

## REVIEW ARTICLE

# Recent progresses in gut microbiome mediates obstructive sleep apnea-induced cardiovascular diseases

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## Abstract

Obstructive sleep apnea (OSA) is a multifactorial sleep disorder with a high prevalence in the general population. OSA is associated with an increased risk of developing cardiovascular diseases (CVDs), particularly hypertension, and is linked to worse outcomes. Although the correlation between OSA and CVDs is firmly established, the mechanisms are poorly understood. Continuous positive airway pressure is primary treatment for OSA reducing cardiovascular risk effectively, while is limited by inadequate compliance. Moreover, alternative treatments for cardiovascular complications in OSA are currently not available. Recently, there has been considerable attention on the significant correlation between gut microbiome and pathophysiological changes in OSA. Furthermore, gut microbiome has a significant impact on the cardiovascular complications that arise from OSA. Nevertheless, a detailed understanding of this association is lacking. This review examines recent advancements to clarify the link between the gut microbiome, OSA, and OSA-related CVDs, with a specific focus on hypertension, and also explores potential health advantages of adjuvant therapy that targets the gut microbiome in OSA.

## KEYWORDS

cardiovascular diseases, gut microbiome, intermittent hypoxia, obstructive sleep apnea, prebiotics, probiotics

## 1 | INTRODUCTION

Obstructive sleep apnea (OSA) is a chronic prevalent condition with a high-cost burden. An estimated 936 million people between the ages of 30 and 69 have OSA.<sup>1</sup> OSA is characterized by recurrent episodes of partial or complete upper airway obstruction that frequently caused intermittent hypoxia (IH) and sleep fragmentation (SF).<sup>2</sup> These pathophysiological processes can result in a series of complications,

including cardiovascular diseases (CVDs), metabolic syndrome, and cognitive function.<sup>3,4</sup> Among these sequelae, CVDs, namely hypertension (HTN), are the most common complication of OSA. Several mechanisms have been postulated for explaining the pro-hypertensive effects of OSA, including endothelial dysfunction, sympathetic nervous system activation, systemic inflammation, and oxidative stress reaction. However, the underlying mechanisms of how OSA leads to HTN remain largely unknown.

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Recently, there has been increasing interest in the gut microbiome. Substantial evidence indicates a robust correlation between the gut microbiome and both OSA and OSA-related CVDs. While intriguing evidence suggests that the gut microbiome plays a significant part in CVDs induced by OSA, specifically HTN, there still remains a limited understanding of this relationship. OSA affects the gut microbial environment and that altered the composition and metabolism of gut microbiome, namely gut dysbiosis. It has been reported that gut dysbiosis interacts with the fundamental mechanisms of OSA, including IH and SF, resulting in elevated inflammation, reduced insulin sensitivity in adipose tissue, and impaired gut barrier function. These pathological changes collectively contribute to the development of OSA. Furthermore, gut microbiome mediates cardiovascular disease-related pathological changes in patients with OSA. In a murine model of OSA, gut dysbiosis contributed to impairment in artery function and increased arterial blood pressure.<sup>5</sup> In another animal model of OSA, it was observed that OSA rats exhibited a decrease in bacterial-produced short-chain fatty acids (SCFAs), which might trigger symptoms of HTN, including an elevation in blood pressure.<sup>6</sup>

Consequently, to elucidate the correlation between the gut microbiome, OSA, and OSA-related CVDs, in particular HTN, this review assesses contemporary research. Additionally, we explore the appliance of therapeutic approaches targeted the gut microbiome in OSA.

## 2 | INTRODUCTION OF GUT MICROBIOME

Bacteria, archaea, fungi, protozoa, viruses, and their collective genomes comprise a microbiome inside and outside the host. It interacts with the host, forms a symbiosis, and maintains a relative balance despite fluctuations.<sup>7,8</sup> The most significant component of the human microbiome is the gut microbiome. It is extremely vulnerable to changes in the internal and external environment and a variety of internal and external environmental factors, including the host's immune response, various drugs, infections, and changes in lifestyle (diet, exercise, smoking, etc.), can all trigger their reactions.<sup>9,10</sup> The gut microbiome has an initial part in maintaining normal gut physiology. It promotes food digestion, helps maturation of the host immune system, and keeps integrality of gut epithelial barrier.

Dysbiosis, a change in the composition of the gut microbiome, is frequently characterized by the following symptoms: decreased microbial diversity, an increase in the Firmicutes to Bacteroidetes ratio (F: B), and a decrease in Bifidobacterium.<sup>11,12</sup> Dysbiosis has been associated

with a variety of disorders, including obesity, insulin resistance (IR),<sup>13</sup> CVDs,<sup>14,15</sup> autoimmune diseases,<sup>16</sup> and neurodegeneration.<sup>17</sup> Chronic diseases previously believed to be associated with a certain lifestyle are now claimed to be related to microbiome.<sup>18</sup> Additionally, it has been reported that the same Western lifestyle might produce an opposing phenotype, which is directly related to the gut microbiome.<sup>19</sup> Although ample research is lacking, there is evidence that the alterations in the gut microbiome of OSA patients are strongly linked to crucial assessment indicators, such as the severity of OSA.

## 3 | GUT MICROBIOME AND OSA

OSA is a common form of sleep-disordered breathing that is associated with various detrimental health outcomes. Several studies have identified dysbiosis in individuals with OSA and have analyzed the gut microbiome of OSA patients. First, Bikov et al<sup>20</sup> divided the participants into OSA group ( $n=19$ ) and non-OSA group ( $n=20$ ). They discovered no significant change in the gut microbiome composition between the non-OSA group and OSA in  $\alpha$ - and  $\beta$ -diversity analyses. However, a separate study has shown that in OSA patients with varying levels of severity, there is a distinct difference in microbiome characteristics between severe OSA subjects and those with no OSA.<sup>21</sup> Notably, a  $\beta$  diversity analysis based on principal coordinate analysis has revealed significant variations in the OSA groups' composition.<sup>21</sup> Secondly, individuals diagnosed with OSA demonstrate an enhancement in beneficial gut bacteria and a reduction in harmful gut bacteria. Patients with OSA showed elevated levels of Proteobacteria, which synthesizes lipopolysaccharide (LPS), associated with systemic inflammation and obesity.<sup>22</sup> Meanwhile, Actinobacteria were significantly downregulated in OSA. Actinobacteria are renowned for producing the sleep-inducing neurotransmitter gamma-aminobutyric acid.<sup>23</sup> Additionally, a negative correlation was observed between Actinobacteria and the number of awakenings in healthy individuals.<sup>24</sup> Therefore, reduced levels of Actinobacteria may exacerbate arousals in OSA.

