

The Multisite Microbiome-Vascular Axis in Health and Disease: From Local Niches to Systemic Consequences

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Abstract

The human microbiome functions as a distributed superorganism that exerts profound systemic control over vascular homeostasis. Here, we systematically synthesize how microbial communities across five distinct anatomical niches—the gut, oral cavity, respiratory tract, skin, and reproductive tract—orchestrate vascular health and disease. While convergent pathways, such as pattern recognition receptor-mediated systemic inflammation, operate across niches, each compartment deploys specialized mechanisms, including gut-derived metabolic signaling, hematogenous dissemination of periodontal pathobionts, and niche-specific mucosal barrier crosstalk. We critically evaluate the mechanistic contributions of these inter-ecosystem networks to the pathogenesis of atherosclerosis, hypertension,

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and vascular inflammation, highlighting robust microbial signatures as emerging diagnostic biomarkers and risk predictors. Finally, we delineate precision therapeutic paradigms that target niche-specific dysbiosis—ranging from targeted microbiome modulation and periodontal interventions to systemic anti-inflammatory frameworks—and outline multi-omics-driven roadmaps to translate microbiome-vascular science into clinical cardiovascular medicine.

Keywords: Microbiome; Cardiovascular diseases; Atherosclerosis; Metabolic diseases; Inflammation; Periodontitis

Re-evaluating the dialogue between microbiome and cardiovascular system

Multifactorial nature of vascular diseases and the central role of chronic inflammation

Cardiovascular diseases (CVDs) are characterized by their profoundly multifactorial pathogenesis. While traditional risk factor management focusing on blood lipids and pressure has made progress, its predictive and explanatory power for residual cardiovascular risk remains limited^[1]. Extensive research has demonstrated that chronic low-grade inflammation is a core pathological mechanism driving the initiation, progression, and acute complications of atherosclerosis, forming a “common pathway” linking various risk factors to ultimate clinical events^[2]. This “inflammation hypothesis” has evolved from a fundamental theory into a diagnostic and therapeutic paradigm supported by robust clinical evidence.

- **Prognostic and guiding value of inflammatory markers:** Systemic inflammatory biomarkers, epitomized by high-sensitivity C-reactive protein (hsCRP), have been confirmed as strong independent predictors of cardiovascular events, irrespective of traditional risk factors. Deeper investigations reveal that even in patients undergoing intensive statin therapy with controlled low-density lipoprotein cholesterol (LDL-C) levels, the presence of residual inflammatory risk (defined as hsCRP ≥ 2 mg/L) is still associated with a significantly elevated risk of adverse events^[3]. This highlights a potential avenue for targeted anti-inflammatory treatments beyond lipid management.
- **Deepened understanding of underlying mechanisms:** Modern research has elucidated the decisive roles of both innate and adaptive immune systems

in the formation and destabilization of atherosclerotic plaques^[4]. For instance, immune cells within the arterial wall, via signaling hubs like the nucleotide-binding oligomerization domain (NOD)-like receptor family pyrin domain containing 3 (NLRP3) inflammasome, continuously produce key pro-inflammatory cytokines such as interleukin-1 β (IL-1 β) and IL-6. These factors not only exacerbate local inflammation and plaque progression but also stimulate hepatocytes to produce CRP, establishing a systemic inflammatory loop^[2].

- **Landmark clinical intervention evidence:** Clinical trials directly targeting inflammatory pathways have provided definitive validation for the “inflammation hypothesis.” The CANTOS trial was the first to demonstrate that anti-inflammatory treatment using a specific IL-1 β -targeting monoclonal antibody (canakinumab) significantly reduced the risk of recurrent cardiovascular events in patients with a history of myocardial infarction and persistently elevated hsCRP, with this benefit being independent of changes in lipid levels^[5]. Subsequent analyses further indicated a direct correlation between the degree of clinical benefit and the reduction in hsCRP, not LDL-C^[6]. The COLCOT and LoDoCo2 trials further showed that low-cost oral anti-inflammatory drug colchicine (primarily inhibiting NLRP3 inflammasome activation) also conferred significant cardiovascular benefits in patients post-myocardial infarction or with chronic coronary artery disease^[7]. Importantly, the CIRT trial (using broad immunosuppression with methotrexate) failed to show cardiovascular benefits, underscoring the importance of specifically targeting atherosclerosis-relevant inflammatory pathways (such as the IL-1 β /IL-6 axis) rather than general immunosuppression^[8].

Therefore, chronic inflammation has been firmly established as a critical, treatable target in CVD. This paradigm shift provides an essential theoretical framework and clinical link for understanding emerging mechanisms beyond traditional risk factors, such as how microbiome dysbiosis acts as a continuous stimulus for chronic inflammation.

The human microbiome: a multi-niche “signaling network”

The human microbiome is far from a homogeneous entity; instead, it represents a highly spatially organized, multi-niche “signaling network” that forms a crucial interface between the host and its external environment^[9]. Traditional research has long focused on the gut microbiota, leading to a “gut-centric” perspective. However, advancements in high-throughput sequencing technologies have revealed that every mucosal and epithelial surface of the human body—from the oral cavity, upper respiratory tract, and lungs to the skin and reproductive tract—is colonized by distinct microbial communities tightly coupled to local physiological functions^[10]. This spatial heterogeneity is not random but is shaped by the unique physicochemical conditions (e.g., pH, oxygen content, and humidity), nutrient availability, host immune tolerance mechanisms, and inter-microbial interactions within each niche, forming a complex ecological-immune-metabolic microenvironment^[11].

For instance, the gut, a nutrient-rich and strictly anaerobic environment, harbors a microbiome whose core functions are to metabolize dietary components and regulate systemic immunity^[12]. The oral cavity, an open, aerobic, and constantly flushed habitat, is characterized by its microbiota forming multi-species biofilms and participating in local immune balance^[13]. The lower respiratory tract, once considered sterile, is now known to host a low-biomass but dynamic microbiota that interacts with the mucosal immune system to maintain lung homeostasis and defense^[14]. Skin microbiota exhibit differential distribution across dry, moist, and sebaceous regions, acting as a primary barrier against pathogen invasion^[15]. The female vagina, predominantly colonized by *Lactobacillus* species, maintains an acidic environment through lactic acid production, crucial for reproductive health^[16].

These microbial communities, distributed across different ecological niches, do not operate in isolation. Instead, they form an interconnected network through the cross-site migration of microbes and their products (e.g., daily swallowing of oral bacteria) and through shared systemic host responses (e.g., immune activation)^[17]. Therefore, understanding the impact of the microbiome on host health (including vascular health) necessitates moving beyond a single niche to adopt a holistic, multi-site, and multi-level “signaling network” perspective.

Evolution of the “microbiome-vascular axis”: from gut to systemic network

The conceptual evolution of the “microbiome-vascular axis” clearly mirrors the deepening understanding within microbiome science itself. Its origin can be traced to the focus on the metabolic functions of the gut microbiota. Represented by trimethylamine N-oxide (TMAO), research discovered that gut microbiota metabolism of dietary choline produces trimethylamine (TMA), which is then converted to TMAO in the liver, directly promoting atherosclerosis^[18]. This finding gave rise to the gut-centric “gut-heart axis” paradigm, positioning the gut as the primary microbial signal source affecting cardiovascular health^[19].

However, this single-axis model struggled to integrate the robust epidemiological evidence accumulated over decades from other ecological niches. The most significant challenge came from the oral cavity. Decades of research confirmed that periodontitis is an independent risk factor for CVDs, with an effect size comparable to many traditional risk factors^[20]. Mechanistic studies revealed that periodontal pathogens can directly invade the bloodstream and colonize the vascular wall, causing damage by triggering local inflammation^[21]. This “oral-vascular” pathway operates independently of gut metabolism, suggesting that the routes by which microbes influence the vasculature are niche-specific. Similarly, research on the skin microbiome found that dysbiosis accompanying chronic inflammatory skin diseases like psoriasis is one of the drivers of the independent increase in cardiovascular risk in patients^[22]. Collectively, these findings indicate that attributing the microbiome’s influence on the vasculature solely to the gut is incomplete; the cardiovascular system is

exposed to a complex, multi-source microbial signaling environment.

In recent years, with the advancement of projects like the Human Microbiome Project (HMP) and the development of spatial multi-omics technologies, a more systemic and integrated “multi-niche microbial network-vascular” paradigm is emerging^[23]. This paradigm posits: First, microbial communities in different niches (gut, oral cavity, skin, respiratory tract, and reproductive tract), owing to their unique ecological-immune-metabolic microenvironments, have evolved specialized functions that influence host physiology (e.g., the gut excels at producing systemic metabolites; the oral cavity excels at direct pathogen invasion)^[24]. Second, these dispersed signals do not act in isolation but produce synergistic, additive, or antagonistic effects through shared downstream pathways (e.g., common activation of systemic low-grade inflammation, innate immune receptors), forming a dynamic signaling network^[25]. Third, interactions also exist between microbial communities of various niches (e.g., oral microbiota influencing the gut through swallowing), providing internal connectivity to this network^[26]. The core argument of this review is that vascular health and disease states are not determined by a single “axis” but are holistically regulated by a spatially distributed, functionally specialized, and internally interconnected systemic microbial signaling system. Understanding the structure, dynamics, and output of this network is crucial for fully elucidating the role of microbes in cardiovascular pathophysiology and for developing precise niche-targeted or system-wide regulatory strategies^[27].

Therefore, we will first elaborate on systemic innate immune activation triggered by pathogen-associated molecular patterns (PAMPs) as a common bridge connecting all ecological niches^[28]. Building on this, we will delve into the niche-specific mechanisms of the gut (metabolites and immune programming), oral cavity (direct pathogen invasion), skin (barrier disruption and local inflammation), and other niches like the lungs and vagina^[29]. This section will provide a mechanistic basis for understanding the “multi-source” and “heterogeneous” nature of microbial signals. Next, we will integrate these mechanisms to illustrate their synergistic and interactive roles in major vascular diseases. The focus

will be on constructing an integrated model, using atherosclerosis and hypertension as examples, to explain how microbial signals from different niches (e.g., gut-derived TMAO, oral pathogens, and skin-derived inflammatory factors) orchestrate a “multi-pronged attack” that, through additive or synergistic effects, collectively drives disease initiation and progression^[30]. Researchers can leverage emerging multi-omics research paradigms in this section to understand disease pathology at a network level^[24]. Finally, we will discuss potential therapeutic strategies based on niche specificity (e.g., probiotics, periodontal therapy) or overall network regulation (e.g., dietary interventions)^[31]. Simultaneously, we will highlight critical bottlenecks in current research regarding establishing causality, understanding dynamic inter-niche interactions, and developing precise intervention tools^[23,26]. The core objective of this review is to propel the field from descriptive phenomenology and single-mechanism studies toward establishing predictable and intervenable systemic network models, thereby laying a solid theoretical foundation for developing next-generation microbiome-based cardiovascular disease prevention and treatment strategies^[27].

Multi-niche microbial modulation of vascular function

Common foundation: microbe-associated molecular patterns and innate immune activation

Despite the vast differences in composition and local function among microbial communities from various niches, a common cornerstone underpins their influence on the distant vascular system: microbe-associated molecular patterns (MAMPs), such as lipopolysaccharide (LPS), lipoteichoic acid, flagellin, and peptidoglycans, act as “danger signals” by activating the host’s innate immune system, leading to systemic low-grade inflammation and endothelial dysfunction^[32]. This process constitutes the “ultimate common pathway” by which multi-niche microbes affect vascular health. In healthy states, tight epithelial barriers confine the vast microbial populations on mucosal and skin surfaces to local environments. However, various factors (e.g., diet, stress, infection, and disease itself) can compromise niche-specific barrier integrity^[33]. In the gut, this manifests as “leaky gut,” where intercellular junctions of intestinal

epithelial cells widen, allowing bacterial products like LPS to translocate into the portal circulation^[34]. In the oral cavity, periodontitis-induced ulceration and bleeding of the periodontal epithelium provide a direct conduit for PAMPs and viable bacteria from dental plaque to enter the bloodstream^[34]. Even disruption of the skin barrier can lead to systemic exposure to local microbial products^[35]. These circulating PAMPs, particularly LPS, are found at elevated plasma levels in patients with metabolic and CVDs, correlating with disease severity^[36].

Circulating PAMPs are primarily recognized by pattern recognition receptors (PRRs) on two cell types: vascular endothelial cells and innate immune cells (e.g., monocytes, macrophages). Among these, the Toll-like receptor (TLR) and NOD-like receptor (NLR) families are critical^[37].

- **Central role of the TLR4/NF- κ B pathway:** LPS from Gram-negative bacteria is the most extensively studied ligand. It first binds to plasma LPS-binding protein (LBP), then is transported to cluster of differentiation 14 (CD14) on the surface of monocytes/macrophages or endothelial cells, ultimately activating the TLR4 receptor complex^[38]. TLR4 activation triggers the myeloid differentiation factor 88 (MyD88)-dependent signaling pathway, leading to the activation of the I κ B kinase (IKK) complex, which then phosphorylates and degrades I κ B proteins, releasing nuclear factor- κ B (NF- κ B)^[39]. Activated NF- κ B translocates into the nucleus, initiating the transcription of numerous pro-inflammatory genes, including tumor necrosis factor- α (TNF- α), IL-1 β , IL-6, and adhesion molecules on endothelial cells (e.g., vascular cell adhesion molecule-1 [VCAM-1], intercellular cell adhesion molecule-1 [ICAM-1])^[40]. These adhesion molecules promote monocyte recruitment to the vascular wall, an initial step in atherosclerosis.
- **NLRP3 inflammasome activation and IL-1 β maturation:** Beyond transcriptional regulation, PAMPs (such as LPS) can provide a “priming signal” (Signal 1), synergizing with a “second signal” from cellular damage or metabolic stress (e.g., reactive oxygen species [ROS], extracellular adenosine triphosphate [ATP]), to activate

the cytoplasmic NLRP3 inflammasome^[41]. Activated NLRP3 inflammasome recruits and activates caspase-1, which cleaves pro-IL-1 β and pro-IL-18 into their mature, biologically active forms^[42]. IL-1 β is an extremely potent pro-inflammatory cytokine that further amplifies local and systemic inflammatory responses. Notably, periodontal pathogens from the oral cavity (e.g., *Porphyromonas gingivalis* [*P. gingivalis*]) are potent activators of the NLRP3 inflammasome^[43]. Activated endothelial cells not only express adhesion molecules but also experience a reduction in nitric oxide (NO) bioavailability due to increased oxidative stress, while releasing vasoconstrictive substances like endothelin-1, leading to dysfunction of endothelial-dependent vasodilation, an early marker of atherosclerosis and hypertension^[44]. Furthermore, continuous exposure to PAMPs can induce endothelial cell senescence and apoptosis^[45].

- **cGAS–STING signaling and macrophage polarization as an integrative immune axis:** Beyond TLR4/NF- κ B and NLRP3 pathways, the cyclic GMP–AMP synthase (cGAS)–stimulator of interferon genes (STING) pathway has emerged as an important innate immune mechanism linking microbial DNA exposure to macrophage-mediated vascular inflammation. As an additional pattern recognition pathway, cGAS–STING expands the repertoire of PAMP sensing beyond membrane and endosomal receptors by detecting aberrant cytosolic DNA signals. This pathway may therefore serve as a critical molecular bridge between microbial translocation, intracellular danger sensing, and chronic vascular immune activation^[46]. Cytosolic DNA derived from translocated bacteria or bacterial extracellular vesicles is sensed by cGAS, leading to cyclic GMP–AMP (cGAMP) production and subsequent STING activation, which triggers TANK-binding kinase 1 (TBK1)–interferon regulatory factor 3 (IRF3) signaling and the expression of type I interferons and inflammatory mediators^[47,48]. Increasing evidence indicates that cGAS–STING signaling regulates macrophage activation and polarization, influencing the balance between pro-inflammatory M1-like and

tissue-reparative M2-like phenotypes^[49]. Dysregulated STING activation may promote persistent inflammatory macrophage responses, oxidative stress, and vascular injury, whereas appropriate macrophage polarization contributes to immune resolution and tissue homeostasis^[50]. Therefore, microbial signals from different niches may regulate vascular inflammation not only through direct endothelial activation but also by reshaping macrophage functional states, highlighting macrophage polarization as an important integrative node connecting microbial exposure with vascular pathology.

Thus, regardless of whether PAMPs originate from the gut, oral cavity, or other ecological niches, once they enter the circulation, they converge on the same highly conserved host innate immune recognition and response system^[51]. Through TLRs and NLRs, these microbial signals transform vascular endothelial cells and circulating immune cells into a pro-inflammatory state, driving chronic low-grade inflammation, endothelial dysfunction, and atherosclerotic lesions^[52]. This pathway explains why seemingly unrelated local microbial dysbiosis (e.g., periodontitis, irritable bowel syndrome, and skin diseases) is associated with an increased systemic

cardiovascular risk^[53]. The cardiovascular benefits observed in clinical trials targeting this pathway (e.g., anti-IL-1 β treatment) also therapeutically validate its central role as a “common pathway”^[5]. Understanding this foundational mechanism is a prerequisite for dissecting the niche-specific contributions (Figure 1).

In a healthy state, diverse local microbiotas at various mucosal and epithelial interfaces promote physiological homeostasis. Mechanisms include the production of beneficial metabolites (e.g., SCFAs and indoles), maintenance of an intact physical barrier, balanced immune responses, colonization resistance, immune education, and the induction of anti-inflammatory cytokines (such as IL-10 and TGF- β) via Treg/Th17 cell balance, leading to systemic tolerance and homeostasis. Conversely, dysbiosis or pathogen dominance across these same body sites drives pathology. This is characterized by the production of harmful metabolites (e.g., TMAO), barrier disruption, imbalanced immune responses, pathogen overgrowth (e.g., *P. gingivalis*, *S. aureus*, and *Malassezia*), overactivation of inflammatory pathways (e.g., IL-23/Th17 pathway, hyperinflammation), and elevated pro-inflammatory cytokines (IL-17, IL-22), ultimately culminating in systemic inflammation, vascular damage, and vascular remodeling.

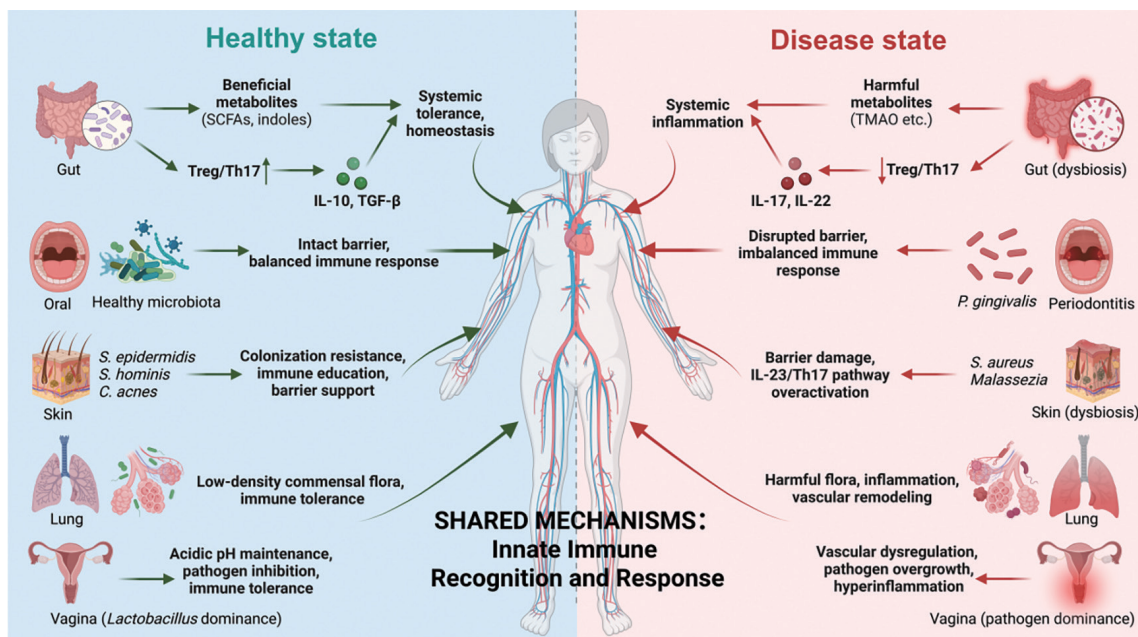


Figure 1: Multi-niche microbial modulation of vascular function.

