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From alpha diversity to zeitgebers: Bacterial gut microbiome associations with sleep and circadian disruption (Part I)

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Abstract

Sleep is a vital behavioral state influencing multiple body systems, including the gut-brain axis, which involves bidirectional communication between the brain and gastrointestinal system. This scoping review examines and provides a comprehensive overview of literature examining the relationship between sleep and the gut microbiome to identify literature gaps. Seventy-four preclinical rodent studies and 65 human translational studies reporting direct sleep and gut microbiome associations were synthesized. We found variable alpha diversity responses to sleep pathology, with decreased alpha diversity more consistent in longer sleep disruption periods. Preclinical studies showed variable phylum-level responses, while in humans, sleep disruption was linked to decreased Bacillota and circadian disruption to increased Bacillota. Unhealthy sleep patterns were commonly associated with reduced levels of beneficial genera such as *Faecalibacterium* and *Lactobacillus*, and increased *Clostridium*, though findings were not consistent across all studies. Recommendations are made to ensure rigorous, reproducible research in this field. The potential for gut microbiome modulation as a therapeutic target is highlighted, with suggested future research directions for preventing sleep disruption and pathology.

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Declaration of Competing Interest

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Author's note

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Registration

Scoping review protocol is registered on Open Science Framework (https://osf.io/) and can be accessed at https://doi.org/10.17605/OSF.IO/69TBR.

Keywords

Gut microbiota; Gut microbiome; Human microbiome; Genomics; Gut-brain signaling; Sleep; Circadian rhythm; Sleep quality; Sleep time; Sleep disruption; Circadian disruption; Scoping review

1. Introduction

1.1. Implications and importance of healthy sleep

Healthy sleep is emerging as a critical preventative strategy for promoting health and reducing the risk of chronic diseases. Far from a passive state, sleep is an active process essential for neurophysiology, immune function, and cardiometabolic health (Irwin, 2015). The American Heart Association's recent inclusion of sleep in updated cardiovascular health recommendations highlights its growing recognition in health promotion and disease prevention (Lloyd-Jones et al., 2022). Sleep is increasingly linked to a range of outcomes, from cognitive and mental health to immune resilience, driving greater interest in translational studies that explore how improving sleep can directly contribute to disease prevention and long-term health promotion (Zheng et al., 2024). Adequate sleep supports essential biological functions, such as clearing neurotoxic waste, repairing DNA, and enhancing memory consolidation. Disruptions in sleep can have cascading effects on brain function, metabolic regulation, and immune responses. The two-process model of sleep regulation, which includeshomeostatic sleep drive and circadian alignment,guides current research by demonstrating how these processes synchronize sleep with the body's physiological needs and environmental cues (Borbély et al., 2016). Misalignment of these processes can result from factors like environmental disruptions, irregular work schedules, or lifestyle choices such as poor diet, lack of physical activity, and alcohol use. Social determinants of health, including socioeconomic status, access to healthcare, and environmental stressors/exposures can also exacerbate sleep difficulties, contributing to the development of sleep disorders (Grandner et al., 2015).

1.2. Sleep disorders and consequences of sleep pathology

Approximately 70 million Americans suffer from chronic sleep disturbances, underscoring the need to prioritize sleep health as a public health goal. According to the CDC, adults who sleep less than seven hours per night are at higher risk for chronic conditions like heart disease, kidney disease, and diabetes compared to those who get adequate sleep (Gallicchio and Kalesan, 2009; Watson et al., 2015). While commonly recognized consequences of sleep disruption include increased stress, mood disturbances, and cognitive deficits, the long-term effects can increase propensity for chronic disease. For example, chronic sleep restriction is linked to cardiovascular disease, metabolic syndrome, type 2 diabetes, and increased cancer risk (Grandner et al., 2014; Li et al., 2022). Cross-sectional studies consistently show that short sleep duration or insomnia is associated with elevated blood pressure, impaired insulin sensitivity, and negative impacts on glucose tolerance, body mass index, and cholesterol levels (Fang et al., 2012; Javaheri and Redline, 2017; Knutson and Van Cauter, 2008).

In addition to these health issues, sleep disruption is connected to behavioral risk factors that worsen overall health. Chronic sleep disturbances increase the risk of obesity by disrupting hunger hormones like ghrelin and leptin, leading to overeating and weight gain. Sleep deprivation also impairs glucose metabolism and reduces physical activity, which exacerbates metabolic disorders. Moreover, irregular and/or poor-quality sleep raises the risk of relapse in individuals with alcohol use disorder by heightening alcohol cravings, impairing decision-making, and increasing subjective anxiety and stress reactivity (Barb et al., 2022; Brooks et al., 2021). Given the interdisciplinary nature of sleep and its impact on health, translational research aims to further explore its relationship with chronic disease risk. While epidemiological studies highlight this connection, effective management and treatment of sleep disorders remain limited and variable in success.

1.3. Relationships of the gut-brain axis with healthy and unhealthy sleep

The gut microbiota, a community of bacteria in the gastrointestinal system, fluctuates diurnally based on food intake, nutrient anticipation, and energy metabolism. This microbiota is essential for metabolite synthesis, lipid absorption, and immune modulation, and disruptions can significantly impact health. A critical flow of information between the brain and gut microbiome (i.e., the community of gut bacteria and collective genes they carry), mediated by metabolites, immune cells, and the vagus nerve, regulates homeostasis, gastrointestinal motility, and immune responses. The gut microbiome also maintains the integrity of tight junctions between epithelial cells, which is crucial for preventing translocation of inflammatory bacterial byproducts and systemic inflammation. Disruptions to this barrier can lead to immune imbalances and a range of inflammatory and metabolic conditions.

The bi-directional communication known as the “gut-brain axis” suggests a link between gut microbiome health and sleep. Research has associated sleep disturbances with changes in gut microbiome composition, such as increases in proinflammatory bacteria like *Escherichia coli* and *Staphylococcus aureus*. These shifts are linked to reduced digestive efficiency, chronic inflammation, obesity, and impaired cognitive function. The reciprocal regulation between sleep and gut microbiome function highlights the gut-brain axis’s role in overall health, especially regarding sleep pathology (Kim and Shin, 2018). However, the exact nature of this relationship—whether sleep disturbances directly alter the microbiome or vice versa—remains unclear. Ongoing research seeks to elucidate the interplay between these systems (Maki et al., 2020b; Moloney et al., 2021).

Primary research on the relationship between sleep and the gut microbiome is rapidly expanding. Therefore, a synthesis of this research is needed to highlight common themes across model systems and identify gaps for future exploration. In this scoping review, we synthesize studies examining the connections between sleep, sleep pathology, and the gut microbiome in both preclinical and clinical study designs, aiming to assess the scope of existing research, what sleep disorders have been studied, the methodologies used and whether they are sufficient in characterizing the global and specific bacterial gut microbiome changes associated with alterations in sleep and circadian physiology.

2. Methods

A scoping review was selected due to the variability in microbiome and sleep measures, allowing for a comprehensive synthesis of preclinical and human research examining relationships between sleep and the gut microbiome. See Maki et al. (2022), for the scoping review protocol, and detailed methods on search strategy, study extraction, and literature synthesis. Briefly, a comprehensive scoping review was conducted by a research librarian using PubMed/MEDLINE, Embase, Scopus, Web of Science, CENTRAL trials, BIOSIS Citation Index, and the Zoological Record databases of primary research studies with no date limits for included studies. The literature search was initially conducted in December 2021 and updated in December 2023 to capture newly published manuscripts and to ensure inclusion of studies available through 2023. Studies that met inclusion criteria were published between 2000 and 2023. All study designs were included in this scoping review which included human studies (adults ≥ 18 years of age) and rodents (preclinical research). Studies were restricted to manuscripts and/or abstracts published in English.

In preclinical research studies, reporting of associations between the bacterial gut microbiome and objective sleep measures and/or interventions disrupting sleep or circadian rhythms were required. In human/translational studies, we required the study to report direct associations between the gut microbiome and either: 1) objective or subjective sleep measures; or 2) sleep pathology and sleep disruption-associated interventions with confirmation of altered sleep via objective sleep monitoring or direct observation. Categorized sleep phenotype variables and models of sleep and circadian disruption or disease in this review are depicted in Fig. 1 and described in detail in the protocol manuscript (Maki et al., 2022). Exclusion criteria included: review articles; outcomes not related to the microbiome; direct analyses of microbiome and sleep models/characteristics not performed; outcomes related to other gut microbiome organisms (virus, protozoa, archaea etc.); intervention that used a symptom of sleep pathology but did not alter or mesaure sleep (i.e. intermittent hypoxia); co-intervention studies lacking a circadian/sleep disruption only group; and other preclinical model organisms. In studies that used additional interventions, if study groups included a sleep or circadian disruption (only) group and control group, the study was included but only relationships between the sleep or circadian disruption and control groups were reported in the review. Two authors (KAM and JA) independently reviewed the title and abstract of 6250 citations using Covidence software, and full text review was also performed on 296 studies by two authors (KAM and JA). After full text review, 139 studies met inclusion criteria and were synthesized (Please see Supplemental Figure S1 for screening flow chart).

In the results synthesis, only comparisons that were tested statistically were reported. For alpha and beta diversity analyses, all results were reported (i.e., increase, decrease, no significant differences, respectively), while in the differential abundance analyses at the individual bacteria level, only significant results were reported due to the data volume. Bacteria at the taxonomic level of phylum are reported according to the current edition of the International Code of Nomenclature of Prokaryotes that was revised in 2022 to facilitate consistency across studies (Oren et al., 2023). All metric reporting frequency figures were generated in JMPv16 (SAS Headquarters, Cary, NC).

3. Results

A total of 74 preclinical (rodent) and 65 translational clinical (human) studies met inclusion criteria for a total of 139 manuscripts and abstracts synthesized in this review (Supplemental Table S1). Across the preclinical studies, 54 used mice as their animal model, while 20 used rats. Most preclinical studies (81 %) exclusively studied male rodents, five reported an equal distribution of males and females, while one study that also reported on polycystic ovary syndrome-associated outcomes exclusively studied female rodents (Supplemental Table S1A). Although some studies analyzed more than one sample site (e.g., fecal sample, invasive colonic content sample), most studies (73 %) included fecal samples for gut microbiome analysis. Additionally, 26 % included cecal/colonic content samples, and less than 10 % of studies included small intestine samples in their gut microbiome analysis (Supplemental Table S1A).

Human and translational studies generally had a balanced representation of male and female participants with an average of 52.85 ± 28.2 % male representation across studies, and fewer than 20 % of the studies had samples where 80 % or more of the participants were male (Supplemental Table S1B). The average age of participants across translational studies was 44.12 ± 16.46 years. Most participants studied across the reviewed studies had a healthy weight, with an average BMI of 24.48 ± 2.58.