The researchers investigated the correlations between the microbiome of OSA and the risk factors for OSA, as well as the basic parameters for assessing OSA. Age and body mass index are main risk factors of OSA. Bikov et al<sup>20</sup> have identified a correlation between the abundance of particular bacteria, such as Proteobacteria or Lactobacillae, and age, as well as body mass index. To evaluate OSA comprehensively, three metrics are utilized: the apnea-hypopnea index, time below 90% oxygen saturation (T90), and the oxygen desaturation index (ODI). These metrics assess OSA individually across three aspects: the

overall count of apneas and hypopneas throughout the sleep cycle, the duration of hypoxia, and the total count of oxygen desaturation events. Baldanzi et al<sup>25</sup> carried out a cross-sectional study examining the associations between gut microbiome and three indicators in a sample of 3570 participants aged 50–64 years. The results revealed a decrease in both richness and evenness of gut microbiome among individuals with OSA, which was linked to the three metrics. However, this is inconsistent with earlier research,<sup>20,21</sup> and this difference could be ascribed to the size of the sample. Additionally, 128 species were found to be associated with T90 and/or ODI. Notably, certain species associated with T90/ODI had either a positive or negative correlation with blood pressure.

Based on the presented evidence, a noteworthy correlation has been observed between gut microbiome and OSA. It is imperative to examine the complex interrelation between the pathology and physiology of OSA and the gut microbiome.

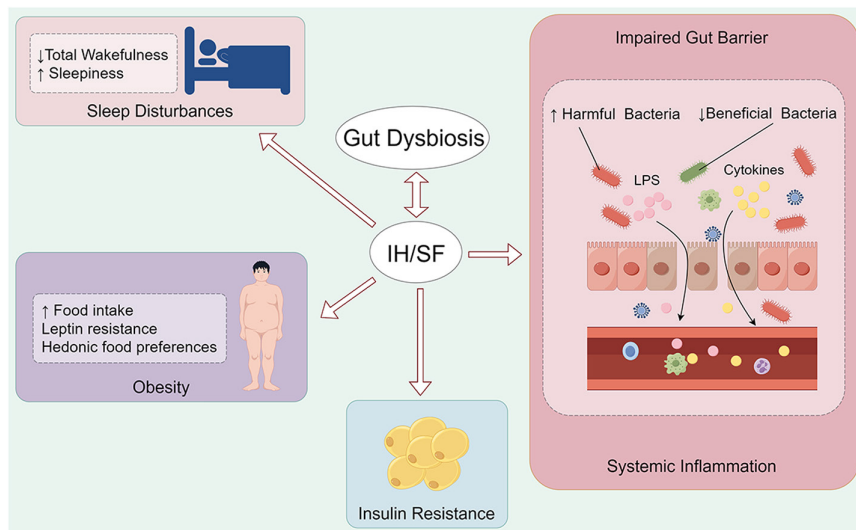
#### 4 | GUT MICROBIOME AND SF

SF is a prevalent sleep disorder with significant impacts on human health. SF significantly impacts the clinical phenotype of OSA,<sup>26</sup> contributing to neuroinflammation, oxidative stress, systemic inflammatory response, cognitive decline, memory impairment, and other common OSA symptoms. SF changes the microbial composition in mice, with more impact observed in the presence of a high-fat diet (HFD).<sup>27</sup> The modified gut microbiome arising from SF may operate via multiple mechanisms, including disruption of the gut's circadian rhythm,<sup>28</sup> leading to enhanced feeding behavior<sup>18</sup> and inflammation responses.<sup>29</sup> The altered gut microbiome resulting from SF

promote the advancement of SF and may even contribute to the pathological changes initiated by SF (Figure 1).

Gut microbiome is associated with SF-related metabolic syndrome. Prolonged exposure to SF in mice results in an elevated food intake without a corresponding increase in caloric expenditure.<sup>30</sup> Also, leptin resistance develops in response to SF exposure. Consequently, subcutaneous and visceral depots accumulate adipose tissue, yielding weight gain even when consuming a standard diet. Ultimately, these factors contribute to the development of obesity. It is worth noting that SF is linked to alterations in hedonic food preferences, including increased snacking and carbohydrate intake.<sup>31</sup> The gut microbiome is believed to have a significant impact on mediating these changes. Research indicates that *Faecalibacterium* and *Bifidobacterium* can boost free fatty acid (FFA) concentrations in males and females, respectively.<sup>32</sup> A significant correlation has been identified between intestinal FFA receptors and appetite.<sup>33</sup> In addition, exposure to OSA leads to an elevation of plasma FFA levels.<sup>34</sup> TUG891, a FFA receptor 4 agonist, displayed significant beneficial effects on body weight, food consumption, and inflammation in the SF model.<sup>35</sup> Moreover, Farré et al<sup>18</sup> discovered that germ-free (GF) mice received fecal pellets from SF-exposed animals reproduced several SF behaviors, including increased food intake, significantly decreased adipose tissue insulin sensitivity, and increased leukocyte presence. Together, it is clear that the gut microbiome is strongly linked to metabolic abnormalities associated with SF and may even be a causative factor for such metabolic dysregulation.