Niche-specific mechanisms I: gut—the “central processor” of metabolism and immunity

Metabolite-mediated remote regulation

- **TMAO: the “accelerator” of atherosclerosis and thrombosis.** Choline, carnitine, and other nutrients are metabolized by gut microbiota (e.g., enzymes encoded by the *cutC/D* gene cluster) to produce TMA, which is then converted to TMAO by hepatic flavin-containing monooxygenases^[54]. TMAO is not merely a risk marker but a directly pathogenic effector molecule. Its mechanisms include: (a) Promoting foam cell formation: TMAO upregulates the expression of macrophage scavenger receptors (e.g., CD36 and SR-A1), enhancing the uptake of oxidized low-density lipoprotein^[55]. (b) Interfering with reverse cholesterol transport: It inhibits bile acid synthesis and reduces hepatic cholesterol 7 α -hydroxylase (CYP7A1) activity, thereby decreasing cholesterol conversion to bile acids and their excretion^[56]. (c) Enhancing platelet reactivity: TMAO increases intracellular calcium ion concentration, promoting platelet activation and aggregation, thus increasing the risk of thrombosis^[57]. (d) Inducing endothelial dysfunction: It promotes ROS production and inflammatory cytokine expression in endothelial cells^[58]. Furthermore, TMAO has been reported to induce endoplasmic reticulum (ER) stress in vascular cells by activating unfolded protein response (UPR) pathways, including protein kinase R-like endoplasmic reticulum kinase (PERK)/C/EBP homologous protein (CHOP) and inositol-requiring enzyme-1 α (IRE1 α)/X-box binding protein 1 (XBP1) signaling, which further promotes endothelial inflammation, oxidative stress, and apoptotic responses. These mechanisms suggest that microbiota-derived TMAO may contribute to vascular injury not only through metabolic dysregulation but also by triggering maladaptive cellular stress responses^[59]. Clinical studies have shown that plasma TMAO levels are independent predictors of cardiovascular events^[17].
- **Short-chain fatty acids (SCFAs): the “guardians” of vascular homeostasis.** Anaerobic gut bacteria ferment dietary fibers to produce SCFAs,

primarily acetate, propionate, and butyrate. They exert widespread vascular protective effects through the following mechanisms: (a) G-protein-coupled receptor pathways: Acetate and propionate are ligands for GPR41 and GPR43, while butyrate has high affinity for GPR109a. These receptors are widely expressed on immune cells, intestinal epithelial cells, and vascular cells. Activating GPR41/43 can inhibit the NF- κ B pathway, reduce pro-inflammatory cytokine production, and regulate gut hormone secretion (e.g., glucagon-like peptide-1 [GLP-1]), indirectly improving metabolism^[60]. (b) Histone deacetylase inhibition: Butyrate is a potent histone deacetylase (HDAC) inhibitor. By inhibiting HDAC, it can increase histone acetylation, regulate gene expression, promote regulatory T cell (Treg) differentiation in the gut, and enhance the expression of antioxidant and anti-inflammatory genes in vascular endothelial cells, improving endothelial function^[61]. Beyond GPCR-mediated effects and epigenetic regulation, SCFAs can also influence vascular homeostasis through activation of the AMP-activated protein kinase (AMPK)/sirtuin 1 (SIRT1)/peroxisome proliferator-activated receptor γ coactivator 1 α (PGC-1 α) signaling axis. This pathway promotes mitochondrial biogenesis, improves oxidative metabolism, and suppresses oxidative stress and inflammatory responses, thereby providing an additional mechanism through which microbial metabolites contribute to endothelial protection and vascular health^[62,63]. Animal models confirm that SCFAs or prebiotic supplementation can lower blood pressure and reduce atherosclerosis^[64].

- **Secondary bile acids: “regulatory switches” with dual roles.** Primary bile acids are modified by gut microbial enzymes (e.g., bile salt hydrolase, 7 α -dehydroxylase) into secondary bile acids, such as deoxycholic acid and lithocholic acid. They act as both signaling molecules and potential toxins: (a) Beneficial signaling: Secondary bile acids are endogenous ligands for farnesoid X receptor (FXR) and G-protein-coupled bile acid receptor 1 (TGR5). Activating FXR helps maintain glucose and lipid homeostasis and exerts

anti-inflammatory effects^[65]. Activating TGR5 can stimulate GLP-1 secretion from intestinal L-cells and inhibit macrophage inflammasome activation^[66]. (b) Potential cytotoxicity: Excess hydrophobic secondary bile acids (e.g., deoxycholic acid) can induce oxidative stress, DNA damage, and promote apoptosis, potentially leading to toxicity in intestinal epithelial and liver cells, and may exacerbate systemic inflammation^[67]. The composition and proportion of the bile acid pool, regulated by the microbiota, are key factors influencing cardiovascular metabolic health.

- **Indole derivatives: regulating vascular homeostasis via the aryl hydrocarbon receptor pathway.** Dietary tryptophan is metabolized by gut microbiota (e.g., *Lactobacillus*, *Bifidobacterium* species) to produce a series of indole derivatives, including indole-3-propionic acid, indole-3-acetic acid, and indole-3-aldehyde. The vascular effects of these metabolites are primarily mediated by activating the aryl hydrocarbon receptor (AhR)^[68]. (a) AhR-mediated endothelial protection: AhR is expressed in endothelial and smooth muscle cells, and its activation upregulates cytochrome P450 enzymes, promoting the clearance of endogenous toxins and enhancing antioxidant defense, thereby maintaining endothelial barrier function^[69]. (b) Anti-inflammatory and immune regulation: AhR signaling plays a critical regulatory role in immune cells. Microbiota-derived indole derivatives, by activating AhR, can promote regulatory T cell differentiation and inhibit excessive Th17 cell activation, thereby reducing systemic inflammation^[70]. (c) Association with atherosclerosis: Animal models show that supplementing indole-producing probiotics or AhR ligands can reduce atherosclerotic plaque burden^[71]. Conversely, in renal insufficiency, another class of tryptophan metabolites—indoxyl sulfate (generated by hepatic sulfation)—accumulates, becoming a uremic toxin that significantly increases cardiovascular risk by inducing oxidative stress, impairing endothelial function, and promoting vascular calcification^[72]. This indicates that the gut microbiota's "shunting" of tryptophan metabolism (producing protective indoles versus

toxic indoxyl sulfate) has a decisive impact on vascular outcomes.

Systemic immune programming

- **Regulating Treg/Th17 balance, setting the inflammatory tone.** Gut microbiota, particularly certain members of *Clostridium* clusters IV and XIVa, induce and expand regulatory T cells in the colonic lamina propria by producing SCFAs (especially butyrate)^[73]. Tregs maintain immune tolerance to commensal bacteria and suppress excessive systemic inflammatory responses by secreting inhibitory cytokines such as IL-10 and TGF- β . Conversely, segmented filamentous bacteria can induce Th17 cell differentiation, which secrete IL-17 and IL-22, important for pathogen defense, but excessive Th17 responses drive autoimmunity and inflammatory diseases^[74]. The gut microbiota directly regulates this critical balance through metabolites and antigens, and its influence can extend systemically. Gut-derived Tregs can exert suppressive functions at distant inflammatory sites (e.g., atherosclerotic plaques)^[75], while dysbiosis-induced excessive Th17 responses are closely linked to hypertension and vascular inflammation^[76].
- **Training innate immunity and myeloid hematopoiesis.** Gut microbiota and their products can influence bone marrow hematopoietic stem and progenitor cells, shaping the development and functional propensity of myeloid cells. For example, microbial signals can "train" macrophage precursors in the bone marrow to produce stronger inflammatory responses to subsequent stimuli^[77]. Circulating microbial metabolites (e.g., propionate) can directly act on bone marrow hematopoietic stem and progenitor cells, affecting their proliferation and differentiation^[78]. This means that the gut microbiota can systemically alter the quantity and quality of the host's mobilizable immune cell pool, thereby profoundly influencing the inflammatory response capacity to vascular injury.

In summary, the gut microbiome, through its potent metabolic capacity, produces directly vasoactive molecules (e.g., TMAO and SCFAs) and acts as a "central

processor” for regulating vascular health by shaping the systemic immune landscape (particularly the Treg/Th17 balance). These two pathways are intertwined (e.g., SCFAs acting as both metabolites and immune modulators), collectively determining the systemic response tone when the host encounters vascular injury stimuli. From a clinical perspective, circulating TMAO has attracted considerable attention as a potential biomarker for cardiovascular risk prediction. Elevated plasma TMAO levels have been associated with increased risks of atherosclerosis, major adverse cardiovascular events, and mortality in clinical cohorts. However, its application in routine clinical practice requires further validation regarding population-specific thresholds, confounding factors, and integration with existing risk assessment models.

Niche-specific mechanisms II: oral cavity—the “outpost” of pathogen invasion and chronic inflammation

Direct hematogenous dissemination and vascular colonization: the pathogen’s “trojan horse” strategy

Periodontal pathogens, exemplified by *P. gingivalis*, are not only local destroyers but also “invaders” capable of systemic dissemination and direct action on the vascular wall.

- **Evidence of circulatory invasion:** Clinical studies using molecular detection techniques have repeatedly identified DNA or RNA of periodontal pathogens in atherosclerotic plaques, thrombi, and aneurysmal tissues^[79]. This association extends beyond nucleic acids; in human and animal arterial plaques, *P. gingivalis* cellular antigens have even been detected via immunohistochemistry^[21]. This suggests that during active periodontitis, bacteria can directly enter the bloodstream through ulcerated gingival epithelium (bacteremia) and evade host immune clearance to achieve remote colonization. *P. gingivalis* has evolved a remarkable ability to survive and replicate within vascular endothelial cells and smooth muscle cells, akin to intracellular pathogens^[80]. It achieves this through its primary virulence factor, gingipains. Gingipains not only degrade the host tissue’s extracellular matrix and tight junction proteins, opening

pathways for bacterial invasion, but also cleave specific cell surface molecules to inhibit host cell apoptosis, thereby creating an intracellular niche conducive to long-term survival^[81]. These findings highlight the potential clinical importance of oral health management in cardiovascular disease prevention. Periodontal screening and treatment may represent a feasible non-cardiac intervention window for reducing systemic inflammatory burden, particularly among individuals with high cardiovascular risk. Future clinical studies should determine whether periodontal intervention can translate microbial modulation into measurable improvements in vascular outcomes.

- **Direct damage to vascular cells by virulence factors:** *P. gingivalis* and its outer membrane vesicles can directly activate Toll-like receptors (e.g., TLR2/4) on endothelial cells, inducing high expression of adhesion molecules like E-selectin, ICAM-1, and VCAM-1, promoting monocyte adhesion and intimal accumulation^[82]. Concurrently, it interferes with endothelial NO synthase activity, reducing the production of vasodilatory and protective NO, and promotes endothelin-1 release, collectively leading to vasoconstriction and endothelial dysfunction^[83]. Gingipains can modify low-density lipoprotein, making it more readily taken up by macrophages, thereby promoting foam cell formation, a core component of atherosclerotic plaques^[84]. *P. gingivalis* infection can upregulate the expression of matrix metalloproteinases (especially matrix metalloproteinase-9 [MMP-9]) in vascular cells. MMP-9 degrades the collagen components of the plaque fibrous cap, weakening its stability and making the plaque prone to rupture, triggering acute thrombotic events^[85].

As an inflammation amplifier: a continuous source of “cytokine storm”

Periodontitis is a chronic inflammatory lesion driven by dysbiosis, incapable of self-repair. This persistently active local inflammatory process acts as a “cytokine factory,” continuously releasing inflammatory mediators into the circulatory system, significantly increasing the systemic inflammatory burden.

Within active periodontal lesions, numerous activated immune cells (neutrophils, macrophages, and T cells) accumulate, producing high concentrations of pro-inflammatory cytokines such as IL-1 β , IL-6, TNF- α , and prostaglandin E2^[86]. These mediators can easily enter the systemic circulation through the rich local capillary network. Studies confirm that serum levels of IL-6, TNF- α , and CRP are significantly higher in patients with severe periodontitis compared to those with healthy periodontium^[87].

The “chronic low-grade inflammation” hypothesis of cardiovascular disease posits that persistent, subclinical systemic inflammation is a key driver of atherosclerosis progression. Periodontitis perfectly fits the definition of such a “continuous stimulus.” It is not a one-time infection but a long-term, chronic process with recurrent acute exacerbations. Even during “quiescent periods,” active immune activity persists beneath the lesion. Therefore, periodontitis is considered an important environmental factor contributing to and maintaining a state of systemic low-grade inflammation^[88]. This sustained inflammatory burden not only directly damages blood vessels but also “primes” the immune system, making it react more intensely to subsequent atherosclerotic stimuli, forming a vicious cycle.

Epidemiological studies, using methods such as Mendelian randomization, have provided support for a causal relationship between periodontitis and cardiovascular disease^[89,90]. More importantly, interventional studies offer direct evidence: successful basic periodontal therapy (scaling, root planing) can significantly reduce serum levels of systemic inflammatory markers like CRP and IL-6^[91]. This indicates that removing this local source of inflammation can directly alleviate the systemic inflammatory burden, mechanistically explaining why treating periodontal disease might yield cardiovascular benefits.

In summary, oral microbial communities, through both “direct seeding” (pathogen dissemination and colonization) and “remote bombardment” (systemic spillover of inflammatory mediators), directly and continuously participate in vascular damage processes, constituting their unique and indispensable mechanisms for influencing cardiovascular health.

Niche-specific mechanisms III: skin—the “regulator” of barrier integrity and local immunity

Microbiota composition and homeostasis maintenance in healthy skin

Healthy skin microbiota is highly site-specific, primarily composed of members from the phyla Actinobacteria, Firmicutes, Proteobacteria, and Bacteroidetes. Core commensals include *Staphylococcus epidermidis*, *Staphylococcus hominis*, *Cutibacterium acnes*, and various *Corynebacterium* species^[92]. These commensals maintain homeostasis through multiple mechanisms: (a) Niche competition and direct inhibition: They secrete antimicrobial peptides (e.g., phenol-soluble modulins from *S. epidermidis*) to inhibit pathogen colonization^[93]. (b) Immune education: They train skin-resident immune cells, promote regulatory T cell (Treg) function, and maintain tolerance to commensals^[94]. (c) Barrier support: They help maintain epidermal acidic pH and stratum corneum integrity through metabolites (e.g., SCFAs)^[95].

Microbiota dysbiosis and barrier disruption: exemplified by psoriasis and atopic dermatitis

In chronic inflammatory skin diseases such as psoriasis and atopic dermatitis (AD), skin microbiota undergoes characteristic dysbiosis, showing decreased diversity and expansion of specific pathogenic bacteria^[96]. In psoriatic plaques, the relative abundance of *Staphylococcus aureus* and *Malassezia* species significantly increases^[97]. In AD, excessive colonization by *S. aureus* is a hallmark feature^[98]. This dysbiosis is not a passive consequence but an active pathogenic factor. Virulence factors secreted by *S. aureus* (e.g., α -toxin, phenol-soluble modulins) can directly lyse keratinocytes, disrupting the physical barrier composed of filaggrin and tight junction proteins^[99]. Following barrier breakdown, MAMPs, allergens, and autoantigens readily penetrate, activating innate immune cells in the dermal layer.

Core immune axis: persistent activation of the IL-23/Th17 pathway

The core of the skin immune response is the IL-23/Th17 axis. Upon recognizing invading antigens, antigen-

presenting cells like dendritic cells produce IL-23. IL-23 drives the expansion of $\gamma\delta$ T cells, Th17 cells, and group 3 innate lymphoid cells (ILC3s), which in turn secrete large amounts of effector cytokines IL-17A, IL-17F, IL-22, and TNF- α ^[100]. IL-17 and IL-22 stimulate keratinocyte hyperproliferation (a typical psoriatic plaque feature) and the production of antimicrobial peptides (e.g., LL-37) and chemokines (e.g., C-X-C motif chemokine ligand 1 [CXCL1], CXCL8), which further recruit inflammatory cells like neutrophils, forming a chronic inflammatory environment characterized by neutrophilic microabscesses^[101]. In AD, although Th2 responses predominate, *S. aureus* colonization can also strongly induce IL-17 and IL-23 production, exacerbating disease severity^[102].

Mechanisms from local inflammation to systemic vascular damage

Active skin lesions are efficient “cytokine factories.” Persistently elevated serum levels of IL-17, IL-23, TNF- α , IL-6, and hsCRP in patients signify a chronic systemic low-grade inflammatory state^[103]. Circulating IL-17A and TNF- α can directly act on vascular endothelial cells, activating the NF- κ B pathway to upregulate adhesion molecule (VCAM-1, ICAM-1) expression, promoting monocyte adhesion and intimal accumulation, while impairing endothelial-dependent vasodilation, which are critical early steps in atherosclerosis^[104]. Cutting-edge research reveals that skin inflammation can remotely affect bone marrow hematopoiesis. Cytokines like IL-23 can induce epigenetic reprogramming of hematopoietic stem and progenitor cells, skewing them toward producing more granulocyte-monocyte progenitors, leading to a continuous output of hyper-reactive inflammatory neutrophils and monocytes from the bone marrow, thereby systematically amplifying the inflammatory response to various stimuli, including vascular injury^[105].

Epidemiological and clinical interventional causal evidence chain

Large-scale cohort studies and meta-analyses confirm that patients with moderate to severe psoriasis have a significantly increased risk of myocardial infarction, stroke, and heart failure, with risk ratios comparable to traditional factors like diabetes and hypertension,

and positively correlated with disease severity and duration^[106]. AD has also been independently associated with an increased risk of hypertension, myocardial infarction, and heart failure^[107]. Effective control of skin inflammation using targeted biologics (e.g., anti-IL-17A, anti-IL-23, anti-IL-12/23, anti-TNF- α) not only significantly reduces serum systemic inflammatory markers but also improves endothelial function^[108]. Furthermore, prospective cohort data show that psoriatic patients receiving effective systemic treatment have lower cardiovascular event rates than those with uncontrolled disease, providing strong supportive evidence for “controlling skin inflammation to reduce cardiovascular risk”^[109].

Skin microbiota dysbiosis, by disrupting the barrier and activating a local immune inflammatory loop centered on IL-23/Th17, leads to systemic spillover of pro-inflammatory cytokines, direct endothelial damage, and bone marrow hematopoietic reprogramming. These collectively drive chronic systemic inflammation, thereby constituting the pathophysiological basis for diseases like psoriasis and AD becoming independent cardiovascular risk factors. This mechanism clearly establishes a logical chain of “skin microbiota dysbiosis → local immune inflammation → systemic inflammation → accelerated vascular disease.”

Niche-specific mechanisms IV: lung—the gatekeeper of local immunity and vascular resistance

Microbiota composition and homeostasis maintenance in healthy lungs

The healthy lower respiratory tract microbiota is characterized by low biomass (abundance approximately one-thousandth of the gut) and high dynamism, with its composition primarily influenced by the balance of inhalation, microaspiration, and mucociliary clearance mechanisms^[110]. Core phyla typically include *Firmicutes*, *Bacteroidetes*, and *Proteobacteria*. Dominant genera vary considerably among individuals, potentially including *Prevotella*, *Veillonella*, and *Streptococcus* species^[111]. The healthy lung microbiota is not passively present but, through continuous dialogue with the host immune system (especially alveolar macrophages),

helps maintain a state of immune tolerance, suppressing excessive inflammatory responses to harmless inhaled antigens^[112].

Microbiota dysbiosis and lung diseases: characteristic changes in COPD and PAH

In diseases such as chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary arterial hypertension (IPAH), lung microbiota undergo characteristic dysbiosis, presenting as reduced alpha diversity and altered community composition^[113]. In COPD patients, the relative abundance of common *Haemophilus*, *Moraxella*, and *Streptococcus* species increases, while potentially beneficial bacteria decrease^[114]. Unique microbial features have also been detected in the lungs of IPAH patients^[115]. This dysbiosis correlates positively with disease severity, frequency of acute exacerbations, and inflammation levels.

