Sleep apnoea, gut dysbiosis and cognitive dysfunction

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Running title: Obstructive sleep apnoea causes gut dysbiosis

Selected Abbreviations

BBB-Blood Brain Barrier; CIH-Chronic Intermittent Hypoxia; CLDN-Claudin; CPAP-Continous Positive Airway Pressure; CSF-Chronic Sleep Fragmentation; GABA-Gamma Aminobutyric Acid; GBA-Gut-Brain Axis; GD-Gut Dysbiosis; GI-Gastrointestinal; HIF-Hypoxia Inducible Factor; IL-Interleukin, LPS-Lipopolysaccharides; OCLN-Occludin; OHSA- Obstructive Sleep Apnoea–Hypopnea Syndrome; OSA-Obstructive Sleep Apnoea; ROS-Reactive Oxygen Species; SCFAs-Short-Chain Fatty Acids; TLR-Toll Like Receptor; TMAO-Trimethyl Amine N-Oxide; TNF-α-Tumor Necrosis Factor-alpha; Treg-Regulatory T cells

Key words: Obstructive sleep apnoea; gut-brain axis; cognition, neuroinflammation, gut dysbiosis; Neuroinflammation

Conflict of Interest

The authors have read the journal's policy and all the authors declared that they have no proprietary, financial, professional, or any other personal interests of any nature or kind in any product or services and/or company that could be construed or considered to be a potential conflict of interests that might have influenced the views expressed in this paper.

Abstract

Sleep disorders are becoming increasingly common, and their distinct effects on physical and mental health require elaborate investigation. Gut dysbiosis (GD) has been reported in sleep-related disorders, but sleep apnoea is of particular significance because of its higher prevalence and chronicity. Cumulative evidence has suggested a link between sleep apnoea and GD. This Review highlights the gut–brain communication axis that is mediated via commensal microbes and various microbiota-derived metabolites [such as short-chain fatty acids (SCFAs), lipopolysaccharide (LPS) and trimethyl amine N-oxide (TMAO)], neurotransmitters (such as γ-aminobutyric acid, serotonin, glutamate, and dopamine), immune cells and inflammatory mediators, as well as the vagus nerve and hypothalamic–pituitary–adrenal (HPA) axis. This Review also discusses the pathological role underpinning GD and altered gut bacterial populations in sleep apnoea and its related comorbid conditions, particularly cognitive dysfunction. The Review also examines the preclinical and clinical evidence, which suggests that prebiotics and probiotics may potentially be beneficial in sleep apnoea and its comorbidities through restoration of eubiosis or gut microbial homeostasis that regulates neural, metabolic, and immune responses, as well as physiological barrier integrity via the gut–brain axis.

Introduction

Sleep disorder is a major global problem imposing a huge economic burden. The international classification of sleep disorders (ICSD)-2 identified 81 types of sleep disorders among humans [1,2]. Subsequently, in the ICSD-3, sleep disorder is classified under 7 major categories "insomnia; parasomnias; sleep-related breathing disorders; circadian rhythm; central disorders of hypersomnolence; sleep-related movement disorders, and other sleep disorders" [3]. According to the Institute of Medicine, approximately, 50-70 million Americans suffer from a sleep disorder [4]. Emerging evidence suggests that there is a strong association between sleep disturbance and gastrointestinal (GI) conditions such as irritable bowel syndrome, inflammatory bowel disease, celiac disease, colon cancer, and acid reflux. The gut microbiome composition is altered in patients diagnosed with obstructive sleep apnoea–hypopnea syndrome (OSAHS). Specifically, functional analysis has revealed a decrease in SCFA-producing bacteria and an increase in the level of proinflammatory enteric pathogens such as gammaproteobacterial class and *Enterobacteriaceae* family, which were accompanied by elevated fasting levels of IL-6 in plasma. These changes in the gut microbiota and its metabolites contribute to the pathophysiology of OHAHS and related metabolic comorbidities [5].

Gut microbiota comprises the trillions of microorganisms residing in the gut. The gut microbiome refers to the collective genomic composition and diversity of the gut microbes. In humans, Bacteroidetes and Firmicutes comprise the major phyla of gut microbes, while the minor phyla include Proteobacteria, Actinobacteria, Verrucomicrobia, and Fusobacteria (Table 1) [6]. The gut microbiota produces an array of metabolites that either directly or indirectly regulate host homeostasis through a variety of signalling pathways via metabolic, endocrine, neural, and immune systems [7]. Other studies have suggested that sleep and gut microbiota are interlinked and disorders and deficiency of either have a negative impact on one another

[8–12]. Thus, several studies indicate that gut microbiota and gut microbial metabolites are key players in sleep modulation [13,14]. Healthy gut microbiota has shown a positive correlation with increased sleep efficiency tagged with adequate time and good quality of sleep. Eubiosis refers to the healthy composition and diversity of gut microbes, while GD refers to the pathogenic imbalance of composition and diversity. Specifically, in GD, there is an increase in pro-inflammatory taxa and a decrease in anti-inflammatory taxa [15]. Among a variety of intestinal phyla, the increased relative abundance of Firmicutes and the Bacteroidetes are found to be associated with better sleep efficiency by regulating the circadian rhythm, food intake, and synthesis of Gamma-aminobutyric acid (GABA) [16,17]. On the other hand, Actinobacteria taxa; *Brevibacterium*, *Corynebacterium*, and *Dermabacter* as well as *Lachinospiraceace* are found to have a negative correlation with sleep efficiency as the number of awakening or waking up after sleep onset (WASO) episodes are higher with their increased relative abundance [17]. GABA is an amino acid secreted by the phyla Firmicutes, Actinobacteria and genus *Bacteroides* that can help promote sleep by acting through the Gut-Brain-Axis (GBA) [18–20]. In contrast, low GABA levels are linked with disrupted sleep and insomnia [21]. Serotonin is a key neurotransmitter primarily synthesized (95%) by the Enterochromaffin cells under the influence of gut microbial activation and is involved in the regulation of sleep as well as emotion, mood, digestion, sexual desires, and stimulation of intestinal peristalsis [22,23].

The current translational review illustrates the pathological events of SA-induced gut dysbiosis including loss of intestinal barrier- and blood-brain barrier (BBB) integrity, endotoxemia, dysfunctional immune signalling, systemic and central inflammatory responses, and oxidative stress. We also discuss the influence of these pathological correlations on cognitive decline, and describe nutritional non-therapeutic approaches aimed at restoring the gut microbial balance, which in turn can improve the symptoms of SA.

Gut-Microbiota-Brain-Axis

The Gut-Microbiota-Brain-Axis maintains the bidirectional exchange of information between the gut microbiome and the central nervous system (CNS). This is achieved via neuro-immuno-endocrine signalling between the central and the enteric nervous system [31]. The GBA maintains top to bottom and bottom-to-top signalling in response to a stressor and maintains gut and body homeostasis. Numerous pathways are associated with gut-brain crosstalk of which the major pathways involved are:

i) Neuronal pathway; autonomic nervous system (ANS), CNS, vagus nerve, enteric nervous system (ENS), neurotransmitters

ii) Immune pathway

iii) Metabolic pathway

iv) Endocrine pathway: Hypothalamic-pituitary-adrenal (HPA) axis [32].

Brain-to-Gut Pathway

This pathway involves all the efferent neuronal signals from the brain in response to the afferent input received from parasympathetic and sympathetic neuronal innervations of the ANS or indirectly from the ENS stimuli (a highly developed neuronal structure of two ganglionated plexi) to the gut wall [33]. The response generated is directed towards the gut through the aforementioned pathways. Along with this, a key non-neuronal pathway, the HPA axis, which is the neuroendocrine system, mediates stress-induced changes by influencing physiological processes such as metabolism, immune response, and neuronal ANS pathways [34]. The brain also directs gut-immune response by modulating the number and degranulation activity of mast cells, and activation of resident immune cells and their receptors via immune mediators such

as cytokines and chemokines [31,35]. Thus, these factors influence gut motility, gut permeability, immunologic response, nutrient absorption, bicarbonate, and mucus secretion, epithelial fluid maintenance, luminal osmolarity, gut microbiome inhabitants, and neurotransmitter secretion.

