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Review Article

Relationship between sleep disorders and gut dysbiosis: what affects what?

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ABSTRACT

Sleep plays a fundamental role in maintaining good psycho-physical health, it can influence hormone levels, mood, and weight. Recent studies, focused on the interconnection between intestinal microbiome and sleep disorders, have shown the growing importance of a healthy and balanced intestinal microbiome for the hosts health. Normally, gut microbiota and his host are linked by mutualistic relationship, that in some conditions, can be compromised by shifts in microbiota's composition, called dysbiosis. Both sleep problems and dysbiosis of the gut microbiome can lead to metabolic disorders and, in this review, we will explore what is present in literature on the link between sleep pathologies and intestinal dysbiosis.

1. Introduction

Sleep disorders encompass a wide spectrum of diseases with significant impact on individual health and on society health costs [1]. These disorders, including, sleep-disordered breathing, sleep deprivation as insomnia, narcolepsy, circadian rhythm disorders, and restless legs syndrome are common in modern society [2]. It is estimated that 40 million of Americans suffer of chronic sleep disorders and these cause around 40,000 cardiovascular deaths annually [3]. Paediatric sleep disorders are common, affecting approximately 25%–40% of children and adolescents [4]. Poor sleep quality and/or quantity in children are associated with consequences on host's health, including academic problems, behavioural problems, developmental and social difficulties, weight abnormalities. These problems can impact also family dynamics and parental or sibling sleep [5]. Worldwide, around 1 billion adults suffer from sleep-disordered breathing (SBD), especially of obstructive sleep apnoea (OSA), and approximately 425 million people with moderate to severe OSA need treatment [6]. Sleep disorders can affect life quality and alter the normal physiological activities of the body leading to metabolic imbalance and increasing the risk of diabetes, hypertension, obesity, depression and cardiovascular disease as heart attack and stroke [2]. Recent studies show a close interconnection between circadian rhythms, sleep disturbances, particularly sleep disordered breathing and comorbidities [7]. The comorbidities more often associated with sleep disorders are primarily mediated via intermittent hypoxia and sleep fragmentation [8,9]. The intermittent hypoxia induces systemic inflammation and free radical production and this pathogenetic aspect could be related with alterations and modifications of gut microbiota. The human gut microbiota is the best studied host-associated microbial ecosystem, it has important immunological, metabolic, and protective roles in human health and lifespan. The human intestine is the home of an abundant and diverse microbial community, mainly composed of bacteria, fungi, and viruses communicating with each other in a harmonic and dynamic equilibrium [10]. The intestinal microbiota can be considered a real organ, since it controls the host digestive system, helping nutrients and drugs metabolism. Like a real organ, the microbiota can replicate and repair itself in response to external stimuli [11]. It can also provide substrates for hormone production, supplying and regulating multiple compounds that reach the circulation and influence the function of distal organs, such as neurotransmitters,

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vitamins, and other nutrients that, indirectly and through unknown mechanisms, can exercise control over the hypothalamic–pituitary–adrenal axis [12]. If for some intestinal disorders, as chronic inflammatory bowel disease, the contribution of the microbiota in pathogenesis has been demonstrated [13],for other pathologies involving distal organs, this contribution is less evident and more difficult to demonstrate. Environmental, psychological, and physical stressors, that promote sleep disorders, can negatively impact on gut microbiota composition and function, affecting host health status. The focus of the present review is to analyse the current literature data to better understand the relationship between sleep disorders and gut microbiota composition.

2. Methods

PubMed/MEDLINE and ScienceDirect database search were performed using the following search terms individually or in combinations: microbiota, sleep disorders, apnea, insomnia, intermittent hypoxia, sleep fragmentation, excessive daytime sleepiness, children. Case report ($\leq$3 patients), letters to the editor, papers not in the English language were excluded. The authors screened the retrieved literature and 16 articles (case control studies) that were considered most relevant for this review were summarize and included in the list of references.