Core mechanism: “reprogramming” of alveolar macrophages

Alveolar macrophages are the primary innate immune cells in the lung, and the local microbiome directly regulates their functional state. Dysbiosis reprograms them from “guardians” to “destroyers” through the following pathways: Commensal microbiota, typically through metabolites like short-chain fatty acids, maintain the oxidative phosphorylation metabolic phenotype of alveolar macrophages, favoring anti-inflammatory and tissue repair functions^[116]. Following dysbiosis, harmful bacteria and their products (e.g., LPS) shift macrophage metabolism toward glycolysis (the “Warburg effect”). This metabolic shift is fundamental to pro-inflammatory phenotype (M1-like) activation, driving the extensive production of IL-1 β , IL-6, and TNF- α ^[117]. PAMPs (e.g., bacterial DNA) and DAMPs (e.g., ATP) released by lung microbiota dysbiosis provide dual signals, continuously activating the NLRP3 inflammasome within alveolar macrophages, leading to caspase-1-mediated maturation and secretion of IL-1 β and IL-18^[118]. IL-1 β is an extremely potent pro-inflammatory factor that can directly act on the pulmonary vasculature. Chronic microbial stimulation leads to alveolar macrophages exhibiting “immune fatigue” or “inflammatory senescence” phenotypes, characterized by reduced ability to clear apoptotic cells

and pathogens, yet increased baseline inflammatory cytokine secretion, forming an inefficient and harmful state of persistent inflammation^[119].

Towards pulmonary arterial hypertension: from inflammation to vascular remodeling

Alveolar macrophages “reprogrammed” by dysbiotic microbiota are a core engine driving pulmonary vascular remodeling in PAH: Macrophages secrete IL-1 β , IL-6, and TNF- α , which can directly stimulate pulmonary vascular endothelial cell activation, promoting endothelial-to-mesenchymal transition; concurrently, they stimulate abnormal proliferation, migration, and apoptosis resistance of pulmonary artery smooth muscle cells, leading to vascular wall thickening and lumen narrowing^[120]. Activated macrophages produce large amounts of ROS, leading to local oxidative stress. ROS not only directly damage vascular cells but also inactivate the vasodilator NO and activate hypoxia-inducible factor-1 α , further promoting pro-proliferative and pro-inflammatory gene expression, forming a “hypoxia-inflammation-vasoconstriction” vicious cycle^[121].

Systemic vascular impact: beyond pulmonary circulation

Chronic lung inflammation has significant systemic consequences: High levels of IL-1 β , IL-6, and TNF- α produced in the lungs can enter systemic circulation, contributing to a systemic low-grade inflammatory state, a known driver of accelerated systemic atherosclerosis^[122]. Lung-derived ROS and inflammatory cells can “spill over” into circulation, consuming systemic antioxidant capacity, leading to increased circulating oxidized lipids and DNA damage products. Systemic oxidative stress is a critical link in endothelial dysfunction and atherosclerosis^[123]. Similar to skin inflammation, persistent lung inflammatory signals may remotely affect the bone marrow, promoting the generation of more pro-inflammatory-prone myeloid cells, thereby systematically exacerbating vascular inflammation^[124].

Evidence and intervention prospects

COPD is a recognized independent cardiovascular risk factor, with patients experiencing significantly increased

risks of myocardial infarction and heart failure^[125]. PAH patients often also have systemic endothelial dysfunction. Animal model studies show that inducing lung microbiota dysbiosis (e.g., through antibiotics or pathogen infection) can exacerbate hypoxia-induced pulmonary hypertension^[126]. Conversely, using broad-spectrum antibiotics to clear certain microbiota or supplementing probiotics in some models can alleviate pulmonary vascular remodeling and inflammation^[127]. Targeting the lung microbiota-immune axis (e.g., through inhaled probiotics, phages, or specific metabolites) or key downstream inflammatory mediators (e.g., anti-IL-1 β treatment) represents potential new strategies for treating PAH and reducing systemic cardiovascular complications in COPD patients^[128]. The lung microbiome, by finely regulating the immunometabolism and inflammatory state of alveolar macrophages, profoundly influences pulmonary vascular resistance and remodeling, acting as an important link in the pathogenesis of pulmonary arterial hypertension. Simultaneously, the lung, as a chronic inflammatory focus, generates “spillover effects” of inflammation and oxidative stress, systematically exacerbating pathological processes in systemic blood vessels.

Niche-specific mechanisms V: vagina—a key regulator of female cardiovascular health

Microbiota composition and homeostasis maintenance in the healthy vagina

The vaginal microbiota of healthy reproductive-aged women is dominated by *Lactobacillus* species, whose relative abundance can reach 70%–90%^[129]. Key species include *L. crispatus*, *L. gasseri*, *L. jensenii*, and *L. iners*. They maintain a healthy vaginal microenvironment through the following mechanisms: (a) Lactic acid production: They convert glycogen into lactic acid, maintaining a vaginal pH of 3.8–4.5, effectively inhibiting pathogen growth^[130]. (b) Pathogen antagonism: They occupy epithelial cell adhesion sites and produce bacteriotoxins, hydrogen peroxide, and other antimicrobial substances to directly antagonize opportunistic pathogens^[131]. (c) Immune modulation: They promote local immune tolerance, maintaining moderate immune surveillance without triggering excessive inflammation^[132].

Microbiota dysbiosis characteristics of bacterial vaginosis

Bacterial vaginosis (BV) is a typical dysbiosis characterized by a significant reduction or absence of *Lactobacillus* (especially hydrogen peroxide-producing strains), replaced by the overgrowth of various anaerobic and facultative anaerobic bacteria, forming a high-diversity biofilm^[133]. Core pathogenic communities include: *Gardnerella vaginalis* is considered a key “keystone” bacterium in bacterial vaginosis (BV). It can form dense biofilms that serve as a structural scaffold, facilitating the attachment, colonization, and growth of other anaerobic bacteria, including *Prevotella* species (such as *P. bivia* and *P. buccae*), *Mobiluncus* species, *Bacteroides* species, and *Sneathia* species^[134]. These bacteria collectively produce a range of virulence factors, such as sialidases, mucinases, and LPSs, that compromise host defenses.

Mechanisms from local dysbiosis to systemic vascular damage

BV-associated pathogens, particularly *Gardnerella vaginalis* and *Prevotella* species, secrete sialidases that degrade sialic acid residues in the cervical mucus barrier, disrupting the mucus gel structure^[135]. This allows bacterial products and even live bacteria to penetrate the barrier, contacting and activating immune cells (e.g., macrophages, dendritic cells) in the cervix and lower uterus. These cells, by recognizing bacterial LPSs and peptidoglycans, activate TLR2/4 signaling pathways, which then strongly activate the NLRP3 inflammasome, leading to the massive release of mature IL-1 β , IL-6, and TNF- α , among other pro-inflammatory cytokines^[136].

During pregnancy, the uterus is a highly vascularized organ. The intense inflammatory factors produced locally in the cervix-decidua can easily enter the maternal circulation. IL-1 β and TNF- α are known potent modulators of vascular function: they can induce oxidative stress in vascular endothelial cells, reduce NO bioavailability, and promote endothelin-1 release, leading to increased vasoconstriction and dysfunction of endothelial-dependent vasodilation^[137]. This inflammatory environment can inhibit the normal invasion of placental syncytiotrophoblasts and lead to an

imbalance between pro-angiogenic factors (e.g., vascular endothelial growth factor [VEGF]) and anti-angiogenic factors (e.g., soluble fms-like tyrosine kinase-1 [sFlt-1]), the latter being central to preeclampsia pathogenesis^[138]. Numerous prospective cohort studies have confirmed that BV diagnosed in early to mid-pregnancy is an independent risk factor for subsequent preeclampsia, with hazard ratios (HR) ranging from 1.2 to 2.0^[139]. This association is more pronounced in severe, early-onset preeclampsia. *Gardnerella vaginalis*: The biofilm it forms not only provides physical protection, but its release of succinic acid can directly inhibit *Lactobacillus* growth and act as a signaling molecule to enhance local inflammatory responses^[140]. *Prevotella* species: Can produce abundant LPSs, but their LPS structure (non-classical 3-hydroxy fatty acids) possesses unique immunostimulatory activity, potentially inducing stronger TLR4-mediated inflammatory responses^[141].

Potential impact on long-term cardiovascular health

Preeclampsia is considered a “stress test” and a warning signal for women’s future risk of CVDs (e.g., hypertension, ischemic heart disease, heart failure)^[142]. Its fundamental pathology involves systemic endothelial damage incurred and potentially entrenched during pregnancy. Therefore, BV, as an intervenable risk factor for preeclampsia, might have effects beyond pregnancy: Chronic, recurrent, or untreated BV could maintain women in a subclinical systemic inflammatory state over the long term, continuously inflicting low-level damage on the vascular endothelium^[143]. Experiencing severe endothelial dysfunction triggered by BV-related inflammation during pregnancy might impair vascular repair mechanisms, increasing the risk of long-term postpartum arteriosclerosis and hypertension^[144]. Research has begun to explore the association between BV and non-pregnant women’s cardiovascular risk markers (e.g., carotid intima-media thickness), providing preliminary support for this long-term impact hypothesis^[145].

The vaginal microbiome, particularly the *Lactobacillus*-dominated steady state, is critical for maintaining local immune balance and barrier function in the female reproductive tract. Dysbiosis, exemplified by BV, through virulence factors of specific pathogens (e.g., *Gardnerella*, *Prevotella*), disrupts the barrier, triggering

a local immune storm centered on the NLRP3/IL-1 β axis, leading to systemic “spillover” of pro-inflammatory cytokines, directly contributing to the pathogenesis of pregnancy-related vascular complications like preeclampsia. This not only reveals the direct intersection of reproductive health and cardiovascular health during pregnancy but also suggests that BV could be an early, intervenable window for cardiovascular risk across a woman’s lifespan. Future research needs to longitudinally track BV history, pregnancy outcomes, and long-term cardiovascular phenotypes, and explore new strategies to improve vascular health by maintaining or restoring vaginal microbiota homeostasis (e.g., using specific probiotic strains)^[146,147].

Niche-specific mechanisms VI: skeletal muscle—the metabolic and immune interface linking microbiota to vascular function

Skeletal muscle is the largest insulin-sensitive organ and a major regulator of systemic metabolism. Although it is not a classical microbial niche, skeletal muscle serves as a critical target of microbiota-derived metabolites and immune signals. Increasing evidence suggests that the interaction between gut microbiota, skeletal muscle metabolism, and vascular function forms a “Muscle–Microbiome–Vascular Triangle”, in which microbial metabolites regulate muscle metabolic homeostasis, inflammatory status, and myokine secretion, thereby influencing endothelial function and vascular remodeling^[148,149].

Microbiota-derived metabolites and skeletal muscle metabolic regulation

The gut microbiome regulates skeletal muscle function mainly through circulating microbial metabolites, including SCFAs and bile acid derivatives. SCFAs, particularly butyrate, promote mitochondrial biogenesis and oxidative metabolism through AMPK and PGC-1 α signaling, while microbial regulation of bile acid metabolism influences insulin sensitivity via FXR/TGR5 pathways^[150,151]. Microbial dysbiosis reduces beneficial metabolite production and promotes mitochondrial dysfunction, impaired glucose utilization, and oxidative stress in skeletal muscle. These metabolic alterations contribute to systemic inflammation and indirectly accelerate endothelial dysfunction and vascular injury.

Muscle inflammation and immune-mediated vascular dysfunction

Skeletal muscle functions as an endocrine organ through the secretion of myokines, which regulate metabolism and vascular homeostasis. However, microbiota imbalance and increased circulating microbial products, particularly LPS, activate TLR4-dependent inflammatory signaling in skeletal muscle, increasing TNF- α , IL-1 β , and NF- κ B activity^[152]. This chronic inflammatory state reduces beneficial myokine signaling and promotes endothelial dysfunction through decreased NO availability, increased oxidative stress, and vascular inflammatory activation. Therefore, skeletal muscle may act as an intermediate immune-metabolic amplifier linking microbial disturbance to systemic vascular damage.

Clinical evidence and therapeutic perspectives

Clinical studies have demonstrated associations between gut dysbiosis, skeletal muscle dysfunction, and cardiovascular risk. Aging-related reductions in microbial diversity and SCFAs-producing bacteria are linked with sarcopenia, chronic inflammation, and increased cardiovascular susceptibility^[153]. Similarly, obesity and type 2 diabetes exhibit combined alterations in gut microbiota, muscle insulin resistance, and endothelial dysfunction^[154]. Microbiota-targeted interventions, including dietary modulation, exercise, probiotics, and metabolite-based therapies, represent potential strategies to improve both muscle and vascular health. However, current evidence remains largely associative, and the causal mechanisms by which specific microbial taxa or metabolites regulate muscle–vascular communication require further validation using integrated multi-omics approaches.

Although niche-specific mechanisms provide important insights into how microbial communities regulate vascular function, their clinical significance extends beyond mechanistic interpretation. Increasing evidence suggests that niche-derived microbial signatures, metabolites, and immune mediators may serve as clinically relevant indicators for cardiovascular risk stratification. For example, circulating microbial metabolites such as TMAO, pathogen-derived components, and inflam-

matory signatures associated with oral or gut dysbiosis may complement conventional cardiovascular risk factors by identifying individuals with elevated residual inflammatory risk. Therefore, understanding niche-specific microbiome–vascular interactions may facilitate the development of personalized diagnostic strategies and early intervention approaches.

Disease integration: synergistic roles of the microbiome network in cardiovascular pathologies

Atherosclerosis: an integrated “multi-pronged attack” model of the microbiome network

The development of atherosclerosis can be viewed as a process continuously “attacked” by multi-source microbial signals. These signals originate from different ecological niches, and through unique yet interrelated mechanisms, collectively shape the fate of plaques.

Within atherosclerotic lesions, macrophages serve as central regulators that determine whether inflammation progresses or resolves. Upon exposure to microbial-derived signals, oxidized lipids, and inflammatory cytokines, circulating monocytes are recruited into the vascular wall and differentiate into heterogeneous macrophage populations with dynamic functional states. Pro-inflammatory macrophages produce cytokines such as TNF- α , IL-1 β , and IL-6, promoting endothelial dysfunction, lipid accumulation, and plaque instability, whereas reparative macrophage phenotypes contribute to efferocytosis, tissue repair, and inflammatory resolution^[155]. Recent single-cell transcriptomic studies have revealed extensive macrophage heterogeneity within atherosclerotic plaques, demonstrating that macrophage states exist along a continuum rather than as simple M1/M2 categories, with local metabolic and inflammatory cues shaping their functional profiles^[156]. Microbial signals may disturb this balance by sustaining inflammatory macrophage activation, impairing efferocytosis, and accelerating necrotic core formation, thereby linking microbiome-derived stimuli to atherosclerotic progression^[157]. Importantly, microbial-derived metabolites may further promote macrophage dysfunction by inducing ER stress and activating the UPR, particularly the XBP1-dependent transcriptional program, which

regulates inflammatory signaling, cellular adaptation, and survival responses. Dysregulated ER stress responses may therefore serve as a mechanistic bridge connecting microbiome-derived metabolic perturbations to persistent macrophage activation and plaque progression^[158].

In addition, microbial-derived DNA and damage-associated mitochondrial DNA released under cellular stress may activate the cGAS–STING pathway in plaque macrophages and endothelial cells. STING activation promotes TBK1–IRF3 signaling and type I interferon production, while its excessive activation significantly drives a phenotypic switch in plaque macrophages, exacerbating pro-inflammatory M1 polarization while suppressing reparative M2 polarization. This dynamic imbalance accelerates oxidative stress, lipid loading, and endothelial dysfunction. Thus, cGAS–STING represents an additional innate immune sensing mechanism linking microbial translocation and cellular stress responses to chronic vascular inflammation and plaque instability via dysregulated macrophage polarization dynamics^[159].

Clinically, the multi-niche microbiome network model suggests that atherosclerosis should not only be considered a lipid-driven disease but also a condition influenced by microbial, metabolic, and immune interactions. This concept may support future risk prediction models incorporating microbial biomarkers alongside conventional cardiovascular parameters. Nevertheless, prospective clinical trials are required to determine whether microbiome-based interventions can reduce plaque progression or cardiovascular events.

Gut: the “nexus of metabolic dysregulation”

The gut microbiome systemically sets the metabolic and inflammatory tone for atherosclerosis (AS) by producing vasoactive metabolites directly.

- **Pro-atherogenic factors—TMAO:** A diet rich in choline/carnitine (e.g., red meat) is metabolized by gut bacteria (e.g., *Firmicutes* species encoding the *cutC/D* gene cluster) to produce TMA, which is converted to TMAO in the liver. TMAO directly

promotes AS and thrombosis by (a) upregulating macrophage scavenger receptors to promote foam cell formation; (b) inhibiting reverse cholesterol transport; and (c) enhancing platelet reactivity^[27,160,161].

- **Vascular protective factors—SCFAs, indole derivatives, and secondary bile acids:** Dietary fibers fermented by gut anaerobic bacteria produce acetate, propionate, and butyrate. They inhibit inflammation by activating GPR41/43 on vascular and immune cells, and upregulate protective gene expression (e.g., antioxidant genes) by inhibiting HDAC. Butyrate also induces regulatory T cells in the gut, systematically suppressing inflammation. Propionate supplementation in animal models significantly reduces hypertensive cardiovascular damage and AS^[64]. Tryptophan is metabolized by gut bacteria (e.g., *Lactobacillus*) to produce indole-3-propionic acid, among others, which are endogenous ligands for the AhR. AhR signaling activation enhances endothelial barrier function, reduces oxidative stress, and promotes regulatory T cell differentiation, thereby exerting anti-AS effects^[162]. Gut bacteria modify primary bile acids to produce deoxycholic acid and lithocholic acid. As ligands for FXR and TGR5, their activation inhibits hepatic lipid synthesis, promotes energy expenditure, and suppresses NLRP3 inflammasome in macrophages, thereby exerting anti-inflammatory and anti-AS effects^[65].

Oral cavity: the “outpost of direct invasion and local inflammation”

Oral pathogens, exemplified by *P. gingivalis*, accelerate AS through direct hematogenous dissemination and systemic inflammation. This bacterium can enter circulation via ulcerated gingival epithelium and utilize its virulence factor gingipains to invade and survive within vascular endothelial cells and smooth muscle cells^[81]. Its direct damage includes: (a) activating endothelial cell TLR2/4, promoting adhesion molecule expression; (b) inducing abnormal proliferation and migration of smooth muscle cells; and (c) upregulating MMP-9 expression within plaques, weakening fibrous cap stability^[90]. Systemic inflammation amplification:

Periodontitis, as a chronic inflammatory focus, continuously releases pro-inflammatory cytokines such as IL-1 β , IL-6, and TNF- α into circulation, significantly elevating the systemic inflammatory burden and providing continuous “fuel” for AS development^[87].

Skin and others: the “amplifiers of persistent immune activation”

Chronic inflammatory skin diseases (e.g., psoriasis) share immunopathological bases with AS.