Gut-to-Brain Pathway

The vagus nerve is the prime modulator that originates from the brainstem and innervates into the ENS and the gut. It comprises 80% afferent and 20% efferent nerve fibres, and thus processes information bidirectionally from the brain and to the gut, regulating the proper functioning of the gut [33,36]. In gut-to-brain signalling, the ENS communicates with harmful pathogens via intestinofugal afferent neurons to sympathetic ganglia and processes information generated from afferent fibres, thereby acting either directly or indirectly on the microbiota and its metabolites [36]. The responses produced are predominantly directed towards the afferent signals generated against metabolites such as short-chain fatty acids (SCFAs), trimethyl amine N oxide (TMAO), serotonin, and hormones such as cholecystokinin and glucagon-like peptide 1 (GLP-1), and peptide tyrosine derived from the Enteroendocrine cells (ECC) of the gut epithelium. Other modulators involved are lipopolysaccharides (LPS), an immunogenic endotoxin derived from the Gram-negative bacteria that causes metabolic endotoxemia resulting in neuronal inflammation in the brain, and low-grade systemic inflammation through the release of proinflammatory cytokines via Toll-like receptor-4 (TLR-4) activation (Figure-1) [35,37,38]. The neuronal and non-neuronal input and output generated are integrated towards the modulation and neuronal development of the microglia, and astrocytes and in the regulation of blood-brain barrier integrity [39–41]. It also is associated with modulating the expression of intestinal epithelial barrier tight junction proteins such as occludin (OCLN),

claudin (CLDN), and zonula occludens (ZO) in the gut, therefore maintaining the integrity and permeability of the gut barrier [42,43]. In contrast, stress is associated with decreased expression of mRNAs encoding these tight junction proteins.

Together, these data indicate the importance of the gut microbiome in orchestrating the regulation and modulation of physiological processes of the host as well as its pathogenic role or association in disease development such as cardiovascular disease, GI disease, metabolic disorder, and neuropsychiatric disorders [44–46].

Sleep disorders and gut dysbiosis

Significant differences have been reported in the diversity, composition, and metabolic activity of the gut microbiota between healthy versus patients with insomnia [47]. A study of microbial composition among young individuals subjected to partial sleep deprivation (SD) demonstrated the presence of metabolic disturbance marked by an increased Firmicutes: Bacteroidetes (F/B) ratio and increased abundance of *Coriobacteriaceae* and *Erysipelotrichaceae*, and lower abundance of *Tenericutes* [48]. Microbial analysis and 16s rRNA sequencing study revealed a decline in *Faecalibacterium* and *Agathobacter*, 3-hydroxybutyric acid, and melatonin in 120 children diagnosed with Autism spectrum disorder (ASD) and sleep disorders [49]. SD-caused astrogliosis, microgliosis, impaired glymphatic clearance, Blood-Brain-Barrier (BBB) disruption, the release of inflammatory cytokines, and altered gut microbe populations linked with neuroinflammation and cognitive impairment. Therefore, therapies that aim to enhance sleep quality and reduce GD can benefit SD [50,51]. In a self-reported sleep quality study, 28 young healthy subjects were assessed using Pittsburgh Sleep Quality Index (PSQI), with microbial diversity (Shannon Index), the F/B ratio, and bacterial taxa. The study revealed a positive correlation between sleep quality and F/B ratio with increased butyragenic genera,

Blautia and *Ruminococcus*. While the genus *Prevotella* was elevated in the self-reported poor sleepers [52]. Reports from the study in a cohort of 59 insomniac patients revealed a negative correlation between the fecal SCFA concentration and sleep duration which may be a due to noradrenaline release via activation of Free Fatty Acid Transporter 3 by the SCFA propionate [53]. SD is associated with the accumulation of Reactive oxygen species (ROS) in the gut of flies and rat models leading to oxidative stress and premature death. This was supported by a supplement of gut-targeted antioxidant enzymes which prevented oxidative damage and extended the survival time of sleep-deprived animals [54].

Similarly, a differential bacterial abundance study between narcolepsy type 1 patients versus the healthy control group revealed a difference in the abundance of taxonomical units within Bacteroidetes, *Bacteroides*, and *Flavonifractor* [55] indicating the role of gut microbiota in the disease condition. Rats that were sleep deprived for 48 hours showed significant compositional differences compared to the control group with a decrease in the relative abundance of the genera *Butyricicoccus*, *Butyricimonas*, *Alistipes*, *Intestinimonas,* and *Lactobacillus,* with an increase in the relative abundance of genus *Streptococcus*. Functional alterations in the rat gut microbiota included a decrease in the 17 Kyoto Encyclopedia of Genes and Genomes (KEGG) metabolic pathway involved in amino acid, carbohydrate, and lipid metabolism with an increase in the 2 KEGG pathway involved in LPS biosynthesis. These changes were reversible after one week of sleep recovery [56].

Sleep apnoea

Despite being often overlooked, underdiagnosed, and underreported, sleep apnoea (SA) has grown to be a significant burden to the healthcare system [57]. SA is a sleep disorder characterized by pauses in breathing or shallow breaths during sleep that lasts for a few seconds

to minutes and blocks the airflow to the brain. SA may occur multiple times throughout the night and is usually accompanied by loud snoring and fragmented sleep. Broadly, SA is classified into two types: Obstructive Sleep Apnoea (OSA) and Central Sleep Apnoea (CSA). OSA is the most predominant type of SA, characterised by the complete cessation of airflow for >10 sec, due to collapsing or narrowing of the airway as the back of the throat fails to keep the airway open, despite the effort to breathe. OSA leads to disrupted breathing patterns and complete pauses in breathing, resulting in intermittent hypoxemia, autonomic fluctuation, and sleep fragmentation. Approximately 34% and 17% of middle-aged men and women meet the diagnostic criteria for OSA, respectively. Although the prevalence of OSA varies by race/ethnicity, sex, and obesity status, sleep disturbances are common and underdiagnosed among middle-aged and older adults [58].

In contrast to SA, hypopnoea is characterised by a partial blockage or narrowing of the airway during sleep, resulting in reduced airflow. The American Academy of Sleep Medicine (AASM) defines hypopnoea as a reduction in airflow during sleep i.e., >30% of baseline, lasting for up to 10 seconds, and accompanied by either oxygen desaturation or an arousal from sleep. Hypoapnoea is associated with a drop in arterial oxyhemoglobin saturation (≤4%) [59,60].

Central sleep apnoea (CSA) occurs when the central nervous system dysfunction disrupts the normal breathing pattern, as the brain fails to send appropriate signals to the muscles that control breathing. Unlike OSA, there is no physical blockage in the airway. A lack of drive to breathe during sleep, which repeatedly results in insufficient ventilation and impaired gas exchange, is the hallmark of CSA [61]. Apnoea hypopnea index (AHI) is a standard to represent the severity of disease where an AHI > 5 per h denotes mild to moderate severity while an AHI>15 per h denotes moderate to severe severity.

The pathophysiological state of sleep apnoea is multifactorial and risk factors need to be addressed to prevent the progression of the disorder. A large number of epidemiological studies have correlated the relationship between OSA and comorbidities associated such as obesity, hypertension (HTN), and diabetes mellitus (DM) [62]. Development and progression of GI diseases are also associated with sleep dysfunction due to changes in inflammatory cytokines resulting in inflammatory bowel disease and gastroesophageal reflux disease. [63]. Patients with sleep apnoea were found to be predisposed to the risk of developing peptic ulcer bleeding in a study population of 35,480 individuals (7096 sleep apnoea vs 28,384 controls) [64]. These findings indicate that sleep apnoea plays a critical role in the development of co-morbid conditions.

Risk factors for OSA include obesity, age (common among males), sex (e.g., post-menopausal status), ethnicity, neck morphology (thickness and circumference), craniofacial (e.g., facial deformities), and upper airway deformities (e.g. narrowing of the pharynx), smoking and alcohol consumption [65,66]. Different studies have revealed a positive association between the consumption of certain foods like unprocessed red meat, high salted foods, carbonated beverages, fried foods, high-fat diet, and OSA as well as its severity.

On the other hand, interventional studies wherein lifestyle modifications in diet, exercise, and weight reduction have reported improvement in the severity of OSA (reduced AHI), mental health, reduced BMI, and daytime somnolence along with improvement in OSA-associated comorbidities [67–69].