3. Gut microbiota

The human intestinal microbiota is composed by Bacteria, Viruses, Fungi, Protozoa and Archaea that live in symbiosis with the host; among these, bacteria are the most represented [14]. The gut microbial colonization starts during the prenatal life [15]. The microbiota organ begins forming during the gestational period with microorganisms belonging to maternal microbiota and, after birth, it enriches itself acquiring new bacterial species from food, environment, and interactions with other people. During the gestational phase, the composition of the gut microbiota depends on maternal microbiota, lifestyle and healthy status [16]. Instead, after birth several factors influence microbiota structure: vaginal or C-section deliver [17], breastfeeding or formula, family environment, geographical location and genetical factors [16]. Since infancy, microbiota composition is not stable but changes, and enriches in biodiversity over time [18]. Its development continues during childhood, especially in the first years of life, and at the age of 3 years old gut microbiota stabilizes, becoming like the adult one in term of composition and diversity [18]. Anyway, environment and external factors, such as the intake of drugs, lifestyle and potential diseases can still perturb microbiota influencing its composition [19]. In a healthy subject gut microbiota is mainly represented for 90% the two phyla Firmicutes and Bacteroidetes, and the remaining 10% is composed by phyla Actinobacteria, Proteobacteria, Fusobacteria, and Verrucomicrobia. Generally, an ecosystem is considered healthy when its biodiversity is high and none of its members take over the others [20]. Gut microbiota performs several important functions, such as play the role of protective barrier versus pathogenic colonization and pathobionts overgrowth, through competition for space and nutrients, production of antibacterial substances and by maintaining the intestinal epithelium integrity [21]. Furthermore, gut microbiota plays important role in food digestion, xenobiotic metabolism, nutrients absorption and vitamins production. The intestinal microbiota can ferment dietary fibers, otherwise indigestible for humans, leading to nutrients production, such as short chain fatty acids (SCFAs), (butyrate, propionate and acetate), which represent an important energy source for colon epithelium cells [22,23]. Moreover, gut microbiota plays an important role in regulating innate and adaptive immunological processes and in modulating intestinal barrier integrity [24]. Several bacterial metabolites play a protective role against pathogens and a potential anti-inflammatory activity. These metabolites are locally released, so they can reach distal sites regulating and triggering many cells signaling pathways. For example, SCFAs can act as suppressors of pro-inflammatory cytokines, mitigating gut inflammation, they can promote mucin synthesis, maintain gut integrity by preventing bacterial translocation [25], and they can stimulate the production of anti-microbial peptides [26]. Polysaccharide A up-regulates the production of some anti-inflammatory cytokines and, at the same time, down-regulates the production of some pro-inflammatory cytokines, as IL-6 and IL-1β [27]. This intense crosstalk between host's immune system and gut microbiota is central to guarantee the correct functioning of the organism [11,28]. Endogenous and exogenous factors such as age, gender, diet, psycho-physical stress can promote an imbalance in gut microbiota composition and function, called dysbiosis. The term dysbiosis indicates the loss of mutualistic relationships within the microbial ecosystem, accompanied in changes in microbiota composition and the overgrowth of potentially pathogenic microbial species, phenomenon known as blooming [29], with a generally reduction in biodiversity [30,31]. Dysbiosis can significantly impact host health and lead to disease states [29]. Recently, microbial dysbiosis has been associated with immunosuppression, metabolic and cognitive disorders and with an increased permeability of the intestinal epithelial barrier. These could provoke the translocation of gut bacteria and toxins into surrounding tissues and systemic circulation, leading to a local and systemic inflammation [32]. In the dysbiosis status, essential nutrients for intestinal epithelium function, such as butyrate and acetate [23] are reduced and the increasing of bacterial toxins, like lipopolysaccharides (LPS), could induce systemic inflammation [33]. Different studies, in animal models and in humans, have linked intestinal dysbiosis to various diseases such as: inflammatory bowel diseases (IBD), irritable bowel syndrome (IBS), obesity, diabetes, cancer, cardiovascular, neurological and psychiatric disorders [28,34,35].