The intestinal damage and chronic low-grade inflammation linked to SF are associated with the gut microbiome. Studies have shown that SF modifies the gut microbiome, leading to an elevation in the Lachnospiraceae family and a decline in the Lactobacillaceae family.<sup>29</sup> The former is associated with intestinal inflammation, whereas the latter



**FIGURE 1** Mechanisms of how the gut microbiome facilitate the development of IH/SF. IH, intermittent hypoxia; SF, sleep fragmentation.

acts as a protective barrier. Moreover, SF lowers antioxidant capacity and depletes the number of goblet cells and colonocyte proliferation.<sup>36</sup> It also intensifies LPS-binding protein circulation levels and stimulates an enhanced inflammatory response.<sup>29</sup> It is reasonable to hypothesize that SF-related alteration in gut microbiome could risk damage to the gut barrier, thereby causing LPS displacement and provoking chronic low-grade inflammation. An *in vitro* study reported that SF mice generated fecal water that resulted in a disruption of the colonic epithelium.<sup>29</sup> Moreover, the transfer of fecal matter from SF mice to GF mice resulted in an increased inflammatory response in the latter.<sup>29</sup> These findings support the abovementioned role of the gut microbiome in SF.

Additionally, studies have reported that probiotic supplements can improve sleep quality,<sup>37</sup> decrease arousal levels,<sup>37</sup> and reduce inflammation and oxidative stress<sup>38</sup> in another sleep disorder, namely sleep deprivation. In the future, there is a need to further investigate the effects of treatments that target gut microbiome on the negative outcomes of SF. In conclusion, the gut microbiome plays a role in mediating certain pathological changes induced by SF.

## 5 | GUT MICROBIOME AND IH

IH affects the arterial partial pressure of oxygen, which could result in a hypoxia/reoxygenation pattern within the gut.<sup>39,40</sup> This pattern adversely impacts the environment of the intestinal epithelium and lead to dysbiosis. Systemic low-grade inflammation caused by IH could also contribute to dysbiosis. In chronic intermittent hypoxia (CIH) mice, beneficial genera like *Clostridium*, *Akkermansia*, and *Bacteroides* reduced in presence while pathogenic genera like *Desulfovibrio* increased.<sup>41</sup> There is increasing evidence indicating the involvement of gut dysbiosis in promoting and facilitating IH (Figure 1).

The gut microbiome has been associated with disturbed sleep patterns seen in IH. IH exposure may impair sleep architecture by reducing total wakefulness and increasing sleepiness.<sup>42</sup> Badran et al<sup>42</sup> undertook a study that transplanted IH mouse microbiome into naive mice, and for the first time, analyzed the sleep patterns of the recipient mice. The treated mice showed disruptions in their sleep patterns, leading to increased sleep duration during the dark phase when these animals are usually more active and engaged in feeding and play. These findings imply that the gut microbiome changes associated with IH can independently cause sleep disturbances in mice. The sleep disorders observed in mice resemble the excessive daytime sleepiness commonly found in individuals with OSA. Hence, the present study highlights the vital role of the

gut microbiome in regulating sleep and suggests a promising therapeutic approach to improving sleep quality and reducing daytime sleepiness in patients with OSA.

The gut microbiome is associated with intestinal damage and systemic inflammatory responses that are linked to IH. CIH damages the colonic mucosa, reducing goblet cells and impairing intestinal tight junctions.<sup>41</sup> These changes may relate with gut microbiome. The gut microbiome and its byproducts have been shown to harm gut barrier function through various mechanisms.<sup>43</sup> IH mice exhibited increased levels of *Desulfovibrio*, a bacterium that adversely impacts the intestinal barrier, contributing to the disruption of the intestinal barrier.<sup>41</sup> Moreover, researchers transplanted IH mice feces into recipient mice, which also exhibited dysbiosis and elevated intestinal permeability.<sup>44</sup> This indicates that gut barrier injury can be mediated, at least in part, by IH-induced alterations in gut microbiome. Dysfunctional gut barriers create an atmosphere for bacterial translocation, leading to inflammation. CIH, as expected, increased circulating pro-inflammatory cytokine<sup>41</sup> and LPS levels.<sup>45</sup> LPS is a by-product of Gram-negative gut bacteria and is a biomarker of intestinal barrier dysfunction.<sup>46</sup>

There exists a link between gut microbiome changes and IR in IH. Abdelnaby et al<sup>44</sup> found that mice exposed to IH developed IR at a faster rate than those exposed to room air. This observation also applied to GF mice via fecal transplantation. Additionally, plasma exosomes, a kind of extracellular vesicle involved in cell communication, were examined in mice who received IH feces. The effects of these exosomes were comparable to those obtained from IH-exposed mice. It led to a decrease in insulin sensitivity and a shift in macrophage polarity toward M1 macrophages.

Moreno-Indias et al<sup>45</sup> have shown that plasma concentrations of LPS in mice exposed to IH remained significantly increased even after 6 weeks of normoxic recovery, surpassing the levels measured after 6 weeks of IH exposure by a factor of one. Moreover, gut dysbiosis still persisted after exposure to normoxia. These findings indicate that the harmful consequences of IH may last for an extended period and require intervention, despite the cessation of IH exposure.