The pathological link between OSA and cardiovascular - cerebrovascular disease

OSA and cardiovascular diseases:

Even though the prevalence of OSA is high, ranging from 40% to 80%, in patients with cardiovascular diseases (CVDs) including hypertension, heart failure, coronary artery disease, pulmonary hypertension, atrial fibrillation, and stroke, OSA is often underrecognized and undertreated in cardiovascular clinical practice [58,70,71]. The prevalence of OSA is notably high among individuals with hypertension, with approximately 30-50% of them found to have both conditions [72]. In particular, up to 80% of patients with resistant hypertension are reported to also have OSA [73]. Even in patients without underlying cardiac disorders, OSA is considered an independent risk factor for atrial fibrillation [74]. Severe OSA has been associated with an increased risk of sudden cardiac death [75]. Among patients with symptomatic heart failure, sleep-disordered breathing is prevalent in 40% to 60% of cases, with OSA accounting for about one-third of those cases [76]. The detrimental effects of OSA on heart failure involve various mechanisms, such as neurohormonal activation, increased oxidative stress and inflammation, fluctuations in preload and afterload due to intrathoracic pressure changes, and exacerbation of systemic hypertension. The repetitive cycles of oxygen deprivation and restoration in OSA can lead to oxidative stress and systemic inflammation, which contribute to the development of coronary atherosclerosis and acute myocardial infarction. OSA has also been linked to coronary artery calcification, unstable plaques, and increased vulnerability, resulting in a twofold higher risk of cardiovascular events or death [77]. Furthermore, OSA is strongly associated with pulmonary hypertension, with reported prevalence as high as 70% to 80% among individuals diagnosed with pulmonary hypertension through right-sided heart catheterization [78]. The main mechanism behind OSA-related pulmonary hypertension is believed to be the constriction of pulmonary arterioles induced by hypoxia, mediated by various signalling pathways involving nitric oxide, endothelin, angiopoietin-1, serotonin, and NADPH-oxidase [79].

Overall, the pathological mechanisms underlying OSA and various cardiovascular diseases [80,81] include hypoxia (decreased oxygen levels) and hypercapnia (increased carbon dioxide levels) during sleep; increased sympathetic nervous system activity that can contribute to oxidative stress, inflammation, and endothelial dysfunction; and sleep fragmentation that can contribute to metabolic dysregulation, insulin resistance, and inflammation. These OSA-induced pathological changes can contribute to the development of cardiovascular diseases, including coronary artery disease and heart failure [80,81].

OSA and Cerebrovascular diseases:

According to a recent meta-analysis [82], the prevalence of obstructive sleep apnoea (OSA) following a stroke is estimated to be 71% [83]. This high prevalence remains consistent across different stages of stroke, including acute, subacute, and chronic phases [82]. OSA not only serves as an independent risk factor for the initial occurrence of a stroke [84] but also increases the risk of stroke recurrence [85]. Additionally, OSA is associated with higher mortality rates and negatively impacts functional and cognitive outcomes among stroke patients. These findings highlight the significant role of OSA in post-stroke complications and outcomes [86].

Pathogenic correlation between sleep apnoea and gut dysbiosis

Sleep fragmentation (SF) and intermittent hypoxia (IH) observed in sleep-related breathing disorders disturb the balance of the gut ecological system resulting in GD [87]. Several lines of evidence report the causal role of sleep apnoea as one of the causative factors for the onset of GD [5,88] whilst others suggest it may be present as a co-morbid condition along with OSA [89]. GD resulting from sleep apnoea can be a causative factor in the generation of hypoxic conditions which may affect the population of oxygen-sensitive bacteria, and cause an increase in GI inflammation and gut permeability [90], as well as systemic inflammation brought on by

oxidative stress on IH exposure and disturbance in metabolic pathways (bile acid and fatty acid metabolism) [91].

Evidence from *in vitro* and *in vivo* (animal) studies

In a mouse model of sleep apnoea, chronic intermittent hypoxia (CIH) associated with an increase in the level of obligate anaerobic bacteria. Mucin-degrading bacteria *Prevotella* and *Desulfovibrio* were elevated along with different species from the *Lachnospiraceae* family that are associated with obesity [28]. Such an increase in bacterial abundance of these microbes has been linked to loss of gut epithelial barrier integrity, increased gut permeability, and elevated endotoxin levels leading to a dysbiotic gut. Likewise, adult guinea pigs effected by CIH demonstrated altered gut microbial richness with carotid body sensitization indicating the role of gut microbiota in the modulation of brainstem activity and autonomic homeostasis via the GBA [92]. Gut dysbiosis is associated with an increased abundance of enteric pathogens and decreased levels of SCFA-producing bacteria and gut metabolites such as indole derivatives, which are negatively correlated with tight junction protein levels in CIH and SF animal models of sleep apnoea [93,94].

In an *in vitro* study, E12 human colon cells showed improved epithelial barrier function on treatment with sodium butyrate (1-10mM concentration) [95]. Butyrate was found to facilitate tight junction proteins expression by inducing the activation of AMPK thereby maintaining the barrier integrity. Tight junction proteins expression (upregulation of OCLN and CLDN-1) in intestinal epithelial cells, inhibition of NLRP3 inflammasome activation, and downregulation of IL-1β are reported with SCFA treatment [96]. Chronic sleep fragmentation (CSF) and CIH were shown to decrease the abundance of clostridium species which is linked to the decrease in the indole derivatives of tryptophan such as 5-hydroxytryptamine and melatonin, the key

regulators of sleep cycles [97]. Tryptophan was found to increase intestinal epithelial barrier integrity and decreased inflammatory response mediated by the calcium-sensing receptor/Ras-related C3 botulinum toxin substrate 1/ phospholipase Cg1 signalling pathway in porcine intestinal epithelial cells [98]. Tryptophan-derived indole and its metabolites such as indole-3-acetamide, indole-3-pyruvate, indole-3-aldehyde, indole-3-acetaldehyde, indole-3-acetic acid, indole-3-propionic acid, and indole-3-lactic acid generated by microbes activate aryl hydrocarbon receptor, a ligand-activated transcription factor, that senses environmental stimuli and toxins, encourages immune cell maturation and decreases pathogen colonization [96]. Administration of indole-containing capsules elicited protective action against Dextran Sodium Sulfate (DSS)-induced epithelial damage in mice [93]. Such studies indicate the role of tryptophan and its metabolites in the promotion of sleep and maintenance of gut homeostasis. Thus, it is evident that an altered gut microbiome due to IH and SF may indirectly worsen sleep apnoea conditions by dysregulation of sleep and loss of epithelial gut barrier integrity [99,100].

Oxidative stress can be attributed to the imbalance in the oxidant and antioxidants in the body. It is a major implication of sleep apnoea and a prime pathological factor in the disruption of the gut microenvironment. Sleep apnoea-associated IH leads to dysregulation of Hypoxia Inducible factor (HIF) isomer, an upregulation of HIF-1, which results in activation of pro-oxidant enzyme genes and downregulation of transcription of antioxidant genes by HIF-2 [101] and leads to an increased level of ROS. An in vitro study in BBB model of endothelial cells HBEC-5i cells produced similar results with an increase in the Nrf2, HIF-1α, and ROS with a significant decrease in the tight junction proteins CLDN-5, VE-cadherin, and ZO-1 [102]. Such high levels of oxidative stress can disrupt the intestinal barrier leading to a leaky gut. However, HIF-1 plays a dual role in human physiology. Apart from its role in the promotion of ROS and development of sleep apnoea-associated comorbidities such as cognitive decline caused by disrupted NMDA signalling, insulin resistance, and hypertension. HIF-1 α is involved in the

maintenance of gut homeostasis by regulating mucin processing and the expression of genes involved in the formation of tight junction proteins. HIF-1 α also decreases inflammation via suppression of NF-κB via inhibition of TAK1 which is required for its downstream activation and by inducing differentiation of Regulatory T cells (Treg) which enhances the production of anti-inflammatory cytokines [103] (Table 2).