- **IL-17/23 axis-driven systemic inflammation:** Skin microbiota dysbiosis (e.g., *Staphylococcus aureus* overgrowth) leads to barrier disruption, activating the skin’s IL-23/Th17 immune axis, producing large amounts of IL-17A and IL-22^[100]. These cytokines enter circulation, directly impairing endothelial function and remotely “training” bone marrow hematopoietic stem cells to produce more pro-inflammatory myeloid cells, thereby systematically exacerbating vascular inflammation^[163]. BV-related dysbiosis is associated with an increased risk of preeclampsia during pregnancy (a form of acute endothelial dysfunction)^[164], suggesting its potential to influence long-term cardiovascular risk by inducing severe vascular inflammatory events.
- **Integrated “multiple hit” hypothesis:** Growing evidence supports a “multiple hit” hypothesis: that simultaneous or sequential dysbiosis from multiple ecological niches exerts additive or even synergistic accelerative effects on AS. Regardless of origin, microbial signals from different niches ultimately converge to activate common host innate immune pathways, such as NF- κ B and the NLRP3 inflammasome, producing ultimate effector molecules like IL-1 β and IL-6. This convergence can lead to an “1 + 1 > 2” amplification of inflammation^[32]. Oral pathogens (e.g., *P. gingivalis*) can, after being swallowed, alter gut microbiota composition and barrier function, thereby affecting the production of gut-derived metabolites (e.g., increasing TMAO, decreasing SCFAs)^[26]. Conversely, systemic inflammation driven by gut dysbiosis may also reduce local oral

immunity, exacerbating periodontitis^[21]. Chronic inflammation in one niche (e.g., psoriasis) leading to systemic low-grade inflammation and “trained immunity” in the bone marrow can make the vascular system respond more rapidly and intensely to attacks from another niche (e.g., oral bacteremia or high TMAO)^[165]. Patients suffering from both periodontitis and gut dysbiosis-related metabolic diseases (e.g., diabetes) have a far greater cardiovascular risk than those with only one of these conditions^[166]. Psoriasis patients complicated with severe periodontitis have higher levels of systemic inflammatory markers and cardiovascular event risk than those with only psoriasis^[167]. Simultaneously administering a high-choline diet (mimicking gut dysbiosis) and oral *P. gingivalis*-infection to mice accelerates aortic plaque formation and inflammation more significantly than either intervention alone^[168]. Similarly, protective signals from different niches can also synergize. For example, gut-produced SCFAs and indole derivatives can systemically enhance immune tolerance and endothelial stability, while healthy oral and skin microbiota reduce systemic inflammatory burden by maintaining local barriers. This holistic healthy microbiome network collectively forms a defense against AS^[23].

Atherosclerosis is a concentrated manifestation of systemic microbiome network imbalance at the vascular level (Figure 2). The gut, oral cavity, skin, and other ecological niches drive plaque progression from different angles through niche-specific mechanisms such as metabolites, direct pathogen invasion, and systemic immune activation. These mechanisms are not independent but engage in profound dialogue at the level of inflammatory pathways, inter-niche interactions, and host immune status, collectively constituting a “multiple hit” scenario. Future research and clinical interventions need to shift from a single-niche perspective to holistic network regulation, for instance, through integrated strategies that combine dietary improvement (gut modulation), periodontal disease treatment (oral control), and skin inflammation management (reducing systemic burden) to prevent and treat atherosclerosis more effectively.

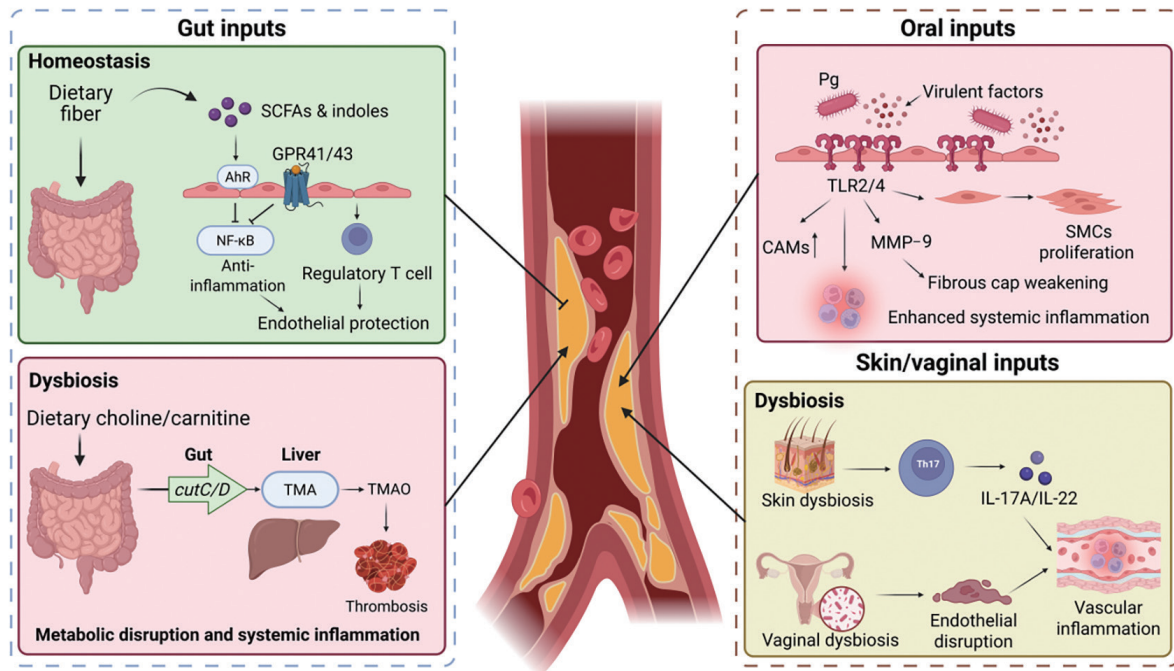


Figure 2: Atherosclerosis is a concentrated manifestation of systemic microbiome network imbalance at the vascular level.

Gut inputs: Under homeostasis, dietary fiber produces SCFAs/indoles to induce anti-inflammatory and endothelial protection. Under dysbiosis, dietary choline/carnitine converts via microbial *cutC/D* into TMA and hepatic TMAO, promoting thrombosis and systemic inflammation. Oral and skin/vaginal inputs: Periodontal pathogens activate TLR2/4 signaling to enhance systemic inflammation and fibrous cap weakening. Skin and vaginal dysbiosis trigger Th17 cells, IL-17A/IL-22, and endothelial disruption to drive vascular inflammation. Center: Cross-section of a blood vessel showing converging multi-site inputs that promote plaque buildup and vascular pathology.

Hypertension: gut-centric regulation and multi-niche modification

Hypertension is a complex manifestation of imbalanced vascular homeostasis. Within the microbiome network, the gut microbiota plays an undeniable “central processor” role, directly regulating blood pressure through metabolic and immune mechanisms. Meanwhile, dysbiosis in other niches such as the oral cavity and lungs acts as “accessory factors,” exacerbating vascular inflammation and resistance, collectively shaping the hypertensive phenotype.

High-salt diet reshapes gut microbiota structure and function

High salt intake rapidly and significantly alters gut microbiota composition, primarily characterized by depletion of *Lactobacillus* species (especially beneficial strains like *L. reuteri*, *L. rhamnosus*) and a reduction in certain members of the *Bacteroidetes* phylum^[169]. Concurrently, inflammation-associated bacterial groups may

relatively increase. A key consequence of this dysbiosis is reduced gut short-chain fatty acid production, particularly a decrease in butyrate and propionate^[170].

SCFA deficiency: the core link connecting microbiota dysbiosis and hypertension

SCFAs are not only energy sources but also crucial blood pressure-regulating signaling molecules. Their deficiency leads to hypertension through the following parallel pathways:

- **Immune dysregulation (Th17/Treg imbalance):** SCFAs, particularly butyrate, are potent inhibitors of histone deacetylase and agonists of the GPR109a receptor. In the intestinal lamina propria, butyrate promotes the differentiation and function of regulatory T cells through epigenetic reprogramming and direct signaling^[61]. High salt diet-induced butyrate reduction weakens Treg’s immunosuppressive function. Concurrently, a high-salt environment directly activates dendritic cells, promoting interleukin-17 production and

Th17 cell polarization via p38/mitogen-activated protein kinase (MAPK) and serum and glucocorticoid-regulated kinase 1 (SGK1) signaling pathways^[171]. Increased Th17 cells migrate to the kidneys and perivascular adipose tissue, producing IL-17, which directly induces vasoconstriction and increased renal sodium reabsorption.

- **Neuroendocrine system activation:** SCFAs (e.g., propionate) can regulate sympathetic nerve activity by activating intestinal enteroendocrine cells or directly acting on GPR41 receptors in blood vessels and kidneys^[172]. SCFA deficiency may release inhibitory control over the sympathetic nervous system. Gut microbiota dysbiosis can affect the activity of the intrarenal and systemic renin-angiotensin-aldosterone system (RAAS). Animal studies suggest that dysbiosis may enhance RAAS's pressor effects by increasing angiotensin II receptor type 1 expression or decreasing angiotensin-converting enzyme 2 expression^[76].
- **Endothelial dysfunction:** SCFAs (especially propionate and butyrate) can directly act on vascular endothelial cells by activating GPR41/GPR43 and inhibiting HDAC, increasing NO bioavailability and reducing ROS production, thereby improving endothelial-dependent vasodilation^[64]; their deficiency directly impairs this protective mechanism. Moreover, reduced SCFAs availability may impair activation of the AMPK/SIRT1/PGC-1 α signaling axis, leading to decreased mitochondrial biogenesis, impaired endothelial energy metabolism, and increased oxidative stress. Loss of AMPK-mediated vascular protection may further promote endothelial inflammation and dysfunction, providing an additional mechanism linking microbiota-derived SCFAs depletion to hypertension development^[62,63].

Roles of other protective gut metabolites

- **Indole derivatives:** Tryptophan metabolized by gut bacteria produces indole-3-propionic acid, indole-3-acetic acid, etc., which are ligands for the AhR. AhR activation in endothelial cells has antioxidant and anti-inflammatory effects, and in immune cells, it can promote Treg differentiation and inhibit Th17 responses^[173]. Impaired AhR

signaling is associated with arterial stiffness and elevated blood pressure.

- **Secondary bile acids:** As endogenous ligands for FXR and TGR5 receptors, secondary bile acids (e.g., ursodeoxycholic acid) can induce vasodilation by activating TGR5 and inhibit hepatic *de novo* lipogenesis and systemic inflammation through FXR signaling^[174]. Microbiota dysregulation-induced changes in the bile acid pool may weaken these protective effects.

Beyond gut-derived metabolites, skeletal muscle-derived myokines represent an additional regulatory layer within the microbiome–vascular axis. Exercise-induced myokines, including IL-6, irisin, and other muscle-derived signaling molecules, can exert anti-inflammatory and metabolic benefits by enhancing endothelial function, improving insulin sensitivity, and modulating immune responses. In particular, transient IL-6 elevation during exercise differs from chronic pathological IL-6 activation, as exercise-induced IL-6 promotes metabolic adaptation and anti-inflammatory pathways rather than sustained vascular inflammation. These muscle-derived signals may counteract microbiota-driven hypertension by improving vascular metabolic homeostasis, suppressing excessive inflammatory activation, and complementing protective microbial metabolites such as SCFAs^[175,176].

Intervention evidence

Supplementation with specific probiotics (e.g., *Lacto-bacillus* species), prebiotics (e.g., inulin, fructooligosaccharides), or direct supplementation with propionate/butyrate has shown clear blood pressure-lowering effects in animal models and preliminary clinical studies^[177], providing reverse validation for the central role of the gut microbiota.

From a therapeutic perspective, microbiome-associated mechanisms may provide new opportunities for hypertension management, particularly in patients with persistent inflammation or metabolic abnormalities despite standard therapy. However, clinical translation requires standardized microbiome profiling methods and well-designed intervention studies to distinguish causal therapeutic targets from disease-associated microbial alterations.

Other vascular diseases: vasculitis and aneurysm—from PAMPs to vascular remodeling

Vasculitis and aneurysm represent destructive pathological remodeling of the vascular wall due to aberrant immune attack. While traditionally considered associated with autoimmunity or genetic factors, growing evidence suggests that microbes and their products—PAMPs—from multiple ecological niches can act as crucial environmental triggers, aberrantly activating the vascular wall's intrinsic immune surveillance system, driving pathological inflammation and tissue destruction.

The vascular wall is not an immunologically inert tissue; its adventitia and media contain resident dendritic cells and macrophages, and both vascular smooth muscle cells (vSMCs) and endothelial cells express functional pattern recognition receptors (PRRs). When circulating PAMP levels are persistently elevated due to niche barrier disruption (e.g., leaky gut, periodontitis), they can infiltrate the vascular wall, be recognized by these PRRs, and thereby initiate an uncontrolled immune response locally^[178].

- **Specific microbial genera and evidence:**

P. gingivalis is the oral pathogen most closely associated with large vessel vasculitis, giant cell arteritis, and abdominal aortic aneurysm (AAA)^[179]. Mediated by its fimbriae and gingipains, *P. gingivalis* can directly invade vascular endothelial cells and smooth muscle cells.

- **NLRP3 inflammasome overactivation:** *P. gingivalis* LPS and secreted gingipains provide strong activation signals, driving the assembly of the NLRP3 inflammasome in vascular wall macrophages and vSMCs, leading to caspase-1-mediated massive maturation and release of IL-1 β and IL-18^[83]. IL-1 β is a central mediator of vascular inflammation, recruiting neutrophils and inducing MMP expression. *P. gingivalis* heat shock protein 60 is highly homologous to human endothelial cell heat shock protein 60 (HSP60). Immune responses targeting *P. gingivalis* may produce cross-reactive antibodies and T cells that mistakenly attack self-vascular tissue, driving autoimmune vasculitis^[180]. Gingipains can directly degrade the extracellular matrix of the vascular wall (e.g.,

elastin, collagen) and induce vSMC apoptosis, directly compromising vascular wall structural integrity and promoting aneurysm formation^[181].

In cases of gut barrier dysfunction, increased translocation of gut-derived PAMPs (e.g., LPS) leads to persistent low-grade endotoxemia. While this systemic immune stimulation does not directly target specific vessels, it can “prime” the systemic immune system, lowering the threshold for vasculitis onset and exacerbating existing vascular inflammation^[182].

Chronic obstructive pulmonary disease or severe skin infections (e.g., *Staphylococcus aureus* bacteremia) can also lead to PAMPs and viable bacteria entering circulation. For example, community-acquired pneumonia is a known trigger for vasculitis and acute expansion of AAA^[183]. These infections, by providing abundant PAMPs, intensely activate intrinsic vascular wall immunity in a short time, potentially acting as a “trigger point” for acute flares or accelerated progression.

Aberrantly activated immune responses lead to vascular destruction through the following pathways:

- **Inflammatory infiltration and tissue destruction:** Cytokines such as IL-1 β , IL-18, and IFN- γ recruit large numbers of neutrophils, cytotoxic T cells, and macrophages to infiltrate the entire vascular wall (vasculitis) or localized areas (aneurysm). Activated immune cells release ROS, proteolytic enzymes (e.g., MMP-2, MMP-9), and granzymes, directly degrading elastic fibers and collagen, destroying the stable structure of the vascular media^[184].
- **Vascular smooth muscle cell dysfunction and apoptosis:** Under the influence of inflammatory factors (e.g., TNF- α , IL-1 β), contractile vSMCs switch to a synthetic/inflammatory phenotype, losing contractile function and secreting more inflammatory mediators. Concurrently, the inflammatory environment induces excessive vSMC apoptosis, causing the vascular wall to lose crucial structural support cells, a key step in aneurysm formation^[185].
- **ER stress as a potential amplifier of vascular wall inflammation:** Chronic inflammatory and

metabolic stress can induce ER stress and activate the UPR, including PERK/CHOP and IRE1 α /XBP1 pathways. While initially protective, persistent UPR activation promotes inflammatory signaling, oxidative stress, and apoptosis. ER stress-mediated CHOP activation contributes to vascular cell apoptosis. In contrast, dysregulated XBP1 signaling modulates inflammatory responses, suggesting that ER stress serves as a molecular link between chronic inflammation, immune dysregulation, and vascular wall destruction^[59,158].

- **Pathological neoangiogenesis:** In chronically inflamed conditions, pathological neovascularization (vasa vasorum) appears in the vascular adventitia and thickened intima. These vessels have incomplete structures, are prone to rupture and hemorrhage, further exacerbating vascular wall inflammation and edema, forming a vicious cycle^[186].
- **Translational prospects:** Detecting immune responses against specific microbes (e.g., anti-*P. gingivalis* antibodies) or circulating PAMP levels may help identify individuals at high risk for vasculitis/aneurysm or assess disease activity^[187]. This mechanism provides new therapeutic targets: aggressively treat periodontitis, manage gut health, and reduce the input of pathogenic PAMPs. Anti-IL-1 β therapy (e.g., canakinumab) or IL-6 receptor antagonists (e.g., tocilizumab) have shown efficacy in some refractory large vessel vasculitis cases^[188], indirectly validating the cytokine-driven pathological process. Drugs targeting intracellular inflammatory signaling pathways, such as Janus kinase (JAK) inhibitors, are also under investigation^[189]. Exploring the modulation of microbiota (e.g., probiotics, prebiotics) to restore immune tolerance may become a long-term adjunctive management strategy. Vasculitis and aneurysm are extreme manifestations of microbiome network dysregulation. PAMPs from multiple ecological niches, including the oral cavity (represented by *P. gingivalis*) and gut, act as environmental triggers by aberrantly activating the intrinsic vascular wall immune system's NLRP3 and other inflammatory pathways, leading to a severe local inflammation

characterized by an IL-1 β storm and mediated by neutrophil and cytotoxic T cell infiltration. This process leads to the destruction of vascular wall structural cells, degradation of the extracellular matrix, and pathological vascular remodeling. Future research needs to utilize multi-omics techniques to elucidate the precise association between specific microbial characteristics and different vasculitis/aneurysm subtypes, and explore precise prevention and treatment strategies based on “anti-dysbiosis” and “anti-aberrant innate immune activation.”

Modifying factors: oral and lung inflammation as “accessory factors”

While the gut is a major driver, chronic inflammation from other ecological niches can act as important “accessory factors,” exacerbating blood pressure fluctuations and target organ damage.

Oral cavity: periodontitis as a persistent inflammatory burden

Periodontitis lesions continuously release IL-1 β , IL-6, and TNF- α into circulation, leading to systemic low-grade inflammation. These cytokines can directly impair vascular endothelial function, promoting oxidative stress and vasoconstriction^[83]. Furthermore, recurrent, low-level bacteremia caused by periodontal pathogens (e.g., *P. gingivalis*) can continuously activate vascular and immune cells, maintaining a pro-inflammatory state. Observational studies consistently show that periodontitis is associated with hypertension prevalence and poor blood pressure control^[190]. Effective periodontal treatment has been shown to modestly but significantly reduce systolic and diastolic blood pressure and improve endothelial function^[88,191]. This indicates that removing this additional inflammatory source can alleviate the overall burden on the vascular system.

Lung: COPD and hypoxic vasoconstriction

Lung microbiota dysbiosis and chronic inflammation in patients with COPD lead to systemically elevated pro-inflammatory cytokines (e.g., IL-6)^[192]. More importantly, chronic intermittent hypoxia caused by COPD is a powerful pressor stimulus. Hypoxia acutely causes

vasoconstriction by activating chemoreflexes and the sympathetic nervous system; long-term, it promotes endothelin-1 production and inhibits NO synthesis via hypoxia-inducible factor-1 α , leading to pulmonary hypertension and systemic vascular remodeling^[121]. COPD is a common comorbidity of secondary hypertension and resistant hypertension. Its blood pressure fluctuations often correlate with the degree of hypoxia, and treating lung disease and improving oxygenation helps control blood pressure.

When gut-centric drivers (e.g., high salt diet-induced Th17 elevation) coexist with persistent inflammatory “accessory factors” from the oral cavity/lungs, additive effects may occur. For instance, a systemic inflammatory background might amplify the activating effect of high salt on immune cells, or reduce vascular responsiveness to antihypertensive drugs, collectively leading to more severe, harder-to-control hypertension.

The microbiome network model of hypertension is gut-centric, with its core lying in diet (e.g., high salt)-induced dysbiosis and the subsequent reduction in protective metabolites (SCFAs, indole derivatives), which elevate blood pressure through dual immune (Th17/Treg imbalance) and neuroendocrine (sympathetic nervous system, RAAS) mechanisms. Chronic inflammation and hypoxia associated with oral periodontitis and lung diseases act as important “accessory factors,” modifying the severity and progression of hypertension by exacerbating systemic inflammation and vascular dysfunction^[193,194]. This suggests that hypertension prevention and treatment require an integrated strategy: optimizing diet and targeting the gut microbiota, and actively managing oral health and respiratory system diseases to achieve comprehensive blood pressure and vascular health maintenance.

Thrombosis: exploring the impact of microbiota metabolites (e.g., TMAO) and systemic inflammation on platelet activity and coagulation-fibrinolysis balance

Thrombosis is the ultimate endpoint of cardiovascular events, its occurrence depending on a delicate balance between platelet activity, coagulation factors, and the fibrinolytic system. Recent research has revealed that

gut microbiome-derived metabolites, acting as systemic messengers, can profoundly influence this balance, encompassing both potent pro-thrombotic factors and crucial anti-thrombotic protective components.