3.1. Objective and subjective sleep phenotype

3.1.1. Sleep duration

3.1.1.1. Preclinical research: Objective sleep duration. Most preclinical studies did not directly measure sleep duration and focused on comparisons between intervention groups. Of studies that objectively measured sleep duration, different methodologies and recording systems were used for sleep quantification including PiezoSleep behavioral tracking (Bubier et al., 2020), invasively implanted electroencephalogram (EEG) and electromyogram (EMG) electrodes with sleep scoring (Maki et al., 2022, 2020a; Thompson et al., 2021), as well as direct observation with (Mo et al., 2023) and without (Wang et al., 2020) video acquisition technology.

No preclinical studies reported measures of alpha diversity or beta diversity in association with sleep duration measures or characteristics (Fig. 2A; Fig. 3A). There were no significant relative abundance (RA) comparisons of bacteria at the phylum or family level in association with sleep duration (Fig. 4A; Fig. 5A). At the genus level, shorter objective sleep duration was associated with a decreased RA of *Bifidobacterium* (Mo et al., 2023) and *Lactobacillus* (Bubier et al., 2020; Mo et al., 2023), and increased RA of *Akkermansia*, *Alistipes*, and *Butyricimonas* (Fig. 6) (Mo et al., 2023). Additionally, the RA of *Odoribacter* was negatively associated with several objective measures of sleep duration including sleep in the light phase, sleep in the dark phase, and percent sleep over the full recording period (Bubier et al., 2020).

3.1.1.2. Human/translational research: Subjective sleep duration and objective sleep duration. Sleep logs were used for the measurement of subjective sleep duration either

as a standalone measure or as validation for actigraphy monitoring. Actigraphy was used in 70 % of studies that quantified objective sleep duration, while polysomnography captured objective sleep time in the remaining studies (Supplemental Table S1B). In all studies reporting subjective sleep duration, usual sleep time (hours/night) was asked and analyzed cross-sectionally. Longitudinal actigraphy data was collected, but sleep data was averaged and used in cross-sectional analyses in relationship with the gut microbiome. Most actigraphy recording periods in the included research lasted approximately one week, while other studies used longer durations of 14–30 days to generate average sleep measures (Supplemental Table S1B).

Most studies investigating the relationship between alpha diversity and sleep duration found no differences (across 24 reported metrics) in alpha diversity when using either objective or subjective measures of sleep duration (Fig. 2B) (Agrawal et al., 2021; Hagen et al., 2019; Jiao et al., 2022; Ko et al., 2019; Mohammadi et al., 2022; Ren et al., 2023; Reutrakul et al., 2020; Smith et al., 2019; Zhong et al., 2021). However, one study reported an increase in Shannon index in individuals with shorter subjective sleep duration (Holingue et al., 2020), one study observed a decrease in both observed operational taxonomic units (OTUs) and Shannon indices with shorter subjective sleep duration (Fei et al., 2021) and one study also reported decreased Inverse Simpson with shorter objective sleep duration in addition to their negative findings (Supplemental Figure S2) (Smith et al., 2019).

Group comparisons of microbiome composition via beta diversity analysis showed group differences in participants reporting usual sleep time of under 7 h/night versus ≥ 7 h/night using different distance matrices including Binary-Jaccard, Bray-Curtis Dissimilarity, Unweighted UniFrac, and Weighted UniFrac (Agrawal et al., 2021; Fei et al., 2021; Ren et al., 2023). Two studies analyzed gut microbiome differences via beta diversity across objective sleep duration groups. One study found no significant differences between shorter and longer sleepers (Reutrakul et al., 2020), while the other identified significant differences between sleep duration groups using Weighted UniFrac distances, but not Unweighted UniFrac (Zhong et al., 2021).

A decreased RA of Bacillota in gut microbiome samples were associated with lower subjective sleep duration (Agrawal et al., 2021). No significant taxa at the family level were reported in association with subjective or objective sleep duration. Shorter objective sleep duration was associated with a decreased RA of *Adlercreutzia* species, including *Adlercreutzia equolifaciens* and *Adlercreutzia muris*, and an increased RA of *Enterococcus* species including *Enterococcus durans* and *Enterococcus faecalis* (Arnoriaga-Rodríguez et al., 2023). An increased RA of *Blautia* (Haimov et al., 2019; Smith et al., 2019; Zhang et al., 2021b) and *Blautia producta* (Arnoriaga-Rodríguez et al., 2023), and decreased RA of other *Blautia* species including *Blautia glucerasea* and *Blautia obeum* (Arnoriaga-Rodríguez et al., 2023) was also seen in individuals with shorter objective sleep duration. Shorter objective and/or subjective sleep duration was associated with a decreased RA of *Alistipes* (Agrawal et al., 2021; Zhong et al., 2021), *Butyricicoccus* (Arnoriaga-Rodríguez et al., 2023; Shimizu et al., 2023), *Faecalibacterium* (Agrawal et al., 2021; Kitami et al., 2020), *Parabacteroides* (Arnoriaga-Rodríguez et al., 2023; Ren et al., 2023), and *Anaerobutyricum hallii* (Ren et al., 2023; Shimizu et al., 2023). Additionally, the RA of *Bacteroides* was increased in

association with shorter subjective sleep duration (Fei et al., 2021; Shimizu et al., 2023) but decreased in subjects with shorter objective sleep duration (Zhong et al., 2021).

3.1.1.3. Key takeaways. Preclinical models did not report broad microbiome diversity measures (i.e., alpha and beta diversity) in relation to sleep duration. Although studies were limited, decreased *Lactobacillus* RA was reported in associated with shorter sleep duration in animal models. Human studies similarly found limited effects on alpha diversity, but beta diversity analyses revealed compositional differences between short and adequate sleepers, particularly when using subjective sleep measures. Shorter sleepers in human studies exhibited an increased RA of *Blautia* and decreased RA of putative butyrate-producing genera including *Faecalibacterium* and *Butyricicoccus*.

3.1.2. Sleep quality

3.1.2.1. Preclinical research: Objective sleep quality. Like sleep duration, most preclinical studies did not directly measure sleep quality and focused on comparisons between intervention groups. Both studies that objectively measured sleep quality quantified sleep latency, but different data collection methods were used including direct observation in one study (Wang et al., 2020), and video acquisition in another (Mo et al., 2023).

There were no measures of global gut microbiome community characteristics (i.e., alpha and beta diversity) that were reported in association with sleep quality measures or characteristics. Similarly, preclinical studies did not report significant comparisons of phylum or family level bacteria in association with sleep quality. Lower objective sleep quality (quantified via sleep latency) was associated with similar taxa as shorter sleep duration including a decreased RA of *Bifidobacterium* and *Lactobacillus*, and increased RA of *Akkermansia*, *Alistipes*, and *Butyricimonas* (Fig. 6) (Mo et al., 2023).

3.1.2.2. Human/translational research: Subjective and objective sleep quality. Most of the studies that measured subjective sleep quality in humans used the Pittsburgh Sleep Quality Index (PSQI; 27 studies; Supplemental Table 1B), followed by five studies that used the Insomnia Severity Index (ISI), and the remaining studies using sleep-associated subscales of other symptom measures (Aizawa et al., 2018; Ganci et al., 2022) or protocol-specific sleep quality measures (Holingue et al., 2020; Holzhausen et al., 2023).

When sleep quality was quantified subjectively (i.e., PSQI, ISI) most studies investigating the relationship between alpha diversity and subjective sleep quality found no differences (across 39 reported metrics) in alpha diversity (Fig. 2B) (Estaki et al., 2023; Hagen et al., 2019; Hope et al., 2023; Li et al., 2023c; Mohammadi et al., 2022; Xie et al., 2023; Yao et al., 2021; Zhang et al., 2022b, 2021a). However, seven studies (across 11 metrics) reported decreased Shannon, Abundance-based Coverage Estimator (ACE), Chao1, Simpson and inverse Simpson indices in association with lower subjective sleep quality (Supplemental Figure S2) (Cai et al., 2021; Grosicki et al., 2020; Hagen et al., 2019; Holzhausen et al., 2023; Xie et al., 2023; Zhang et al., 2021a; Zhou et al., 2022). In contrast, all three studies using objective measures of sleep quality reported decreased alpha diversity with lower objective sleep quality in at least one metric tested (Hagen et al., 2019; Holzhausen et al., 2023; Smith et al., 2019). For example, Chao1, Shannon, inverse Simpson, and richness

indices were associated with decreased sleep efficiency (Holzhausen et al., 2023; Smith et al., 2019), and ACE, Chao1, Shannon, Simpson, and inverse Simpson metrics, but not richness, were associated with increased wakefulness after sleep onset (WASO) (Hagen et al., 2019; Holzhausen et al., 2023; Smith et al., 2019).

Most studies found no beta diversity differences when comparing subjects with higher versus lower subjective sleep quality, using the same distance matrices that were applied to compare differences in beta diversity across sleep duration groups (Supplemental Figure S3), aside from three studies reporting significant differences in beta diversity using Weighted UniFrac or Bray-Curtis Dissimilarity matrices (Holzhausen et al., 2023; Xie et al., 2023; Yao et al., 2021). Only one study compared differences in beta diversity using objective measures of sleep quality, and significant compositional group differences were found in patients with higher and lower sleep latency and sleep efficiency, respectively (Holzhausen et al., 2023).

At the taxonomic level of phylum, significant differential abundance comparisons were reported in six studies in association with subjective sleep quality and four in association with objective sleep quality (Supplemental Table S6). Associations of the RA of Bacteroidota with subjective and objective sleep quality was conflicting across the reviewed studies (Fig. 4B). For example, Bacteroidota RA was reported to be decreased (Bellikci-Koyu et al., 2021; Yao et al., 2021) and increased (Grosicki et al., 2020) in association with poor subjective sleep quality via PSQI, decreased (Smith et al., 2019) and increased (Haimov et al., 2019) in association with lower objective sleep quality via sleep efficiency, and decreased (Smith et al., 2019) and increased (Haimov et al., 2019) in association with lower objective sleep quality via WASO. The ratio of Bacillota to Bacteroidota (commonly reported as the Firmicutes: Bacteroidetes [F:B] ratio, which will be maintained in this manuscript) has been reported as a broad indicator of gut microbiome composition (Benedict et al., 2016; Bowers et al., 2020; Gao et al., 2019; Grosicki et al., 2020; Maki et al., 2020b), although the clinical utility of this ratio for health and disease discrimination has been questioned (Tilg and Kaser, 2011). Across the studies included in this review, the F:B ratio was also conflicting, and reported to be decreased (Grosicki et al., 2020; Tuason et al., 2019) and increased (Yao et al., 2021) in association with low subjective sleep quality. Other bacteria demonstrated more consistent relationships with objective sleep quality including a decreased RA of Lentisphaerota (Haimov et al., 2019), a decreased RA of Verrucomicrobiota (Chen et al., 2022; Haimov et al., 2019), and an increased RA of Spirochaetota (Chen et al., 2022) in association with lower objective sleep quality via sleep efficiency or WASO. The RA of *Ruminococcaceae* was significantly decreased in association with lower objective sleep quality measured through WASO and sleep efficiency (Fig. 5B) (Haimov et al., 2019), while the RA of *Erysipelotrichaceae* was significantly increased in individuals with lower subjective sleep quality (Bellikci-Koyu et al., 2021; Tanaka et al., 2022; Zhang et al., 2022b).

