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Immunological Mechanisms of the Gut–brain–cardiovascular Axis in Coronary Heart Disease with Comorbid Anxiety and Depression

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ABSTRACT

Coronary heart disease (CHD) is frequently accompanied by anxiety and depression, conditions that markedly worsen cardiovascular outcomes. Increasing evidence indicates that immune dysregulation, driven by gut microbiota alterations, plays a central role in linking psychological disorders with cardiovascular pathology through the gut–brain–cardiovascular axis. This narrative review systematically summarizes recent advances in the immunological mechanisms underlying CHD complicated by anxiety and depression. We focus on gut microbiota–immune interactions, inflammatory signaling pathways, immune-related microbial metabolites, and neuroimmune communication that collectively shape cardiovascular and mental health. Relevant studies addressing immune biomarkers, cytokine profiles, intestinal barrier dysfunction, and immune-modulating therapeutic strategies were critically analyzed. Gut microbiota dysbiosis contributes to intestinal barrier impairment and translocation of microbial products, leading to activation of innate and adaptive immune responses. Elevated pro-inflammatory cytokines, including interleukin 6 and tumor necrosis factor α, serve as key mediators linking systemic inflammation with atherosclerosis and neuropsychiatric symptoms. Microbial metabolites, such as trimethylamine N-oxide, exacerbate immune-driven vascular inflammation, whereas short-chain fatty acids exert immunoregulatory and anti-inflammatory effects. Neuroimmune mechanisms, including hypothalamic–pituitary–adrenal (HPA) axis activation and immune modulation of autonomic function, further integrate psychological stress with cardiovascular immune injury. Immune dysregulation represents a unifying mechanism connecting gut microbiota imbalance, neuropsychiatric disorders, and coronary heart disease. Targeting immune–microbiota interactions within the gut–brain–cardiovascular axis may offer novel diagnostic biomarkers and immunomodulatory therapeutic strategies for CHD patients with comorbid anxiety and depression. This immunological perspective provides a translational framework for future research and integrated clinical management.

Keywords: Anxiety; Atherosclerosis; Brain-gut axis; Comorbidity; Coronary disease; Cytokines; Depressive disorder; Gastrointestinal microbiome; Inflammation; Neuroimmunomodulation

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INTRODUCTION

Coronary heart disease (CHD), a major global health threat, exhibits an extremely high prevalence of comorbid anxiety and depression among its patients. We strictly adhered to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), and the International Classification of Diseases, Eleventh Revision (ICD-11), diagnostic criteria for clinically diagnosed anxiety and depression. Subclinical symptoms were explicitly distinguished from clinical disorders in all analyses, as this distinction critically impacts immunological pathways and cardiovascular outcomes.[1] Traditional research often attributes this comorbidity to psychological-social factors and neuroendocrine dysregulation, but the emerging gut–brain–cardiovascular axis has provided a novel framework for uncovering underlying mechanisms.[2]

The gut microbiota establishes bidirectional networks with the brain and cardiovascular system through neural, immune, and metabolic pathways.[3] The vagus nerve, a key neural pathway, transmits microbial signals to influence brain emotional centers, while microbial metabolites, such as short-chain fatty acids (SCFAs), regulate neurotransmitter synthesis in the brain.[4] Dysbiosis-induced intestinal barrier damage leads to endotoxin translocation, triggering systemic inflammation and promoting atherosclerosis and depressive-like behaviors.[5] Metabolic byproducts, such as trimethylamine N-oxide (TMAO), accelerate atherosclerosis, whereas SCFAs exhibit anti-inflammatory and neuroprotective effects, playing critical roles in these comorbidities.[6]

Within this axis, the pathological mechanisms of CHD and anxiety/depression are highly intertwined. Pro-inflammatory cytokines, such as interleukin 6 (IL-6), drive both atherosclerosis and depression, while gut microbial dysmetabolism characterized by reduced SCFAs and elevated TMAO simultaneously impairs cardiovascular and neurologic functions.[7] Hyperactivation of the hypothalamic–pituitary–adrenal (HPA) axis is a shared feature, and the microbiota influences HPA regulation through multiple pathways, perpetuating a pathological vicious cycle.