Pro-thrombotic drivers: TMAO and systemic inflammation

TMAO, produced by gut microbiota (e.g., *Firmicutes* species rich in *cutC/D* genes) metabolizing dietary choline/carnitine, is currently the most potent microbiota-derived pro-thrombotic molecule. Its mechanisms extend beyond simple biomarker association: TMAO can promote intracellular calcium ion release within platelets (via specific membrane receptors or by inducing intracellular ROS production), significantly enhancing platelet aggregation induced by various agonists (e.g., collagen, adenosine diphosphate [ADP]), and making platelets more prone to forming dense, fibrin-rich thrombi^[195]. TMAO can stimulate vascular endothelial cells and monocytes to express tissue factor, a key initiator of the extrinsic coagulation cascade^[196]. Plasma TMAO levels are independently associated with both arterial thrombotic events (e.g., myocardial infarction, stroke) and venous thromboembolism risk, and can predict residual thrombotic risk in patients receiving antiplatelet therapy^[197].

Chronic low-grade inflammation, triggered by multi-niche microbial dysbiosis (e.g., periodontitis, leaky gut), creates a “hypercoagulable state” through multiple pathways: Inflammatory cytokines (e.g., IL-1 β , TNF- α) inhibit endothelial cell expression of thrombomodulin and endothelial protein C receptor, while inducing expression of von Willebrand factor and tissue factor, shifting the endothelium from an anticoagulant to a procoagulant surface^[198]. Activated neutrophils release neutrophil extracellular traps (NETs), whose DNA backbone provides a scaffold for platelet and coagulation factor adhesion, and whose histones and myeloperoxidase directly damage endothelium and activate coagulation factor XII, driving the contact activation pathway^[199]. IL-6 drives hepatic synthesis of acute phase proteins, including fibrinogen, increasing thrombus matrix concentration. Concurrently, inflammation upregulates plasminogen activator inhibitor-1, inhibiting the fibrinolytic system^[200].

Anti-thrombotic protective factors

A healthy gut microbiome maintains vascular homeostasis and normal coagulation balance by producing protective metabolites.

- **SCFAs:** Maintaining endothelial homeostasis and moderate inflammation. SCFAs (butyrate, propionate, and acetate), produced by anaerobic bacteria (e.g., *Faecalibacterium prausnitzii*, *Roseburia*) fermenting dietary fiber, exert pleio-tropic protective effects: SCFAs enhance endothelial barrier function, inhibit pro-inflammatory factor expression, and maintain NO bioavailability by activating endothelial cell GPR41/43 receptors and inhibiting HDAC, thereby protecting the endothelium from procoagulant stimuli^[64]. Emerging evidence suggests that SCFAs may participate in regulating platelet number and function by affecting megakaryocyte maturation and platelet production, though direct antiplatelet aggregation mechanisms require further elucidation^[201].
- **Indole derivatives:** Stabilizing vessels via AhR signaling. Indole-3-propionic acid and other indoles, produced by *Lactobacillus* and *Bifidobacterium* metabolizing tryptophan, are endogenous aryl hydrocarbon receptor ligands.
- **Enhanced endothelial barrier:** Upon activation, AhR signaling can strengthen tight junctions between endothelial cells, reducing the leakage of harmful substances and inflammatory cells, and maintaining the integrity of the vascular wall^[202]. AhR signaling in immune cells can inhibit NLRP3 inflammasome activation and promote regulatory T cell function, thereby systematically reducing the inflammatory burden that drives thrombosis^[163]. Notably, in renal insufficiency, indoxyl sulfate (a uremic toxin) produced via another tryptophan metabolic pathway becomes a potent pro-thrombotic uremic toxin, promoting thrombosis by inducing oxidative stress and endothelial dysfunction. This highlights the importance of the microbial metabolic “direction”^[191].

Integrated perspective and clinical significance

Thrombotic risk essentially results from a dynamic interplay between “pro-thrombotic” (TMAO) and “protective” (SCFAs, indoles) metabolites produced by the gut microbiome, and between “systemic inflammation” triggered by multi-niche microbes and protective immune “regulation” by the gut. Combining plasma TMAO levels with SCFA-related microbiota abundance or protective metabolite levels may more accurately assess individual thrombotic risk than a single indicator. Reshaping the microbial metabolic network through targeted dietary changes (increasing dietary fiber, reducing red meat), prebiotics/probiotics (increasing SCFA- and indole-producing microbiota), or small molecule inhibitors (inhibiting microbial TMA lyase) has become a cutting-edge strategy for preventing thrombosis^[203]. Concurrently, controlling distant inflammatory foci like periodontitis is also an important measure to reduce systemic inflammatory burden and hypercoagulable states. The microbiome profoundly and directly participates in the regulation of thrombosis through its metabolites. Pro-thrombotic factors such as TMAO and protective factors such as SCFAs and indole derivatives collectively act on platelets, endothelial cells, and the coagulation-fibrinolysis system, determining the tendency for thrombosis. This provides a new scientific basis for understanding thrombotic diseases at the level of “microbe-host metabolic interaction” and for developing novel anti-thrombotic strategies.

Translational prospects and challenges

The mechanistic insights described in previous sections provide the foundation for exploring microbiome-based biomarkers, risk assessment approaches, and therapeutic strategies in cardiovascular medicine.

Diagnostic and prognostic biomarkers: decoding circulating microbial “signals”

Circulating microbial metabolites: a direct readout of function

- **TMAO:** As the most established microbiota-derived pro-atherogenic metabolite, plasma TMAO levels have been repeatedly validated in large

prospective cohorts as an independent predictor of major adverse cardiovascular events. Its predictive power surpasses traditional risk indicators and can identify patients with “residual risk” even after statin therapy^[197,204]. Detecting its upstream precursors (γ -butyrobetaine, crotonobetaine) can further improve predictive accuracy^[28]. Mechanistically, TMAO directly contributes to pathogenesis by promoting platelet hyperreactivity, foam cell formation, and endothelial dysfunction, making it not just a biomarker but an intervenable pathogenic link.

- **Phenylacetylglutamine:** Another metabolite produced by gut microbiota metabolism of aromatic amino acids is strongly associated with thrombosis risk, adverse outcomes in heart failure, and all-cause mortality in chronic kidney disease patients. Its mechanism involves interfering with adrenergic receptor signaling^[191].

Compared to harmful metabolites, low levels of circulating protective metabolites may also hold significant risk assessment value. Low plasma or fecal concentrations of butyrate and propionate are associated with hypertension, insulin resistance, and increased systemic inflammation^[201]. As GPR41/43 agonists and HDAC inhibitors, their deficiency implies an impairment of vascular anti-inflammatory and endothelial protective mechanisms. In addition to measuring microbial metabolites directly, downstream host signaling responses may provide complementary indicators of microbial functional activity. Activation markers of the AMPK/SIRT1/PGC-1 α pathway, including phosphorylated AMPK, SIRT1 expression/activity, and PGC-1 α -mediated mitochondrial regulation signatures, may serve as potential indicators of protective microbial functions, reflecting the capacity of microbiota-derived metabolites to maintain vascular metabolic homeostasis and endothelial resilience^[62,63]. However, the short half-life and low concentration of SCFAs in blood, coupled with high detection technical requirements, are major challenges for their routine use as biomarkers. Reduced levels of protective indole-3-propionic acid and other AhR ligands are associated with atherosclerosis severity and endothelial dysfunction^[205]. Conversely, in patients with renal insufficiency, elevated indoxyl sulfate (a

uremic toxin) is a strong predictor of cardiovascular events and mortality^[72]. This highlights the importance of monitoring the balance in tryptophan metabolic “shunting.” Metabolite profiles (e.g., TMAO/SCFA ratio, indole derivative profile) may better reflect the overall functional state of the microbiome than single indicators, providing a more comprehensive risk assessment.

Microbial DNA and pathogen-specific antibodies: evidence of infection and translocation

- **Circulating microbial DNA:** Detecting cell-free microbial DNA (cf-mbDNA) in plasma is a sensitive method for assessing microbial translocation and occult infections. Metagenomic sequencing can not only detect bacterial DNA but also identify its ecological niche of origin. For example, in patients with heart failure or aneurysm, microbial DNA originating from the gut (e.g., *Enterobacteriaceae*) or oral cavity (e.g., *P. gingivalis*, *Fusobacterium nucleatum*) can be detected in plasma^[206]. Its abundance correlates with inflammation levels and prognosis. The presence of cf-mbDNA directly demonstrates functional impairment of niche barriers (leaky gut, oral epithelial breakdown) and systemic immune exposure, serving as active evidence driving chronic inflammation. However, clinical application of cf-mbDNA remains limited by several technical issues. Due to its extremely low abundance, detection is vulnerable to contamination during sample processing and sequencing, requiring strict quality control and standardized protocols. Moreover, although metagenomic sequencing can identify microbial signatures, accurately tracing their original ecological niche remains challenging, and the presence of microbial DNA does not necessarily indicate viable microorganisms or active infection. Therefore, longitudinal validation and integration with functional biomarkers are needed before cf-mbDNA can serve as a definitive indicator of microbiota-driven cardiovascular pathology.
- **Pathogen-specific antibodies:** Serum antibody titers against specific pathogens reflect the host’s

long-term, cumulative immune exposure history. High levels of serum IgG antibodies against *P. gingivalis* gingipains or *Aggregatibacter actinomycetemcomitans* leukotoxin are independently associated with coronary artery disease and stroke risk^[207]. These antibodies are not only infection markers but may also contribute to vascular damage through mechanisms like molecular mimicry. Antibody titers are relatively stable and easy to detect, making them suitable as surrogate markers for chronic, subclinical infectious burden in large-scale epidemiological studies. Nevertheless, antibody-based biomarkers also have limitations. They mainly reflect previous immune exposure rather than current microbial activity, and antibody persistence may obscure the temporal relationship between infection and disease development. In addition, host factors such as immune status, genetic background, and cross-reactive immune responses may influence antibody levels. Thus, pathogen-specific antibodies should be interpreted as indicators of cumulative microbial burden rather than direct evidence of active infection, and their clinical relevance requires confirmation through integration with sequencing and inflammatory biomarkers.

Multi-niche microbiota signature profiles: towards system biology assessment

Research has found that gut microbiota dysbiosis (e.g., reduced diversity, decreased butyrate-producing bacteria) and oral microbiota dysbiosis (enrichment of periodontal pathogens) often coexist, and both synergistically increase cardiovascular risk^[26]. Concurrently analyzing fecal and salivary microbiota may identify high-risk phenotypes with specific “gut-oral” co-dysbiosis patterns. Combining metagenomics (microbial genes), metabolomics (circulating metabolites), and host immunomics (cytokines, antibodies) data, using machine learning algorithms, can build risk scoring systems with predictive power far exceeding single indicators^[208]. For example, a model integrating high TMAO, low SCFAs, high anti-*P. gingivalis* antibodies, and specific gut microbiota gene signatures could more accurately identify vulnerable plaques or thrombotic patients.

Current status and challenges

Currently, plasma TMAO and specific pathogen antibodies are at the forefront of translational application, with some already used for risk stratification in clinical studies, and TMAO detection kits are under development. Most biomarkers remain correlational and require causal and disease-specific validation in prospective intervention studies. Metabolite detection methods (e.g., mass spectrometry), cf-mbDNA extraction and sequencing protocols, and antibody detection standards urgently need standardization. The microbiome and its metabolites are highly susceptible to short-term influences from diet and medications (especially antibiotics and PPIs); distinguishing between “state” and “trait” biomarkers is a major challenge. Optimal healthy ranges for protective and harmful metabolites need to be defined in large-scale healthy populations.

Circulating microbial metabolites, represented by TMAO, SCFAs, and indole derivatives, along with cf-mbDNA and pathogen-specific antibodies, collectively form a multi-layered, information-rich toolbox of biomarkers. They reveal the dynamic influence of the microbiome on the cardiovascular system from three dimensions: function, translocation, and immune memory. Despite challenges such as standardization and causal validation, integrating multi-niche, multi-omics data is expected to yield a new “microbiome risk score” for CVDs, transforming diagnostic and therapeutic models toward earlier, more precise, and more etiology-driven approaches.

Targeted intervention strategies

Niche-specific precision intervention

- **Gut interventions:** Aim to reduce harmful products, increase protective metabolites, and reshape immune balance.
- **Increase dietary fiber/prebiotics:** Directly provide substrates for SCFA-producing commensal bacteria (e.g., *Faecalibacterium prausnitzii*, *Roseburia*). Randomized controlled trials show that supplementing inulin, fructooligosaccharides, etc., can significantly increase fecal butyrate levels, improve insulin sensitivity, and modestly lower blood pressure^[209]. High-fiber diets (e.g.,

whole grains, legumes, vegetables) are the most natural and effective strategy to boost SCFAs and reduce TMAO precursors.

- **Limit red meat, egg yolks, and other high-choline/L-carnitine foods:** Directly reduces the substrate supply for TMAO. Clinical trials confirm that vegetarian or Mediterranean dietary patterns can rapidly and significantly lower plasma TMAO levels^[210].
- **Next-generation probiotics:** No longer limited to traditional *Lactobacillus* and *Bifidobacterium*, strains screened for specific functions are a hot topic. For example, certain *Lactobacillus* and *Bifidobacterium* strains have been shown to degrade TMAO precursor choline *in vivo* or enhance gut barrier function^[211]. Indole-producing probiotics (e.g., certain *Lactobacillus plantarum* strains) are also under investigation, aiming to enhance AhR-mediated vascular protection.
- **Synthetic microbiota communities:** “Live biotherapeutic products” composed of multiple bacteria with defined complementary functions (e.g., containing SCFA producers, indole producers, and barrier-enhancing bacteria) are entering clinical trials, aiming for more stable and effective functional reshaping^[212].
- **Fecal microbiota transplantation (FMT):** Still in the exploratory stage in cardiovascular medicine. Preliminary studies show that FMT from healthy donors to patients with metabolic syndrome can temporarily improve insulin sensitivity and alter recipient microbiota. However, its long-term safety, efficacy, and donor screening criteria are not yet clear; it is currently used more for studying causality than for routine treatment^[213].
- **TMA lyase inhibitors:** Such as 3,3-dimethyl-1-butanol and its derivatives, can specifically inhibit bacterial CutC/D enzymes, blocking TMA generation. In animal models, they effectively reduce TMAO and suppress atherosclerosis, and are in early clinical development^[203].
- **FXR/TGR5 agonists:** Obeticholic acid and other FXR agonists are approved for primary biliary cholangitis. Their metabolic improvement and anti-inflammatory effects suggest potential value in CVDs, with relevant cardiovascular outcome trials underway^[214].

- **Oral interventions:** Focus on controlling local inflammation and pathogen burden.
- **Professional periodontal treatment:** Including supragingival scaling, subgingival scaling, and root planing. High-quality randomized controlled trials confirm that effective periodontal treatment not only improves local health but also significantly reduces systemic inflammatory markers (e.g., hsCRP, IL-6) and improves vascular endothelial function^[88]. For individuals with existing cardiovascular disease, periodontal treatment is considered an important adjunctive measure for secondary prevention.
- **Antiseptic mouthwashes:** Containing chlorhexidine or essential oils can assist in plaque control. Emerging research focuses on “oral probiotics,” such as lozenges containing *Lactobacillus reuteri*, aiming to inhibit periodontal pathogen colonization competitively. Preliminary results show improved gingival health and reduced pro-inflammatory mediators in saliva^[215].
- **Skin interventions:** Prioritize active disease control. For psoriasis, AD, etc., actively controlling disease activity itself is a means to reduce cardiovascular risk.
- **Systemic treatment and biologics:** Using biologics targeting the IL-23/Th17 pathway (e.g., ustekinumab, guselkumab) or TNF- α (e.g., adalimumab) not only clears skin lesions but also significantly reduces systemic inflammatory markers in patients’ serum and has been preliminarily observed to potentially reduce the risk of major adverse cardiovascular events^[216]. This provides the strongest interventional evidence for “controlling local inflammation to improve systemic vascular outcomes.”
- **Regular use of emollients:** To maintain the skin barrier, reducing colonization and invasion opportunities for pathogenic bacteria like *Staphylococcus aureus*.

Holistic network regulation: anti-inflammatory dietary patterns

Given the dialogue between different niche microbiomes and their shared influence by similar dietary substrates,

adopting holistic dietary patterns is the most actionable and sustainable strategy for regulating the microbiome network.

- **Mediterranean diet:** As the gold standard for anti-inflammatory diets, its characteristics (rich in dietary fiber, polyphenols, Omega-3 fatty acids, moderate fermented foods, restricted red meat and processed foods) can positively impact multiple niches simultaneously: significantly increasing gut microbiota diversity, abundance of SCFA-producing bacteria, and circulating SCFA levels, while reducing TMAO^[217]. Foods rich in polyphenols (from olive oil, nuts, and red wine) have antimicrobial and anti-inflammatory properties that may help maintain oral microbiota balance. Through its anti-inflammatory and antioxidant properties, it directly reduces the vascular inflammatory burden. Large randomized controlled trials (e.g., PREDIMED) have confirmed that the Mediterranean diet significantly reduces the incidence of cardiovascular events in high-risk populations, with part of its benefit attributed to gut microbiota mediation^[218].
- **Dietary approaches to stop hypertension (DASH) diet:** Emphasizing fruits, vegetables, whole grains, and low-fat dairy, it has also been shown to alter gut microbiota and lower blood pressure beneficially.
- **Exercise-based microbiome modulation:** Regular physical activity represents an important lifestyle intervention targeting the microbiome-vascular axis. Exercise can enhance gut microbial diversity, increase SCFA-producing bacteria, and improve intestinal barrier function, thereby reducing microbial translocation and systemic inflammation. Moreover, exercise-induced myokines, including IL-6 and irisin, can enhance AMPK/SIRT1/PGC-1 α -mediated metabolic regulation and improve endothelial function. Unlike chronic pathological IL-6 elevation, transient exercise-induced IL-6 promotes metabolic adaptation and immune regulation, providing a complementary mechanism to counteract microbiota-driven vascular injury^[178,179].

Challenges

Despite promising prospects, the path to translation still faces challenges:

- **Individual variability:** Due to differences in baseline microbiota, genotypes, and lifestyles, individual responses to the same intervention (e.g., probiotics, dietary fiber) vary greatly. Future efforts require personalized recommendations based on microbiome characteristics.
- **Causality and long-term outcomes:** More large-scale, long-term randomized controlled trials with hard endpoints (e.g., myocardial infarction, stroke) are needed to definitively prove whether adjusting specific microbes or their functions can prevent cardiovascular events.
- **Standardization and safety:** For FMT, live biotherapeutic products, and novel probiotics, clear efficacy evaluation standards and long-term safety monitoring systems need to be established.

A system of intervention strategies targeting the microbiome-vascular axis is taking shape. Clinically, a holistic anti-inflammatory pattern like the Mediterranean diet should be advocated as a foundation, combined with targeted niche management (e.g., treating periodontitis, controlling skin inflammation). At the research frontier, the focus is on developing next-generation probiotics and precise small-molecule metabolic enzyme inhibitors. Through such multi-level, personalized integrated interventions, we hope to truly transform microbiome science into a new generation of tools for improving cardiovascular health.

Unanswered questions and future directions

Causality confirmation: moving beyond association to mechanistic proof

Currently, the vast majority of evidence remains at the correlational level. To establish that microbiome changes are the cause, not merely a consequence, of cardiovascular disease, a dual breakthrough is required:

- **Developing advanced humanized animal models:** Traditional germ-free mouse models

colonized with human microbiota are insufficient to mimic the human multi-niche network. Future research needs to develop multi-niche humanized models, for example, by simultaneously colonizing mice with human oral and gut microbiota in their respective sites, and simulating perturbations like oral infections or high-salt diets. This would allow, under controlled conditions, the elucidation of complete causal chains demonstrating how specific bacterial species or metabolites (e.g., direct invasion by *P. gingivalis* or persistent exposure to TMAO) trigger endothelial dysfunction, hypertension, or plaque formation^[219]. Such models are indispensable platforms for validating the “multiple hit” hypothesis and testing targeted interventions.