## 6 | MOLECULAR MECHANISMS BETWEEN GUT MICROBIOME AND OSA

Leaky gut is characterized by chronic elevation of intestinal permeability. It has been suggested that this phenomenon fosters systemic inflammation. Normally, the intestinal barrier prevents the transmission of harmful



agents to the internal environment. However, compromised intestinal integrity can facilitate the entry of harmful substances, such as pathogens, pro-inflammatory substances, and antigens, leading to the development of diseases or inflammation.<sup>47</sup> One such substance is LPS, also known as endotoxin, is a major cell wall component of Gram-negative bacteria. It is released during infection or the lysis of Gram-negative bacteria. The gut microbiome is the biggest reservoir of Gram-negative bacteria, making it the primary source of circulating LPS. Although serum LPS concentration is typically low, compromised intestinal barrier integrity can cause an increase in LPS levels.<sup>48</sup> Elevated LPS levels can activate the Toll-like receptor 4 (TLR4)/nuclear factor-kappaB (NF-κB) pathway, resulting in a systemic inflammatory response that contributes to the development of various diseases. Numerous studies have shown that OSA is a well-established cause of tight junction dysfunction and increased circulating LPS levels.<sup>46</sup>

Individuals with OSA experience narrowing or collapse of the upper airway during sleep, leading to episodes of apnea or hypopnea. Craniofacial abnormalities, such as excessive or elongated soft palate tissue, are a common contributing factor to upper airway stenosis in OSA.<sup>49</sup> Su et al<sup>50</sup> discovered a noteworthy increase in blood vessels in the lamina propria of the soft palate tissue of OSA patients. The study also revealed significantly higher levels of TLR4, p-NF-κB p65, vascular endothelial-derived growth factor, and matrix metalloproteinase-9 in the soft palate of OSA patients compared to controls. The TLR4/NF-κB pathway promotes the production of vascular endothelial-derived growth factor and matrix metalloproteinase-9, contributing to the angiogenesis of the soft palate in OSA patients. The experiment confirmed the up-regulation of the TLR4/NF-κB pathway in the soft palate of OSA patients, which may be linked to the activation of the TLR4 receptor by high mobility group protein box 1. However, the impact of dysbiosis and elevated circulating LPS on OSA has not yet been investigated. Furthermore, a separate study found that individuals with moderate-to-severe OSA exhibited elevated levels of TLR4 in their carotid plaques when compared to both control groups and those with mild OSA.<sup>51</sup>

In previous studies, the role of the TLR4/NF-κB pathway has also been investigated in animal models of OSA. It has been suggested that IH-mediated organ damage may be associated with the activation of this pathway. Zhang et al<sup>52</sup> found that the TLR4/NF-κB pathway plays a vital role in IH-related renal injury. They conducted a study on TLR4 knockout mice and TLR4 wild-type (WT) C57BL/6J mice exposed to normal air or CIH. In comparison with TLR4 knockout mice, the WT mice exhibited renal insufficiency and histological damage. Additionally, CIH treatment led

to a significant accumulation of macrophages and fibroblasts, release of pro-inflammatory cytokines, and renal fibrosis in WT mice. The controls also showed a notable increase in the expression of myeloid differentiation primary-response protein 88 and NF-κB p65 in the kidney. In a separate study, Zou et al<sup>53</sup> found that TLR4 deficiency effectively prevented lung injury induced by IH. The study discovered that TLR4-deficient (TLR4<sup>-/-</sup>) mice did not exhibit any noticeable lung changes, while C57BL/6J mice exposed to IH showed severe alveolar septal thickening, alveolar constriction, structural disruption, leukocyte infiltration, and hemorrhage. Furthermore, C57BL/6J-IH mice had higher expression of NF-κB p65 protein than TLR4<sup>-/-</sup> mice. The TLR4/NF-κB pathway may also be associated with SF-induced damage. Liu et al<sup>54</sup> utilized the modified multi-platform sleep deprivation method to simulate rapid eye movement sleep deprivation, a common method for SF modeling. The rapid eye movement sleep-deprived rats exhibited prolonged sleep latency and shortened sleep duration compared to the control group. Additionally, the sleep-deprived rats displayed significant cognitive impairment and pathological injury in the hippocampus and cortex. In the model group, TLR4, p-NF-κB p65, and phosphorylated NF-κB inhibitor(IκB) alpha levels were significantly higher than those in the control group.

These findings suggest that the activation of the pro-inflammatory TLR4/NF-κB pathway may be a mechanism that links OSA to its associated target-organ damage. However, the substances that activate the TLR4 receptor were not investigated. Additionally, the potential link between OSA-induced dysfunction of the intestinal barrier and increased levels of circulating LPS with TLR4 activation was not explored. Future research should prioritize investigating the relationship between leaky gut and OSA by targeting the TLR4/NF-κB pathway.

## 7 | OSA, GUT MICROBIOME, AND CVDs

It is widely acknowledged that a correlation exists between OSA and CVDs. Furthermore, these two conditions are known to interact with each other. Furthermore, evidence of interaction between these two conditions exists, with OSA affecting between 40% and 80% of patients with HTN, heart failure, coronary artery disease, pulmonary HTN, atrial fibrillation (AF), and stroke.<sup>55</sup> Individuals diagnosed with OSA are more susceptible to developing CVDs, which can lead to a worse prognosis.<sup>56</sup>

In addition to the direct damage that OSA inflicts on the cardiovascular system, the gut microbiome and its metabolites can also exert an impact on it. In fact, there