Interventions targeting this axis, such as probiotics, fecal microbiota transplantation, and dietary modifications, have shown promise in preclinical and early clinical studies by improving symptoms, modulating microbial metabolism, and reducing inflammation.[8] However, clarifying causal relationships between the microbiota and disease, unraveling molecular mechanisms, exploring personalized therapies, and validating long-term safety remain critical. Future integrative multi-omics research holds potential to redefine prevention and treatment paradigms for these comorbidities. This narrative review was conducted following a systematic literature search strategy to ensure comprehensive coverage of the current evidence on the immunological mechanisms of the gut–brain–cardiovascular axis in CHD with comorbid anxiety and depression.

Mechanisms of Gut Microbiota in Coronary Heart Disease

A growing body of evidence indicates that dysbiosis of the gut microbiota plays a pivotal role in the development of CHD and its comorbid conditions of anxiety and depression. This occurs through 3 interconnected pathways that operate as an integrated pathological network.[12–22]

First, the TMAO–endothelial–neuroinflammatory axis is considered: The microbial metabolism of dietary components, such as choline, carnitine, and phosphatidylcholine, results in the production of TMAO. This metabolite directly contributes to the acceleration of atherosclerosis through the activation of the NOD-like receptor protein 3 (NLRP3) inflammasome and endothelial inflammation. Concurrently, TMAO is capable of crossing the blood–brain barrier, where it induces microglial activation and behaviors akin to depression. Prospective studies involving human participants (n=1821 patients with CHD) have demonstrated that elevated levels of TMAO (>5 μM) serve as an independent predictor of both major adverse cardiovascular events (MACE) (hazard ratio [HR]=1.68, p<0.001) and the onset of depression (odds ratio [OR]=1.42, p=0.003) over a 2-year follow-up period. These findings establish TMAO as the primary bidirectional mechanistic link.

Second, the SCFA–vagal–autonomic axis is considered.[23–32]

The depletion of butyrate-producing bacteria undermines the integrity of the intestinal barrier, facilitating the translocation of lipopolysaccharides, which exacerbates systemic inflammation and disrupts autonomic regulation mediated by the vagal nerve. This dual impact fosters arrhythmogenesis and sensitizes central anxiety circuits. Notably, fecal butyrate

levels<20 mM are associated with decreased heart rate variability (r=0.52) and increased anxiety scores (r=−0.44) in cardiac patients. Furthermore, the dysbiotic alteration in tryptophan metabolism diverts precursor availability from serotonin synthesis toward the neurotoxic kynurenine pathway, leading to the overactivation of the HPA axis and aggravating cortisol-induced endothelial damage. It is crucial to recognize that these mechanisms are interdependent: cardiovascular dysfunction impacts the intestinal microenvironment through diminished gut perfusion and autonomic dysregulation, establishing a self-perpetuating vicious cycle in which each component exacerbates the others. This interconnected framework, with TMAO as the central factor, influenced by SCFA deficiency and tryptophan dysmetabolism, elucidates the limited efficacy of interventions targeting isolated pathways and underscores the necessity for comprehensive strategies that modulate the entire axis. Simultaneously, increased serum phenylacetylglutamine (PAGln) levels are linked to dyslipidemia and the formation of vulnerable plaques.[51–54]

In summary, these findings indicate that gut dysbiosis plays a pivotal role in orchestrating a complex pathological cascade in CHD. This cascade is characterized by increased levels of pro-atherogenic metabolites, such as TMAO and PAGln, compromised integrity of the intestinal barrier, and heightened oxidative stress (OS), all of which collectively contribute to the acceleration of atherosclerotic progression and the exacerbation of cardiovascular dysfunction.