Consistent associations with lower objective or subjective sleep quality were reported across several taxa (Fig. 7). For example lower sleep quality was associated with a decreased RA of *Alloprevotella* (Chen et al., 2022; Yao et al., 2021), *Anaerofilum* (Chen et al., 2022), *Desulfovibrio* (Gao et al., 2022; Yao et al., 2021), *Erysipelotrichaceae UCG-003* (Chen

et al., 2022; Smith et al., 2019), *Intestinibacter* (Zhang et al., 2021a), *Lachnospira* (Gao et al., 2022; Haimov et al., 2019; Li et al., 2020), *Oscillospira* (Haimov et al., 2019), *Ruminococcus* (Grosicki et al., 2020; Haimov et al., 2019), *Subdoligranulum* (Gao et al., 2022; Holzhausen et al., 2023), and *Sutterella* (Gao et al., 2022; Smith et al., 2019; Xie et al., 2023), along with *Streptococcus* species *S. mutans* (Ganci et al., 2022), *S. salivarius* (Zhang et al., 2021a), and *S. sanguinis* (Ganci et al., 2022). An increased RA of *Candidatus Soleaferrea* (Chen et al., 2022), *Coprococcus* (Holzhausen et al., 2023; Smith et al., 2019; Zhang et al., 2021a; Zhou et al., 2022), *Enterococcus* (Chen et al., 2022; Ganci et al., 2022), *Fusicatenibacter* (Zhou et al., 2022), and *Oscillibacter* (Zhou et al., 2022) were also reported in subjects with lower objective or subjective sleep quality. Finally, there were bacterial genera that had conflicting associations, and an equal number of studies reported a significantly increased or decreased RA of *Bacteroides* (Ganci et al., 2022; Gao et al., 2022; Li et al., 2020; Liu et al., 2019), *Bifidobacterium* (Chen et al., 2022; Ganci et al., 2022; Louis-Jacques et al., 2019), *Blautia* (Grosicki et al., 2020; Haimov et al., 2020; Li et al., 2020; Masyutina et al., 2021; Smith et al., 2019; Tanaka et al., 2022; Xie et al., 2023; Zhang et al., 2021a), *Clostridium* (Ganci et al., 2022; Haimov et al., 2020; Holzhausen et al., 2023; Zhang et al., 2022b, 2021a; Zhou et al., 2022), *Faecalibacterium* (Estaki et al., 2023; Evans et al., 2017; Kitami et al., 2020; Li et al., 2020; Masyutina et al., 2021), and *Lactobacillus* (Aizawa et al., 2018; Ganci et al., 2022; Jackson et al., 2014) in association with lower subjective and/or objective sleep quality.

3.1.2.3. Key takeaways. Relationships between sleep quality and alpha or beta diversity were not reported in preclinical studies, and taxonomic comparisons were similarly limited. In human studies, associations between sleep quality and alpha diversity were more consistent when sleep quality was measured objectively rather than subjectively; all studies using objective measures reported decreased alpha diversity in individuals with poor sleep. At the genus level, poor sleep quality was consistency associated with decreased RA of *Lachnospira*, *Ruminococcus*, *Subdoligranulum*, and *Sutterella*, and increased *Coprococcus* and *Enterococcus.* However, findings at higher taxonomic levels and for several commonly reported genera were inconsistent across studies.

3.2. Models or disorders of sleep pathology

3.2.1. Preclinical and human/translational experiments of sleep disruption, restriction or deprivation and human sleep disruption-associated disease:

Mechanical sleep disruption models and REM-specific sleep disruption models encompassed most of the preclinical studies meeting inclusion criteria with 23 and 18 studies, respectively (Supplemental Table S1A).

3.2.1.1. Preclinical research: Paradoxical (REM) sleep disruption. The Modified Multiple Platform Method was used in all studies studying paradoxical (i.e. REM sleep in humans) sleep disruption in association with the gut microbiome, and approximately 40 % of studies disrupted paradoxical sleep continuously for 3 days (Supplemental Table S1A). Other studies used a range of 7 days to as long as 6–8 weeks of total paradoxical sleep disruption with intervention lengths (aside from continuous) ranging from 6 h/day to 20 h/day (Supplemental Table S1A).

Half of the studies using models of paradoxical sleep disruption reported decreases in alpha diversity across 23 metrics (Supplemental Figure S2), with decreases in ACE, Chao1, Shannon, richness, and Simpson indices after the intervention period (Gao et al., 2023a, 2021b, 2019; Gu et al., 2022; Ma et al., 2019; Wang et al., 2022b; Yang et al., 2023a; Zhang et al., 2022a, 2021c). Additionally, seven studies reported increased alpha diversity (Gao et al., 2023a, 2021b, 2019; Gu et al., 2022; Ma et al., 2019; Wang et al., 2022b; Zuo et al., 2022), and six reported no difference in alpha diversity (Gao et al., 2023a, 2019; Gu et al., 2022; Ma et al., 2019; Yang et al., 2023a; Zhang et al., 2021c) across the same number of metrics (12 each) after paroxysmal sleep disruption. Notably, Simpson index comprised of 50 % of reported increased alpha diversity metrics, and all studies that reported no differences in alpha diversity performed paroxysmal sleep disruption for seven days or less (Supplemental Table S4). Beta diversity comparisons were performed in a subset of studies using paroxysmal sleep disruption. Interventions lasting 7–28 days led to significant group differences in gut microbiome composition between intervention animals and controls (Gu et al., 2022; Wang et al., 2022b), whereas three day intervention periods did not (Zhang et al., 2021c) (Supplemental Table S5).

Paroxysmal sleep disruption was associated with consistent responses of gut microbiota bacteria at taxonomic levels from phylum to species across studies (Supplemental Figures S4–S7). For example, the F: B ratio was increased in the intervention group versus controls in all studies that reported this analysis (Gao et al., 2019; Wang et al., 2022b; Zuo et al., 2022). Additionally, with one exception, paroxysmal sleep disruption led to an increase in the RA of Bacillota (Gao et al., 2023a; Gao et al., 2020, 2021a; Gao et al., 2021b; Gao et al., 2019; Gu et al., 2022; Zuo et al., 2022) and Pseudomonadota (Gao et al., 2021a, 2021b; Ma et al., 2019; Zhang et al., 2021c) and decrease in the RA of Bacteroidota (Gao et al., 2023a; Gao et al., 2020, 2021a; Gao et al., 2021b; Gao et al., 2019; Gu et al., 2022; Luo et al., 2023; Wang et al., 2022b; Wu et al., 2022; Zuo et al., 2022) and Verrucomicrobiota (Gao et al., 2021b; Gu et al., 2022; Ma et al., 2019) in intervention animals versus controls. Paroxysmal sleep disruption was associated with an increased RA of *Lachnospiraceae* (Gao et al., 2019; Gu et al., 2022) and *Moraxellaceae* (Gao et al., 2020, 2019), and a decreased RA of *Prevotellaceae* in intervention animals versus controls (Gao et al., 2020, 2021a).

An increased RA of *Aeromonas* (Gao et al., 2023a, 2020, 2019), *Clostridium* (Pang et al., 2023; Wang et al., 2022b; Wu et al., 2022), *Clostridium perfringens* (Luo et al., 2023), *Oscillospira* (Gu et al., 2022; Ma et al., 2019), *Parabacteroides* (Gao et al., 2020; Gu et al., 2022; Ma et al., 2019; Zhang et al., 2023), *Roseburia* (Gao et al., 2020; Zhang et al., 2022a), and *Ruminococcus* (Ma et al., 2019; Zuo et al., 2022) was reported in intervention animals versus controls in response to paroxysmal sleep disruption. Conversely, paroxysmal sleep disruption resulted in a decreased RA of *Akkermansia* (Gao et al., 2023a, 2019; Gu et al., 2022; Ma et al., 2019), *Bacteroides* (Gao et al., 2020, 2019; Wu et al., 2022), *Bifidobacterium* (Luo et al., 2023; Wu et al., 2022; Zuo et al., 2022), *Faecalibacterium* (Gao et al., 2021b, 2023b, 2019), *Lactobacillus* (Gao et al., 2020; Luo et al., 2023; Wang et al., 2022b; Wu et al., 2022), *Prevotellaceae UCG-001* (Gao et al., 2020; Zhang et al., 2022a), and *Rikenellaceae RC9 group* (Gao et al., 2020; Zhang et al., 2022a).

3.2.1.2. Preclinical research: Pharmacologic sleep disruption. All studies that using a pharmacologic model of sleep disruption used para-chlorophenylalanine (PCPA), a selective inhibitor of tryptophan hydroxylase, to induce insomnia in rodents (Supplemental Table S1A). Doses of PCPA varied, with most studies administering 300 mg/kg via intraperitoneal (IP) injection or 400 mg/kg IP, although one outlier study only used 40 mg/kg IP of PCPA for sleep disruption. Studies administered PCPA for either two or three days, and the time from the final PCPA injection to specimen collection for gut microbiome analysis also varied, ranging from 7 to 15 days (Supplemental Table S1A).

Across all studies that used PCPA for pharmacologic sleep disruption, most studies found no differences in alpha diversity between the sleep disrupted and control animals (Liu et al., 2023; Tang et al., 2021; Yang et al., 2023b; Yu et al., 2022) (Supplemental Figure S2, Supplemental Table S4). The one study with increased alpha diversity in association with pharmacologic sleep disruption found significant increases in measures of richness (ACE, Chao1, and observed features indices) but Shannon and Simpson indices were not significantly different (Yao et al., 2022). The two studies that reported beta diversity comparisons between pharmacologic sleep disruption versus control animals used similar PCPA doses and waiting periods after last PCPA injection before gut microbiome samples were analyzed (Tang et al., 2021; Yang et al., 2023b). Significant differences in beta diversity were seen using Weighted UniFrac distances (Yang et al., 2023b), but when Bray-Curtis dissimilarity matrices were employed, there were no differences between intervention and control groups (Supplemental Figure S3) (Tang et al., 2021).