4. Sleep disturbances and gut microbiota linked in a bidirectional axis

It has long been suspected that gut microbiota may affect sleep quality, and on the other hand, psychological states can alter gut health through the brain–gut–microbiome axis (MGBA). To date, there are some studies that have investigated the link between gut microorganisms and sleep disorders, but this relationship remains unclear [27]. The MGBA is a bidirectional axis in which the gut and the brain communicate constantly, assuming the correct functioning of both the vagal system and the neuroimmune and circulatory systems [36]. This interaction is determined by several metabolites, neurotransmitters and neuromodulators, as polyphenolic derivatives, vitamins, amines, short chain fatty acids (SCFAs) produced by the intestinal microbiota through fermentative processes, also assuring the integrity of the epithelial barrier [36]. The gut microbiota contributes to production of serotonin's precursors and fundamental signal molecules for central nervous (CNS) and neuroendocrine system (NES), through modifications of the tryptophan pathway. Kennedy and collaborators showed that germ-free (GF) animals with extremely low levels of circulating tryptophan, can be normalized by a healthy microbiota colonization, demonstrating that the levels of circulating tryptophan depend on microbiota [37]. It has been estimated that 90% of the humans' serotonin is produced by intestinal bacteria [38]. Several species belonging to Firmicutes phylum possess tryptophan decarboxylase gene [39] codifying for an enzyme that catalyse the

decarboxylation of L-tryptophan to tryptamine which, in turn, is converted to serotonin by tryptamine 5-hydroxylase [40]. It has been recently shown that Corynebacterium genus is capable of synthesizing serotonin [41]. Serotonin has a broad spectrum of functions, due to its ability to act simultaneously as hormone and neurotransmitter: it acts on mood, on pain perception, it intervenes in the control of appetite and eating behaviour, and it stimulates intestinal peristalsis [42]. Furthermore, serotonin is a precursor of melatonin that regulates the sleep–wake cycle through daily endocrine fluctuations, and recent studies show a direct correlation between host's melatonin concentrations and some intestinal bacteria. There are growing evidences that members of the phyla Bacteroidetes, Firmicutes and Actinobacteria can influence sleep quality regulating food intake and circadian rhythm, producing γ-aminobutyric acid (GABA), a neurotransmitter involved in melatonin's synthesis and glutamate, a somnogenic factor [43–46].