is a causal link between the gut microbiome and CVDs.<sup>57</sup> Gut microbiome is found to promote myocardial damage in ST-elevation myocardial infarction (STEMI) patients. Chen et al<sup>58</sup> introduced fecal samples from such patients into GF mice. The outcome suggested that STEMI combined with fecal microbiota transplantation (FMT) treatment decreased baseline cardiac function and increased left ventricular stiffness, thereby affecting the contractility of recipient mice. After undergoing surgery for myocardial infarction, mice that received STEMI-FMT showed a surprisingly high mortality rate. Interestingly, supplementing mice with butyrate led to a decrease in infarct size and an improvement in cardiac mechanical properties, especially in the presence of a healthy gut microbiome. Additionally, butyrate treatment showed a cardioprotective effect that depended on the dosage. Together, these findings imply that during a myocardial infarction, coexisting dysbiosis of the gut microbiome plays a role in exacerbating cardiac damage and that butyrate has a protective impact on the myocardium. Trimethylamine N-oxide (a microbial metabolic product) and its precursors have been linked to a higher risk of significant adverse cardiovascular incidents and all-cause mortality, irrespective of traditional risk factors for CVDs.<sup>59</sup> Jin et al<sup>60</sup> report that trimethylamine N-oxide treatment impaired cardiac function and T-tubule network in mice. Dysbiosis of the gut microbiome has been shown to have detrimental effects on ischemic stroke through the brain-gut axis. Patients with ischemic stroke have been discovered to have significant gut dysbiosis. In mice used as an ischemic stroke model, proximal middle cerebral artery occlusion (MCAO) increased intestinal permeability and translocation of the gut microbiome and bacterial toxins. Infarct volume and dysfunction following FMT were significantly higher in recipient mice (3 days before distal MCAO) receiving feces from stroke mice (previously had proximal transient MCAO). On the other hand, recipient mice who received feces (beginning on the day of proximal MCAO) had a significantly reduced gut dysbiosis and infarct volume. Additionally, probiotics and prebiotics use can enhance stroke results.<sup>61</sup> Alterations in the gut microbiome composition may be a mediator of aging-related AF. According to Zhang et al,<sup>62</sup> compared to young mice, aged mice showed changed gut microbiome composition and higher circulating LPS (primarily gut-metabolized). A significant increase in AF and a higher incidence of burst pacing-induced AF were observed in young mice that received fecal transplants from older mice. However, the antagonistic potential of *R. sphaeroides* LPS significantly reduced the occurrence and duration of AF in aged-FMT rats and significantly alleviated AF.

There is also some direct research on the relationship between OSA, the gut microbiome, and CVDs. According to Xue et al,<sup>63</sup> IH and hypercapnia accelerate the development of atherosclerosis, especially in the pulmonary artery. The 3,3-dimethyl-1-butanol (a microbial trimethylamine production inhibitor) may also partially inhibit its growth. The cardiac transcriptome is influenced by the microbiome during normoxia and intermittent hypoxia and hypercapnia (IHH) treatment, as reported by Zhou et al.<sup>64</sup> After administering IHH to both conventional and GF mice for 2 weeks, researchers discovered 192 differentially expressed genes (DEGs) in the hearts of conventional mice and just 161 in GF mice with minimal overlap. This indicates that the presence or absence of gut microbiome leads to heterogeneous cardiac responses during exposure to IHH. Interestingly, in conventional mice, 24% of the DEGs detected had a role in regulating transcription from the DNA template. By contrast, DEGs in the heart of GF mice induced by IHH mostly participated in regulating biological functions or activities, for instance, the circadian rhythm and cell cycle. Furthermore, SF exposure resulted in an increase in mean arterial pressure in mice. This manifestation could potentially be linked to a decrease in the abundance of bacteria that produce SCFAs.<sup>65</sup>

## 8 | OSA, GUT MICROBIOME, AND HTN

The gut microbiome of hypertensive patients often has some characteristics. Unlike the healthy populations, both pre-hypertensive and hypertensive populations usually have markedly decreased microbial richness and diversity, and distinct metagenomic composition.<sup>66,67</sup> For example, bacteria associated with healthy status are reduced in HTN, such as *Lactobacillus*<sup>66,68</sup> and *Oscillibacter*.<sup>66,67</sup> Disease-linked bacteria overgrow in HTN, such as *Parabacteroides*.<sup>66,67</sup> Of note, SCFAs-producing bacteria like *Clostridium butyricum* (*C. butyricum*) are normally less prevalent in HTN. SCFAs are known for regulating the blood pressure by SCFAs receptor.

In the last 5 years, the relation between gut microbiome and blood pressure has moved from association to causation, with researches that have used supplementation with specific strains or microbial metabolites, and FMT. A meta-analysis of 14 human randomized and controlled trials has shown that probiotic supplementation can notably reduce blood pressure.<sup>69</sup> Another study described a causal relationship with FMT from one normotensive control and two untreated hypertensive patients to GF mice.<sup>67</sup> When compared to control mice, HTN mice had greater systolic blood pressure (SBP), diastolic

blood pressure, mean blood pressure, and heart rates after 10 weeks following transplantation.

This causal relationship can also be seen in OSA-related HTN and gut microbiome. One of the earliest investigations verified the association by FMT. The researchers mimicked OSA in rats by inflating a tracheal balloon in sync with the sleep cycle.<sup>70</sup> Rats developed HTN after being subjected to OSA and HFD. By contrast with control group, OSA combined with HFD led to a significant alteration in composition of gut microbiome. Using Phylogenetic Investigation of Communities by Reconstruction of Unobserved States, the researchers predicted that several steps in the butyrate metabolism pathway would be downregulated. Afterwards, to identify the role of the gut in OSA-induced HTN, they transplanted cecal contents obtained from OSA + HFD rats into the intestinal tract of recipient rats, who were not anticipated to have HTN. The recipient rats showed an increase in blood pressure. Thus, current evidences suggest that the gut microbiome contributes to the development of OSA-induced HTN.

## 9 | MOLECULAR MECHANISMS BETWEEN GUT MICROBIOME AND OSA, CVDs, AND HTN

Accumulating evidence suggests an important role of microbiome in blood pressure control. It has been hypothesized that one of the main mechanisms involved is the gut-derived LPS/TLR4 pathway activation. The activation of the gut-derived LPS/TLR4 pathway is primarily caused by excessive LPS production, which enters the circulation and activates vascular or heart TLR4. Furthermore, intestinal barrier damage is a critical step in this process. Excessive production of LPS is the primary cause of its activation, which then enters the circulation and activates vascular or heart TLR4. Additionally, damage to the intestinal barrier is a critical step in this process.<sup>71</sup>

Gut-derived LPS/TLR4 pathway is believed to have a strong association with CVDs. Several studies have shown that people with an increased risk of developing the blood major adverse cardiovascular events, such as heart attack and stroke, exhibit the heightened levels of LPS.<sup>72,73</sup> Zhang et al<sup>74</sup> discovered that *Desulfovibrio desulfuricans* (*D. desulfuricans*) worsened the progression of atherosclerosis in apolipoprotein E-deficient mice. The study suggests that treatment with *D. desulfuricans* led to increased gut permeability and elevated serum LPS levels in apolipoprotein E-deficient mice. Additionally, *D. desulfuricans* activated the endothelial TLR4/NF- $\kappa$ B pathway. The researchers used TAK-242, a specific inhibitor of TLR4 that blocks interactions between TLR4. As anticipated,

TAK-242 treatment significantly reduced the lesion area in the aorta and decreased the mRNA expression levels of TLR4 and NF- $\kappa$ B, without affecting LPS levels. This study indicates that the gut-derived LPS/TLR4 pathway activation may have a proatherosclerotic effect.