While responses in bacterial RA at the phylum level to pharmacologic sleep disruption were generally consistent, they were not as uniform as those observed with paroxysmal sleep disruption. Nevertheless, across studies, pharmacologic sleep disruption was associated with a decreased RA of Bacillota (Mo et al., 2023; Tang et al., 2021; Wang et al., 2020), and increased RA of Verrucomicrobiota (Mo et al., 2023; Wang et al., 2020). The RA of Bacteroidota was reported to be increased (Mo et al., 2023; Tang et al., 2021) and decreased (Qiao et al., 2022) in response to PCPA administration in intervention animals versus controls (Supplemental Figure S4). Of note, Qiao et al. (2022) used much smaller PCPA doses (40 mg/kg), in comparison with the other pharmacologic sleep disruption interventions. At the family level, pharmacologic sleep disruption was associated with a significantly decreased RA of *Porphyromonadaceae* in intervention animals versus controls (Qiao et al., 2022; Si et al., 2022).

An increase in the RA of *Blautia* (Si et al., 2022; Yu et al., 2022), *Clostridium* (Hong et al., 2020; Yu et al., 2022), *Escherichia* (Mo et al., 2023; Si et al., 2022), and *Sutterella* (Qiao et al., 2022; Si et al., 2022) was reported in intervention animals after pharmacologic sleep disruption. Pharmacologic sleep disruption also resulted in decreased RA of *Aerococcus* (Tang et al., 2021; Yu et al., 2022), *Faecalibaculum* (Liu et al., 2023; Tang et al., 2021), and *Rothia* (Liu et al., 2023; Yu et al., 2022) in the intervention group (Supplemental Figure S6). The response of *Parabacteroides* to pharmacologic sleep disruption was mixed, with significant increases (Hong et al., 2020; Si et al., 2022) and decreases (Qiao et al., 2022) in RA reported. Like the disparate Bacteroidota RA response, the study reporting decreased *Parabacteroides* also used a smaller dose of PCPA medication.

3.2.1.3. Preclinical research: Mechanical sleep disruption (sleep restriction/ fragmentation and sleep deprivation). Commercially available sleep disruption cages were used for mechanical sleep disruption in most of the reviewed studies, and sleep disruption interventions occurred < 24 h per day in 78 % of studies in this category. Mechanical sleep disruption duration ranged from shorter periods of 5–8 h to longer periods of 20–21 h per day (Supplemental Table S1A). Shorter term mechanical sleep disruption experiments ranged from 1 to 7 days, where chronic experiments ranged from 4 to 6 weeks. The impact of sleep disruption on sleep characteristics were only measured with EEG/EMG in one study, where it was demonstrated that animals acclimated to the sweeper bar and sleep time was not different from controls after two weeks of sleep disruption (Maki et al., 2020b).

Mechanical sleep disruption interventions lasting greater than 24 h ranged from sleep fragmentation experiments where a bar was moving at 2–3-minute increments to sleep deprivation where rodents were prevented from obtaining any sleep during the length of the intervention period (Supplemental Table S1A). The continuous sleep fragmentation experiments lasted 6 days in one study and 10 weeks in another, but objective sleep measures were not collected to evaluate the impact of the sweeper bar on sleep time or architecture. Sleep deprivation was achieved via gentle handling and forced locomotion (Supplemental Table S1A). Like sleep disruption, EEG electrodes were placed in only one of the studies to ensure no sleep was obtained during the intervention period (Everson and Toth, 2000). Sleep deprivation occurred at shorter periods of 1–3 days in most studies, but one study studied the microbial effects of longer durations of sleep deprivation, quantifying selected bacteria in gastrointestinal samples at 5, 10, 15 and 20 days of sleep deprivation (Everson and Toth, 2000).

Recovery periods post mechanical sleep disruption/sleep deprivation was evaluated in a subset of studies (Supplemental Table S1A). Most studies measured gut microbiome responses to recovery post intervention in periods of approximately one week, while other studies continued to monitor animals as long as 14–20 days post sleep disruption.

Total sleep deprivation lasting 48–72 h (Fang et al., 2023; Wang et al., 2022c), but not 24 h (Wang et al., 2022c), was associated with decreased alpha diversity, including measures of richness (Chao1) and richness/evenness (Shannon and Simpson indices) (Supplemental Table S4). Conversely, alpha diversity was not found to be different from controls when animals were allowed to sleep undisturbed for some portion of the day in mechanical sleep disruption interventions under seven days (El Aidy et al., 2020; Maki et al., 2020b; Triplett et al., 2020). Studies employing longer sleep disruption interventions showed mixed results regarding alpha diversity in rodents (Supplemental Table S4). For example, some reported a decrease in alpha diversity in the intervention group compared to controls between days 7 and 21 (Maki et al., 2020b; Zhang et al., 2017; Zhao et al., 2023), while others found no differences in alpha diversity during the same period, even extending up to 6 weeks of sleep disruption (Khannous-Lleiffe et al., 2021; Li et al., 2023b; Liu et al., 2022; Maki et al., 2020b; Sanford et al., 2021; Triplett et al., 2020; Zhang et al., 2017). Both studies that measured alpha diversity responses during recovery post sleep disruption reported no differences between intervention and control rodents when sleep disruption was stopped in the recovery phase (Supplemental Table S4) (Bowers et al., 2020; Maki et al., 2020b).

No studies compared differences in beta diversity in the preclinical sleep deprivation interventions. One study with sleep disruption/fragmentation > 24 h compared group beta diversity differences in distal ileal, cecal and fecal samples using Bray-Curtis dissimilarity and Weighted UniFrac distance measures (Triplett et al., 2020). After six days of continuous mechanical sleep disruption, distal ileal samples showed significant group differences using Weighted UniFrac distances; however, these differences were not replicated with Bray-Curtis distances or in the other sample types (Triplett et al., 2020). All studies that reported beta diversity comparisons in sleep disruption interventions < 24 h/day used Bray-Curtis dissimilarity or Weighted UniFrac distances in their models (Supplemental Table S5). Sleep disruption interventions of one week or less showed mixed effects: one study reported significant beta diversity differences (Li et al., 2023b), three studies reporting no differences (El Aidy et al., 2020; Maki et al., 2020b; Zhang et al., 2017), and one study found group differences after two days, but not four days, of mechanical sleep disruption (Bowers et al., 2020). Mechanical sleep disruption interventions of 7–14 days, and 21–28 days did not result in group differences in one study (Maki et al., 2020b), but six weeks of sleep disruption resulted in group beta diversity differences (using Bray-Curtis dissimilarity) that were consistent across distal ileal, cecal, and fecal samples in another (Triplett et al., 2020). These significant beta diversity differences between intervention and control animals were not maintained when Weighted UniFrac distance measures were used for data reduction (Triplett et al., 2020). Only one study compared gut microbiome composition differences post-sleep disruption, which reported significant group differences between intervention and control animals (Maki et al., 2020b).

In preclinical models of mechanical sleep disruption, responses in the RA of Actinomycetota was the only bacteria at the phylum level that had consistent responses in more than one study (Bowers et al., 2020; Poroyko et al., 2016b). Studies reported both increases and decreases in the RA of Bacillota, Bacteroidota, and Pseudomonadota in intervention animals compared to controls (Supplemental Figure S4). Specifically, approximately an equal number of studies observed an increase and a decrease in Bacillota (Bowers et al., 2020; Li et al., 2023a; Maki et al., 2020b; Poroyko et al., 2016b; Zhao et al., 2023), Bacteroidota (Li et al., 2023a; Maki et al., 2020b; Poroyko et al., 2016b; Wang et al., 2022a; Zhao et al., 2023), and Pseudomonadota (Maki et al., 2020b; Triplett et al., 2020; Zhao et al., 2023). Taxa classified to the family level had more uniform responses to mechanical sleep disruption (Supplemental Figure S5). For example, all studies that reported significant taxa comparisons consistently demonstrated an increased RA of *Erysipelotrichaceae* (Poroyko et al., 2016a; Triplett et al., 2020). In contrast, a decreased RA of *Coriobacteriaceae* was observed following mechanical sleep disruption, regardless of whether the intervention occurred during the light or dark phase (Sanford et al., 2021). A decreased RA of *Lactobacillaceae* and increased RA of *Clostridiaceae* in response to mechanical sleep disruption was observed in ileal, colonic, and fecal samples (Bowers et al., 2020; Poroyko et al., 2016b; Triplett et al., 2020; Zhao et al., 2023). All studies but one reported an increased RA of *Ruminococcaceae* (Poroyko et al., 2016b; Triplett et al., 2020) and *Turicibacteraceae* (Sanford et al., 2021; Triplett et al., 2020) in response to mechanical sleep disruption, and this effect was also observed in ileal, cecal and fecal samples.

Mechanical sleep disruption resulted in an increased RA of *Bacteroides* (Fang et al., 2023; Li et al., 2023a; Triplett et al., 2020), *Escherichia* (Everson and Toth, 2000; Maki et al., 2020b), *Odoribacter* (Li et al., 2023a; Zhao et al., 2023), *Romboutsia* (Li et al., 2023a; Maki et al., 2020b), *Streptococcus* (Li et al., 2023a; Wang et al., 2022c), and several *Lachnospiraceae* genera including *Lachnospiraceae bacterium A2, Lachnospiraceae UCG-006,* and *Lachnospiraceae UCG-008* (Maki et al., 2020b). A decreased RA of *Akkermansia* (Li et al., 2023a), *Akkermansia muciniphila* (Li et al., 2023b; Wang et al., 2022a), *Bifidobacterium* (Bowers et al., 2020; Li et al., 2023a), *Dubosiella* (Khannous-Lleiffe et al., 2021; Li et al., 2023a), *Intestinimonas* (Li et al., 2023a; Wang et al., 2022c), and *Lactobacillus* (Fang et al., 2023; Li et al., 2023a; Triplett et al., 2020) was also reported in response to mechanical sleep disruption in intervention animals (Supplemental Figure S6). Interestingly, the RA of *Parabacteroides* was reported to be increased in shorter sleep disruption interventions under two weeks (Oldfield et al., 2016; Triplett et al., 2020) but was decreased in when longer interventions in 3–4 weeks were employed (Maki et al., 2020b).