4.1. Studies currently present in the literature on gut microbiota composition and sleep disorders

4.1.1. Sleep-related breathing disorders (SBD)

To date, in literature, there are several papers that correlate intestinal dysbiosis with sleep disturbances in murine models and human patients, Table 1. In a recent review, Mashaqi et al. show how intestinal dysbiosis could act as a mediator between obstructive sleep apnea syndrome (OSAS) and systemic hypertension. OSAS is one of the most common sleep-related respiratory disorders, characterized by intermittent hypoxia (IH) and sleep fragmentation (SF) [47,48], that can lead to intestinal barrier disruption and microbiota composition alteration [7]. In a recent study, Tripathi et al. showed modifications of the gut microbiome, with an increase of different species know to affect the host's inflammatory status, in adult mice (Ldlr−/−) fed with high-fat diet (HFD) subjected to intermittent episodes of hypoxia and hypercapnia to mimic the changes in blood gases that occur in severe OSAS [49]. In the study of Collado et al., the connection between gut microbiota and primary snoring was examined in a cohort of 43 children (27 snorers and 16 controls) at the age of 2 years. The snorers were non-obese children, metabolically healthy. Interestingly, confounding factors such as passive smoking, alcohol consumption during pregnancy and other different stressors, which could have interfered with the composition of the gut microbiota, were excluded from the study [50]. Significant differences in microbial structure between snorers and controls were found. The snoring children manifest a lower microbial diversity and richness respect to non-snorers with a higher abundance of members of the Proteobacteria phylum in snorers (in particular, at family level with higher abundances of Enterobacteriaceae and Erysipelotrichaceae). A significant increase of Firmicutes/Bacteroidetes ratio (F/B) and a reduced Actinobacteria/Proteobacteria ratio (A/P) was found in snorers compared with controls, suggesting that snoring can affect the gut microbiota and have a few long-term consequences [51]. The recent work of Ko C–Y et al., revealed gut microbial dysbiosis in patients with different severities of OSAS. It underlines how the events of IH and SF that occur in these patients may lead to microbial dysbiosis, with an increase of pathogens levels, overgrowth of Enterobacteriaceae family, and reduced levels of SCAFs producing species. Those changes, induce local and systemic inflammatory responses, increasing pro-inflammatory cytokines production, in particular IL-6, leading to intestinal barrier dysfunction and to metabolic comorbidities [52]. Previously, two studies demonstrated an increased intestinal mucosal permeability, a decreasing tight junction integrity, an increased bacterial translocation and gut cytokine production related to these events both in vitro, using two epithelial cell lines in which hypoxia/reoxygenation was recreated than in vivo in which ischemia/reperfusion was induced in mice [53]. In the IH rodent model have also been observed alterations in the gut microbiome, with an increase of anaerobic bacteria abundance and higher levels of circulating LPS, due to the anoxic intestinal environment recreated, suggesting that IH can affect gut microbiome and endotoxins level [54]. Also, the study of Morenos-Indias et al. has shown an increase of the F/B ratio in animal models exposed to intermittent hypoxia respect to controls. The toxins produced by several bacteria, included the lipopolysaccharides (LPS) by Gram-negative bacteria, are normally related to a low-grade systemic inflammation. Increased levels of these molecules

Table 1
Summary of the illustrated studies. Notes: HI = intermittent hypoxia; OSAS = obstructive sleep apnea syndrome; F/B ratio = ratio between Firmicutes and Bacteroidetes; A/P ratio = ratio between Actinobacteria/Proteobacteria; SCAFs = short chain fatty acids; (Ldlr −/− mice) = mice deficient in the LDL receptor.

Author of the study and year of publication	Model Rodent/ Human	Object of the study	Results
Xu Dz et al., 1999 [53]	Rodent	Mice in which ischemia/reperfusion was induced	Increased intestinal mucosal permeability, bacterial translocation, gut cytokine production
Grotz MR et al., 1999 [54]	Rodent	Rodents exposed to intermittent hypoxia (HI)	Gut microbiota alterations and increased of endotoxin levels
Kheirandish-Gozal L et al., 2014 [57]	Human	OSA children prone to obesity	Increased production of pro-inflammatory molecules
Moreno Indias I et al., 2015 [56]	Rodent	HI Mice	Increased production of inflammatory mediators and bacterial translocation
Moreno Indias I et al., 2016 [55]			
Benedict C et al., 2016 [59]	Human	Human with short-term sleep loss	Increased of Firmicutes and Bacteroidetes (F/B) ratio
Poroyko VA et al., 2016 [33]	Rodent	Mice in which sleep fragmentation was induced	Metabolic homeostasis disruption and alteration of F/B ratio
Tripathi A et al., 2018 [49]	Rodent	(Ldlr−/−) mice fed with high-fat diet, subjected to intermittent hypoxia/hypercapnia	Modifications in gut microbiota composition
Collado et al., 2019 [51]	Human	2 years old children with primary snoring	Increased F/B ratio and reduction of A/P ratio
Ko C–Y et al., 2019 [52]	Human	Adults with different OSAS severity	Gut microbial dysbiosis, decrease of bacterial species producing SCAFs and production increase of pro-inflammatory cytokines.
Smith RP et al., 2019 [27]	Human	Young males' patients with sleep fragmentation	Identification of some phyla and taxa related to sleep health
Liu B. et al., 2019 [61]	Human	Humans with insomnia	Gut microbiota alteration and decrease of F/B ratio
Valentini F. et al., 2020 [58]	Human	OSAS Children	Gut microbiota diversity reduction and increase of bacterial species related to inflammation

Table 2
Summary of the illustrated studies. Notes: OSAS = obstructive sleep apnea; HFD = high fat diet; GABA = γ-aminobutyric acid; FMT = faecal microbiota transplantation; FMT-RA = naïve mice transplanted with faecal microbiota of mice normally exposed to room air (RA); FMT-HI = naïve mice transplanted with faecal microbiota of mice subject to intermittent hypoxia (HI).