Evidence from Clinical studies

Clinical data in both adults and children have reported consistent information on the alterations in the gut microbiota species with/exposed to IH and SF. An increase in gut proteobacteria phylum, Gammaproteobacteria class, *Lactobacillae* family, *lachnospiraceae*, *Lactobacillus* and *Roseburia* genera were observed in the compromised gut of OSA patients. These results were in accordance with the report produced by Poroyko et al except a decrease in the abundance of the *lactobacillae* family was observed in CSF subjects [24,25,108]. Increased arousal was correlated with a reduction in the population of Actinobacteria in the gut of patients with OSA, which in turn was associated with a decrease in the production of GABA, a major neurotransmitter that promotes sleep. An increase in glutamate and a decrease in GABA levels have also been reported in the insular cortex of OSA patients [109]. An elevated level of glutamate is observed under chronic hypobaric-hypoxia conditions associated with augmented caspase-3 protein expression along with increased expression of NMDA and AMPA receptors which can lead to neuronal apoptosis and neuronal death via excitotoxicity, implicating the role of glutamate excitotoxicity in cognitive dysfunction [110]. This presents a new area of research to understand the role of gut dysbiosis in glutamate-mediated cognitive dysfunction via alteration in the glutamate-producing gut microbes and their metabolism.

The microbes related to inflammation such as Proteobacteria, *Clostridiaceae, Oscillospiraceae*, *Klebsiella*, and the barrier integrity disrupter strains - *Bacteroides fragilis*, *Faecalibacterium prausnitzii*, and *Desulfovibrionaceae* were found to be elevated in the gut of OSAS [111]. IH was found to signal via ROS-dependent activation of MAP Kinases leading to dysregulation of junction proteins in the gut resulting in increased intercellular gaps [112]. All such observations can be linked to alterations in intestinal barrier function and sleep disturbances (Table 3).

Gut microbial-derived metabolites and sleep apnoea

Short-chain fatty acids

Short-chain fatty acids **(**SCFAs) are gut-microbial derived metabolites, the major products of anaerobic fermentation of partially and non-digestible polysaccharides such as dietary fiber and resistant starch in the large intestine [113,114]. These metabolites are involved in maintaining gut harmony by promoting intestinal barrier integrity, mucus production, and anti-inflammatory activity through Treg regulation in the gut [115]. The four SCFAs produced via anaerobic fermentation of fibers are acetate, butyrate, propionate, and formate. However, acetate, propionate, and butyrate can also be produced from amino acid metabolism. Apart from the local effects of SCFAs in the gut such as the promotion of gut health via maintaining gut barrier integrity, and mucus production, they also act centrally via gut-brain communication [116].

Although the mechanistic pathways through which SCFAs act still need to be further studied, the current understanding is that they mainly act via two mechanisms; inhibition of histone deacetylases and activation of G-protein-coupled receptors with SCFAs communicating to the brain via the GBA directly through systemic circulation or indirectly via neurotransmitters,

hormones, and cytokines [117]. OSA-induced gut dysbiosis in a rat model was shown to be associated with a decrease in Treg cells which is responsible for suppressing inflammatory immune responses whilst an increase in the level of TH17 and TH1 cells are responsible for the production of pro-inflammatory mediators including IL-17 and Tumour Necrosis Factor-alpha (TNF- α). An interleukin (IL)-17 neutralizing antibody was found to decrease TNF- α and TH1 responses with an increase in Treg in the brain, cecum, and ileum, depicting a significant role of gut dysbiosis and proinflammatory responses in OSA [15]. Since SCFAs are known to limit local inflammation in the gut via their role in the development of colonic Treg cells and in preventing the infiltration of neutrophils by engaging with G protein-coupled receptor GPR43, a reduction in the number of major SCFA-producing gut microbial phyla such as firmicutes may be a contributing factor for the exaggerated inflammatory response in sleep apnoea patients [118]. Decreased levels of SCFAs have been implicated in the dysfunction of the gut mucosal barrier due to the activation of TLRs signalling by pathogen-associated molecular patterns (PAMPs) from bacteria viruses, and fungi (Figure-1). SCFAs play an immunoregulatory role by supplementing nutrition to intestinal epithelial cells, strengthening gut barrier function, inducing differentiation of intestinal epithelial goblet cells, and mucus secretion [119]. In turn, these effects reduce sleep apnoea-related sympathetic activation, protect the body against endotoxemia and microbial metabolite-mediated systemic inflammation, and encourage gut homeostasis.

Lipopolysaccharide

The bacterial LPS represents a component of the outer membrane of Gram-negative bacteria and is a strong potentiator of innate immunity in humans. In LPS, a primary immunostimulatory core is found in its carbohydrate-lipid component, or lipid A [120]. LPS

acts as both a neurotoxin and immunotoxin, enhances the accumulation of ROS and RNS accumulation, neuronal inflammation, and neurodegeneration via activation of microglia, TLR4/NF-κB, and the p38/c-Jun N-terminal kinase signalling pathways (Figure-1) [38]. The loss of gut barrier integrity allows the leakage of LPS from the gut to the systemic circulation and this may result in the endotoxin-induced systemic inflammation observed in sleep apnoea [121,122].

When the gut barrier is weakened, LPS enters the systemic circulation via TLR4 stimulation of dendritic cells which activates NF-κB and leads to the recruitment of neutrophils, macrophages, and infiltration of proinflammatory cytokines, with a downstream inflammatory response [94]. A clinical study in both adult and pediatric OSA patients has reported an elevated level of systemic LPS-binding protein (LBP), a surrogate marker of inflammation in OSA. A positive correlation was found between LBP and Body mass index (BMI) wherein systemic low-grade endotoxemia and systemic inflammation were more profound in higher BMI and AHI states [122,123]. This relationship between gut dysbiosis, elevated LPS level, and inflammation has also been found in other disease conditions such as venous thromboembolism and type 2 diabetic patients with chronic kidney disease [124,125]. Furthermore, C57BL/6J mice treated with the IH-LPS group showed more serious inflammation, oxidative stress terminal deoxynucleotidyl transferase dUTP nick ends labelled-positive cells than RA-LPS treated group, indicating the ill effect of IH in worsening acute lung injury [126]. Altered gut microbiota affects lipid homeostasis, increasing free fatty acids and LPS, causing activation of TLR receptor-associated proinflammatory factors such as IL-6, monocyte chemoattractant protein-1 (MCP-1), TNF-α, and the pro-apoptosis protein Bax (Figure-1) [97].

Trimethylamine N-oxide

TMAO is a gut metabolite derived from choline, L-carnitine, betaine, and other choline-rich compounds present in the diet. These precursors are converted by gut microbes and enzymes to TMA, which enters the liver via the portal circulation and are further metabolized by hepatic flavin monooxygenases to TMAO [127]. Elevated TMAO levels are linked with cardiovascular diseases, neurological and sleep disorders, metabolic diseases, and cancer [128–133]. Mice treated with TMAO showed an increased abundance of senescent cells in the hippocampal CA3 region, mitochondrial impairment, superoxide production, and reduction in the expression of synaptic plasticity-related-protein through the downregulation of the mTOR signalling pathway. Other changes included synaptic damage and neuronal senescence with resultant cognitive dysfunction [134]. Gut microbiome-derived TMAO metabolite levels were associated with proinflammatory cytokine levels, neuroinflammation, and markers of astrocyte activation, while an inverse relationship was found with performance on NIH Toolbox Cognition Battery tests of memory and fluid cognition [135]. Elevated ROS, NLRP3 inflammasome, mitochondrial dysfunction, and enhanced pyroptosis linked inflammatory death of oligodendrocytes with increased TMAO levels [136]. Thus, the pyroptosis of oligodendrocytes via the ROS/NLRP3 inflammasome signalling pathway is related to sleep apnoea-gut dysbiosis-induced cognitive impairment.

The association of diet and host taxonomy is a major factor in the bacterial gene coding enzymes carnitine oxygenase, choline-TMA lyase, and betaine reductase, which are responsible for TMA production [137]. Reports support the involvement of gut microbial composition in the modulation of TMAO levels such as the colonization of TMA producer *C. sporogenes* in gnotobiotic mice which was associated with a significant surge in serum TMAO and cecal levels of TMA [138]. Understanding factors responsible for TMAO production is important to modulate the TMAO level and prevent TMAO-rooted disorders.

A multi-ethnic cohort adiposity phenotype study revealed an association of TMAO with *Prevotella*, *Mitsuokella*, *Fusobacterium*, *Desulfovibrio*, and bacteria belonging to the families *Ruminococcaceae* and *Lachnospiraceae*, as well as the methanogen *Methanobrevibacter smithii* [139]. A recent study discovered the bacterium *Ihubacter massiliensis* to be a key microbe for TMA/TMAO production through an oral carnitine challenge test in a gnotobiotic mouse model [140]. These data suggest that TMAO levels are linked with the anaerobic or obligately anaerobic bacterial populations. Similar data were reported in the gut microbiome of OSA patients where there was an elevation in certain genera of *Ruminococcaceae* and *Lachnospiraceae* [141]. In other disease conditions such as preeclampsia, patients with gut dysbiosis exhibited increased fecal and plasma levels of LPS and increased plasma TMAO levels, indicating the direct connection between the gut microbiota and the level of the metabolites [142]. In contrast to prior studies, Hoyles et al showed that dietary TMAO at a physiologically relevant concentration has a favourable effect on modulating the integrity of the BBB and cognition in mice [143]. However, discrepancies concerning the possible impact of TMAO on human health still need to be addressed.