3.2.1.4. Human/translational research: Sleep deprivation and sleep restriction. Gut microbiome responses to total sleep deprivation in humans was analyzed in two studies, where participants were kept awake for 24 h and 40 h, respectively (Supplemental Table S1B). In sleep restriction experiments where participants were given a shortened sleep opportunity, the amount of time allowed in bed varied across studies, with shorter sleep opportunities ranging from 2 to 3 h, and longer opportunities ranging from 4 to 5 h (Supplemental Table S1B). The chronicity of sleep restriction experiments also varied across studies, where shorter sleep restriction experiments lasted from 2 to 3 days, and longer experiments lasted from 5 to 7 days. Recovery periods post sleep deprivation/sleep restriction were monitored in three studies ranging from shorter monitored recovery periods of 8 h to longer recovery periods of 2–7 nights. In three studies that included recovery periods, recovery sleep characteristics were objectively quantified using either PSG (Benedict et al., 2016; Wang et al., 2021) or actigraphy (Gao et al., 2023b).

Sleep deprivation had a robust effect on alpha diversity in humans, but response varied based on the metric evaluated (Supplemental Figure S2). Simpson indices decreased, on average, in one study after 24 h of sleep deprivation (Gao et al., 2023b), but were not significantly different from baseline in another study after 24 and 40 h of sleep deprivation, respectively (Supplemental Table S4) (Wang et al., 2021). Conversely, in the same study, average Shannon indices increased after 24 h of sleep deprivation (Gao et al., 2023b), but were again not significantly different from baseline after either sleep deprivation lengths in the other study (Wang et al., 2021). Like Shannon and Simpson indices, average richness, Chao1 and ACE measures differed across the two studies, suggesting more research is needed to confirm how gut microbiome alpha diversity responds to sleep deprivation in humans. In the study that monitored post-sleep deprivation recovery for one week, the decrease in Simpson and increase in ACE, Chao1, and Shannon indices from baseline persisted to the end of the seven-day recovery period (Gao et al., 2023b). Sleep restriction did not have the same impact on gut microbiome alpha diversity, and decreased microbial richness was only demonstrated in the one study that used the shortest sleep opportunity (2 h) for sleep restriction (Karl et al., 2023). Other measures of alpha diversity were not

significantly different in the same study or across other studies that restricted subjects' sleep (Benedict et al., 2016; Gao et al., 2023b; Karl et al., 2023; Zhang et al., 2017).

Sleep deprivation for 24 h resulted in group differences in beta diversity in both studies (Gao et al., 2023b; Wang et al., 2021), but significant within-group differences in gut microbiome community characteristics from baseline were not maintained after 2 days of sleep deprivation (Supplemental Table S5) (Wang et al., 2021). Like alpha diversity, sleep restriction did not have the same impact as sleep deprivation on overall gut microbiome composition differences. Sleep restriction to 5 h/sleep per night for 7 days led to within-group differences in microbiome composition from baseline (Gao et al., 2023b), but this effect on beta diversity was not replicated in shorter durations of sleep restriction in other studies (Benedict et al., 2016; Karl et al., 2023; Zhang et al., 2017).

Statistically significant responses of individual bacteria to sleep deprivation or sleep restriction at the taxonomic levels of phylum to species were not reported in many human studies. The F:B ratio was reported in three studies, where it was increased (Benedict et al., 2016) and decreased (Gao et al., 2023b) in response to sleep restriction, and decreased (Gao et al., 2023b) in response to sleep deprivation. The RA of *Erysipelotrichaceae* and *Coriobacteriaceae* increased in subjects after two days of sleep restriction (Benedict et al., 2016), while the RA of two putative short chain fatty acid fermenters, *Alloprevotella* and *Prevotella*, were significantly decreased after 40 h of sleep deprivation (Wang et al., 2021).

3.2.1.5. Human/translational research: Narcolepsy, insomnia, obstructive sleep apnea, and REM sleep disorders. Across studies that evaluated gut microbiome community characteristics in subjects with sleep-associated disorders, most studies studied patients with insomnia and obstructive sleep apnea (OSA) (Supplemental Table 1B). Other disorders involving sleep pathology in association with the gut microbiome were only evaluated in single studies (i.e., idiopathic REM sleep behavior disorder and narcolepsy). Most studies compared patients with the sleep-associated disorders to controls and used cross-sectional analyses in their group comparisons.

Alpha diversity was generally similar between controls and individuals with sleep-associated disorders (Supplemental Figure S2). In patients with narcolepsy and OSA, nearly all measures of alpha diversity were comparable to controls (Ko et al., 2021; Lu et al., 2022; Zhang et al., 2021b). Similarly, in subjects with insomnia, most alpha diversity metrics showed no significant differences, except for the Chao1 index, which was significantly decreased in three studies (Li et al., 2020; Liu et al., 2019; Masyutina et al., 2021). Beta diversity analyses were reported in only two studies evaluating the gut microbiome in insomnia (Li et al., 2020; Zhou et al., 2022), and one study in narcolepsy (Zhang et al., 2021b). Patients with narcolepsy had significantly different gut microbiome communities from control subjects (Zhang et al., 2021b), while among patients with insomnia, one study reported significant microbiome differences from controls (Li et al., 2020), while the other did not (Zhou et al., 2022).

Bacteria at the phylum level that were significantly differentially abundant in OSA versus controls were reported in one study, where patients with OSA had a decreased RA of

Bacteroidota and an increased F:B ratio versus control subjects (Lu et al., 2022). In patients with insomnia, the RA of Actinomycetota was increased (Li et al., 2020; Masyutina et al., 2021), and the RA of Bacillota was decreased (Li et al., 2020; Liu et al., 2019). Significant associations of taxa at the family level were not reported in the context of many sleep-associated disorders, with the exception that the RA of *Prevotellaceae* was increased in patients with REM sleep behavior disorder versus controls (Heintz-Buschart et al., 2018). At the genus level, OSA was associated with a decreased RA of *Alistipes* (Ko et al., 2019; Lu et al., 2022) and *Dialister* (Ko et al., 2019, 2021). Patients with insomnia had an increased RA of *Blautia* and *Eubacterium hallii*, and a decreased RA of *Faecalibacterium*, *Lachnospira*, and *Prevotella* compared to control subjects (Li et al., 2020; Masyutina et al., 2021). *Oscillibacter* and *Roseburia* consistently showed decreased RA across multiple sleep pathology groups, with both OSA and insomnia patients exhibiting lower levels of these taxa compared to controls (Supplemental Figure S6) (Ko et al., 2019, 2021; Li et al., 2020; Lu et al., 2022; Zhou et al., 2022).

3.2.1.6. Key takeaways. Preclinical sleep disruption models produced distinct microbiome signatures depending on intervention type. Paradoxical (REM) sleep disruption was associated with increased Bacillota RA and decreased RA of Bacteroidota, *Akkermansia*, *Bacteroides*, *Bifidobacterium*, *Faecalibacterium*, and *Lactobacillus* across multiple studies. In contrast, pharmacologic sleep disruption showed opposite phylum-level changes, with decreased Bacillota and increased Verrucomicrobiota. Genus-level responses to mechanical sleep disruption were the more consistent, including increased RA of *Bacteroides*, *Escherichia* and several genera within the *Lachnospiraceae* family, along with decreased RA of *Akkermansia*, *Bifidobacterium*, and *Lactobacillus*. In humans, acute sleep deprivation altered both alpha and beta diversity within 24 h, whereas sleep restriction required longer durations (5–7 days) to produce changes in microbiome composition. Among individuals with sleep-related disorders, decreased RA of *Faecalibacterium* was reported in patients with insomnia, while reduced *Oscillibacter* and *Roseburia* were observed in both insomnia and OSA compared with controls.

3.2.2. Preclinical and human/translational experiments involving circadian disruption

3.2.2.1. Preclinical research: Biological circadian disruption. Central circadian control of sleep and wake are regulated by several complementary proteins that generate a feedback loop to drive the approximately 24-hour rhythms of physiological processes across many organisms including rodents and humans. CLOCK and BMAL1 form a protein complex that control sleep-wake cycles and influence many sleep characteristics including sleep duration and quality (Kondratov et al., 2006; Laposky et al., 2005), and PERIOD (1/2) proteins interact with CLOCK and BMAL1 in a regulatory feedback loop that directs cellular biological activity timing (Schrader et al., 2024). Similarly, NPAS2 is a transcription factor that has many similar roles to CLOCK and is an important regulator of sleep homeostasis and circadian rhythmicity (DeBruyne et al., 2007). In preclinical studies of circadian disruption and gut microbiome community characteristics, biological circadian disruption was achieved using *Clock*, *Bmal1*, *Period*, and *Npas2* gene knockout mouse models (Supplemental Table S1A).

All three studies that reported associations between biological circadian disruption and alpha diversity observed alpha diversity changes in circadian-associated knockout models (Supplemental Figure S2), but alpha diversity responses varied significantly across model systems. For example, measures of microbial richness increased in *Per2* knockout mice (Zhen et al., 2022), decreased in *Per1/2* knockout mice (Thaiss et al., 2014), and were not significantly different in *ClockΔ19* knockout mice (Voigt et al., 2016) versus controls. Similarly, Shannon and Simpson indices were significantly increased in *Per2* knockouts (Zhen et al., 2022), and decreased in *ClockΔ19* knockouts versus control mice (Voigt et al., 2016), respectively. Only two studies reported beta diversity comparisons across biological circadian disruption groups (Liang et al., 2015; Voigt et al., 2016). Compositional differences in the gut microbiome were not significant between *ClockΔ19* knockout and control mice (Voigt et al., 2016). However, significant beta diversity differences were observed between *Bmal1* knockout and control mice using Unweighted UniFrac distances, although these differences were not replicated with Weighted UniFrac distances in the same study (Liang et al., 2015).

Response of bacteria at the phylum level to biological circadian disruption were reported in one study, where *Bmal1* knockout mice had a significant decrease in the RA of Pseudomonadota, and increase in the RA of Saccharibacteria versus controls (Liang et al., 2015). Significant responses of family-level bacteria to biological circadian disruption were not reported, and at the genus level, an increased RA of *Rikenella* was the only taxa differentially abundant in intervention animals versus controls in response to circadian disruption (Liang et al., 2015; Zhen et al., 2022).

3.2.2.2. Preclinical research: Circadian light alteration intervention. Circadian light interventions varied across studies, with some studies shifting light cycles more than once per week, others weekly, and one study shifting every two weeks (Supplemental Table S1A). Other circadian light interventions included continuous light exposure, continuous dark exposure or short light exposure (i.e., 8 h light and 16 h dark). Like the type of light exposure, the duration of interventions varied across circadian light alteration studies varying from periods of 2–4 weeks, 8–10 weeks and 12–16 weeks (Supplemental Table S1A).