Author of the study and year of publication	Model	Object of the study	Results
Ganesh BP et al., 2018 [72]	Rodent	Administration of starch Hylon VII and *Clostridium butyricum* in a rat model of OSA fed with HFD	Prevention of acetate decrease and reduction of adverse effects on gut microbiota composition, intestinal inflammation and hypertension
Lin A et al., 2019 [70]	Rodent	Administration of *Lactobacillus fermentum* to normal mice and to short-term insomnia model mice	Sleep improvement in insomnia model mice
Yu L et al., 2020 [71]	Rodent	Mice treated with milk containing high or low levels of GABA respect to positive control (diazepam)	Prolonged sleep duration and decreased sleep latency in positive controls and high dose GABA treated mice
Badran M et al., 2020 [74]	Rodent	FMT from HI or RA mice to naïve mice	differences in the gut microbiota composition of the FMT-RA and FMT-HI and improvement of sleep duration and quality in FMT-RA

and of lipopolysaccharide binding protein (LBP), marker of bacterial translocation, were found in the blood of mice exposed to IH, along with other inflammatory mediators such as interleukin 6 (IL-6) and tumour necrosis factor alpha (TNF-α) [55,56]. Moreover, in children with OSA prone to obesity, elevated LBP circulating levels and an inflammatory status have been reported [57]. In a recent pilot study in OSAS children, Valentini F. et al., found an increase in F/B ratio and in inflammation-related strains and a less diversity in these patients respect to control group. Moreover, they observed a correspondence between these results and sleep parameters [58]. From these studies it emerges that both in adult and paediatric OSA patients the "leaky gut" created by intermittent hypoxia is found to be related with higher plasmatic LPS levels and inflammatory mediators such as IL-6, that are responsible for the low-grade systemic inflammation [52,54,56,58] (see Table 2).

