a Treg-dependent manner.[152] Likewise, the susceptibility to cardiac ventricular arrhythmias was significantly lower in propionate-treated mice, indicating viable links between SCFAs and arrhythmia development.[152] Moreover, Tang et al. demonstrated that gut microbe-derived SCFAs would benefit cardiac repair, reduce the size of infarct area and improve outcomes after MI through modulation of immune composition in mice model.[153] In $ApoE^{-/-}$ mice, elevated levels of butyrate due to inoculation with the butyrate-producer *Roseburia intestinalis* led to ameliorated atherosclerosis.[154] Overall, the possible mechanisms behind SCFAs and CVDs are manifold and need to be elucidated.

A growing number of microbe-derived metabolites, including a variety of aromatic amino acid products like uremic toxins and indole, are thought to potentially favor disease pathogenesis via the aryl hydrocarbon receptor.[155,156] Phenylacetylglutamine (PAGln), a phenylalanine-derived metabolite interacts with adrenergic receptors, was reported to induce hyperreactivity of platelet and be associated with incident risk for major adverse cardiac events in an independent cohort.[157] The emphasis is given on the complexities of translating these metabolic signatures into practical clinical biomarkers used to identify patients at risk of CVDs, particularly in terms of whether these changes can lead to new therapeutic strategies like dietary interventions and microbial adjustments.

Other potential microbial aspects in the development of CVDs

Oral microorganisms and cardiovascular risk

The oral cavity is also colonized with a highly heterogeneous microbial community,[158] oral infections occur frequently in humans and often cause caries, gingivitis, and periodontitis,[159] which can lead to edematous swelling and high bleeding tendency, facilitating the transmission of these periodontal pathogens into the bloodstream via the injured oral epithelium along with their by-products or inflammatory mediators (e.g., IL-1 or TNF-α).[160] Within this complexity, an ever-growing number of oral bacteria have been associated with CVDs, and particularly hypertension[161] and atherosclerosis (Figure 3).[162] Bacterial DNA of

oral origin (e.g., *Streptococcus mutans*) and periodontopathogens such as *Porphyromonas gingivalis* and *Treponema denticola* has been frequently detected in atherosclerotic lesions suggesting that bacteria may be rapped at the site of the atherosclerotic lesion and act as potent inducers which may increase inflammatory activity.[163–166] The pathogen-associated molecular patterns (PAMPs, e.g., LPS or peptidoglycan), found commonly on many different pathogens, can bind to a limited number of pattern-recognition receptors (PRRs) expressed on both macrophage and endothelial cells, and through subsequent intracellular signaling trigger the inflammatory response,[167,168] leading to a more vulnerable plaque, thereby increasing the risk of CVDs. Some of these receptors include toll-like receptors (TLRs), nucleotide-binding oligomerization domains (NODs), CD14, complement receptor-3, lectins, and scavenger receptors.[169–171] In addition to recognizing PAMPs, these receptors are also involved in the uptake of oxidized LDL by macrophages, which play a causative role in exacerbating atherosclerosis.[172]

Oral diseases and CVDs share a large set of overlapping risk factors, such as smoking, diabetes mellitus, age, obesity, and poor socioeconomic conditions,[173] as well as common genetic susceptibility variants[174] and biomarkers,[175] suggesting a possible common pathophysiology of periodontitis and CVDs. Previous observational studies have supported an association between periodontitis and atherosclerosis independent of known confounders; however, the evidence did not support a causative relationship.[176] Recently, it was inspiring that a population-based cohort study containing 247,696 participants in Korea demonstrated oral hygiene improvements such as frequent tooth brushing and regular dental visits for professional cleaning were associated with 9% and 14% significantly lower risk of cardiovascular events after multivariable adjustment.[177] Considering as a highly feasible and daily manageable intervention to prevent CVDs, in the near future, randomized controlled trials would require a large population, an adequate follow-up length, and an ethically acceptable control group to elucidate the effects of oral hygiene behaviors on attenuating the cardiovascular risk originating from periodontal disease and dental caries.