- **Large-scale randomized controlled trials (RCTs):** More large-scale, long-term RCTs with hard clinical endpoints (e.g., myocardial infarction, stroke) are needed. For example, RCTs on periodontal therapy (evaluating its effect on secondary prevention of cardiovascular events) and RCTs on small molecule inhibitors of microbiota metabolism (e.g., TMA lyase inhibitors for cardiovascular outcomes) will provide the most direct causal evidence^[203]. Researchers should concurrently use genetic tools such as Mendelian randomization to assess potential causal relationships between specific microbial characteristics and cardiovascular risk at the population level^[220].

Network dynamics: deconstructing inter-niche “dialogue”

The human body is a continuous ecosystem, and the microbial communities in various niches are not isolated islands. They engage in active “cross-niche dialogue,” and their dynamic interactions are key to understanding overall network effects.

- **Oral-gut axis:** Billions of oral bacteria are swallowed daily, continuously “seeding” the gut. Research shows that colonization by periodontal pathogens like *P. gingivalis* can alter gut microbiota composition, reduce SCFA-producing commensals, and exacerbate gut inflammation and barrier damage^[27]. Conversely, systemic immune

states driven by gut dysbiosis may also affect local oral immunity, forming a vicious cycle. Future longitudinal studies are needed to clarify the directionality of this influence, key mediators (live bacteria, bacterial vesicles, specific metabolites, or inflammatory factors), and their specific contributions to systemic vascular inflammation.

- **Gut-distant organ axis:** Preliminary evidence suggests that gut microbiota influence distant organ health through metabolites and immune modulation. For example, gut-derived SCFAs may affect alveolar macrophage function via circulation; gut microbiota dysbiosis may influence the severity of skin diseases like psoriasis^[221]. The existence of these axes implies that gut-targeted interventions may yield systemic benefits beyond metabolism, and their mechanisms urgently need elucidation.
- **Spatiotemporal multi-omics:** Developing spatiotemporal multi-omics technologies that can simultaneously analyze microbial communities, metabolomes, and host immunomes from multiple niches (e.g., collecting dental plaque, stool, and blood samples concurrently) at multiple time points is crucial for mapping dynamic interaction networks^[23].

Individualization and precision medicine: from “averaged” data to personalized blueprints

The microbiome exhibits extreme inter-individual variability, meaning a “one-size-fits-all” intervention is bound to fail. The future direction is to leverage artificial intelligence and systems biology to achieve truly personalized management.

- **Integrated multi-omics risk profiling:** By integrating individual multi-niche metagenomics (oral, gut microbiota genes), blood metabolomics (TMAO, SCFAs, indole derivatives, etc.), immunomics (cytokines, pathogen-specific antibodies), and host genomics data, machine learning algorithms can build a multi-dimensional risk prediction model^[208]. This model would not only more accurately predict an individual’s future cardiovascular risk but also identify the predominant risk mechanisms (e.g., “high TMAO type,” “low

SCFA type,” “high oral pathogen load type,” or “mixed type”).

- **Highly tailored intervention strategies:** Clinicians can highly customize intervention strategies based on the risk profile above. For “high TMAO type” individuals, strict red meat diet restrictions may be recommended, along with considering CutC/D enzyme inhibitors or specific choline-degrading probiotics. Dietitians would emphasize high-fiber diets and supplementation with specific prebiotics/probiotics (e.g., *Faecalibacterium prausnitzii*-related preparations) for “low SCFA/high inflammation type” individuals to increase protective metabolites. For “oral pathogen-driven type” individuals, intensified periodontal therapy and oral microbiota management would be central. Clinicians can concurrently monitor dynamic changes in individual risk profiles before and after intervention to achieve a precise “assess-intervene-reassess” closed-loop management^[222].

Beyond microbiota-directed interventions, targeting downstream innate immune pathways may provide an additional therapeutic strategy for microbiome-driven vascular diseases. The cGAS–STING pathway represents a potential novel target, as it integrates microbial DNA sensing, mitochondrial stress responses, and chronic inflammatory activation in vascular cells and macrophages. Pharmacological modulation of STING activity or inhibition of excessive downstream signaling may help reduce type I interferon responses, macrophage inflammatory polarization, and endothelial dysfunction while preserving essential host immune surveillance. Future studies should determine whether cGAS–STING inhibition can selectively suppress pathological vascular inflammation without compromising antimicrobial defense.

Research on the microbiome-vascular axis stands at the threshold of moving from phenomenology to mechanistic elucidation and precise intervention. The key to this breakthrough lies in adopting systems biology thinking and cutting-edge technological tools. By constructing complex causal models, elucidating cross-niche network dynamics, and leveraging AI to map individualized functional profiles, we aim to unlock all the mysteries of how the microbiome influences

vascular health. This will not only catalyze novel diagnostic biomarkers and targeted therapies (such as next-generation probiotics, precision antimicrobial peptides, or metabolic enzyme modulators) but will fundamentally reshape the paradigm of cardiovascular disease prevention and management, shifting from “treating the sick” to “preventing illness based on ecological health.”

Conclusion

From “microbiome-vascular axis” to “systemic ecological network”: a paradigm revolution and future navigation in cardiovascular medicine

We stand on the brink of a revolution in cardiovascular disease understanding and prevention. The traditional “pipeline repair” model, which focused solely on the heart and vessels as targets, has reached its therapeutic limits due to its restricted ability to explain the fundamental drivers of disease. This review systematically unveils the human microbiome—a “spatially organized, functionally specialized systemic ecological network”—offering a groundbreaking, fundamental perspective to overcome this bottleneck. This is far more than discovering a few new risk markers or therapeutic targets; it is a profound paradigm shift from “treating downstream symptoms” to “regulating upstream ecology.”

Current research has successfully drafted a dynamic “eco-vascular” interaction landscape: The gut, as the “central metabolic and immune processor,” launches “metabolic attacks” via harmful metabolites like TMAO, while simultaneously building “protective shields” through short-chain fatty acids and indole derivatives. The oral cavity, functioning as the “outpost of direct invasion and chronic inflammation,” deploys “targeted strikes” by pathogens such as *P. gingivalis*. The skin and lungs act as “amplifiers of systemic inflammation,” continuously supplying inflammatory “fuel” via the IL-23/Th17 axis or hypoxia-inflammation cycles. The vaginal microecology reveals a unique, female-specific role as an “immune storm initiator” intimately linked to pregnancy-related vascular crises. Regardless of their origin, these signals ultimately converge on two major common pathways: systemic low-grade inflammation (centered on the NLRP3/IL-1 β axis) and

immune-metabolic dysregulation (marked by Th17/Treg imbalance and endothelial metabolic dysfunction). This explains why seemingly unrelated local ecological imbalances (e.g., periodontitis, psoriasis, irritable bowel syndrome) share similar cardiovascular risks. From precise modulation of gut metabolic output through diet and prebiotics, to eliminating inflammatory sources via periodontal treatment, and blocking specific cytokine storms using biologics, we already possess initial “niche-specific” intervention tools. Holistic approaches like the Mediterranean diet further demonstrate the feasibility of benefiting cardiovascular health by shaping the overall microbiome environment. However, this landscape remains static, blurred, and fragmented. We view the microbiome as an “organ,” yet we have not fully grasped its operational rules as a “complex adaptive system.” Researchers must overcome this core challenge in the next decade.

A leap in deepening understanding: from “correlation” to “causality” and “mechanism”

Future research must transcend mere association to establish causal chains *in vivo* using spatiotemporal multi-omics dynamic tracking. This requires:

- **Developing “human eco-vascular” digital twin models:** Integrating individual genomic, multi-niche longitudinal metagenomic/metabolomic/immunomic data, and leveraging artificial intelligence to construct predictive models capable of simulating quantitative relationships between microbiome network dynamics and vascular phenotype outputs. Such models could virtually test interventions and guide personalized solutions.
- **Deconstructing the molecular language of “cross-niche dialogue”:** Focusing on breakthroughs in axes like the “oral-gut axis” and “gut-skin axis.” It is crucial to determine whether live bacteria migration, bacterial vesicles, specific metabolites (e.g., succinic acid produced by oral microbiota affecting the gut), or remotely trained immune cells act as messengers. This demands the development of single-cell spatial transcriptomics and metabolic imaging technologies to map microbial signals and host cell dialogues *in situ* within tissues.

A leap in precision control: from “single intervention” to “ecosystem remodeling”

Future interventions will no longer be simple labels like “probiotics” or “antibiotics” but will involve “precision engineering” and “homeostatic remodeling” of the microbial ecosystem.

- **Next-generation live biotherapeutics:** Designing engineered probiotics with “sense-and-respond” capabilities. For example, engineering gut-colonizing bacteria to real-time sense inflammatory markers (e.g., high calcium ions) and *in situ* express and release anti-inflammatory peptides or specific enzymes to degrade TMA precursors. Even envisioning the development of “immunomodulatory probiotics” that can specifically target local inflammatory sites within the vascular wall.
- **Precise application of phage therapy:** For specific harmful bacteria implicated in cardiovascular disease (e.g., TMA-producing *Firmicutes*, periodontal pathogens), developing highly specific phage cocktail therapies to achieve “precision weeding” without disrupting the overall ecosystem.
- **Ecological perspective on small molecule drugs:** Developers must systematically evaluate the long-term impact of drugs on multi-niche microbiomes. Future “cardiovascular protective drugs” may possess dual properties of improving host metabolism and promoting a beneficial microbial ecosystem.

A leap in preventive medicine paradigm: from “disease management” to “healthy ecosystems”

The greatest imagination lies in positioning microbiome health management as a core pillar of cardiovascular health management.

- **“Microbiome-vascular health” lifelong records:** Individuals would establish digital health records from youth, including key niche microbiota characteristics (oral, gut), metabolome profiles, and immune markers. Artificial intelligence would analyze these records to warn of vascular

ecological imbalance risks years before clinical indicators become abnormal.

- **Personalized eco-nutrition:** Based on an individual's microbiome functional characteristics (e.g., SCFA production capacity, TMA conversion efficiency), algorithms would generate entirely personalized dietary recommendations, enabling “eating for your microbes to protect your blood vessels.”
- **Ecological interventions for environment and behavior:** Systematically investigate how sleep, stress, exercise, and other factors specifically influence different niche microbiomes and their vascular effects, thereby developing comprehensive “protect the heart by protecting the microbes first” lifestyle prescriptions.

In conclusion, we call upon the entire field to collectively move toward a new paradigm of “Vascular Ecological Medicine.” This requires:

- **Interdisciplinary big science collaboration:** Integrating cardiovascular medicine, microbiology, immunology, computational science, bioengineering, and nutrition to form interdisciplinary teams and launch a global “Human Vascular Ecosystem Project.”
- **Regulatory and clinical pathway innovation:** Promoting regulatory agencies to establish new evaluation frameworks for live biotherapeutics and microbiome-oriented therapies, incorporating “assessing and managing microbiome health” into standard primary and secondary prevention guidelines for CVDs.
- **Public science and education:** Elevating public awareness that “oral health is heart health” and “gut health impacts vascular longevity,” promoting ecological maintenance measures such as oral hygiene and high-fiber diets to the same level of public health strategy as smoking cessation and blood pressure control.

The human microbiome is not a stranger to our cardiovascular system but an intrinsic, interdependent “internal ecosystem.” Understanding and wisely utilizing this ecosystem means we are finally beginning to grasp and safeguard the health of the heart and blood

vessels at the most fundamental level of life's symbiotic relationships. This is not only the next wave of disease treatment, but also the starting point for building a new medical philosophy focused on maintaining health and preventing disease.

Author contributions

Yanhua Tang and Tingtao Chen conceived the study and were responsible for frame conception. Wu Liu was responsible for writing the manuscript. Xinyi Zhang was responsible for data visualization/drawing. Jingyu Wang, Yonggang Shi, Heng Yang, Congcong Li, and Wanqi Lan contributed to literature retrieval and format adjustment for each section. All authors reviewed, edited, and approved the final version of the manuscript and agreed to its publication.

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This review does not involve animal or human experiments.

Data availability statement

No datasets were generated or analyzed for this work.

AI statement

The authors used (GPT-4, online version) as a language-editing tool to improve grammar, clarity, and readability. The AI tool was not used for data analysis, data generation, image processing, or scientific content creation. All outputs were carefully reviewed and verified by the authors, who take full responsibility for the final content.

Conflicts of interest

The authors declare no conflict of interest.

References

1. Libby P. The changing landscape of atherosclerosis. *Nature*. 2021;592(7855):524-533.

2. Ridker PM. From C-reactive protein to interleukin-6 to interleukin-1: moving upstream to identify novel targets for atheroprotection. *Circ Res*. 2016;118(1):145-156.
3. Pradhan AD, Aday AW, Rose LM, Ridker PM. Residual inflammatory risk on treatment with PCSK9 inhibition and statin therapy. *Circulation*. 2018;138(2):141-149.
4. Martínez-Hervás S, González-Navarro H. Anti-inflammatory therapies for cardiovascular disease: signaling pathways and mechanisms. *Rev Esp Cardiol (Engl Ed)*. 2019;72(9):767-773.
5. Thompson PL, Nidorf SM. Anti-inflammatory therapy with canakinumab for atherosclerotic disease: lessons from the CANTOS trial. *J Thorac Dis*. 2018;10(2):695-698.
6. Ridker PM, MacFadyen JG, Everett BM, et al. Relationship of C-reactive protein reduction to cardiovascular event reduction following treatment with canakinumab: a secondary analysis from the CANTOS randomised controlled trial. *Lancet*. 2018;391(10118):319-328.
7. Tardif JC, Kouz S, Waters DD, et al. Efficacy and safety of low-dose colchicine after myocardial infarction. *N Engl J Med*. 2019;381(26):2497-2505.
8. Ridker PM, Everett BM, Pradhan A, et al. Low-dose methotrexate for the prevention of atherosclerotic events. *N Engl J Med*. 2019;380(8):752-762.
9. Gilbert JA, Blaser MJ, Caporaso JG, Jansson JK, Lynch SV, Knight R. Current understanding of the human microbiome. *Nat Med*. 2018;24(4):392-400.
10. Lloyd-Price J, Abu-Ali G, Huttenhower C. The healthy human microbiome. *Genome Med*. 2016;8(1):51.
11. Martinez-Guryn K, Leone V, Chang EB. Regional diversity of the gastrointestinal microbiome. *Cell Host Microbe*. 2019;26(3):314-324.
12. Thaiss CA, Zmora N, Levy M, Elinav E. The microbiome and innate immunity. *Nature*. 2016;535(7610):65-74.
13. Lamont RJ, Koo H, Hajishengallis G. The oral microbiota: dynamic communities and host interactions. *Nat Rev Microbiol*. 2018;16(12):745-759.
14. Dickson RP, Huffnagle GB. The lung microbiome: new principles for respiratory bacteriology in health and disease. *PLoS Pathog*. 2015;11(7):e1004923.
15. Byrd AL, Belkaid Y, Segre JA. The human skin microbiome. *Nat Rev Microbiol*. 2018;16(3):143-155.
16. Zhu B, Tao Z, Edupuganti L. Roles of the microbiota of the female reproductive tract in gynecological and reproductive health. *Microbiol Mol Biol Rev*. 2022;86(4):e0018121.
17. Agnoletti D, Piani F, Cicero AFG, Borghi C. The gut microbiota and vascular aging: a state-of-the-art and systematic review of the literature. *J Clin Med*. 2022;11(12):3557.
18. Ierardi E, Sorrentino C, Principi M, Giorgio F, Losurdo G, Di Leo A. Intestinal microbial metabolism of phosphatidylcholine: a novel insight in the cardiovascular risk scenario. *Hepatobiliary Surg Nutr*. 2015;4(4):289-292.
19. Brown JM, Hazen SL. The gut microbial endocrine organ: bacterially derived signals driving cardiometabolic diseases. *Annu Rev Med*. 2015;66:343-359.
20. Herrera D, Sanz M, Shapira L, et al. Periodontal diseases and cardiovascular diseases, diabetes, and respiratory diseases: summary of the consensus report by the European Federation of Periodontology and WONCA Europe. *Eur J Gen Pract*. 2024;30(1):2320120.
21. Arimatsu K, Yamada H, Miyazawa H, et al. Oral pathobiome induces systemic inflammation and metabolic changes associated with alteration of gut microbiota. *Sci Rep*. 2014;4:4828.
22. Ahlehoff O. Psoriasis and cardiovascular disease: epidemiological studies. *Dan Med Bull*. 2011;58(11):B4347.
23. Integrative HMP (iHMP) Research Network Consortium. The integrative human microbiome project. *Nature*. 2019;569(7758):641-648.
24. Lloyd-Price J, Arze C, Ananthakrishnan AN, et al. Multi-omics of the gut microbial ecosystem in inflammatory bowel diseases. *Nature*. 2019;569(7758):655-662.
25. Kurtzman GM, Horowitz RA, Johnson R, Prestiano RA, Klein BI. The systemic oral health connection: biofilms. *Medicine (Baltimore)*. 2022;101(46):e30517.
26. Kitamoto S, Nagao-Kitamoto H, Hein R, Schmidt TM, Kamada N. The bacterial connection between the oral cavity and the gut diseases. *J Dent Res*. 2020;99(9):1021-1029.
27. Peters BA, Burk RD, Kaplan RC, Qi Q. The gut microbiome, microbial metabolites, and cardiovascular disease in people living with HIV. *Curr HIV/AIDS Rep*. 2023;20(2):86-99.
28. Nemet I, Saha PP, Gupta N, et al. A cardiovascular disease-linked gut microbial metabolite acts via adrenergic receptors. *Cell*. 2020;180(5):862-877.e22.
29. Chen YE, Fischbach MA, Belkaid Y. Skin microbiota-host interactions. *Nature*. 2018;553(7689):427-436.
30. Aron-Wisnewsky J, Prifti E, Belda E, et al. Major microbiota dysbiosis in severe obesity: fate after bariatric surgery. *Gut*. 2019;68(1):70-82.
31. Shariff S, Kwan Su Huey A, Parag Soni N, et al. Unlocking the gut-heart axis: exploring the role of gut microbiota in cardiovascular health and disease. *Ann Med Surg (Lond)*. 2024;86(5):2752-2758.
32. Furman D, Campisi J, Verdin E, et al. Chronic inflammation in the etiology of disease across the life span. *Nat Med*. 2019;25(12):1822-1832.
33. Martel J, Chang SH, Ko YF, Hwang TL, Young JD, Ojcius DM. Gut barrier disruption and chronic disease. *Trends Endocrinol Metab*. 2022;33(4):247-265.
34. Olsen I, Singhrao SK. Is there a link between genetic defects in the complement cascade and *Porphyromonas gingivalis* in Alzheimer's disease?. *J Oral Microbiol*. 2020;12(1):1676486.
35. Ch'ng CC. Rebalancing of the skin microbiome with an emollient 'plus' for effective management of atopic dermatitis: a mini review. *Med J Malaysia*. 2024;79(2):203-205.
36. Jayashree B, Bibin YS, Prabhu D, et al. Increased circulatory levels of lipopolysaccharide (LPS) and zonulin