Epidemiological Analysis of CHD and Anxiety/Depression

First, the prevalence of anxiety and depression among CHD patients is notably high, and these psychological issues exhibit an alarming accelerating trend over time. In a prospective study of CHD patients, the incidence of anxiety rose from 42.6% at baseline to 51.1% at 36 months, while depression rates increased from 33.3% to 43.7%.[33] This temporal progression markedly contrasts with the relatively stable prevalence rates observed in the general population during comparable periods, highlighting the disease-specific psychological deterioration within CHD cohorts. The clinical implications of this escalating comorbidity are profound, as the concurrent presence of anxiety and depression significantly undermines the prognosis of CHD. Notably, this comorbidity heightens the risk of non-cardiac rehospitalization, increases the incidence of MACE, and is independently associated with a 1.5- to 2-fold increase in mortality risk compared to CHD patients without these mental health conditions.[34,36] The association between anxiety disorders and coronary endothelial dysfunction has also been validated in female CHD patients, suggesting a potential mechanism linking anxiety to CHD complications.[35]

In CHD patients, comorbid anxiety and depression not only affect mental health but are also linked to increased risks of cardiovascular events. Studies show that their comorbidity correlates with higher all-cause mortality in CHD patients.[36] Additionally, these conditions may exacerbate CHD progression through mechanisms such as inflammation and OS.[37] To better manage mental health in CHD patients, early identification and intervention for anxiety and depression should be prioritized clinically. Psychological interventions and pharmacotherapy can effectively alleviate these symptoms, potentially improving cardiovascular outcomes.[38] Mental health management for CHD patients should be integrated into comprehensive treatment strategies to enhance quality of life and long-term prognosis.

Epidemiological Studies on Gut Microbiota in Anxiety and Depression

Gut microbiota is closely associated with anxiety and depression. Studies reveal significant alterations in gut microbiota diversity (α and β diversity), increased abundance of pro-inflammatory species, and reduced levels of SCFA-producing bacteria in patients with anxiety disorders and depression. Specifically, these patients exhibit lower α diversity, indicating reduced richness and evenness of microbial species in the gut.[39] β diversity changes further suggest substantial differences in microbial community composition between individuals. Such reduced diversity may be linked to functional dysbiosis of the gut microbiome, impacting host mental health.[40] Elevated pro-inflammatory species, such as Enterobacteriaceae and *Desulfovibrio*, are particularly abundant in depression patients. These microbes activate host immune systems via pro-inflammatory cytokine production, contributing to chronic inflammation, a key pathological mechanism in anxiety and depression.[41] Reduced SCFA-producing bacteria weaken gut barrier integrity and anti-inflammatory capacity. SCFAs, such as butyrate and propionate, are crucial for maintaining gut health, regulating immune responses, and influencing host

mental states through energy provision to intestinal epithelial cells and modulation of neuroimmune functions.

Significant differences in gut microbiota composition are observed among psychiatric patients with distinct clinical phenotypes. Techniques such as quantitative PCR and 16S rRNA sequencing enable detailed analysis of these variations and underlying mechanisms. Gut microbiota diversity and abundance may differ across psychiatric disorders, reflecting disease-specific pathophysiological processes. For instance, a study on ulcerative colitis (UC) patients using high-throughput sequencing found that while microbial diversity and abundance were similar across glucocorticoid-responsive subgroups, compositional heterogeneity directly correlated with functional differences in microbial metabolism.[42] Another study employing 16S rDNA sequencing demonstrated age-related shifts in gut microbiota structure among healthy adults, which may contribute to cognitive decline and reduced anti-inflammatory/anticancer efficacy.

The Brain–cardiovascular Axis and Mental Health

The brain–cardiovascular axis is closely linked to mental health. Brain-derived neurotrophic factor (BDNF), a key molecule in this axis, is involved in the pathogenesis of comorbid cardiovascular disease (CVD) and mental disorders (MD). The brain–cardiovascular axis serves as a bidirectional pathway connecting the central nervous system and cardiovascular system, playing a critical role in the shared mechanisms of CVD and MD. In recent years, BDNF has emerged as a focal molecule in research on CVD and MD, attracting significant attention. By binding to TrkB receptors and activating multiple signaling pathways, BDNF exerts multifaceted functions in both the nervous and cardiovascular systems. It may contribute to the pathogenesis of CVD and MD by modulating inflammatory responses, OS, and the HPA axis, positioning it as a promising target for future diagnosis and therapy.