Neuroanatomical alterations and sleep apnoea

The hypothalamus which is the smart coordinator of the brain is responsible for various neurobehavioral-related functions including memory. Sleep apnoea is the most common cause of a drop in the blood oxygen level during sleep and is related to a higher oxygen desaturation index in OSA patients [144]. A study conducted on 83 OSA patients of age between 51-88 years showed that oxygen desaturation was related to reduced cortical thickness in the bilateral temporal lobes, which is a key factor in neurodegeneration [145]. Neuroimaging data has presented a decrease in hypothalamus volume on exposure to hypoxic conditions with a linear

relationship with memory dysfunction and information processing in sleep apnoea patients [146]. In addition to structural abnormalities, functional connectivity anomalies are also observed in the hypothalamus of individuals with sleep apnoea. These anomalies are primarily seen in the sensorimotor, frontoparietal, and semantic/default mode networks and are closely related to neurocognitive impairment [147]. Antibiotic-induced gut-microbial alterations in newborn mice elicited behavioural impairment due to a reduction in adult neurogenesis, long-term potentiation, and altered gene expression via overexpression of lipocalin-2 and leucine-rich α2-glycoprotein in the hippocampus. These changes were responsible for the inhibition of spine maturation and synaptic dysfunction and led to impaired memory. [148,149]. A four-year follow-up study in 1110 participants with OSA revealed age and sex-dependent association of OSA with white matter integrity and cognitive impairment on polysomnography, diffusion tensor imaging, and cognitive assessment. [150]. Focal reduction in gray matter volume in the left hippocampal region left posterior parietal cortex, and right superior frontal gyrus was reported in OSA patients. However, such findings were reversible on 3 months of treatment with continuous positive air pressure therapy (CPAP) along with improvement in executive functioning, mood, and memory [151]. Assessment of OSA patients revealed extensive alterations including changes in the axonal connections to the hippocampus, amygdala, and cerebral peduncle. Reduced axonal integrity in the ventral medial prefrontal cortex, and frontal cortex and alterations in axon linking major structures in the limbic system, pons, frontal, temporal, and parietal cortices, and projections to and from the cerebellum were reported by performing diffusion tensor imaging and fractional anisotropy [152]. Patients with severe OSA showed a reduction in grey matter volume in the right temporal lobe and left cerebellum [153]. Impairments in cognitive areas, mood, sleepiness and white matter abnormalities reported in OSA patients were almost completely reversed with 12 months of CPAP treatment followed by significant improvement in memory, attention and executive functioning, and white matter

integrity [154]. Obese patients with OSA showed an increase in total respiratory resistance and peripheral airway resistance with decreases in lung volume compared to obese patients without OSA, implying the effect of OSA in inducing structural and functional changes in the lung [155].

Based on these findings, the anatomical changes in the brain may affect the behavioural, learning, and memory functions based on the brain region affected. Therefore, in all such cases, timely treatment and therapeutic intervention may be necessary to prevent disease-associated anatomical changes that lead to cognitive decline.

Sleep apnoea-related gut dysbiosis and cognitive decline

The BBB regulates brain physiology by maintaining chemical and nutritional exchanges [156]. Preclinical [157] and clinical studies [158] have revealed that disruption in the BBB can lead to behavioural and memory deficits. Sleep apnoea and gut dysbiosis are the major causative factors for the loss of BBB and intestinal membrane integrity ultimately resulting in systemic and neuronal inflammation [159,160]. Epidemiological studies have linked OSA as an important risk factor for Alzheimer's disease and *in vivo* studies in animals have also revealed the association of CIH in the progression of pathological tau phosphorylation and may be an OSA-associated pathway in cognitive impairment [161,162]. Exposure to CIH caused an increase in phosphorylated tau seeding and spread in the brain and was found to exacerbate synaptic plasticity deficits in P301S mice [161]. BBB disruption is one of the hallmarks of neurodegenerative disease and is responsible for cognitive impairment. The role of the gut microbiome in the maintenance of the BBB was demonstrated in germ-free mice with a reduction in the expression of tight junction proteins such as OCLN and CLDN-5 resulting in increased BBB permeability, while exposure of the germ-free mice to pathogen-free bacteria

upregulated tight junction protein expression and decreased BBB permeability, indicating the role of gut microbiota in the modulation of BBB permeability (Figure-1) [39].

In an *in vitro* study in the HBEC-5i cell line, Voirin et al showed that BBB leakage was caused by OSA. Wherein sera of OSA patients transferred to HBEC-5i cells demonstrated increased permeability and a decrease in tight junction protein expression, indicating BBB leakage [163]. In addition to sleep apnoea, gut dysbiosis also contributes to oxidative stress via hyperexpression of nitric oxide, inhibition of cyclooxygenase (COX) activity, and decreased O_2 consumption by mitochondria as a negative result of hydrogen sulfide, increased proinflammatory gene expression, and a decrease in SCFA-producing bacteria [164,165]. Oxidative stress imparts detrimental effects on the brain's microvascular endothelial cells (BMVECs), astrocytes, pericytes, and tight junctions in the brain. It causes BBB disruption by lysosomal dysfunction, pericytes, astrocytes, and BBB leakage [166]. Gut dysbiosis results in the generation of ROS which further activates the Nuclear factor kappa B (NF-kB) pathway leading to increased inflammation and neuronal cell death (Figure-1) [167].

Numerous data have presented the negative impact of lack of proper sleep on the decline in cognition [168–170]. This may be interrelated with the decline in major GABA-producing bacteria *Bifidobacterium* in the gut of OSA adolescent patients [19]. Growing evidence has suggested that serotonin apart from its action on mood, sleep, digestion, and emotion, also plays a part in boosting the learning rate which may be achieved through the hippocampal 5HT1A receptor-mediated cAMP/PKA/CREB signalling pathway [171–173]. A decline in the tryptophan decarboxylase-producing firmicutes phylum, which produces the neurotransmitters like serotonin and melatonin, can be correlated with a decline in cognitive ability [16,109,173], and may also play a key role in regulating tauopathy-related cognitive decline.

Sleep apnoea, gut dysbiosis, and neuroinflammation

The immune cells act as an interface in the GBA to sense, mitigate and respond to any alterations in the physiological state. Gut microbiota regulates the homeostasis between immune tolerance and host defence. Disruption of the normal gut microbial balance presents negative effects on the brain in addition to its commensal region [174,175]. Loss of gut barrier integrity leads to infiltration of pathobionts and toxic metabolites causing GBA dysregulation and inflammation [176]. Microglia, a resident innate cell in the brain, functions by generating a local immune response to injury or infection thereby supporting a healthy brain and spinal cord [177]. It also plays a crucial role in neuronal plasticity, learning, and memory [178] which may be affected by the CIH experienced by patients with sleep apnoea. Gut bacterial synthesized products such as outer membrane vesicles (OMVs) were found to cause cognitive impairment by promoting astrocyte and microglial activation, increasing BBB permeability, and activating the glycogen synthase kinase 3β pathway that leads to tau phosphorylation [179].

Adult rats subjected to CIH showed a region-based difference in the microglial inflammatory gene expression of iNOS, IL-6, IL-1β, TNFα, COX-2, and innate immune receptor TLR4 expression in the brain. Exposure to IH resulted in differential microglial activation in a different region of CNS leading to neuroinflammation (figure -1) [180,181]. The NLRP3 inflammasome pathway is also associated with microglial activation. It mediates caspase-1 activation and responds to microbial infection and cellular damage by the secretion of proinflammatory cytokines IL-1β/IL-18 [182]. In NLRP3 knockout mice, there is a reported decrease in microglial activation on exposure to CIH, which promotes parkin-dependent mitophagy which protects against neuroinflammation [183]. Proinflammatory cytokines TNF-α and IL-6 are highly expressed in OSA. These cytokines result in the activation of NF-κB which has been linked as a prime modulator in the inflammatory pathway in sleep apnoea [184,185].