Host ecological acclimation and adaptation powered by gut microbiome

The gut microbiome and its hosts are no longer heralded as autonomous entities, but rather as holobionts. As such, their collective genomes forge a hologenome, and these concepts afford a holistic view of biological complexity.[178] Therefore, while human evolution undoubtedly shaped the gut microbiome via changes in factors such as host genetic background, dietary habits, and social behavior during the admixture and introgression processes of human ancestors,[179–181] we believe genetic interactions between the gut microbiome and hosts might play an essential role in increasing a host's acclimation capacity (individual level) and adaptation capacity (population level), even modulating disease severity.[182] One of the examples in humans suggested that the gut bacterium *Bacteroides plebeius* in Japanese individuals has acquired genes encoding carbohydrate active enzymes, which are absent in the human genome, from the seaweed-associated bacterium *Zobellia galactanivorans* in non-sterile food (i.e., sushi).[183] Additionally, the differences in digestion ability due to allelic variations of human genes *LCT* (encoding lactase) and *AMY1* (encoding salivary amylase) could be modified by *Bifidobacterium* (a lactose-metabolizing genus),[184] *Ruminococcus* (a resistant-starch fermentation genus),[185] or other functionally redundant microbes, thus may mitigate energetic trade-offs and contribute to host-adaptive evolution. Similar patterns were also observed when humans encounter environmental fluctuations,[186] and some commensal bacteria can even determine the phenotype of hosts carrying risk alleles for inflammatory disease.[182]

Obviously, these reciprocal interactions facilitate rapid adjustments in host phenotypes across much shorter timescales compared with the classic models of selective pressure on the human genome. A better understanding of the relationship between the host genome and gut microbiome in the context

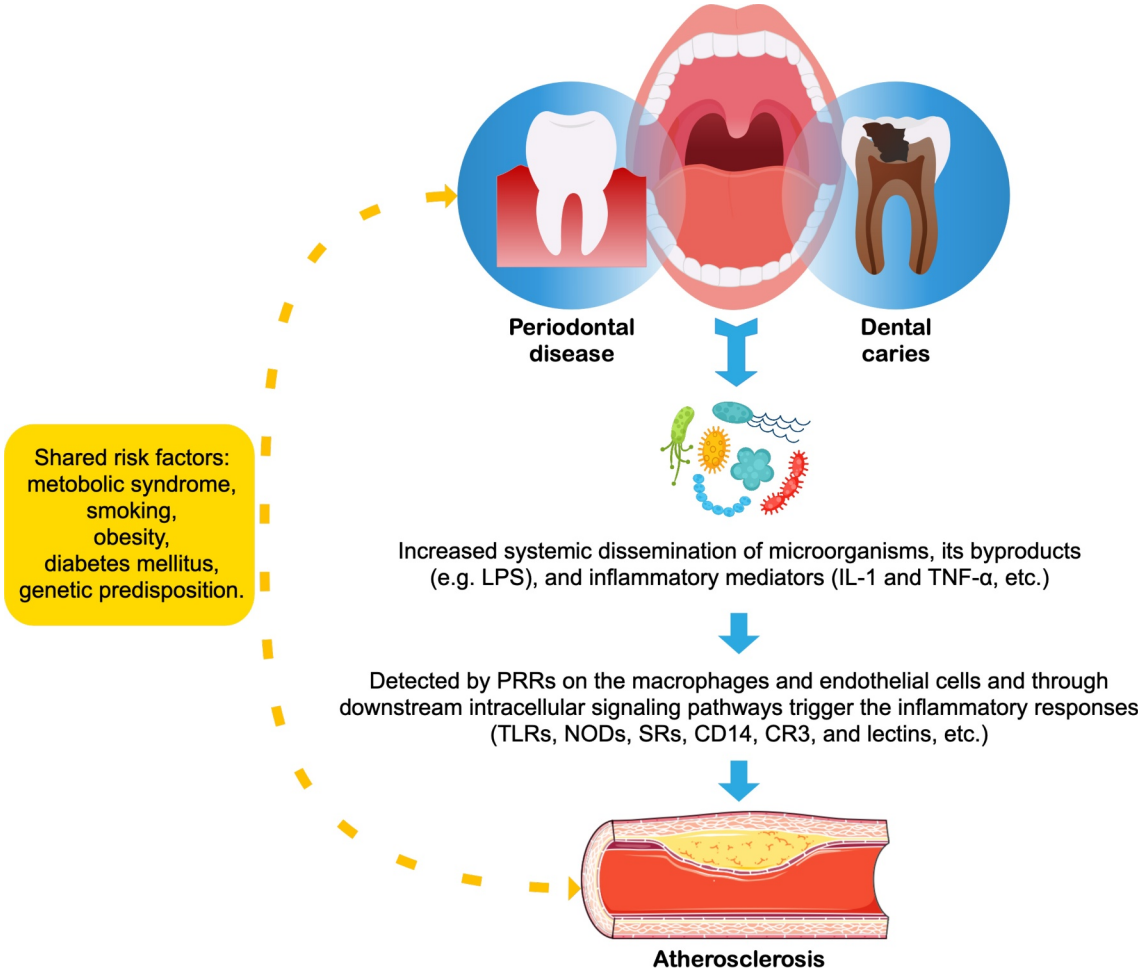

Figure 3. Relationship between atherosclerosis and oral diseases. LPS = lipopolysaccharide; TNF-α = tumor necrosis factor; TLRs = toll-like receptors; NODs = nucleotide-b inding oligomerization domains; SRs = scavenger receptors; CR3 = complement receptor-3.