There is increasing evidence indicating the significant involvement of gut-derived LPS in HTN. Vascular function is widely regarded as the direct cause of high blood pressure. The primary actors in vascular function are the endothelial and smooth muscle cells.<sup>75</sup> Numerous studies have investigated endothelial dysfunction triggered by LPS. Exposure to LPS, both through ex vivo incubation and in vivo intraperitoneal administration, has been shown to impair the aortic vasodilatory response to acetylcholine.<sup>76</sup> Su et al<sup>71</sup> modeled metabolic hypertension (MH) in rats by feeding them a diet high in sugar and fat, along with excessive alcohol. After 5 weeks of modeling, the MH rats exhibited significant increases in SBP and mean blood pressure. In comparison with rats fed normal chow and water, the model group exhibited a decrease in intestinal diversity and an impaired intestinal barrier. This was demonstrated by the loss of colonic villi and the downregulation of protein expression levels of zonula occludens-1, occludin, and claudin-1 when compared to normal rats. Additionally, the model group had higher serum levels of LPS. Vessels from MH rats also exhibited detached endothelial cells, smooth muscle cell hypertrophy and reduced endothelial nitric oxide synthase (eNOS) levels. eNOS produces vascular nitric oxide (NO) by using L-arginine as a substrate. Nitric oxide is a crucial molecule released by endothelial cells. Endothelial dysfunction, which underlies the pathogenesis of CVDs, is commonly characterized by reduced bioavailability of NO.<sup>77</sup> Thus, reduced levels of eNOS reflected impaired endothelial dysfunction. In this study, it was also found that MH increased the expression of TLR4 and the phosphorylation of I $\kappa$ B kinase-beta, I $\kappa$ B alpha, and NF- $\kappa$ B p65 in rat vessels.<sup>71</sup> Therefore, it was concluded that the LPS-dependent activation of TLR4 is responsible for vascular structural and functional dysfunction in MH. Furthermore, LPS/TLR4 pathway may decrease eNOS levels, impairing endothelial function. Robles-Vera et al<sup>78</sup> discovered significant gut dysbiosis and endotoxemia in spontaneously hypertensive rats (SHR) compared to Wistar Kyoto rats (WKY). The vasodilatory response to the endothelium-dependent dilator acetylcholine was weaker in the aorta of the SHR than that of the WKY. In both WKY and SHR, this acetylcholine-induced vasorelaxation was entirely dependent on NO from the endothelium, as NG-nitro-L-arginine methyl ester, an eNOS inhibitor, completely inhibited acetylcholine-induced relaxation. The bioavailability of NO is heavily dependent on the reactive oxygen species (ROS) generated by NADPH oxidase in the endothelium,

in addition to eNOS. In aortic rings from SHR, NADPH oxidase ROS production increased by approximately 60%, whereas in WKY, it did not. In aortic homogenates, TLR4 mRNA levels were approximately 8 times higher in SHR than in WKY. Notably, supplementing with probiotics and SCFAs can attenuate these changes. Taken together, these studies demonstrate that the gut dysbiosis may mediate the production of ROS and decrease the level of eNOS through the LPS/TLR4 pathway. This can lead to disruption of NO signaling and endothelial dysfunction.

Moreover, increased LPS levels triggered vascular inflammation through TLR4 activation. Vascular inflammation is widely acknowledged as a key precursor of endothelial dysfunction and the inciting factor in HTN. Many clinical studies have reported a positive association between levels of inflammatory markers and blood pressure.<sup>79</sup> Yuan et al<sup>80</sup> demonstrated that LPS treatment of EA.hy926 cells resulted in higher levels of I $\kappa$ B and NF- $\kappa$ B phosphorylation compared to the control group. Additionally, LPS treatment raised the levels of typical inflammatory cytokines, interleukin 6 (IL-6), and tumor necrosis factor-alpha (TNF- $\alpha$ ), in EA.hy926 cells. Likewise, LPS treatment in mice led to significant inflammatory cell infiltration in vascular tissues. In the aortae of LPS mice, the mRNA levels of IL-6, TNF- $\alpha$ , and TLR4 were elevated. Importantly, in WT mice, the injection of LPS led to a notable rise in NF- $\kappa$ B activation. However, this effect was not observed in TLR4<sup>-/-</sup> mice, which further supports the hypothesis that TLR4 activation is necessary for LPS-induced vascular inflammation.<sup>76</sup>

In conclusion, the gut-derived LPS/TLR4 pathway induces vascular dysfunction and inflammation by disrupting NO signaling and promoting an inflammatory response, ultimately leading to elevated blood pressure. These findings are consistent with the clinically observed phenotype. Patients with OSA exhibit reduced circulating NO and impaired endothelium-dependent vasodilation.<sup>81</sup> In addition, as a well-studied pathological process, the LPS/TLR4 pathway has been implicated in the disease phenotype of OSA. The gut-derived LPS/TLR4 pathway has been shown to play a pro-cardiovascular role in animal models of HTN. However, there is currently no conclusive evidence to confirm the role of this molecular mechanism

in the OSA combined with HTN model. Future work should give priority attention to verifying whether this pathway is involved in the development of OSA-related HTN. Moreover, manipulating the microbiome and metabolome may be a promising treatment strategy to block the cascade of responses generated by leaky gut in OSA patients.