Treatments used in sleep apnoea and its co-morbid conditions

Sleep apnoea and nutrition

A diet rich in red/processed meat with a low whole grain and diet quality was found to aggravate OSA, along with a marked decrease in slow-wave sleep (N3 sleep) quality, correlating the disease severity with dietary intake [186]. In an epidemiological study of Cypriot patients with OSA, a higher intake of macronutrients and antioxidant vitamins was found to be positively correlated with disease severity [187]. Healthy diets rich in fruits and low in processed foods [188] and an anti-inflammatory diet were associated with lower OSA risk as well as disease severity [189]. Several studies have linked diet as an independent factor in the development of insulin resistance in sleep apnoea [190–192]. A meta-analysis of randomized controlled trials of probiotics on glycaemic control has revealed probiotics' modest role in improving insulin resistance [193,194].

Dietary changes to restore gut dysbiosis and improve sleep

Consuming a diet rich in fiber, particularly prebiotic fibers found in fruits, vegetables, whole grains, and legumes, promotes the growth of beneficial bacteria or anti-inflammatory taxa in the gut [195,196]. These beneficial bacteria help produce SCFAs, which help to establish gut eubiosis. Foods rich in omega-3 fatty acids (e.g., fatty fish, walnuts), antioxidants (e.g., berries, leafy greens), and spices (e.g., turmeric, ginger) may help reduce inflammation in the body, including the airway tissues affected by OSA [197–199]. By identifying and avoiding trigger foods (commonly including spicy foods, high-fat foods, caffeine, alcohol, and carbonated beverages), individuals may experience fewer OSA-related symptoms during sleep.

Conventionally, a healthy diet and adequate nutrition help establish and maintain a healthy gut ecosystem. Different studies have revealed that sleep is affected by the nutritional status of the body. Lack of carotene, selenium, dodecanoic acid, calcium, and hexadecanoic acid was

associated with difficulty in falling asleep [200]. Diets rich in tryptophan, melatonin, cherries, and zinc supplements may play a beneficial role in improving sleep quality [201]. A randomized, double-blinded, placebo-controlled trial in a healthy population has shown that consumption of zinc-rich food is linked with improved onset and latency of sleep [202]. Various other dietary nutrients such as carbohydrates, fatty acids (omega 3 polyunsaturated fatty acid), vitamin B6/12, vitamin C, vitamin D, and amino acids such as tryptophan, tyrosine, glutamine, and GABA have proven to be beneficial in improving sleep quality and promoting sleep [203–205]. These data indicate that nutritional interventions can be used as a potential strategy in OSA treatment and its management.

Conventional treatment for OSA

The most popular therapeutic strategy for preventing upper airway collapse in sleep apnoea currently is CPAP therapy [206,207]. Mandibular advancement devices (MAD) are another option for treating OSA but can cause temporomandibular joint discomfort [208]. The use of CPAP and MAD in the treatment of OSA is not directly linked to changes in the gut microbiome. However, no research data investigating the direct influence of CPAP or MAD on the gut microbiome has been established. Nonetheless, maintaining a healthy gut microbiota through dietary choices, can have broader benefits for overall health and potentially complement the effectiveness of CPAP or MAD therapy. Therapies that target gut dysbiosis are potential novel therapies that can be adjuvant to OSA standard treatment and can potentially translate into benefits regarding the morbidities associated with OSA.

Special nutritional interventions: probiotics and prebiotics

Probiotics and prebiotics are special nutritional supplements that help restore and maintain the balance of the gut microbiome [209]. Probiotics are supplements containing living microorganisms that support and build up a healthy gut population while prebiotics supports

the growth of commensals [210]. Probiotics elicit beneficial properties via various mechanisms by modulating immune response, decreasing inflammation, increasing antibody response, and the production of gut metabolites such as SCFAs. Probiotics also prevent the colonization of pathogenic bacteria by competing for nutrients, secretion of antimicrobial compounds such as bacteriocin, decreasing luminal pH, and production of microbial enzymes such as β-galactosidase and bile salt hydrolase to improve digestion of lactose in lactose intolerance. Probiotics also promote increased expression of tight junction proteins to maintain gut barrier function [211]. Deviation from the normal F/B ratio is considered a hallmark of gut dysbiosis. The acute intervention of probiotics supplements such as *Lactobacillus* species: *acidophilus*, *rhamnosus*, *plantarum*, and *Bifidobacterium* species: *lactis*, and *longum* improved the proliferation of goblet cells and intestinal crypts cells [180–182] as well as protected the intestinal epithelium and restored gut microbiota diversity in a mouse model of radiation-induced intestinal injury [212]. Administration of dietary prebiotics, lactoferrin, and milk fat globule membrane in rats was found to enhance rapid eye movement sleep and also attenuate the stress-induced decrease in the alpha gut microbial diversity [213]. The gut metabolite butyrate has emerged as a source of sleep-promoting signals. Oral and intraportal administration of the butyrate prodrug tributyrin in mice showed a significant increase in non-rapid eye movement sleep. However, similar results were not observed in the case of systemic and subcutaneous administration indicating the role of the hepatoportal system in the role of sleep modulation via intestinal microbiota [214]. Synbiotics can promote the synthesis of butyrate which may help in the promotion of sleep [215].

The OSA-associated comorbidities such as vascular dysfunction due to altered gut microbiota as a result of CIH were mitigated by concurrent administration of probiotics in a murine model of sleep apnoea [105]. Similarly, another study conducted on OSA and hypertension in an animal model found a low level of cecal acetate correlated with the OSA in the rat model of

OSA. Such observations were reversed by the administration of probiotic *C. butyricum* and prebiotic Hylon by reducing OSA-induced dysbiosis, epithelial goblet cells loss, mucus barrier thinning, and activation of brain microglia leading to prevention of OSA-induced gut inflammation and hypertension [106]. *Lactobacillus rhamnose* GG strain showed a reduction in the TMAO level and modulated the Th1/Th2 cytokine imbalance, regulating systemic and immunological homeostasis in high salt diets and CIH-exposed rats. Administration of the prebiotic fructo- and galacto-oligosaccharides, modulated the gut microbiota and SCFAs but was not able to ameliorate cardiorespiratory dysfunction in CIH-exposed rats [216]. Together, the data suggest that the restoration of a healthy microbial population via dietary intervention with pre- and probiotics and synbiotics presents a potential therapeutic strategy to address gut dysbiosis associated with a different array of sleep disorders.

The current narrative review has summarised the clinical and experimental studies related to gut dysbiosis and sleep-related breathing disorders and associated cognitive dysfunction. Studies on conventional and germ-free mice as well as clinical studies in patients with OSA were examined in this review. However, there is a need for systematic studies and meta-analyses of SA-induced gut dysbiosis.

Conclusion

An emerging body of research suggests a potential link between sleep apnoea and GD, highlighting the intricate relationship between respiratory health and the gut microbiome. Sleep apnoea, affecting more than one billion of the world's population, poses a huge socioeconomic burden, mitigating the urgency of early diagnosis and development of effective therapeutic approaches. Preclinical and clinical data have evidenced the linear relationship between sleep apnoea and GD. Several correlational studies in human and animal models revealed the main

pathophysiological mechanisms underlying sleep apnoea-induced GD. These include disruption of gut barrier- and BBB integrity, a reduction in the abundance of anti-inflammatory microbial taxa (SCFA-producing bacteria), and an increase of proinflammatory microbial taxa (alterations in B/F ratio), and elevated levels of enteric pathogens, and circulating TMAO and endotoxin LPS. Such changes lead to the activation of the immunogenic response and the release of gut-mediated inflammatory mediators via NRLP3 and TLR4/NF-kB, which results in neuroinflammation and neuronal death. Additionally, lifestyle factors such as obesity and poor diet, commonly associated with sleep apnoea, can further exacerbate gut dysbiosis, leading to a vicious cycle of reciprocal interactions between sleep apnoea and the gut microbiome.