4.1.2. Sleep deprivation and sleep fragmentation (WASO)

Others specific sleep disorders have been widely studied in animal models and humans, with the aim to demonstrate how partial or prolonged sleep loss or disruption could affect the composition of the intestinal microbiota. Benedict and collaborators demonstrated that short-term sleep loss induces indirect effects on human microbiota altering the ratio between Firmicutes and Bacteroidetes. The F/B ratio appeared to double, after two days of partial sleep deprivation (PSD) versus normal sleep (NS) [59]. Studies in mice have shown similar results too. Mice in which sleep fragmentation was experimentally induced, fed on a low-fat diet, showed an increase in food intake and changes in gut microbiota composition, with alteration of F/B ratio and a reduced percentage of species belonging to the phylum of Actinobacteria. These changes promote metabolic homeostasis disruption leading to systemic and adipose tissues inflammation, probably through microbial metabolites' translocation and insulin resistance. These alterations were reversible if sleep fragmentation was induced discontinuously [33]. It has also been recently shown in mice that a 5-days sleep interruption has an impact on the microbiome and metabolome that lasts at least four days after the end of this sleep interruption leading to reduced levels of beneficial bacteria, altered metabolic functions of the microbiome, and changed faecal levels of bacterial metabolites [60]. A recent study has determined a correlation between gut microbiome and sleep physiology in a population of young male patients, using actigraphy, cognitive and neurobehavioral tests, gut microbiome sequencing, and the measurement of some immune system markers [27]. The results of this study show a positive correlation between gut microbiome diversity and richness and quality sleep, as well as a negative correlation between microbiome diversity and sleep fragmentation (WASO), identifying certain phyla and taxa related to sleep health. Specifically, Smith and collaborators found that richness within the phyla Bacteroidetes and Firmicutes was positively correlated with sleep efficiency, while only the phylum Bacteroidetes was negatively correlated with WASO. Moreover, the richness within the Actinobacteria phylum was negatively correlated with the number of awakenings. Since intestinal microorganisms regulate and interact with the immune system, the researchers tested the correlations between IL-6 (important factor that regulates sleep), intestinal microbiota and sleep. The concentration of IL-6 was positively correlated with microbiota diversity and sleep measures, such as time spent in bed and total sleep time. It was observed that, some bacteria belonging to Proteobacteria family were positively correlated with IL-6. The mechanism underlying this microbiota-sleep-immune system remains unknown [27]. Liu et al. through the analysis of faecal samples collected from twenty volunteers divided into insomnia group and control group, based on sleep parameter, observed that the insomnia disorder was associated to significant structural and functional modifications of the intestinal microbiota. The insomnia group showed an alteration of the gut microbiota (both in α-than in β-diversity) and the co-occurrence analysis showed a gut flora interaction network significantly altered in this group compared to control [61]. Furthermore, a decrease in the F/B ratio was also detected in gut microbiota of insomnia group and bioinformatic algorithm predicted an enrichment of gram-negative and potential pathogenic taxa in this group respect to control. The decrease in the F/B ratio contrast with the increase in this ratio shown in previous studies about sleep deprivation or restriction. Although insomnia and sleep deprivation may lead to similar sleep's reductions, they showed different consequences for what concerns dysbiosis of the gut microbiota and metabolisms. Liu and collaborators also found that in insomnia group there was an increase of both vitamin B6 catabolism and folate (vitamin B9) biosynthesis, while arachidonic acid biosynthesis was decreased [61]. Even if further investigations are required, several research studies have showed that gut microbiota and its metabolites are linked in a bidirectional axis with sleep disorders. Diurnal rhythm disruption could negatively affect sleep and lead to gut microbiota unbalance [62,63] by producing changes in community structure, in ecological parameters of the microbial ecosystem [64–67], and on inflammatory state of the organism [68]. This brief discussion clearly shows that a close interaction between sleep and microbiota exists. Probably there is a bidirectional interaction in which sleep disturbances can lead to changes in the microbiota and vice versa.

5. Manipulation of gut microbiota to increase sleep quality or quantity

Recently, microbiota has been considered as a new therapeutic target for sleep disorders in different studies. Collado and collaborators, in the study conducted on children with primary snoring, proposed the manipulation of the intestinal microbiota as a new