Light/dark reversal, constant darkness, and constant light exposure were associated with decreased alpha diversity in fecal, cecal or jejunal samples across 14 metrics (Supplemental Figure S2) in four studies (Cheng et al., 2021; Hu et al., 2022; Li et al., 2021; Thompson et al., 2021), three studies (Olekhnovich et al., 2021; Sun et al., 2022; Zhang et al., 2022c), and one study (Olekhnovich et al., 2021), respectively. In six studies, mice exposed to circadian light alteration conditions showed no significant differences in alpha diversity of cecal or fecal microbiome samples versus controls. Weekly light-dark cycle reversal had mixed effects on beta diversity (Supplemental Figure S3); two studies reported no group differences (Thompson et al., 2021; Voigt et al., 2014), whereas two reported significant differences in gut microbiome community characteristics between intervention and control groups (Cheng et al., 2021; Li et al., 2021). Continuous light exposure had a more consistent effect, with significant differences between intervention and control rodents observed in both studies reporting beta diversity comparisons (Chu et al., 2019; Deaver et al., 2018).

Circadian light alteration interventions were associated with consistent responses of gut microbiota bacteria at the phylum level across light intervention studies (Supplemental Figure S4). A decreased RA of Bacteroidota was reported in animals exposed to circadian light shifting interventions (Koh et al., 2021; Li et al., 2021), continuous light exposure (Chu et al., 2019), and continuous darkness exposure (Sun et al., 2022; Zhang et al., 2022c) versus controls. Similarly, the F:B ratio was increased in response to circadian light shifting (Koh et al., 2021; Li et al., 2021) and constant darkness exposure (Sun et al., 2022), and the RA of Pseudomonadota was increased in response to circadian light shifting (Hu et al., 2022) and constant darkness exposure (Zhang et al., 2022c). The response of Bacillota to circadian light shifting was mixed, with one study reporting a decrease in RA (Hu et al., 2022) and another reporting an increased RA (Koh et al., 2021). Nevertheless, the RA of Bacillota consistently increased in response to continuous light exposures including constant light exposure (Chu et al., 2019) and constant darkness exposure (Sun et al., 2022; Zhang et al., 2022c).

Circadian light alteration exposures resulted in a decreased RA of *Ruminococcaceae* (Cheng et al., 2021; Hu et al., 2022; Li et al., 2021) and *Desulfovibrionaceae* (Cheng et al., 2021; Li et al., 2021) in intervention animals versus controls (Supplemental Figure S5). The effects of circadian light interventions on other taxa were less consistent, with studies reporting both significant increases and decreases in the abundance of *Christensenellaceae* (Cheng et al., 2021; Kim et al., 2019; Li et al., 2021; Thaiss et al., 2014), *Erysipelotrichaceae* (Hu et al., 2022; Li et al., 2021), and *Prevotellaceae* (Li et al., 2021; Thaiss et al., 2014). At the genus level, circadian light interventions were associated with an increased RA of *Akkermansia* (Hu et al., 2022; Sun et al., 2022), *Alloprevotella* (Chu et al., 2019; Hu et al., 2022), *Clostridium* (Khalyfa et al., 2017; Koh et al., 2021), *Ileibacterium* (Cheng et al., 2021; Hu et al., 2022; Li et al., 2021), and *Parasutterella* (Chu et al., 2019; Hu et al., 2022; Zhen et al., 2022). Conversely, altered light exposures led to a decreased RA of *Alistipes* (Li et al., 2021; Sun et al., 2022), *Bacteroides* (Koh et al., 2021; Li et al., 2021; Zhang et al., 2022c), *Bacteroides thetaiotaomicron* (Koh et al., 2021), *Odoribacter* (Chu et al., 2019; Li et al., 2021), *Phascolarctobacterium* (Li et al., 2021; Thaiss et al., 2014), and *Ruminococcus* (Li et al., 2021; Thaiss et al., 2014) versus controls (Supplemental Figures S6–S7).

3.2.2.3. Human/translational research: Circadian rhythm disruption. Human studies of circadian rhythm disruption were mostly observational, with only three studies manipulating sleep characteristics to alter circadian rhythms (Supplemental Table S1B). Two interventions used modest changes shifting sleep time by 2–4 h for one night or extending time in bed for 1 h per night for two weeks, where the third study was more extreme combining circadian misalignment with 3-hour sleep restriction to evaluate the cumulative impact of sleep and circadian disruption on the gut microbiome. The observational studies of circadian rhythm disruption ranged from evaluating the effect of rotating work shifts, interventional travel, and alterations in sleep regularity with gut microbiome community characteristics, respectively.

Alpha diversity of gut microbiome samples decreased (Shannon, Inverse Simpson and Chao1 indices) in subjects with reduced sleep regularity in one study (Holzhausen et al., 2023); however, across most studies, alpha diversity showed no significant association

with circadian rhythm disruption (Supplemental Figure S2) (Liu et al., 2020; Mortaş et al., 2020; Withrow et al., 2021). Lower objective sleep regularity was associated with significant differences in beta diversity compared with higher sleep regularity (Estaki et al., 2023), whereas night shift workers did not differ significantly in microbiome community composition from day shift workers (Mortaş et al., 2020).

Observational and interventional studies of circadian rhythm disruption (i.e., night shift schedules, altered sleep or wake times, and experimentally shifted bedtimes) were associated with an increase in the RA of Bacillota (Mortaş et al., 2020; Shochat et al., 2019), and an increase in the RA of Mycoplasmatota (Supplemental Figure S3) (Liu et al., 2020; Shochat et al., 2019). Lower objective sleep regularity was associated with a decreased RA of *Ruminococcaceae* (Shochat et al., 2019). Conversely, subjects working night shift had an increased RA of *Dorea formicigenerans* and *Dorea longicatena* versus subjects on the day shift (Mortaş et al., 2020).

3.2.2.4. Key takeaways. Preclinical circadian disruption induced by light manipulation decreased Bacteroidota and *Ruminococcaceae* across multiple interventions, including light/dark shifts, constant light, and constant darkness. Genus-level changes were consistent across light-based interventions, with increased *Akkermansia*, *Alloprevotella*, *Clostridium*, *Ileibacterium*, and *Parasutterella*, and decreased *Alistipes*, *Bacteroides*, *Odoribacter*, *Phascolarctobacterium*, and *Ruminococcus*. In contrast, biological circadian disruption using gene knockout models produced inconsistent diversity responses that varied by the specific circadian gene disrupted. In humans, circadian disruption associated with shift work and irregular sleep timing was characterized by increased Bacillota abundance and minimal changes in overall microbiome diversity.

4. Discussion

This comprehensive synthesis of the existing literature studying sleep and gut microbiome associations in humans and rodents demonstrated consistent findings that offer significant insight and consensus of gut microbiome responses to sleep and circadian disruption. For example, alpha diversity responses to sleep and circadian disruption were inconsistent and showed variability in alpha diversity under conditions like lower sleep quality, sleep deprivation, and circadian misalignment in both rodents and humans. Beta diversity responses to sleep and circadian disruptions were more consistent, often showing significant differences between disrupted and control groups in humans and rodents. Although the specific metrics (e.g., Bray-Curtis, UniFrac) varied, both humans and rodents commonly exhibited shifts in beta diversity under conditions like sleep deprivation, paroxysmal sleep disruption, and circadian misalignment, indicating changes in overall microbial composition. Additionally, sleep and circadian disruptions were associated with increased Bacillota and decreased Bacteroidota, although the response to sleep disruption alone was more variable. This pattern was observed under conditions of lower sleep quality, shorter sleep duration, sleep disruption (e.g., paroxysmal sleep disruption, insomnia), and circadian misalignment (e.g., night shift work, light alteration). These changes were often accompanied by an increase in the F:B ratio, highlighting a shift in major microbial phyla to sleep disturbances.

At the family level, both humans and rodents exhibited inconsistent changes in response to sleep and circadian disruptions, with some families like *Ruminococcaceae* and *Lachnospiraceae* showing mixed patterns of increase or decrease across studies. While certain families were implicated in preclinical and translational research, the direction and consistency of bacterial abundance changes varied across different types of sleep disruptions and model systems. Poor sleep quality and sleep disruption decreased beneficial genera such as *Faecalibacterium* and *Bifidobacterium*, while genera like *Akkermansia* and *Clostridium* frequently increased, particularly under circadian disruption, in both humans and rodents.

4.1. Assessment of sleep and gut microbiome research methodologies and their effectiveness in characterizing gut microbiome responses to sleep pathology

A substantial number of preclinical and translational research studies have explored the relationship between sleep and the gut microbiome, with 74 rodent studies and 65 human studies meeting the inclusion criteria for this review. However, there was considerable variability across study designs, including differences in sleep disruption methods, duration of interventions, and microbiome analysis methodologies and metrics reported.

In preclinical research, sleep and circadian disruption interventions varied widely across studies, using different models and intervention lengths. For paradoxical sleep disruption, all studies used the Modified Multiple Platform Method, but durations ranged from continuous disruption for 3–7 days to 12 h/day over 3–8 weeks. In pharmacologic sleep disruption, PCPA was also used in all studies to induce insomnia, but medication doses varied ranging from 40 mg/kg to 450 mg/kg over 2–3 days. Mechanical sleep disruption was used in models of sleep deprivation, sleep restriction and sleep fragmentation, with interventions ranging from 5 to 21 h per day in non-sustained interventions to continuous sleep deprivation 24 h/day, lasting from 1 day to 9 weeks. In circadian disruption models, different light alterations included continuous dark exposure, continuous light exposure, and time shifts (6- to 8-h shifts or light-dark cycle reversals) applied at intervals of 3 days to 2 weeks, over 2–16 weeks. Biological sleep disruption involved knockout models of various genes involved in circadian regulation, such as *ClockΔ19, Per1/2*, *Per2*, and *Bmal1* to examine the gut microbiome impacts of genetic circadian disruption.

In clinical studies, a range of interventions and observational methods were also used to assess subjective and objective sleep parameters. The PSQI was used in most studies involving quantification of subjective sleep quality, with a smaller subset using tools like the ISI or other sleep quality questionnaires. Approximately an equal number of studies measured sleep duration using either self-reported sleep times or objective sleep patterns through actigraphy or polysomnography. Objective sleep quality and regularity were also quantified using similar methodologies as objective sleep duration and included measures such as WASO and sleep efficiency. Observational studies in individuals with sleep-related disorders, including narcolepsy, insomnia, OSA, and idiopathic REM sleep behavior disorder, were conducted to compare gut microbiome differences with control groups, primarily through cross-sectional analyses. Interventions for sleep deprivation involved 24- to 40-h sleep deprivation protocols, followed by recovery sleep, while sleep restriction studies, ranging from 2 to 7 days, allowed sleep opportunities between 2 and 5

h. Finally, circadian disruption interventions included delayed bedtimes, sleep extension, and observational studies focused on international travel, shift work, and irregular bedtimes, with intervention lengths ranging from 1 day to 2 weeks.