Targeted interventions aimed at establishing eubiosis, such as probiotics, prebiotics, or fecal microbiota transplantation, may hold promise as adjunctive therapies in the management of sleep apnoea in clinical settings. Lifestyle interventions such as an increase in physical activity promoting weight loss and encouraging healthy dietary choices should be emphasized in sleep apnoea subjects. Supplementation of prebiotics and probiotics has been shown to establish eubiosis and control vascular dysfunction and glycaemic control by reducing the insulin resistance conferred by sleep apnoea. Furthermore, addressing sleep apnoea through appropriate treatment modalities, such as CPAP therapy or oral appliances, may not only alleviate respiratory symptoms but also potentially restore gut microbial balance. A multidisciplinary and coordinated treatment approach involving sleep medicine specialists, gastroenterologists, and registered dietitians can significantly improve clinical outcomes.

Although the results of correlational studies investigating gut dysbiosis and OSA have shown discrepancies, these may be attributed to factors such as heterogeneity in study populations (including variations in age, body mass index, and comorbidities); methodological variations (including differences in sampling methods, DNA extraction techniques, sequencing platforms,

and bioinformatics pipelines), confounding factors (including dietary factors and lifestyle such as physical activity, smoking, and medication use), and the complex nature of the gut microbiome. OSA is a complex disorder with multifaceted etiology, different phenotypes and severity levels, and the inclusion of participants with different OSA characteristics across studies may contribute to the observed discrepancies. Longitudinal studies with larger sample sizes, more comprehensive assessments, and consideration of confounding factors are needed to better evaluate the dynamic interplay between OSA and GD in humans to produce more consistent and reliable findings in future research.

Acknowledgment

The authors thank their respective institutions for providing the required infrastructure to produce this manuscript.

Conflict of Interest

The authors have read the journal's policy and all authors declare that they have no proprietary, financial, professional, or any other personal interests of any nature or kind in any product or services and/or company that could be construed or considered to be a potential conflict of interests that might have influenced the views expressed in this paper.

Author Contributions

SBC, AMM, AGR, SRP, and TMM conceptualization, manuscript editing, and compilation; TD, literature collection, original manuscript drafting, and illustrations; TAH, PD, MB, and MAB assisted in manuscript drafting and image editing. All authors approved the final version of the paper that was submitted for publication.

Funding details

No funding was received for conducting this study.

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Table 1: Gut microbiota in normal vs OSA patients

Bacterial phyla	Normal gut microbial population - genus level	Microbial population elevated in OSA/IH exposure/SF	Reference
Actinobacteria	*Corynebacterium, Bifidobacterium, atopobium*	↓Actinobacteria, ↓*Bifidobacteriaceae*	[24] [25]
Firmicutes	*Lactobacillus, Bacillus, Clostridium, Dialister, Enterococcus, Ruminicoccus, Faecelibacterium, Roseburia, Staphylococcus*	↑*Megamonas*, *Lactobacillus*, *Megasphaera*, *Coprococcus*, *Ruminococcus*_1, *Lachnospira*, *Lachnoclostridium*, and *Lachnospira* ↑*Mogibacteriaceae*, *Lachnospiraceae*, and *Clostridiaceae* families ↓*Faecalibacterium*, *Ruminococcaceae*, *Dialister* and *Oscillibacter*, Clostridium_XlVa, *Ruminococcus_gnavus*, *Eubacterium coprostanoligenes*, *Blautia*, *Roseburia*	[5] [26] [27] [28] [29] [24] [30]

Bacteriodetes	*Sphingobacterium, Bacteriotides, Tanerella, Parabacteriotides, Alistipes, prevotella*	↑*Prevotella* and *Muribacululaceae* ↑ Increased F/B ratio ↓*Bacteriodes, Alistipes, Odoribacter, Turicibacter, Peptococcaceae and Erysipelotrichaceae*	[26] [27] [28] [24] [30]
Proteobacteria	*Escherichia, Shigella, Desulfovirbo, Biliphila,Hhelicobacter*	↑Proteobacteria, Gammaproteobacteria and *Enterobacteriaceae family* ↑Putative pathobionts- *Raoultella spp., Methylobacterium*	[5]
Fusobacteria	*Fusobacterium*	↓*Fusobacterium*	[27]
Verrucomicrobia	*Akkermansia*	↓ *Akkermansia muciniphila*	[30]

Table 2: Preclinical evidences

Model	OSA model	Methodology	Relative microbial/metabolite data	Observation	References
Pathogen-free C57BL/6	IH exposure for 6 weeks: 40 sec 21% O2followed by 20 sec 5% O2 -6 h/day	16S rRNA pyrosequencing, Bioinformatic analysis, Endotoxin assay	↓ Bacteroidetes and ↑Firmicutes and *Deferribacteres* IH group showed positive correlations between the abundance of *Mucispirillum* and *Desulfovibrio* and a negative correlation between the abundance of *Lactobacillus* and *Ruminococcus*	Following six weeks of normoxic recovery mimicking CPAP therapy showed normalizing the gut microbiota.	[104]

C57Bl/6J mice naïve mice-FMT	IH 6 weeks 21% FIO_2 and 6% FIO_2, 20 cycles/h for 12 h/day	16s rRNA sequencing, Sleep recordings using piezoelectric approaches	FMT-IH group showed: ↑ the abundance of *Lachnospiraceae* from the phylum Firmicutes, *Prevotella*, and *Muribacululaceae* from the phylum Bacteroidetes, and ↓ the abundance of *Alistipes* from the phylum Bacteroidetes when compared to FMT-RA	Change in the gut microbial flora induced by IH exposures can produce sleep disturbances in the absence of concurrent IH. This suggests that IH-induced gut dysbiosis may play role in mediating sleep disturbance.	[26]
C57BL/6J naïve mice- FMT	IH 6 week 21% FIO2and 6% FIO2, 20 cycles	16S rRNA amplicon sequencing	IH-FMT group showed: ↑ the abundance of *Lachnospiraceae* and	IH-FMT mice exhibited a typical cardiovascular disturbance of sleep apnea, and impairments in aortic and coronary artery function with	[105]

	h−1 for 12 h day−1	Arterial blood pressure (aBP) and coronary artery and aorta function testing	*Ruminococcaceae* from the phylum Firmicutes and *Prevotellaceae* and Muribaculaceae from the phylum Bacteroidetes, ↑the abundance of *Lactococcus* and *Bifidobacterium* on treatment with VSL3 (probiotics)	increased aBP and TMAO levels, which were reversed by probiotic administration.	
Eight weeks old male Long Evans rats	Implantation of endotracheal obstruction device	16S rRNA analysis	HFD-OSA + Prebiotic: ↑*Bifidobacterium*, ↑*Ruminococcus*, *Blautia*, and *Colinsella*	C.butyricum and Hylon administration restored the cecum acetate concentration in the HFD-OSA treated group and decreased OSA-induced dysbiosis, epithelial	[106]

			HFD-OSA + Probiotic: ↑*Clostridiales*	goblet cells loss, mucus barrier thinning, and activation of brain microglia ($p<0.05$ for each).	
C57BL/6J mice	IH exposure: 10% O_2 for 240s, followed by 21% O_2 for 120 s along with High-Fat Diet	16S rRNA gene amplicon sequencing KEGG-based PICRUSt Metagenome functions analyses	CIH intervention inhibited Bacteroidetes and *Faecalibacterium prausnitzii* CIH alone significantly ↑ abundances of *Lactobacillus spp*. and *Alistipes* spp., *and* ↓ abundances of *Feacalibaculum rodentium* and *Clostridium spp*	Following HFD supplementation, CSF exhibited a drop in Bacteroidetes and an increase in Proteobacteria, resulting in an intestinal microbiota that was pro-inflammatory. The function and composition of the fecal microbiota, as well as host metabolism, are negatively impacted by CIH and CSF; these findings offer fresh information	[97]

			↑ Actinobacteria and *Desulfovibrio*, Causing proinflammatory intestinal dysbiosis CIH+HFD intervention: ↓ *Eisenbergiella massiliensis, Fournierella massiliensis, Intestinimonas spp.*, and *A. muciniphila*.	about the individual and combined effects of CSF, HFD, and CIH on lipid disorders.	
Ldlr−/− and *ApoE*−/− mouse models	IHH -mice in short periods (~4 min) ↓ in O_2 (from 21% to 8%)	16S rRNA sequencing Metabolome	Unclassified strains from the families *Ruminococcaceae, Mogibacteraceae,*	The bacterial strain altered in IHC has been associated with metabolic and cardiovascular comorbidities as well as inflammatory conditions	[107]

	and ↑ in CO_2 (from ~0.5% to 8%) separated by alternating periods (~4 min) of normoxia ($[O_2]$ = 21%) and normocapnia ($[CO_2]$ = ~0.5%) with 1- to 2-min ramp intervals for10 h per day during the light cycle.	Untargeted liquid chromatography-tandem mass spectroscopy LC-MS/MS	*Lachnospiraceae*, and *Clostridiaceae* depicted IHH-associated alterations.	which indicates a common mechanistic pathway in OSA-associated cardiovascular conditions.	
10-week-old *Apoe*$^{-/-}$ mice	1 week of 4 min cycle of IH	16S rRNA gene amplicon	Verrucomicrobia, Firmicutes, and	A significant change in the diurnal dynamics of metabolome and fecal	[30]