## 10 | THERAPEUTIC CONSIDERATIONS

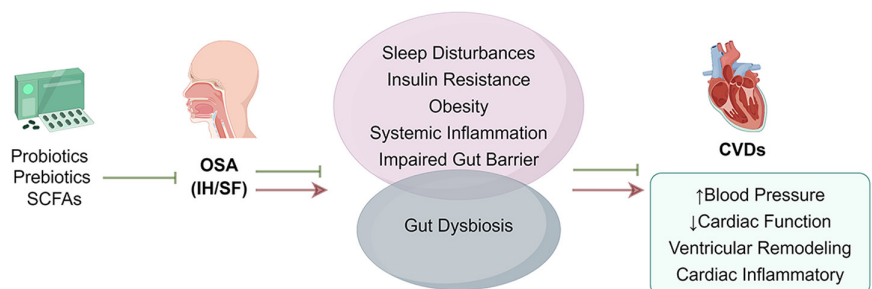
The goals of treatment for OSA are to reduce symptoms, improve quality of life, reduce complications, and decrease mortality. As stated above, the gut microbiome plays a role in the pathological processes of both OSA and its cardiovascular complications. Adjuvant therapies targeting the gut microbiome, such as probiotics and prebiotics supplements, SCFAs supplements, and FMT, are currently undergoing preclinical and clinical testing due to their potential impact on OSA. These therapies may soon have applications in clinical settings.

### 10.1 | Probiotics and prebiotics

Probiotics are presently defined as live bacteria that, when consumed in sufficient quantities, provide advantageous health effects to the host.<sup>82</sup> Probiotics can affect various internal pathways or the intestinal barrier directly, resulting in the regulation of metabolism and immunity.<sup>83,84</sup> The present prebiotic concept pertains to “a substrate utilized selectively by host microorganisms leading to health benefit.”<sup>85</sup> Prebiotics can combat enterogenous infections due to their anti-adhesive characteristics against enteropathogens and enterotoxins,<sup>86</sup> while stimulate selectively the growth and/or activity of probiotic bacteria.<sup>87</sup> Certain probiotics and prebiotics have shown to have positive effects in relation to cardiovascular complications in OSA through experimental and clinical research (Figure 2).

*C. butyricum*, a commensal bacterium in the human gut, is a member of the *Clostridium* genus.<sup>88</sup> *C. butyricum* ferments undigested dietary fibers and synthesizes

**FIGURE 2** The probiotics, prebiotics, and SCFAs supplements may reduce the progression of OSA and the cardiovascular morbidity. CVDs, cardiovascular diseases; IH, intermittent hypoxia; OSA, obstructive sleep apnea; SF, sleep fragmentation; SCFAs, short-chain fatty acids.





SCFAs, especially butyrate and acetate.<sup>89</sup> Hylon VII is a resistant corn starch that serves as a substrate for bacterial fermentation and SCFAs generation. Study has demonstrated that its consumption results in elevated concentrations of butyrate in the caecum, as well as acetate and butyrate in fecal matter.<sup>90</sup> Ganesh et al<sup>6</sup> established rat model of OSA by implanting an endotracheal obstruction device into rat and evaluated the impact of *C. butyricum* and Hylon VII supplementation on HTN in OSA rats with one billion CFU of *C. butyricum* or 20% high amylose corn starch Hylon VII. OSA rats and sham rats are, respectively, randomized to HFD, HFD + Hylon, or HFD + *C. butyricum* group. They found that HFD-fed rats showed increased SBP after 1 and 2 weeks of OSA, as compared with sham rats. In contrast, there was no substantial difference in SBP between OSA and sham rats in the HFD + Hylon or HFD + *C. butyricum* groups. That means the Hylon and *C. butyricum* can prevent SBP elevation in OSA without affecting SBP in normotensive sham rats. Furthermore, the number of mucus-producing goblet cells in the cecum decreased, and the mucus barrier thickness that spans the distance from luminal bacteria to the underlying epithelium was reduced by OSA. These changes were countered by *C. butyricum* and Hylon.

*Lactobacillus rhamnosus* GG (LGG) is a member of the *Lactobacillus* genus, which comprises a substantial portion of the human microbiota. LGG is the most common probiotic available. It has the ability to adhere to the intestinal mucosa, improve the epithelial barrier, and concomitantly inhibit pathogen adhesion. Additionally, it modulates type 1 immune responsiveness.<sup>91</sup> To develop the condition of obesity in OSA, Xu et al<sup>92</sup> treat the mice with a high-fat high-fructose diet and IH. Based the model, they investigated the effects of LGG (10<sup>9</sup> CFU bacteria/day) and LGG cell-free supernatant (dose equivalent to 10<sup>9</sup> CFU bacteria/day). Transthoracic echocardiography analysis revealed that IH-exposed obese mice exhibited an increase in left ventricular internal systolic diameter and left ventricular end systolic volume, as well as a decrease in EF%. However, these alterations were absent in high-fat high-fructose diet/IH + LGG mice. Furthermore, the myocardium did not exhibit IH-induced structural disorganization in both LGG and LGG cell-free supernatant groups. These findings illustrated the anti-ventricular remodeling and cardio protection ability of LGG in OSA. Additionally, LGG diminished the IH-elevated cardiac inflammatory level in obese mice. In another investigation, important differences were observed between normal diet (ND), CIH + ND, high salt diet (HSD), and CIH + HSD rats.<sup>93</sup> CIH + HSD rats showed increased blood pressure and altered gut microbiome composition, particularly in *Lactobacillus*. For 4 weeks of LGG intervention,

CIH + HSD rats were sequentially divided into ND, HSD, and ND + LGG groups averagely and randomly. Importantly, LGG therapy resulted in a significant reduction in blood pressure compared to controls and their blood pressure before intervention.

Beyond that, other probiotics like bifidobacterium has been found worked in cardiovascular models. Lu et al<sup>94</sup> reported that the growth of HTN and vascular remodeling in SHR was inhibited by *Bifidobacterium longum* CCFM752. Nevertheless, these abilities have yet to be confirmed in an OSA-related HTN model.