The neural, mechanical, and biochemical pathways of the brain–cardiovascular axis play a pivotal role in regulating human physiology, cognitive function, and emotional states. Neural pathways involve interactions between the autonomic nervous system and central autonomic networks in the brain; mechanical pathways involve mechanosensitive receptors, particularly those expressing Piezo protein channels, which transmit blood pressure signals via peripheral and cerebral vasculature connections; biochemical pathways include endogenous compounds that serve as critical mediators of neurocardiovascular function.[43] Immune mechanisms of the brain–cardiovascular axis also play a significant role in the progression of cardiovascular and neurologic diseases. Circulating immune mediators, including immune cells and cytokines from adaptive and innate immune systems, facilitate bidirectional communication between the heart and brain. Cardiovascular disease can impair cognitive function, while brain pathology may lead to cardiac complications.[44]

In cardiovascular disease, the roles of neuroimmune regulation and inflammation are often underestimated. The heart–brain axis (HBA) engages in bidirectional communication through complex autonomic/hormonal and cytokine networks, playing a critical role in common pathologies. Central and peripheral neurogenic pro-inflammatory factors exhibit complex bidirectional relationships in conditions such as stroke, arrhythmias, and cardiomyopathies.[45] The vascularization, neural innervation, and inflammatory processes of the HBA hold significant clinical implications. The axis's integrity, relying on inflammation, vascular anatomy/function, and neuroregulation, is frequently disrupted or dysregulated during major pathologies (e.g., myocardial infarction or stroke), leading to long-term impacts on overall health and future disease risk.[46] BDNF's influence in the HBA extends beyond neuroregulation to cardiovascular function. Its multifaceted roles in inflammation, OS, and neuroendocrine regulation offer novel insights and strategies for the prevention, diagnosis, and treatment of cardiovascular disease and mental disorders.

Higher cardiovascular health levels are associated with a lower risk of depression and anxiety, and maintaining good cardiovascular health may exert a protective effect on mental health. The brain–cardiovascular axis likely plays a significant regulatory role in these relationships. The connection between cardiovascular health and mental health has been substantiated across multiple studies. Research indicates that individuals with optimal cardiovascular health experience a significantly reduced risk of developing depression and anxiety. One study analyzed the association between cardiovascular health scores (CVH) and the incidence of depression and anxiety, revealing that those with higher CVH scores exhibited markedly lower risks of these conditions. Another study also demonstrated a significant link between improvements

in cardiovascular health and reductions in depressive symptoms, further underscoring the potential protective role of cardiovascular health on mental well-being.[47]

Beyond mental health, cardiovascular health may influence neurodegenerative diseases through the brain–cardiovascular axis. Studies show that individuals with robust cardiovascular health exhibit lower levels of biomarkers associated with neurodegenerative disorders, reinforcing the importance of cardiovascular health in preserving neurological function.[48] The cardiovascular-brain health relationship has also been validated in other research, suggesting that optimizing cardiovascular health could help mitigate stroke and cognitive impairment risks.[49] Improving cardiovascular health not only benefits mental health but may also enhance quality of life by reducing symptoms of anxiety and depression. A study highlighted those enhancements in cardiovascular health correlate with reductions in anxiety and depressive symptoms, positively impacting patients' quality of life.[50] Furthermore, improved cardiovascular health might lower cardiovascular event risks by improving mental health outcomes, emphasizing the critical role of mental health management in cardiovascular optimization.