therapeutic goal in these children to restore the intestinal eubiosis lost respect to the healthy subject [51]. In a study on mice by Thompson RS and collaborators has been showed that the administration through diet of probiotics can improve sleep quality, controlling brain function and stress responses [69]. Probiotics with some benefits on host's psychophysical health are named "psychobiotics" and some of them, through the brain–gut–microbiome axis, could ameliorate sleep conditions [70]. Yu and collaborators have recently demonstrated in mice, the potential beneficial effects of fermented milk rich of GABA on anxiety management and sleep quality. In this study, mice were divided into different groups based on the treatment received (high or low levels of GABA contained in the milk). The negative control group and the positive control group were treated with saline solution and diazepam, respectively, and the sleep improvement test was performed by injecting sodium pentobarbital in mice and going to see what happening. Only mice treated with fermented milk containing a high dose of GABA, and the group treated with diazepam (positive control) showed prolonged sleep duration and decreased sleep latency after sleep induction. In this study it has been also shown that the administration of high-dose GABA fermented milk leads to modification of gut microbiota composition, particularly in beta diversity, increasing the relative abundances of species note to produce SCFAs [71]. The study of Lin A. et al. demonstrated the time- and dose-dependent effects of the psychobiotic *Lactobacillus fermentum* strain PS150TM on sleep improvement, in normal mice and in a short-term insomnia model mice, proposing its use as diet supplement in sleep disorders [70]. In another study, Ganesh and collaborators demonstrated the importance of prebiotics, probiotics, and acetate in preventing hypertension in a rat model of OSA fed with a high fat diet, in which a decrease of SCAFs producing bacteria has been documented [72]. They analysed the role of corn starch Hylon VII as a prebiotic [72,73], and *Clostridium butyricum* as probiotic to increase SCFAs production. They have seen that the administration of *C. butyricum* and Hylon prevented the decrease of acetate concentration and reduced the adverse effects of OSAS on the microbiota, in addition to prevent the loss of epithelial goblet cell, the thinning of mucus barrier and brain microglia activation. Moreover, they showed that a pre-infusion of acetate, directly into cecum, was able to prevent gut inflammation and hypertension in these rats. This demonstrates that acetate plays a key role in OSAS-induced hypertension and that the administration of probiotics and prebiotics, able to increase cecal acetate concentrations, could have a protective role against OSAS complications, gut permeability, microbiota's alteration, brain functions and blood pressure [72]. Recently, Badran M. et al., showed how the transplantation of faecal microbiota from mice subject to intermittent hypoxia (HI) or from mice normally exposed to room air (RA) could influence the duration and quality of sleep of the transplanted naïve mice. Furthermore, this study illustrates the differences in the gut microbiota composition of the two groups of transplanted naïve mice (FMT-RA and FMT-HI) and gut microbiota similarities between donor and fecal transplant recipient mice [74]. Therefore, there are different studies related to sleep disorders that, to obtain a sleep qualitative and/or quantitative improvement, tried to manipulate gut microbiota, obtaining a positive outcome. However, we have not yet certainties on microbiological markers (specific species) and key metabolites related to these pathologies. Thus, understanding how intestinal microorganisms affect host's sleep could place the basis for the improvement of sleep through gut microbiota manipulation.

6. Conclusion

There are several evidences that gut microbiota could influence mental states and affect sleep quality and circadian rhythm of the host, as well as it is known that psycho-physiological stress can influence microbiota composition [70]. Sleep is a physiological state that is basically linked to the immune system and the gut microbiota composition, exerting a systemic action through metabolic mediators, seems to be associated with sleep regulation [75]. The most studies illustrated in this review agree that an alteration of the intestinal bacterial composition, with an increase of F/B ratio and a disruption of intestinal barrier is associated with sleep disturbances [8,33,51,59]. Both in adult and paediatric patients with sleep-related breathing disorders the intestinal permeability is found to be related with higher plasmatic LPS levels and inflammatory mediators, and no major differences between the intestinal microbiota composition of adults compared to children, were reported. Small differences between the microbial composition related to sleep disorders breathing and sleep deprivation disorders are described but a causal-effect link between these disorders and gut microbiota composition has not been identified. To understand if this causal connection exists, studies on gut microbiota should not be based only on microbiota's taxonomic characterization but on functional and metabolic approaches of the microbial ecosystem. Further investigations are needed to comprehend the role that the intestinal microbiota plays in modulating sleep, and the mechanism by which it may or may not promote sleep, identifying the molecules involved and the exact action. Multifactorial pathologies such as sleep disturbances, require multidisciplinary approaches to identify strategies aimed at avoiding negative consequences on human health. These strategies could be based on lifestyle adjustment, personalized diet, administration of prebiotics and "psycobiotics", to counteract dysbiosis potentially associated with sleep disorders [10]. The question "what influences what" is therefore still open and studies aimed at understanding whether intestinal dysbiosis may represent a potential predisposing or aggravating risk factor for these disorders, could be of great help in the management of patients with these diseases.

Author contributions

BN, SS writing—original draft preparation, ME, GDN, GR; visualization, SS, MPV, FP, ME.; supervision. All authors have read and agreed to the published version of the manuscript.

Conflict of interest

The authors declare no conflict of interest.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2021.08.003.

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