In addition to the abovementioned effects, probiotics and prebiotics could aid in managing CVDs by regulating metabolic disorders encompassing obesity and diabetes,<sup>95</sup> reducing cholesterol levels,<sup>96</sup> and curbing oxidative stress.<sup>97</sup> Collectively, it is evident that the data from these experimental studies demonstrate considerable cardiovascular advantages associated with the ingestion of probiotics and prebiotics in OSA. However, further mechanistic studies and more clinical studies in OSA patients are required.

## 10.2 | SCFAs

SCFAs are generated by the gut microbiota during the fermentation of dietary fiber, which includes acetate, butyrate, and propionate. SCFAs have multiple physiological impacts both inside and outside of the colon. Locally, they increase mucosal blood flow and stimulate the growth of colonic epithelial cells. Furthermore, they can regulate intestinal barrier function and maintain intestinal homeostasis. Unlike most other types of cells, which utilize glucose as their primary energy source, colonocytes mainly use SCFAs, especially butyrate, for energy.<sup>98</sup> Butyrate enhances Mucin2 expression, and thereby improving the intestinal physical barrier.<sup>99</sup> Outside of the colon, SCFAs possesses an anti-inflammatory characteristic. Butyrate suppressed neuroinflammation induced by chronic alcohol exposure by reducing pro-inflammatory cytokines TNF- $\alpha$ , interleukin-1beta, and IL-6 in the brain. It also regulated the polarization of M1/M2 microglia and downregulated TLR4/NF- $\kappa$ B activation.<sup>100</sup> SCFAs play a crucial role in regulating immune function. Butyrate increases the expression of aryl hydrocarbon receptor and hypoxia-inducible factor 1 $\alpha$ , which enhances the production of interleukin-22 in group 3 innate lymphoid cells and CD4<sup>+</sup> T cells by binding to G-protein receptor 41.<sup>101</sup> In addition, SCFAs can affect metabolic state of the host. Insulin secretion in islet  $\beta$ -cells is regulated by SCFAs through FFA2 and FFA3 receptors.<sup>102</sup> Moreover, SCFAs stimulate leptin release in mouse adipose tissue and adipocytes via the G protein-coupled receptor41.<sup>103</sup>

The role of SCFAs was also validated in the OSA-induced HTN model (Figure 2). Ganesh et al<sup>6</sup> found the rats developed HTN, after gavaged with cecal and colonic contents of HTN rats which caused by a combination of OSA and HFD. To determine the specific substance responsible for HTN in the gut contents, they analyzed the gut microbiota profile and metabolism. Their investigation revealed a decrease in both acetate-produced bacteria and acetate level in OSA + HFD rats. Then, they examine the effect of acetate supplementation (cecal infusion of acetate). Acetate infusion reduced the heightened mRNA level of cecal interleukin-1 $\alpha$  and interleukin-6 mRNA in OSA rats. It is worth noting that there was no significant difference in the interleukin-1 $\alpha$  and interleukin-6 mRNA levels between the OSA + acetate group and the sham group. Since its known that OSA accompanied by HFD leads to HTN, they next measured SBP. SBP of OSA + acetate rats were not remarkably different from sham group. It is evidence that acetate supplementation can prevent OSA-related inflammation and HTN.

### 10.3 | FMT

FMT is a procedure in which fecal material containing gut microbiota from a healthy donor is infused into the gastrointestinal tract of a recipient patient.<sup>104</sup> FMT is a therapy recommended for instances of recurrent or refractory *Clostridium difficile* infection.<sup>105</sup> FMT also conducted for inflammatory bowel disease, specifically ulcerative colitis, in several clinical trials.<sup>106–108</sup> While multiple variables, like administered dose, varied in the studies mentioned, the overarching results seem to demonstrate that FMT may lead to clinical remission of ulcerative colitis. In type 2 diabetes, FMT effectively improved IR and mended impaired islets.<sup>109</sup>

Given the implication of gut microbiome and its metabolites in the progression of OSA and many pathological manifestations of OSA can be transmitted via FMT, it seems plausible to suggest that FMT could present a feasible advantage for OSA. As stated earlier, FMT is currently being utilized in animal models to investigate whether gut microbiota play a part in mediating pathological processes linked to OSA. It has not yet been implemented therapeutically. However, the present clinical indication for FMT in humans remains limited to recurrent or refractory *Clostridium difficile* infection. To date, FMT is not indicated for human non-gastrointestinal diseases.

## 11 | SUMMARY

The influence of the gut microbiome on the host has been extensively investigated in the context of OSA. According

to recent findings, the gut microbiome plays a crucial role in OSA. IH and SF, the fundamental features of OSA, have been found to induce alterations in the gut microbiome, aggravate gut permeability, modify microbial metabolites, and trigger low-grade chronic inflammatory, metabolic syndrome, and sleep disturbance. Based on the current evidence, some researchers have established the causal association between the gut microbiome and OSA. Among them, the gut-derived LPS/TLR4 pathway appears to play a significant role. Furthermore, interventions targeting the gut microbiome, including probiotic and prebiotic supplements, SCFAs supplements, and FMT, have demonstrated the ability to mitigate pathophysiology triggered by OSA. Of note, in animal models, probiotic or prebiotic supplements display promise as a therapy for CVDs arising from OSA. Further randomized and controlled trials are necessary to demonstrate the efficacy of using probiotics or prebiotics as an adjunct therapeutic remedy in preventing, eliminating, or reducing complications associated with OSA.

### AUTHOR CONTRIBUTIONS

Xiaotong Zhang: Writing—original draft, Conceptualization; Haifen Zhang: Investigation; Shuai Li: Investigation; Fan Fang: Conceptualization; Yanran Yin: Supervision; Qiang Wang: Writing—review & editing.

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### CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

### DATA AVAILABILITY STATEMENT

Stored in repository.

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