Despite the broad range of study models and sleep-related conditions covered, the limited number of studies for each specific condition or intervention type made it difficult to pinpoint gut microbiome differences that were directly attributable to the underlying sleep pathology. The diversity in sleep disruption methods, intervention lengths, and representation of studies introduced considerable variability, making it challenging to differentiate between the effects of sleep disturbances and those of the specific interventions used. This was further complicated in clinical studies by the range of sleep disorders and measurement tools applied, such as subjective versus objective sleep metrics, which varied widely across studies. Leveraging complementary sleep measurement tools and metrics could support the development of more accurate sleep phenotypes. For example, combining the sleep regularity index with sleep duration may better capture habitual sleep patterns and circadian alignment, both of which are emerging indicators of sleep health. While the studies synthesized in this review provide valuable insight into potential links between sleep and the gut microbiome, heterogeneity in study design and small sample sizes present challenges for direct comparisons across studies. The taxonomic variability observed likely reflects both true biological differences between cohorts, including baseline microbiome composition, dietary patterns, host genetics, and environmental exposures, as well as differences in methodological approaches. Although greater standardization of research methods, particularly with respect to interventional protocols, sleep measurement tools, and reporting of key covariates such as diet, would help distinguish biological heterogeneity from methodological artifacts and more clearly isolate microbiome changes associated with sleep or circadian pathology, integrating assessments such as metabolite profiling and functional gene analysis (as discussed in **Part II** of this review) may offer more robust and mechanistically informative endpoints for understanding sleep-microbiome relationships across diverse populations.

A wide variety of metrics were employed across both alpha and beta diversity gut microbiome analyses, with differing degrees of reliability and consistency in their findings. For alpha diversity, commonly used metrics included Chao1, Shannon index, Simpson index, ACE, and observed features. Shannon and Chao1 indices were among the most frequently used, appearing consistently across different models of sleep disruption, circadian disruption, and sleep quality assessments. While these metrics provided mixed results, Shannon and Chao1 were often the most reliable in detecting decreases in alpha diversity, especially in response to sleep quality disruptions and in insomnia models. On the other hand, metrics like Simpson and ACE indices showed less consistent associations, sometimes indicating both increases and decreases in diversity or no change at all, particularly in rodent sleep disruption models.

Distance matrices such as Bray-Curtis Dissimilarity, Weighted UniFrac, and Unweighted UniFrac were the most commonly used in beta diversity analyses. Weighted UniFrac and Bray-Curtis emerged as the most reliable and efficient distance matrices employed to detect differences in microbial community structure, particularly in human studies examining

objective sleep quality and sleep disruption models. These metrics were able to detect group differences in beta diversity in several studies assessing subjective and objective sleep disturbances. However, it is worth noting that some inconsistencies existed, with certain studies finding no differences using these same metrics, particularly when examining sleep duration. Interestingly, only one study used Aitchison distance for beta diversity, despite recent literature recommending the use of Aitchison distance to effectively handle the compositional nature of microbiome data, providing a more robust and accurate analysis of community structure (Bastiaanssen et al., 2023; Gloor et al., 2017). Future research using Aitchison distance for beta diversity analyses will validate and potentially refine existing data on gut microbiome composition differences across sleep or circadian pathology groups.

4.2. Shared and disparate human and rodent gut microbiome associations with sleep and circadian pathology

4.2.1. Themes across responses to lower sleep quality and shorter sleep duration: In preclinical research, there was limited data on alpha diversity associations with objective and subjective measures of sleep duration and quality. Associations between subjective sleep quality and alpha diversity in clinical studies produced mixed results; however, most studies using objective sleep quality measures found significant relationships between poor sleep quality and decreased alpha diversity (Fig. 2). Several studies examining beta diversity across subjective sleep duration groups reported significant differences using metrics such as Binary Jaccard, Bray-Curtis, Weighted UniFrac, and Unweighted UniFrac, suggesting a potential reporting bias toward significant findings (Fig. 3). Conversely, most studies did not find beta diversity differences associated with subjective sleep quality, particularly when using Weighted UniFrac and Bray-Curtis distances, which consider the composition and abundance of taxa. Only one study examined objective sleep quality in relation to beta diversity, and found differences associated with both sleep latency and sleep efficiency, highlighting the need for further research on objective sleep quality and the gut microbiome.

Similar to alpha and beta diversity findings, no preclinical studies reported eligible phylum- or family-level differential abudance results for objective sleep quality or sleep duration. In humans, lower subjective sleep duration was associated with decreased RA of Bacillota, whereas no other bacterial phyla showed significant associations with subjective or objective sleep duration (Fig. 4). Similarly, no significant taxa at the family level were reported in association with subjective or objective sleep duration in humans or rodents, but the RA of *Ruminococcaceae* was decreased in association with two markers of lower objective sleep quality (WASO and sleep efficiency) in humans (Fig. 5). In rodents, there was a decreased RA of *Bifidobacterium* and *Lactobacillus*, and increased RA of *Akkermansia* and *Alistipes* in response to shorter sleep duration and lower sleep quality (Fig. 6), but these relationships were not reflected in human microbiome associations with sleep quality or duration (Fig. 7).

4.2.2. Themes across responses to sleep disruption: Both humans and rodents showed mixed alpha diversity responses under sleep disruption. In rodent models, there were both increases and decreases in alpha diversity, depending on the type (e.g., mechanical or pharmacologic) and duration of the sleep disruption. In preclinical research, sleep

deprivation interventions lasting more than 24 h consistently led to decreased alpha diversity. In cases of sleep disruption where animals could sleep for part of the day, no change in alpha diversity was observed for interventions under one week. Sleep disruption lasting 7–21 days produced mixed results, with some studies reporting decreased alpha diversity and others finding no change. In contrast, sleep disruption lasting 28 days or longer generally showed no alpha diversity differences. Similarly, human cohort studies of sleep disorders (e.g., insomnia and OSA) reported mixed findings, with some showing decreased alpha diversity and others finding no significant differences. The limited research on sleep deprivation in humans suggests sleep deprivation leads to differences in alpha diversity, but these results require future validation. Ongoing research is particularly relevant as many professions including military personnel and healthcare providers require extended wakefulness mimicking these conditions. Alpha diversity responses to sleep restriction in humans were less consistent, likely due to variability in sleep opportunity length, timing, and duration of restriction across studies (Fig. 2). In both rodent and human studies, beta diversity responses to sleep disruption were also mixed (Fig. 3). Rodent sleep disruptions under 7 days generally showed no significant differences, while longer durations (7–21 days) often led to significant changes, particularly when assessed with Weighted UniFrac and occasionally with Bray-Curtis dissimilarity. In humans, 24-h sleep deprivation resulted in significant beta diversity differences from baseline, but these differences were not maintained at 48 h. Beta diversity findings in association with sleep-associated disorders were not reported in many studies, likely due to a reporting bias of significant findings across manuscripts.

Phylum-level analyses typically revealed increases in Bacillota and decreases in Bacteroidota in human sleep disruption studies (Fig. 4), and rodent studies mirrored these trends, with various sleep disruption models (e.g., paroxysmal sleep disruption, pharmacologic sleep disruption). Paroxysmal sleep disruption was associated with the most consistent responses of phylum-level taxa, with multiple studies citing an increased RA of Bacillota and Pseudomonadota, and decreased RA of Bacteroidota in the intervention animals versus controls. At the family level, changes were variable, but several studies reported a decreased RA of *Lactobacillaceae* in response to sleep disruption in rodents and decreased RA of *Ruminococcaceae* in response to circadian disruption in both humans and rodents (Fig. 5). In both human and rodent models of sleep disruption, the RA of *Faecalibacterium* was decreased and *Blautia* was increased in preclinical models of paroxysmal and pharmacologic sleep disruption and human sleep pathologies including OSA and insomnia (Fig. 6; Fig. 7). In preclinical sleep disruption models, the RA of *Akkermansia* and *Akkermansia muciniphila* decreased in response to paroxysmal and mechanical models of sleep disruption, while the RA of *Prevotella* decreased in association with human sleep deprivation experiments and sleep disorders (e.g., OSA and insomnia). Alterations in taxa linked to mucin and complex carbohydrate metabolism, intestinal barrier maintenance, and anti-inflammatory functions may influence metabolic health and inflammation; however, continued mechanistic studies are needed to clarify the functional consequences of sleep disruption.

Both humans and rodents showed consistent reductions in *Lactobacillus* and *Faecalibacterium* in response to sleep disruption, particularly with REM sleep deprivation

in rodents and with insomnia or sleep restriction in humans. Increased *Oscillospira* and *Clostridium* were also reported across preclinical and translational sleep disruption studies, including mechanical or paroxysmal sleep disruption in rodents, and insomnia or obstructive sleep apnea in humans.

4.2.3. Themes across responses to circadian disruption: Circadian light alterations produced mixed effects on alpha diversity, varying by the metric used (e.g., Shannon, Simpson index) and the type of light exposure; however, constant darkness exposure consistently reduced alpha diversity across studies (Supplemental Table S4). Similar varied responses in alpha diversity were reported with preclinical biologic circadian disruption and human circadian disruption models, although decreased alpha diversity was consistently reported in individuals with lower sleep regularity. Observational or experimental shifted circadian rhythm paradigms were associated with an increased RA of Bacillota in humans and rodents, and increased RA of Pseudomonadota in preclinical models, including circadian light shifting and constant darkness exposure (Fig. 4). Additionally, both humans and rodents exposed to circadian disruptions, such as circadian light alteration or shift work, exhibited increases in the F:B ratio. In rodent models, constant light or dark exposure increased the F:B ratio by increasing the RA of Bacillota and decreasing the RA of Bacteroidota, where similar increases in Bacillota were also observed in individuals with circadian misalignment (i.e., night shift workers). Concordant bacterial responses to circadian disruption at the level of genus were only demonstrated in preclinical research, with several studies reporting a decreased RA of *Bacteroides*, *Lactobacillus*, *Phascolarctobacterium*, and *Ruminococcus*, and an increased RA of *Akkermansia*, *Bifidobacterium*, *Enterorhabdus*, and *Parasutterella* (Fig. 6). Future and ongoing research in human models of circadian disruption will confirm the cross-species replication of these findings across model systems and conditions.