	Exposure reduction of O_2 from 21% to 8% and elevation of CO_2 from 0.5% to 8%, followed by alternating periods of 4 min of normoxia and normocapnia with 1- to 2-min ramp intervals 10 h per day during the light cycle.	sequencing and untargeted liquid chromatography-mass spectrometry (LC-MS)	Bacteroidetes were also affected by the IHC conditions. ↓ *Akkermansia muciniphila* IHC conditions associated with the cooccurrence of *Ruminococcaceae* and tauro-beta-muricholic acid (TbMCA) Control conditions associated with the co-occurrence of *Coriobacteriaceae* and	microbiome was observed in IHC with an increase in the proinflammatory and proatherogenic bacterial strain and their metabolite.	

			chenodeoxycholic acid (CDCA)		

Table 3: Clinical Evidences

Sample size	Study design	Methodology	Relative abundance of microbial data in OSA	Observation	References
16 children were grouped into OSAS and healthy cohorts.	Pilot study	16S rRNA sequencing, Nocturnal pulse oximetry, polysomnography	↑Proteobacteria, *Clostridiaceae*, *Oscillospiraceae*, *Klebsiella*, *Desulfovibrionaceae*, *Coriobacteriaceae* and *Erysipelotrichaceae* ↓*Faecalibacterium*, *F. prausnitzii* (inhibits NFkB pathway), *Actinobacteria*	OSAS children showed an increase in gut inflammation and gut barrier disrupter-related strains while a reduced abundance of healthy microbial strains may be due to exposure to IH in children.	[111]

			↑ *Bifidobacterium* spp (in particular *B. reuteri, B. aerophilum*, and *B. sanguini*), *Butyrricoccus faecihominis, Eubacterium coprostagnoligenes, Paraprevotella clara, Veillonella parvula Bacteroides fragilis*		
93 patients with OSAHS n=40 (5 < AHI ≤ 15),	---------	16S rRNA pyrosequencing, Polysomnography and	↓ Fecal counts of *Megasphaera, Dialister, Faecalibacterium, Oscillibacter*, and *Ruminococcaceae*	Homocysteine levels are altered in OSAHS patients. The findings raise the possibility that changes in the gut microbiota may also play a part in the	[5]

n=23 (15 < AHI ≤ 30) and n=20 controls (AHI ≤ 5)		bioinformatics analysis	↑↑ *Faecalibacterium*, *Howardella*, and *Oscillibacter genera* in controls) ↑ Proinflammatory enteric pathogens Gammaproteobacteria class and *Enterobacteriaceae* family ↑ R*aoultella spp.*, *Methylobacteriu*m-putative pathobionts	pathophysiology of metabolic comorbidities in OSAHS patients.	

43 children (n = 27 snorers and n = 16 controls) Inclusion criterion: Snorers- children snoring ≥ 3/ week. Controls- children snoring ≤ 3/ week	Prospective, Observational CHILD-SLEEP birth cohort study,	16S rRNA gene amplicon sequencing Bioinformatics analysis	↑ Proteobacteria phylum, *Erysipelotrichaceae*, and *Enterobacteriaceae* families ↑ F/B ratio observed in snorers compared to controls.	In children with sleep-disordered breathing (SDB), the early change of the gut microbiota or restoring the gut microbiota to a normal level may appear as a potential therapeutic target.	[8]
52 hypertensive patients:	Observational, Case-controlled study	16s rRNA sequencing	F/B ratio > in group C than in groups A and B.	Hypertensive-OSA patients were associated with worse gut dysbiosis. Increased inflammation-associated	[27]

Group A (cotrol-[AHI] < 5, n = 15), Group B 5 < AHI < 20, n = 17), and Group C (AHI > 20, n = 20)			In OSA, ↓ The abundance of *Bacteroides* and *Prevotella* (SCFA-producing bacteria) ↑ Inflammation-related bacteria such as *lactobacillus*	bacterial strain and decreased SCFA-producing bacteria may result in enhanced inflammation and increase the risk of comorbidities.	
19 OSA patients and 20 non-OSA controls	Cross-sectional study	16S rRNA Cardiorespiratory polygraphy (n = 13) and polysomnography	OSA patients elicited: ↑ *Lactobacillae*, *Roseburia* Proteobacteria, including Gammaproteobacteria ↓ Actinobacteria phylum	The microbial changes presented such as the abundance of Proteobacteria, Gammaproteobacteria, *Lactobacillus*, and *Lactobacillae* (all $p < 0.05$) were correlated with disease severity and dyslipidemia, while the abundance of Proteobacteria and	[25]

				Gammaproteobacteria was related to hypertension and cardiovascular disease (all $p < 0.05$)	
3,570 individuals aged 50–64 from the Swedish CardioPulmonary bioImage Study (SCAPIS)	Cross-sectional study	Deep shotgun metagenomics	OSA patients showed a positive correlation with *Collinsela* aerofacines, *Blautia* obeum, *C. comes*, *R. gnavus*, and *M. glycyrrhizinilyticus* of which *Collinsela aerofacines* was associated with increased systolic blood pressure.	This is the largest study to date that has depicted that OSA-related hypoxia is associated with specific microbiota features. The OSA-related hypoxia parameters total sleep time (T90) and oxygen desaturation index (ODI), were independently associated with 59 and 97 gut microbiota species.	[108]

Figure Legends

Figure 1. The pathogenic role of sleep apnoea in cerebral inflammation and gut dysbiosis

A) Chronic intermittent hypoxia (CIH) and Sleep fragmentation (SF) induced variations in the gut microbial flora and the metabolites involved in the Gut-brain-axis (GBA) communication via four primary pathways: Vagus nerve; Hypothalamic pituitary adrenal (HPA) axis; Immunological pathway; Neurotransmitters and Neuropeptides. Sleep apnoea results in a reduction in sleep and cognition promoting neurotransmitter levels of Gamma-aminobutyric acid (GABA) and serotonin, and causes an imbalance of the normal gut ecosystem, ultimately leading to gut dysbiosis and neuronal inflammation in the brain.

B) Loss of Blood Brain Barrier (BBB) integrity as a result of a decrease in the tight junction protein levels of Occludin (OCLN) and Claudin (CLDN) leads to the passage of neurotoxin, immunotoxin, and bacterial metabolites such as Lipopolysaccharide (LPS), Outer membrane vesicles (OMVs), NOD-like Receptor Proteins-3 (NLRP3), and associated Damage Associated Molecular Patterns (DAMPs) which activates innate immune receptors on microglia and astrocytes via pattern recognition receptors such as Toll-Like Receptor 4 (TLR4) on immune cells, leading to the release of proinflammatory mediators such as Interleukins IL-6 and IL-1β, Tumor necrosis Factor (TNF-α), increased Reactive Oxygen Species (ROS) and chemokines, resulting in neuroinflammation and neurodegeneration.

C) Microbial imbalance as a result of gut dysbiosis leads to a decrease in tight junction proteins OCLN, CLDN-1, and goblet cell expression in the gut epithelial cells. Low levels of Short-Chain Fatty Acids (SCFAs) in a dysbiotic gut contributes to the reduction in tight junction proteins and Regulatory T cells (Treg) expression and in

parallel, the level of anti-inflammatory cytokines IL-10 and Transforming Growth Factor (TGF-β). The translocation of LPS, Trimethylamine N-oxide (TMAO), pathobionts, and other gut metabolites via leaky gut results in activation of the pattern recognition receptor TLR4 on binding with Pathogen associated molecular patterns (PAMPs), which activates intestinal immune cells which then causes the release of cytokines IL-1,6,8, 17, Nuclear factor kappa B (NF-kB), and the downstream inflammatory pathway leading to local gut inflammation.