- signify novel biomarkers of proinflammation in patients with type 2 diabetes. *Mol Cell Biochem.* 2014;388(1-2):203-210.
37. Zheng D, Liwinski T, Elinav E. Inflammasome activation and regulation: toward a better understanding of complex mechanisms. *Cell Discov.* 2020;6:36.
 38. Mogensen TH. Pathogen recognition and inflammatory signaling in innate immune defenses. *Clin Microbiol Rev.* 2009;22(2):240-73, Table of Contents.
 39. Liu T, Zhang L, Joo D, Sun SC. NF- κ B signaling in inflammation. *Signal Transduct Target Ther.* 2017;2:17023-17023.
 40. Pober JS, Sessa WC. Evolving functions of endothelial cells in inflammation. *Nat Rev Immunol.* 2007;7(10):803-815.
 41. Swanson KV, Deng M, Ting JP. The NLRP3 inflammasome: molecular activation and regulation to therapeutics. *Nat Rev Immunol.* 2019;19(8):477-489.
 42. Jiang H, Gong T, Zhou R. The strategies of targeting the NLRP3 inflammasome to treat inflammatory diseases. *Adv Immunol.* 2020;145:55-93.
 43. Park E, Na HS, Song YR, Shin SY, Kim YM, Chung J. Activation of NLRP3 and AIM2 inflammasomes by *Porphyromonas gingivalis* infection. *Infect Immun.* 2014;82(1):112-123.
 44. Steven S, Frenis K, Oelze M, et al. Vascular inflammation and oxidative stress: major triggers for cardiovascular disease. *Oxid Med Cell Longev.* 2019;2019:7092151.
 45. Gorabi AM, Kiaie N, Khosrojerdi A, et al. Implications for the role of lipopolysaccharide in the development of atherosclerosis. *Trends Cardiovasc Med.* 2022;32(8):525-533.
 46. Jiang H, Ji Y, Shang T, et al. The cGAS-STING signaling pathway: a central regulator and novel therapeutic target in skeletal muscle pathophysiology. *Biochem Pharmacol.* 2026;248:117854.
 47. Liu H, Zhu X, Wang J, et al. Mechanisms and therapeutic potential of the cGAS-STING signaling pathway in macrophage activation and polarization. *Biochem Pharmacol.* 2026;250(Pt 2):118031.
 48. Ablasser A, Chen ZJ. cGAS in action: expanding roles in immunity and inflammation. *Science.* 2019;363(6431):eaat8657.
 49. Shang T, Xu H, Yao X, et al. Dual role of macrophages in skeletal muscle atrophy: mechanisms and therapeutic strategies. *Biochem Pharmacol.* 2026;244:117589.
 50. Murray PJ, Allen JE, Biswas SK, et al. Macrophage activation and polarization: nomenclature and experimental guidelines. *Immunity.* 2014;41(1):14-20.
 51. Fitzgerald KA, Kagan JC. Toll-like receptors and the control of immunity. *Cell.* 2020;180(6):1044-1066.
 52. Soehnlein O, Libby P. Targeting inflammation in atherosclerosis—from experimental insights to the clinic. *Nat Rev Drug Discov.* 2021;20(8):589-610.
 53. Wang Z, Kaplan RC, Burk RD, Qi Q. The oral microbiota, microbial metabolites, and immuno-inflammatory mechanisms in cardiovascular disease. *Int J Mol Sci.* 2024;25(22):12337.
 54. Wang Z, Klipfell E, Bennett BJ, et al. Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. *Nature.* 2011;472(7341):57-63.
 55. Koeth RA, Wang Z, Levison BS, et al. Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. *Nat Med.* 2013;19(5):576-585.
 56. Tan X, Liu Y, Long J, et al. Trimethylamine N-oxide aggravates liver steatosis through modulation of bile acid metabolism and inhibition of farnesoid X receptor signaling in nonalcoholic fatty liver disease. *Mol Nutr Food Res.* 2019;63(17):e1900257.
 57. Zhu W, Gregory JC, Org E, et al. Gut microbial metabolite TMAO enhances platelet hyperreactivity and thrombosis risk. *Cell.* 2016;165(1):111-124.
 58. Seldin MM, Meng Y, Qi H, et al. Trimethylamine N-oxide promotes vascular inflammation through signaling of mitogen-activated protein kinase and nuclear factor- κ B. *J Am Heart Assoc.* 2016;5(2):e002767.
 59. Ji Y, Jiang Q, Chen B, et al. Endoplasmic reticulum stress and unfolded protein response: roles in skeletal muscle atrophy. *Biochem Pharmacol.* 2025;234:116799.
 60. Kimura I, Inoue D, Maeda T, et al. Short-chain fatty acids and ketones directly regulate sympathetic nervous system via G protein-coupled receptor 41 (GPR41). *Proc Natl Acad Sci U S A.* 2011;108(19):8030-8035.
 61. Fellows R, Denizot J, Stellato C, et al. Microbiota derived short chain fatty acids promote histone crotonylation in the colon through histone deacetylases. *Nat Commun.* 2018;9(1):105.
 62. Chen J, Liu B, Yao X, et al. AMPK/SIRT1/PGC-1 α signaling pathway: molecular mechanisms and targeted strategies from energy homeostasis regulation to disease therapy. *CNS Neurosci Ther.* 2025;31(11):e70657.
 63. Wang J, Gu J, Li X, Sun H, Yang X. The central role of the AMPK/SIRT1/PGC-1 α signaling axis in skeletal muscle physiology and pathology and its targeted therapeutic strategies. *Pharmaceuticals (Basel).* 2026;19(7):1056.
 64. Bartolomeus H, Balogh A, Yakoub M, et al. Short-chain fatty acid propionate protects from hypertensive cardiovascular damage. *Circulation.* 2019;139(11):1407-1421.
 65. Jiang C, Xie C, Lv Y, et al. Intestine-selective farnesoid X receptor inhibition improves obesity-related metabolic dysfunction. *Nat Commun.* 2015;6:10166.
 66. Pols TW, Nomura M, Harach T, et al. TGR5 activation inhibits atherosclerosis by reducing macrophage inflammation and lipid loading. *Cell Metab.* 2011;14(6):747-757.
 67. Qi Y, Jiang C, Cheng J, et al. Bile acid signaling in lipid metabolism: metabolomic and lipidomic analysis of lipid and bile acid markers linked to anti-obesity and anti-diabetes in mice. *Biochim Biophys Acta.* 2015;1851(1):19-29.

68. Skov-Jepesen SM, Kobylecki CJ, Jacobsen KK, Bojesen SE. Aryl hydrocarbon receptor repressor (AHR) methylation predicts risk of vascular disease: a cohort study of the general population. *Int J Surg*. 2024;110(11):6953-6961.
69. Jin UH, Lee SO, Sridharan G, et al. Microbiome-derived tryptophan metabolites and their aryl hydrocarbon receptor-dependent agonist and antagonist activities. *Mol Pharmacol*. 2014;85(5):777-788.
70. Li T, Gao C, Wu B, Chen Y. Increased circulating trimethylamine N-oxide contributes to endothelial dysfunction in a rat model of chronic kidney disease. *Biochem Biophys Res Commun*. 2018;495(2):2071-2077.
71. Liu W, Wang J, Yang H, et al. The metabolite indole-3-acetic acid of *Bacteroides ovatus* improves atherosclerosis by restoring the polarisation balance of M1/M2 macrophages and inhibiting inflammation. *Adv Sci (Weinh)*. 2025;12(11):e2413010.
72. Nemet I, Li XS, Haghighi A, et al. Atlas of gut microbe-derived products from aromatic amino acids and risk of cardiovascular morbidity and mortality. *Eur Heart J*. 2023;44(32):3085-3096.
73. Arpaia N, Campbell C, Fan X, et al. Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation. *Nature*. 2013;504(7480):451-455.
74. Wang Y, Yin Y, Chen X, et al. Induction of intestinal Th17 cells by flagellins from segmented filamentous bacteria. *Front Immunol*. 2019;10:2750.
75. Josefowicz SZ, Niec RE, Kim HY, et al. Extrathymically generated regulatory T cells control mucosal Th2 inflammation. *Nature*. 2012;482(7385):395-399.
76. Karbach SH, Schönfelder T, Brandão I, et al. Gut microbiota promote angiotensin II-induced arterial hypertension and vascular dysfunction. *J Am Heart Assoc*. 2016;5(9):e003698.
77. Khosravi A, Yáñez A, Price JG, et al. Gut microbiota promote hematopoiesis to control bacterial infection. *Cell Host Microbe*. 2014;15(3):374-381.
78. Li G, Lin J, Zhang C, et al. Microbiota metabolite butyrate constrains neutrophil functions and ameliorates mucosal inflammation in inflammatory bowel disease. *Gut Microbes*. 2021;13(1):1968257.
79. Figuero E, Sánchez-Beltrán M, Cuesta-Frechoso S, et al. Detection of periodontal bacteria in atheromatous plaque by nested polymerase chain reaction. *J Periodontol*. 2011;82(10):1469-1477.
80. Atanasova KR, Yilmaz O. Looking in the *Porphyromonas gingivalis* cabinet of curiosities: the microbe, the host and cancer association. *Mol Oral Microbiol*. 2014;29(2):55-66.
81. Lin J, Huang D, Xu H, Zhan F, Tan X. Macrophages: a communication network linking *Porphyromonas gingivalis* infection and associated systemic diseases. *Front Immunol*. 2022;13:952040.
82. Zhang J, Xie M, Huang X, et al. The effects of *Porphyromonas gingivalis* on atherosclerosis-related cells. *Front Immunol*. 2021;12:766560.
83. Lai YJ, Chuang YC, Wang YL, et al. Taiwanese green propolis suppresses NLRP3 inflammasome activation and induces Nrf2/HO-1 pathway to reduce periodontal pathogen-induced endothelial inflammation. *Arch Oral Biol*. 2025;178:106364.
84. Saki N, Haybar H, Maniati M, Davari N, Javan M, Moghimian-Boroujeni B. Modification macrophage to foam cells in atherosclerosis disease: some factors stimulate or inhibit this process. *J Diabetes Metab Disord*. 2024;23(2):1687-1697.
85. Miyabe M, Nakamura N, Saiki T, et al. *Porphyromonas gingivalis* lipopolysaccharides promote proliferation and migration of human vascular smooth muscle cells through the MAPK/TLR4 pathway. *Int J Mol Sci*. 2022;24(1):125.
86. Oliveira SB, Silveira ALPA, Kim YJ, et al. Effect of non-surgical treatment in diabetes-associated periodontitis on immune/inflammatory and oxidative stress biomarkers: a pilot study. *J Diabetes Complications*. 2025;39(4):108999.
87. D'Aiuto F, Gkranias N, Bhowruth D, et al. Systemic effects of periodontitis treatment in patients with type 2 diabetes: a 12 month, single-centre, investigator-masked, randomised trial. *Lancet Diabetes Endocrinol*. 2018;6(12):954-965.
88. Saffi MAL, Rabelo-Silva ER, Polanczyk CA, et al. Periodontal therapy and endothelial function in coronary artery disease: a randomized controlled trial. *Oral Dis*. 2018;24(7):1349-1357.
89. Gupta V, Dawar A, Das SK, et al. Cardiovascular biomarkers in periodontitis: a systematic review and meta-analysis. *Oral Dis*. 2026;32(2):278-287.
90. Hajishengallis G, Chavakis T. Local and systemic mechanisms linking periodontal disease and inflammatory comorbidities. *Nat Rev Immunol*. 2021;21(7):426-440.
91. Hajishengallis G. The inflammophilic character of the periodontitis-associated microbiota. *Mol Oral Microbiol*. 2014;29(6):248-257.
92. Oh J, Voigt AY. The human skin microbiome: from metagenomes to therapeutics. *Nat Rev Microbiol*. 2025;23(12):771-787.
93. Nakatsuji T, Chen TH, Narala S, et al. Antimicrobials from human skin commensal bacteria protect against *Staphylococcus aureus* and are deficient in atopic dermatitis. *Sci Transl Med*. 2017;9(378):eaah4680.
94. Scharschmidt TC, Vasquez KS, Truong HA, et al. A wave of regulatory T cells into neonatal skin mediates tolerance to commensal microbes. *Immunity*. 2015;43(5):1011-1021.
95. Sanford JA, Gallo RL. Functions of the skin microbiota in health and disease. *Semin Immunol*. 2013;25(5):370-377.
96. Olejniczak-Staruch I, Ciężka M, Sobolewska-Szytych D, Narbutt J, Skibińska M, Lesiak A. Alterations

- of the skin and gut microbiome in psoriasis and psoriatic arthritis. *Int J Mol Sci.* 2021;22(8):3998.
97. Boix-Amorós A, Badri MH, Manasson J, et al. Alterations in the cutaneous microbiome of patients with psoriasis and psoriatic arthritis reveal similarities between non-lesional and lesional skin. *Ann Rheum Dis.* 2023;82(4):507-514.
 98. Byrd AL, Deming C, Cassidy SKB, et al. *Staphylococcus aureus* and *Staphylococcus epidermidis* strain diversity underlying pediatric atopic dermatitis. *Sci Transl Med.* 2017;9(397):eaal4651.
 99. Fujii K. Pathogenesis of cutaneous T cell lymphoma: involvement of *Staphylococcus aureus*. *J Dermatol.* 2022;49(2):202-209.
 100. Hawkes JE, Yan BY, Chan TC, Krueger JG. Discovery of the IL-23/IL-17 signaling pathway and the treatment of psoriasis. *J Immunol.* 2018;201(6):1605-1613.
 101. Sánchez-Rodríguez G, Puig L. Pathogenic role of IL-17 and therapeutic targeting of IL-17F in psoriatic arthritis and spondyloarthropathies. *Int J Mol Sci.* 2023;24(12):10305.
 102. Bonzano L, Borgia F, Casella R, Miniello A, Nettis E, Gangemi S. Microbiota and IL-33/31 axis linkage: implications and therapeutic perspectives in atopic dermatitis and psoriasis. *Biomolecules.* 2023;13(7):1100.
 103. Bellinato F, Gisondi P, Marzano AV, et al. Characteristics of patients experiencing a flare of generalized pustular psoriasis: a multicenter observational study. *Vaccines (Basel).* 2023;11(4):740.
 104. Chen S, Crother TR, Ardit M. Emerging role of IL-17 in atherosclerosis. *J Innate Immun.* 2010;2(4):325-333.
 105. Tsiogka A, Gregoriou S, Stratigos A, et al. The impact of treatment with IL-17/IL-23 inhibitors on subclinical atherosclerosis in patients with plaque psoriasis and/or psoriatic arthritis: a systematic review. *Biomedicines.* 2023;11(2):318.
 106. Vaengebjerg S, Skov L, Egeberg A, Loft ND. Prevalence, incidence, and risk of cancer in patients with psoriasis and psoriatic arthritis: a systematic review and meta-analysis. *JAMA Dermatol.* 2020;156(4):421-429.
 107. Thyssen JP, Halling-Overgaard AS, Andersen YMF, Gislason G, Skov L, Egeberg A. The association with cardiovascular disease and type 2 diabetes in adults with atopic dermatitis: a systematic review and meta-analysis. *Br J Dermatol.* 2018;178(6):1272-1279.
 108. Rivers JP, Powell-Wiley TM, Dey AK, et al. Visceral adiposity in psoriasis is associated with vascular inflammation by ¹⁸F-Fluorodeoxyglucose positron-emission tomography/computed tomography beyond cardiometabolic disease risk factors in an observational cohort study. *JACC Cardiovasc Imaging.* 2018;11(2 Pt 2):349-357.
 109. Wu JJ, Sundaram M, Cloutier M, et al. The risk of cardiovascular events in psoriasis patients treated with tumor necrosis factor- α inhibitors versus phototherapy: an observational cohort study. *J Am Acad Dermatol.* 2018;79(1):60-68.
 110. Zhou P, Zou Z, Wu W, et al. The gut-lung axis in critical illness: microbiome composition as a predictor of mortality at day 28 in mechanically ventilated patients. *BMC Microbiol.* 2023;23(1):399.
 111. Natalini JG, Singh S, Segal LN. The dynamic lung microbiome in health and disease. *Nat Rev Microbiol.* 2023;21(4):222-235.
 112. Mould KJ, Moore CM, McManus SA, et al. Airspace macrophages and monocytes exist in transcriptionally distinct subsets in healthy adults. *Am J Respir Crit Care Med.* 2021;203(8):946-956.
 113. Mithradas N, Sudhakar U, Shanmugapriya K, Jeddy N, Ram S. The oral-lung microbiome dysbiosis: unravelling its role in implications for chronic obstructive pulmonary disease (COPD) pathogenesis. *J Oral Maxillofac Pathol.* 2024;28(4):619-625.
 114. Hussell T, Lui S, Jagger C, Morgan D, Brand O. The consequence of matrix dysfunction on lung immunity and the microbiome in COPD. *Eur Respir Rev.* 2018;27(148):180032.
 115. Ma R, Cheng L, Song Y, et al. Altered lung microbiome and metabolome profile in children with pulmonary arterial hypertension associated with congenital heart disease. *Front Med (Lausanne).* 2022;9:940784.
 116. Cox DJ, Connolly SA, Ó Maoldomhnaigh C, et al. Human airway macrophages are metabolically reprogrammed by IFN- γ resulting in glycolysis-dependent functional plasticity. *Elife.* 2024;13:RP98449.
 117. Cirovic B, de Bree LCJ, Groh L, et al. BCG vaccination in humans elicits trained immunity via the hematopoietic progenitor compartment. *Cell Host Microbe.* 2020;28(2):322-334.e5.
 118. Leszczyńska K, Jakubczyk D, Górka S. The NLRP3 inflammasome as a new target in respiratory disorders treatment. *Front Immunol.* 2022;13:1006654.
 119. Valenzi E, Tabib T, Papazoglou A, et al. Disparate interferon signaling and shared aberrant basaloid cells in single-cell profiling of idiopathic pulmonary fibrosis and systemic sclerosis-associated interstitial lung disease. *Front Immunol.* 2021;12:595811.
 120. Cansu DÜ, Korkmaz C. Pulmonary hypertension in connective tissue diseases: epidemiology, pathogenesis, and treatment. *Clin Rheumatol.* 2023;42(10):2601-2610.
 121. Xu D, Hu YH, Gou X, et al. Oxidative stress and anti-oxidative therapy in pulmonary arterial hypertension. *Molecules.* 2022;27(12):3724.
 122. Sweis JJG, Sweis NWG, Alnaimat F, et al. Immune-mediated lung diseases: a narrative review. *Front Med (Lausanne).* 2023;10:1160755.
 123. Agarwal SK, Heiss G, Barr RG, et al. Airflow obstruction, lung function, and risk of incident heart failure: the atherosclerosis risk in communities (ARIC) study. *Eur J Heart Fail.* 2012;14(4):414-422.
 124. Alysandratos KD, Herriges MJ, Kotton DN. Epithelial stem and progenitor cells in lung repair and regeneration.