Pathological Effects of Anxiety and Depression on the Brain–cardiovascular Axis

In patients with CHD, the presence of anxiety and depression may influence cardiovascular health through multiple mechanisms. First, these conditions are closely associated with dysregulation of the HPA axis, leading to increased secretion of stress hormones, such as cortisol.[55,56] Excessive cortisol release not only triggers inflammatory responses but also exacerbates OS, thereby damaging vascular endothelial cells and impairing cardiac function.[57,58] Studies indicate that anxiety and depression are strongly linked to endothelial dysfunction in CHD patients. Endothelial dysfunction serves as an early marker of atherosclerosis and may contribute to cardiovascular events.[59] Additionally, these psychological states may influence cardiac autonomic regulation, elevating the risk of cardiovascular incidents.[60,61] Psychological stress and emotional distress are also recognized as significant triggers for cardiovascular events in CHD patients. Stress activates the sympathetic nervous system and HPA axis, inducing physiological changes such as heightened inflammation and endothelial damage.[62]

Anxiety and depression impact cardiovascular health in CHD patients through multiple pathways, including HPA axis activation, inflammation, OS, endothelial cell damage, and autonomic dysregulation. Clinically, managing psychological well-being alongside traditional cardiovascular risk factors is crucial for improving patient outcomes. These conditions may also negatively affect vascular stiffness, with stronger associations observed during active disease phases.[63] Anxiety may interact with cerebral perfusion, worsening cognitive impairment. In elderly cardiovascular patients, higher anxiety scores correlate with reduced frontal lobe perfusion and memory deficits, and the combined effects of low frontal perfusion and anxiety further exacerbate cognitive decline. The pathophysiological impact of comorbid mood disorders in CHD critically depends on diagnostic classification. Clinically diagnosed depression demonstrates a robust association with elevated systemic inflammation and 30% higher cardiovascular mortality compared to non-depressed CHD patients. In contrast, subclinical symptoms show significantly attenuated inflammatory responses and lack independent cardiovascular risk elevation. This dichotomy arises from differential HPA axis dysregulation: clinical diagnosis activates the NF-κB pathway via glucocorticoid resistance, while subclinical symptoms maintain partial immune homeostasis. The ICD-11 diagnostic framework further emphasizes functional impairment as a key discriminator, explaining why symptom burden alone does not trigger the gut–brain–cardiovascular inflammatory cascade observed in full clinical disorders.

Application of Gut Microbiota Analysis in Coronary Heart Disease

High-throughput sequencing of fecal samples from CHD patients reveals significant differences in gut microbiota diversity and composition compared to healthy individuals, including lower proportions of the phylum Bacteroidetes and higher proportions of the firmicutes in CHD patients.[65] Studies confirm that CHD patients exhibit reduced bacteroidetes and elevated firmicutes ratios, suggesting these microbial shifts may correlate with disease onset and progression.[66] Reduced gut microbiota diversity in CHD patients often leads to dysbiosis, which may impair cardiovascular health.[67]

CHD patients also show altered abundances of specific microbial groups. For instance, the order lactobacillales is more prevalent in CHD patients, while *bacteroides* and *prevotella* species are less abundant.[68]

These compositional changes may promote atherosclerosis progression by influencing metabolic pathways and inflammatory responses. Selecting among gut microbiota diagnostic approaches for CHD patients with psychiatric comorbidity requires balancing invasiveness, accuracy, and clinical feasibility.[69]

Our data suggest that anxiety and depression collectively contribute to an increased cardiovascular burden through convergent mechanisms, including neuroendocrine dysregulation, systemic inflammation, endothelial damage, and autonomic imbalance. This interaction establishes a self-perpetuating cycle that exacerbates the severity of CHD and increases the risk of adverse cardiac events. The microbiota–gut–brain–cardiovascular axis forms a network where microbial imbalance connects metabolic issues, neuroinflammation, and heart problems. This interaction sustains the link between CHD, anxiety, and depression, offering a potential therapeutic target to break the cycle of mental and cardiac disorders.

STATEMENT OF ETHICS

This is a narrative review based on published literature. No human participants or animals were directly involved in this study. Therefore, approval from an ethics committee and informed consent were not required. All original studies cited herein involving human subjects were conducted in accordance with the Declaration of Helsinki and approved by the respective institutional review boards of those studies.

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Not applicable.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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Not applicable.

DATA AVAILABILITY

All data supporting the findings of this study are available within the cited articles and their respective public repositories.

AI ASSISTANCE DISCLOSURE

Not applicable.

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