of adaptive evolution will add another dimension to our knowledge as we moved with our microbes through time and space. Therefore, intertwined processes with host genetics must be considered when exploring the potential of the gut microbiome to influence CVDs pathogenesis. Currently, no study has tested the hypothesis and its biological relevance in an eco-evolutionary trajectory, investigating host genome–microbiome interactions in a wider range of human populations will help researchers go beyond collections of anecdotes to form the foundation of a theory that takes microbiome contributions to host physiology and disease progression into account in a formal framework. Microbial transplantations may help to demonstrate the effect of the gut microbiome on host phenomes, combining with metagenomics and other meta-omics approaches to reveal mechanisms underlying genotype-phenotype variation involving simultaneous pathological changes in diverse levels that contribute to disease risk. Furthermore, as microbial gene repertoires are highly malleable, it offers not only the metagenomic plasticity that expedites host acclimation and adaptation, but exciting prospects for novel therapies.

Conclusions and future perspectives

Although our understanding of how the gut microbiome impacts the pathogenesis of CVDs is still rudimentary, the rate at which new discoveries are emerging is impressive. As outlined, there is overwhelming evidence that microbe-related processes, in general, are linked to multiple CVD-relevant phenotypes, including but not limited to atherosclerosis, blood pressure, platelet reactivity and thrombosis potential, cardiac rhythm, lipid metabolism, and vascular inflammation, which provides us with exciting

areas of investigation to translate it into microbiome-based clinical or pharmaceutical practice. Unsurprisingly, inhibitors of TMA formation that targeting microbial TMA lyases have been developed, which could reduce TMAO levels and reverse atherosclerosis in mice models.[187] Moreover, bile acid activation of FXR can inhibit NF-κB pathway, thereby ameliorating inflammation and improving myocardial function;[188] TGR5 agonists can exert a cardioprotective function and improve myocardial response to physiologic, inotropic, and hemodynamic stress in mice,[189] and thus may consider their roles in the treatment of heart failure in the future. Whereas dietary interventions, prebiotics and probiotics, antibiotics, and fecal microbiota transplantation (FMT) are all potential candidates showing the ability to favorably alter gut microbial profiles and its functional output in some human studies, results are highly variable, and findings from animal models have not yet been transformed to evidence of clinical efficacy, and large, prospective interventional studies will be needed to validate these gut microbiome-targeted therapeutics.[190]

In light of recent findings of adherence to a Mediterranean diet or discontinuation of dietary red meat consumption is negatively associated with TMAO levels,[98,191] and high-fiber diet or acetate supplementary being beneficial to reducing blood pressure and cardiac fibrosis,[192] dietary interventions could be a logical and accessible next step for targeting the gut-heart axis. However, one challenge with particular relevance to microbiome research is the tremendous inter-individual variations in the gut microbiome configuration,[193] and the following host metabolism occasioned by dietary interventions was also person-specific.[194,195] Hence, personalized diet recommendations based on an individual's microbiome, particular responders to a specific food, as well as personal health information including physiologic parameters and family history would become a new rational design for prevention and treatment of disease, and the exploration of precision medicine will progress immensely.

Given the complexity and heterogeneity of the gut microbiome, as well as the state-of-the-art technological advances, a meta-omics approach holds the promise as a path toward unraveling host–microbiome interactions and assessing causality in clinical settings. However, the current application of meta-omics integrations in the field of CVDs has so far been limited. Obviously, one of the main reasons for this is inadequate research design and lack of standardized methods. The parallel measurements on multiple omics layers and proper preprocessing are important for removing outliers and non-biological variations and increasing the comparability between data from different studies. In the coming future, standardized meta-omics pipelines and updated bioinformatic methods with high-resolution of microbial taxa characterization at the strain level can effectively capture a holistic view of pathogenic mechanisms, and ultimately achieve more comprehensive phenotyping of our physiology to select composite diagnostic or prognostic biomarkers for risk stratification and precision medicine, realizing the full potential of this field.

Author Contributions

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