- Annu Rev Physiol.* 2021;83:529-550.
125. Yang YL, Xiang ZJ, Yang JH, Wang WJ, Xu ZC, Xiang RL. Association of β -blocker use with survival and pulmonary function in patients with chronic obstructive pulmonary and cardiovascular disease: a systematic review and meta-analysis. *Eur Heart J.* 2020;41(46):4415-4422.
 126. Moutsoglou DM, Tatakis J, Prisco SZ, et al. Pulmonary arterial hypertension patients have a proinflammatory gut microbiome and altered circulating microbial metabolites. *Am J Respir Crit Care Med.* 2023;207(6):740-756.
 127. Hassanein EHM, Sayed GA, Alzoghbi AM, et al. Azithromycin mitigates cisplatin-induced lung oxidative stress, inflammation and necroptosis by upregulating SIRT1, PPAR γ , and Nrf2/HO-1 signaling. *Pharmaceuticals (Basel).* 2022;16(1):52.
 128. Marsland BJ, Gollwitzer ES. Host-microorganism interactions in lung diseases. *Nat Rev Immunol.* 2014;14(12):827-835.
 129. Ravel J, Brotman RM, Gajer P, et al. Daily temporal dynamics of vaginal microbiota before, during and after episodes of bacterial vaginosis. *Microbiome.* 2013;1(1):29.
 130. Pace RM, Chu DM, Prince AL, Ma J, Seferovic MD, Aagaard KM. Complex species and strain ecology of the vaginal microbiome from pregnancy to postpartum and association with preterm birth. *Med.* 2021;2(9):1027-1049.
 131. Kumherová M, Veselá K, Kosová M, Mašata J, Horáčková Š, Šmidrkal J. Novel potential probiotic lactobacilli for prevention and treatment of vulvovaginal infections. *Probiotics Antimicrob Proteins.* 2021;13(1):163-172.
 132. Elovitz MA, Gajer P, Riis V, et al. Cervicovaginal microbiota and local immune response modulate the risk of spontaneous preterm delivery. *Nat Commun.* 2019;10(1):1305.
 133. Muzny CA, Cerca N, Elnaggar JH, Taylor CM, Sobel JD, Van Der Pol B. State of the art for diagnosis of bacterial vaginosis. *J Clin Microbiol.* 2023;61(8):e0083722.
 134. Shvartsman E, Hill JE, Sandstrom P, MacDonald KS. *Gardnerella* revisited: species heterogeneity, virulence factors, mucosal immune responses, and contributions to bacterial vaginosis. *Infect Immun.* 2023;91(5):e0039022.
 135. Gilbert NM, Lewis WG, Li G, Sojka DK, Lubin JB, Lewis AL. *Gardnerella vaginalis* and *Prevotella bivia* trigger distinct and overlapping phenotypes in a mouse model of bacterial vaginosis. *J Infect Dis.* 2019;220(7):1099-1108.
 136. Zhang X, Chen Y, Zhu K, Yu X, Zhao J. Characteristics of vaginal microbiota in pregnant women with cervical insufficiency and its association with adverse pregnancy outcomes. *Pak J Med Sci.* 2025;41(5):1381-1387.
 137. Phipps EA, Thadhani R, Benzinger T, Karumanchi SA. Pre-eclampsia: pathogenesis, novel diagnostics and therapies. *Nat Rev Nephrol.* 2019;15(5):275-289.
 138. Rana S, Lemoine E, Granger JP, Karumanchi SA. Preeclampsia: pathophysiology, challenges, and perspectives. *Circ Res.* 2019;124(7):1094-1112.
 139. Li X, Tian Z, Cui R, et al. Association between pre-gestational vaginal dysbiosis and incident hypertensive disorders of pregnancy risk: a nested case-control study. *mSphere.* 2023;8(3):e0009623.
 140. Delgado-Diaz DJ, Tyssen D, Hayward JA, Gugasyan R, Hearps AC, Tachedjian G. Distinct immune responses elicited from cervicovaginal epithelial cells by lactic acid and short chain fatty acids associated with optimal and non-optimal vaginal microbiota. *Front Cell Infect Microbiol.* 2019;9:446.
 141. Koren O, Konnikova L, Brodin P, Mysorekar IU, Collado MC. The maternal gut microbiome in pregnancy: implications for the developing immune system. *Nat Rev Gastroenterol Hepatol.* 2024;21(1):35-45.
 142. Tooher J, Thornton C, Makris A, Ogle R, Korda A, Hennessy A. All hypertensive disorders of pregnancy increase the risk of future cardiovascular disease. *Hypertension.* 2017;70(4):798-803.
 143. Turpin R, Tuddenham S, He X, Klebanoff MA, Ghanem KG, Brotman RM. Bacterial vaginosis and behavioral factors associated with incident pelvic inflammatory disease in the longitudinal study of vaginal flora. *J Infect Dis.* 2021;224(12 Suppl 2):S137-S144.
 144. Sugulle M, Fiskå BS, Jacobsen DP, Fjeldstad HE, Staff AC. Placental senescence and the two-stage model of preeclampsia. *Am J Reprod Immunol.* 2024;92(1):e13904.
 145. Escalda C, Botelho J, Mendes JJ, Machado V. Association of bacterial vaginosis with periodontitis in a cross-sectional American nationwide survey. *Sci Rep.* 2021;11(1):630.
 146. Abavisani M, Sahebi S, Dadgar F, Peikfalak F, Keikha M. The role of probiotics as adjunct treatment in the prevention and management of gynecological infections: an updated meta-analysis of 35 RCT studies. *Taiwan J Obstet Gynecol.* 2024;63(3):357-368.
 147. van de Wijgert J, Verwijs MC. Lactobacilli-containing vaginal probiotics to cure or prevent bacterial or fungal vaginal dysbiosis: a systematic review and recommendations for future trial designs. *BJOG.* 2020;127(2):287-299.
 148. Bindels LB, Delzenne NM. Muscle wasting: the gut microbiota as a new therapeutic target? *Int J Biochem Cell Biol.* 2013;45(10):2186-2190.
 149. Ticinesi A, Nouvenne A, Cerundolo N, et al. Gut microbiota, muscle mass and function in aging: a focus on physical frailty and sarcopenia. *Nutrients.* 2019;11(7):1633.
 150. McLaren DG, Han S, Murphy BA, et al. DGAT2 inhibition alters aspects of triglyceride metabolism in rodents but not in non-human primates. *Cell Metab.* 2018;27(6):1236-1248.e6.
 151. Mancin L, Wu GD, Paoli A. Gut microbiota-bile acid-

- skeletal muscle axis. *Trends Microbiol.* 2023;31(3):254-269.
152. Singh VK, Munro K, Jia Z. A novel calmodulin- β -PIX interaction and its implication in receptor tyrosine kinase regulation. *Cell Signal.* 2012;24(9):1790-1796.
 153. Claesson MJ, Jeffery IB, Conde S, et al. Gut microbiota composition correlates with diet and health in the elderly. *Nature.* 2012;488(7410):178-184.
 154. Qin J, Li Y, Cai Z, et al. A metagenome-wide association study of gut microbiota in type 2 diabetes. *Nature.* 2012;490(7418):55-60.
 155. Tabas I, Bornfeldt KE. Macrophage phenotype and function in different stages of atherosclerosis. *Circ Res.* 2016;118(4):653-667.
 156. Evans BR, Schulz J, Triantafyllidou V, et al. ChemR23 prevents phenotypic switching of vascular smooth muscle cells into macrophage-like foam cells in atherosclerosis. *Cardiovasc Res.* 2026;122(2):195-213.
 157. Spann NJ, Garmire LX, McDonald JG, et al. Regulated accumulation of desmosterol integrates macrophage lipid metabolism and inflammatory responses. *Cell.* 2012;151(1):138-152.
 158. Jiang H, Li Z, Wang J, Sun H, Qi L. Regulatory mechanisms of XBP1 in tumorigenesis and cancer progression: challenges and therapeutic strategies. *Pharmaceuticals (Basel).* 2026;19(7):993.
 159. Jiang H, Li Z, Li X, et al. The cGAS-STING pathway in tumor immunity: dual roles, regulatory mechanisms, and precision therapeutic strategies. *Front Pharmacol.* 2026;17:1844637.
 160. Alka Ahuja, Saraswathy Mp, Nandakumar S, Prakash FA, Kn G, Um D. Role of the gut microbiome in diabetes and cardiovascular diseases including restoration and targeting approaches- a review. *Drug Metab Bioanal Lett.* 2022;15(3):133-149.
 161. Orjichukwu CK, Orjichukwu RO, Akpunonu PK, Ugwu PC, Nnabuike SG. Microbiome and heart failure: a comprehensive review of gut health and microbiota-derived metabolites in heart failure progression. *Med Sci (Basel).* 2025;13(4):302.
 162. Rothhammer V, Borucki DM, Tjon EC, et al. Microglial control of astrocytes in response to microbial metabolites. *Nature.* 2018;557(7707):724-728.
 163. Coppin E, Zhang X, Ohayon L, et al. Peripheral ischemia imprints epigenetic changes in hematopoietic stem cells to propagate inflammation and atherosclerosis. *Arterioscler Thromb Vasc Biol.* 2023;43(6):889-906.
 164. Li P, Wang H, Guo L, et al. Association between gut microbiota and preeclampsia-eclampsia: a two-sample mendelian randomization study. *BMC Med.* 2022;20(1):443.
 165. Christ A, Günther P, Lauterbach MAR, et al. Western diet triggers NLRP3-dependent innate immune reprogramming. *Cell.* 2018;172(1-2):162-175.e14.
 166. Sanz M, Ceriello A, Buysschaert M, et al. Scientific evidence on the links between periodontal diseases and diabetes: consensus report and guidelines of the joint workshop on periodontal diseases and diabetes by the international diabetes federation and the European federation of periodontology. *Diabetes Res Clin Pract.* 2018;137:231-241.
 167. Han JH, Park JW, Han KD, Park JB, Kim M, Lee JH. Smoking and periodontitis can play a synergistic role in the development of psoriasis: a nationwide cohort study. *Dermatology.* 2022;238(3):554-561.
 168. Huang X, Xie M, Wang Y, et al. *Porphyromonas gingivalis* aggravates atherosclerotic plaque instability by promoting lipid-laden macrophage necroptosis. *Signal Transduct Target Ther.* 2025;10(1):171.
 169. Surma S, Okopień B, Murphy AJ, Banach M. High salt intake and atherosclerosis progression-not only via blood pressure: a narrative review. *Nutrients.* 2025;17(21):3464.
 170. Duttaroy AK. Role of gut microbiota and their metabolites on atherosclerosis, hypertension and human blood platelet function: a review. *Nutrients.* 2021;13(1):144.
 171. Kleinewietfeld M, Manzel A, Titze J, et al. Sodium chloride drives autoimmune disease by the induction of pathogenic Th17 cells. *Nature.* 2013;496(7446):518-522.
 172. Poll BG, Cheema MU, Pluznick JL. Gut microbial metabolites and blood pressure regulation: focus on SCFAs and TMAO. *Physiology (Bethesda).* 2020;35(4):275-284.
 173. Polonio CM, McHale KA, Sherr DH, Rubenstein D, Quintana FJ. The aryl hydrocarbon receptor: a rehabilitated target for therapeutic immune modulation. *Nat Rev Drug Discov.* 2025;24(8):610-630.
 174. Porez G, Prawitt J, Gross B, Staels B. Bile acid receptors as targets for the treatment of dyslipidemia and cardiovascular disease. *J Lipid Res.* 2012;53(9):1723-1737.
 175. Yi J, Chen J, Yao X, et al. Myokine-mediated muscle-organ interactions: molecular mechanisms and clinical significance. *Biochem Pharmacol.* 2025;242(Pt 2):117326.
 176. Wang Y, Zhang J, Wang J, et al. The dual role of interleukin-6 in the pathophysiology of skeletal muscle: mechanisms, challenges, and therapeutic prospects. *Pharmaceuticals (Basel).* 2026;19(6):868.
 177. Setayesh A, Karimi M, Asbaghi O, et al. Effects of probiotics and synbiotics supplementation on blood pressure in adults with prediabetes and type 2 diabetes mellitus: a grade-assessed systematic review and dose-response meta-analysis. *Probiotics Antimicrob Proteins.* 2026;18(2):3303-3317.
 178. La Barbera L, Macaluso F, Fasano S, Grasso G, Ciccio F, Guggino G. Microbiome changes in connective tissue diseases and vasculitis: focus on metabolism and inflammation. *Int J Mol Sci.* 2022;23(12):6532.
 179. Susin C, Stadler AF, Haas A, Albandar JM. Periodontal

- manifestations of systemic diseases. *J Periodontal Res.* 2025.
180. Wang X, Chen L, Wei J, et al. The immune system in cardiovascular diseases: from basic mechanisms to therapeutic implications. *Signal Transduct Target Ther.* 2025;10(1):166.
 181. Barbadoro P, Ponzio E, Coccia E, et al. Association between hypertension, oral microbiome and salivary nitric oxide: a case-control study. *Nitric Oxide.* 2021;106:66-71.
 182. Violi F, Nocella C. Editorial: gut permeability-related endotoxemia and cardiovascular disease: a new clinical challenge. *Front Cardiovasc Med.* 2023;10:1118625.
 183. Kori M, Cig D, Arga KY, Kasavi C. Multiomics data integration identifies new molecular signatures for abdominal aortic aneurysm and aortic occlusive disease: implications for early diagnosis, prognosis, and therapeutic targets. *OMICS.* 2022;26(5):290-304.
 184. Lai CH, Chang CW, Lee FT, et al. Targeting vascular smooth muscle cell dysfunction with xanthine derivative KMUP-3 inhibits abdominal aortic aneurysm in mice. *Atherosclerosis.* 2020;297:16-24.
 185. Wei X, Li Y, Jiang T, et al. Terazosin attenuates abdominal aortic aneurysm formation by downregulating *PEG3*, expression to inhibit vascular smooth muscle cell apoptosis and senescence. *Eur J Pharmacol.* 2024;968:176397.
 186. Matsuda Y, Terada T, Tetsuo Y, Tsumoto T. Partially thrombosed giant basilar tip aneurysm that remarkably decreased in size after stent-assisted coiling associated with the disappearance of neovascularization. *Neuroradiology.* 2022;64(4):837-841.
 187. Kręgielczak A, Dorocka-Bobkowska B, Słomski R, Oszkinis G, Krasinski Z. Periodontal status and the incidence of selected bacterial pathogens in periodontal pockets and vascular walls in patients with atherosclerosis and abdominal aortic aneurysms. *PLoS One.* 2022;17(8):e0270177.
 188. Hellmich B, Agueda A, Monti S, et al. 2018 update of the EULAR recommendations for the management of large vessel vasculitis. *Ann Rheum Dis.* 2020;79(1):19-30.
 189. Roger I, Milara J, Montero P, Cortijo J. The role of JAK/STAT molecular pathway in vascular remodeling associated with pulmonary hypertension. *Int J Mol Sci.* 2021;22(9):4980.
 190. Tapias Ledesma MÁ, Tapias Martínez P, Martín-Pero Muñoz L, Muñoz García JC. Association diabetes between sociodemographic variables, hypertension, hypercholesterolemia and periodontal disease. *Aten Primaria.* 2018;50(7):445-446.
 191. Chen X, Zhang H, Ren S, et al. Gut microbiota and microbiota-derived metabolites in cardiovascular diseases. *Chin Med J (Engl).* 2023;136(19):2269-2284.
 192. Li W, Liu W, Yang H, Wang X, Wang Z, Liu Z. Oral infection with periodontal pathogens induced chronic obstructive pulmonary disease-like lung changes in mice. *BMC Oral Health.* 2024;24(1):850.
 193. Yang J, Liu J, Gu H, et al. Gut microbiota, metabolites, and pulmonary hypertension: mutual regulation and potential therapies. *Microbiol Res.* 2025;299:128245.
 194. Shremo Msdi A, Wang EM, Garey KW. Prebiotics improve blood pressure control by modulating gut microbiome composition and function: a systematic review and meta-analysis. *Nutrients.* 2025;17(15):2502.
 195. Reiner MF, Müller D, Gobbato S, et al. Gut microbiota-dependent trimethylamine-N-oxide (TMAO) shows a U-shaped association with mortality but not with recurrent venous thromboembolism. *Thromb Res.* 2019;174:40-47.
 196. Cheng X, Qiu X, Liu Y, Yuan C, Yang X. Trimethylamine N-oxide promotes tissue factor expression and activity in vascular endothelial cells: a new link between trimethylamine N-oxide and atherosclerotic thrombosis. *Thromb Res.* 2019;177:110-116.
 197. Khan QA, Asad M, Ali AH, et al. Gut microbiota metabolites and risk of major adverse cardiovascular events and death: a systematic review and meta-analysis. *Medicine (Baltimore).* 2024;103(22):e37825.
 198. Stark K, Massberg S. Interplay between inflammation and thrombosis in cardiovascular pathology. *Nat Rev Cardiol.* 2021;18(9):666-682.
 199. Grilz E, Mauracher LM, Posch F, et al. Citrullinated histone H3, a biomarker for neutrophil extracellular trap formation, predicts the risk of mortality in patients with cancer. *Br J Haematol.* 2019;186(2):311-320.
 200. Iba T, Levy JH. Inflammation and thrombosis: roles of neutrophils, platelets and endothelial cells and their interactions in thrombus formation during sepsis. *J Thromb Haemost.* 2018;16(2):231-241.
 201. Nogal A, Valdes AM, Menni C. The role of short-chain fatty acids in the interplay between gut microbiota and diet in cardio-metabolic health. *Gut Microbes.* 2021;13(1):1-24.
 202. da Silva JF, Bolsoni JA, da Costa RM, et al. Aryl hydrocarbon receptor (AhR) activation contributes to high-fat diet-induced vascular dysfunction. *Br J Pharmacol.* 2022;179(12):2938-2952.
 203. Roberts AB, Gu X, Buffa JA, et al. Development of a gut microbe-targeted nonlethal therapeutic to inhibit thrombosis potential. *Nat Med.* 2018;24(9):1407-1417.
 204. Qi J, You T, Li J, et al. Circulating trimethylamine N-oxide and the risk of cardiovascular diseases: a systematic review and meta-analysis of 11 prospective cohort studies. *J Cell Mol Med.* 2018;22(1):185-194.
 205. Zhang Y, Li S, Fan X, Wu Y. Pretreatment with indole-3-Propionic acid attenuates lipopolysaccharide-induced cardiac dysfunction and inflammation through the AhR/NF-κB/NLRP3 pathway. *J Inflamm Res.* 2024;17:5293-5309.

206. Joshi C, Bapat R, Anderson W, Dawson D, Hijazi K, Cherukara G. Detection of periodontal microorganisms in coronary atheromatous plaque specimens of myocardial infarction patients: a systematic review and meta-analysis. *Trends Cardiovasc Med*. 2021;31(1):69-82.
207. Rahimi A, Afshari Z. Periodontitis and cardiovascular disease: a literature review. *ARYA Atheroscler*. 2021;17(5):1-8.
208. Fromentin S, Forslund SK, Chechi K, et al. Microbiome and metabolome features of the cardiometabolic disease spectrum. *Nat Med*. 2022;28(2):303-314.
209. So D, Whelan K, Rossi M, et al. Dietary fiber intervention on gut microbiota composition in healthy adults: a systematic review and meta-analysis. *Am J Clin Nutr*. 2018;107(6):965-983.
210. Wang Z, Bergeron N, Levison BS, et al. Impact of chronic dietary red meat, white meat, or non-meat protein on trimethylamine N-oxide metabolism and renal excretion in healthy men and women. *Eur Heart J*. 2019;40(7):583-594.
211. Chen T, Wang J, Liu Z, Gao F. Effect of supplementation with probiotics or synbiotics on cardiovascular risk factors in patients with metabolic syndrome: a systematic review and meta-analysis of randomized clinical trials. *Front Endocrinol (Lausanne)*. 2023;14:1282699.
212. Khanna S, Sims M, Louie TJ, et al. SER-109: an oral investigational microbiome therapeutic for patients with recurrent *Clostridioides difficile* infection (rCDI). *Antibiotics (Basel)*. 2022;11(9):1234.
213. Proença IM, Allegretti JR, Bernardo WM, et al. Fecal microbiota transplantation improves metabolic syndrome parameters: systematic review with meta-analysis based on randomized clinical trials. *Nutr Res*. 2020;83:1-14.
214. Shah RA, Alkhouri N, Kowdley KV. Emerging drugs for the treatment of non-alcoholic steatohepatitis: a focused review of farnesoid X receptor agonists. *Expert Opin Emerg Drugs*. 2020;25(3):251-260.
215. İnce G, Gürsoy H, İpçi ŞD, Cakar G, Emekli-Alturfan E, Yılmaz S. Clinical and biochemical evaluation of lozenges containing *Lactobacillus reuteri* as an adjunct to non-surgical periodontal therapy in chronic periodontitis. *J Periodontol*. 2015;86(6):746-754.
216. Martinez-Moreno A, Ocampo-Candiani J, Garza-Rodriguez V. Psoriasis and cardiovascular disease: a narrative review. *Korean J Fam Med*. 2021;42(5):345-355.
217. Ghosh TS, Rampelli S, Jeffery IB, et al. Mediterranean diet intervention alters the gut microbiome in older people reducing frailty and improving health status: the NU-AGE 1-year dietary intervention across five European countries. *Gut*. 2020;69(7):1218-1228.
218. Meslier V, Laiola M, Roager HM, et al. Mediterranean diet intervention in overweight and obese subjects lowers plasma cholesterol and causes changes in the gut microbiome and metabolome independently of energy intake. *Gut*. 2020;69(7):1258-1268.
219. Walter J, Armet AM, Finlay BB, Shanahan F. Establishing or exaggerating causality for the gut microbiome: lessons from human microbiota-associated rodents. *Cell*. 2020;180(2):221-232.
220. Kurilshikov A, Medina-Gomez C, Bacigalupe R, et al. Large-scale association analyses identify host factors influencing human gut microbiome composition. *Nat Genet*. 2021;53(2):156-165.
221. van der Does AM, Amatngalim GD, Keijser B, Hiemstra PS, Villenave R. Contribution of host defence proteins and peptides to host-microbiota interactions in chronic inflammatory lung diseases. *Vaccines (Basel)*. 2018;6(3):49.
222. Kolodziejczyk AA, Zheng D, Elinav E. Diet-microbiota interactions and personalized nutrition. *Nat Rev Microbiol*. 2019;17(12):742-753.