4.2.4. Limitations identified in this literature synthesis and recommendations for future research: This literature synthesis identified limitations in the current body of research that studied relationships between pathologic sleep and the bacterial communities of the gut microbiome. Most studies used male rodents, and there was significant variability in intervention types, duration, and length across preclinical and human studies, complicating synonymous comparisons and data synthesis. Establishing standardized protocols for sleep disruption and consistent model systems would improve cross-study comparability. Differences in intervention length (e.g., sleep deprivation, restriction), and preclinical circadian light alterations were notable, and inconsistent doses of pharmacological agents, like PCPA, impacted bacterial responses to study interventions. The wide range of alpha diversity metrics used, and differences in how they are interpreted (e.g., richness measures like observed ASVs and Chao1), along with the infrequent use of Aitchison distances for beta diversity, highlights the need for standardized analytical approaches aligned with current best practices in the field. Establishing guidelines for best practices related to microbiome-associated research questions and developing standardized recommendations for metric reporting, like existing standards for sequencing metadata (i.e., minimum information about a marker gene sequence [MIMARKS]), will be crucial for consistency and comparability across studies (Yilmaz et al., 2011).

In human research, cross-sectional and associational study designs predominated, limiting the exploration of temporal responses of microbiome community characteristics in association with varying markers of sleep phenotypes or pathology. There was a reporting bias toward significant findings, with limited beta diversity comparisons presented in many studies. Moreover, preclinical research often lacked objective measures of sleep duration and quality, and alpha diversity was rarely analyzed in relation to these variables. Future research should prioritize developing longitudinal research designs, incorporating mechanistic approaches, and applying standardized diversity metrics to enhance our understanding of sleep-microbiome interactions. Additionally, incorporating both humans and rodents in future research will facilitate cross-species comparisons to deepen our understanding of shared and unique mechanisms across preclinical and translational research designs.

There are limitations that are important to mention in the discussion of our research synthesis. We exclusively focused on the bacterial microbiota. Although the gastrointestinal microbiome also includes viruses, fungi, and archaea and research on these organisms is expanding, we limited the scope to bacteria because of the extensive available literature and its direct relevance to the outcomes of this review. Nevertheless, as continued research emerges on relationships between other organisms in the gut microbiome and sleep, future synthesis of these associations will be of interest. Additionally, the included studies featured participants with varying comorbidities, and there was significant heterogeneity in the tests, statistical cutoffs, and covariates controlled for across research designs. Notably, dietary intake was not controlled in many studies, despite being a major determinant of gut microbiome composition. This represents a key confounder, and future research should aim to examine the interacting effects of sleep and circadian disruption with dietary factors to better isolate causal mechanisms. This variability prevented robust quantitative comparisons across studies and limited our ability to calculate effect sizes. As a result, although we identified trends in gut microbiome responses to sleep disruption, the diversity and inconsistency of reported metrics complicated synthesis within a comprehensive statistical framework. Finally, it is important to note that information regarding metabolic and signaling byproducts or mediators produced by the bacterial gut microbiome is absent in this synthesis. This omission stems from the volume of included studies, comprehensive nature of the sleep and circadian disruption methodologies reviewed, and the varied metrics reported across studies that were covered in this review, as dictated by our scoping review protocol (Maki et al., 2022). As many studies also quantified functional metabolites, neurotransmitter precursors, or immune mediators alongside microbial composition, we will synthesize these data in Part 2 of this review. This complementary analysis will focus on functional and signaling correlates of sleep and circadian disruption, providing further insight into how microbial metabolism and the production of bioactive compounds may contribute to sleep disturbances and their physiological consequences. Ongoing study of candidate mechanisms, particularly through longitudinal designs, will be critical for identifying causal links between sleep and circadian disruption and increased risk for disease.

5. Conclusions

In this review, we provide a comprehensive summary of current evidence on the gut microbiome and sleep, emphasizing how disrupted sleep impacts gastrointestinal microbial communities. Several taxa emerged as potentially relevant across studies, with some findings suggesting increases in bacteria associated with inflammation and metabolic dysfunction (e.g., *Clostridium*, *Enterobacteriaceae*), while others reported decreases in taxa linked to beneficial functions such as short-chain fatty acid production (e.g., *Faecalibacterium*, *Lactobacillus*). These patterns identify candidate bacterial groups that warrant future study as potential biomarkers or therapeutic targets, and require confirmation in additional cohorts and experimental models. However, the variability in comorbidities, metrics, and methodologies across studies complicates interpretation and limits cross-study comparability. There remains a lack of human research directly assessing the effects of circadian misalignment on microbiome diversity and composition. To advance the field, it is crucial to establish rigorous guidelines for best practices and standardized metric reporting. Such efforts will clarify the pathways linking sleep and circadian disruption-associated gut microbial shifts to metabolic and immune dysregulation, and will support translational research to develop and test microbiome targeted interventions to prevent or treat sleep disruption and related disease risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2026.106578.

Abbreviations:

ACE	Abundance-based Coverage Estimator
BMI	Body Mass Index
DNA	Deoxyribonucleic Acid
EEG	Electroencephalogram

EMG	Electromyogram
F:B Ratio	Firmicutes: Bacteroidetes Ratio represented as Bacillota: Bacteroidota in this manuscript
IP	Intraperitoneal
ISI	I, nsomnia Severity Index
OSA	Obstructive Sleep Apnea
OUT	Operational Taxonomic Unit
PCPA	Para-chlorophenylalanine
PSQI	Pittsburg Sleep Quality Index
RA	Relative Abundance
REM	Rapid Eye Movement
WASO	Wake After Sleep Onset

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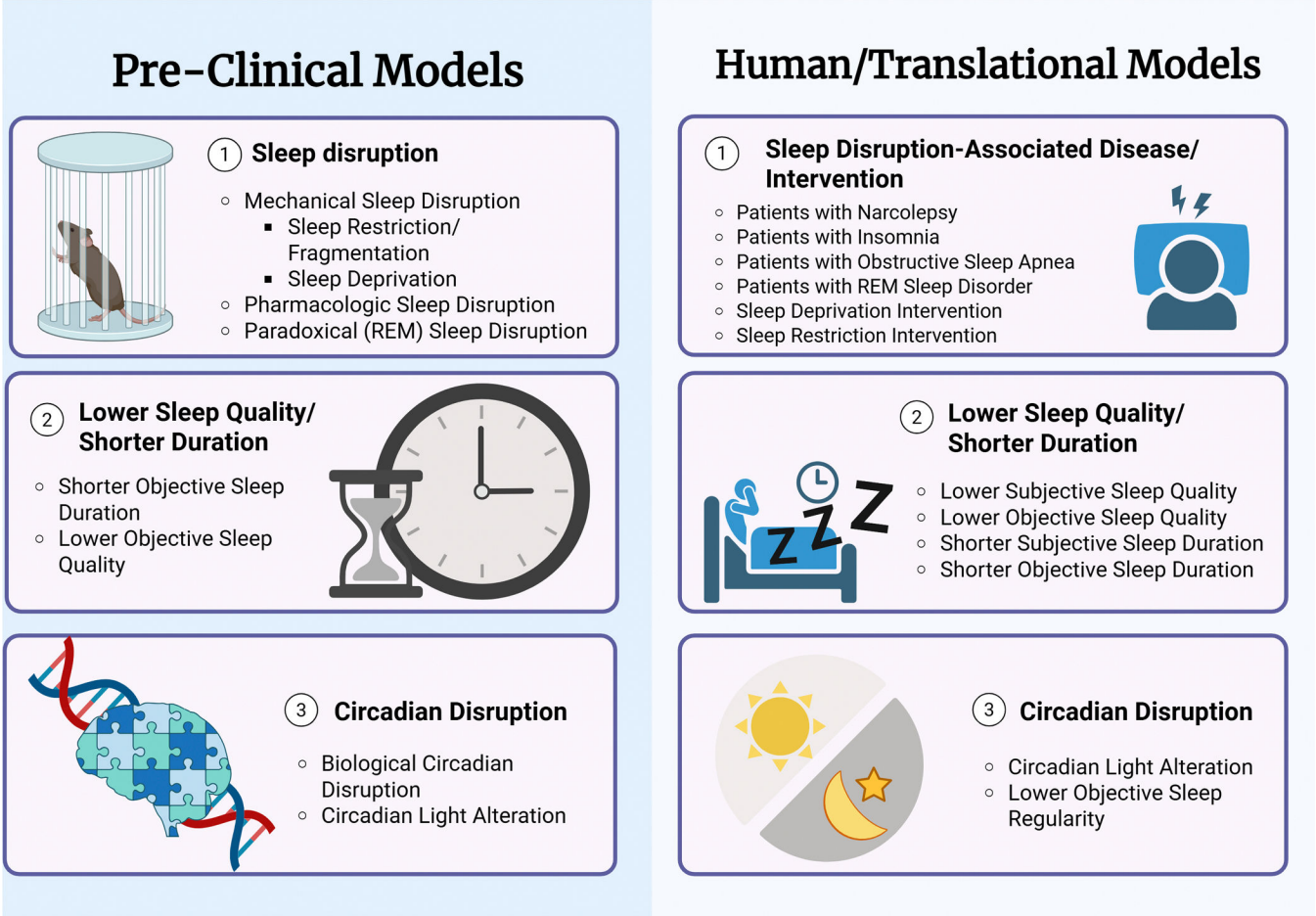

Fig. 1.

Preclinical and Human Models of Sleep and Circadian Disruption or Disease. Legend. Preclinical and Human Models of Sleep and Circadian Disruption or Disease. On the left panel, preclinical models or phenotype of sleep and circadian disruption are depicted. Sleep disruption is classified as research models of mechanical sleep disruption (including sleep restriction/fragmentation and sleep deprivation), pharmacologic sleep disruption, and paradoxical (rapid eye movement [REM]) sleep disruption. Lower sleep quality/shorter duration is classified from sources measuring objective sleep duration and/or objective sleep quality. Circadian disruption is classified as research models of biological circadian disruption and circadian light alteration. The right panel represents interventions, diseases or characteristics associated with sleep or circadian disruption. Sleep disruption-associated disease/intervention is categorized as patients with diagnosed sleep-associated disorders (e.g., narcolepsy, insomnia, obstructive sleep apnea, and REM sleep disorder), along with sleep deprivation or sleep restriction interventions. Lower sleep quality/shorter duration is classified from sources measuring subjective sleep duration, objective sleep duration, subjective sleep quality, and/or objective sleep quality. Circadian disruption is classified as interventions or observational studies that involve alternate light exposures (i.e., shift workers, crossing time zones) and from sources measuring objective sleep regularity. Created in BioRender. Maki, K. (2025) https://BioRender.com/jg7yn5b.

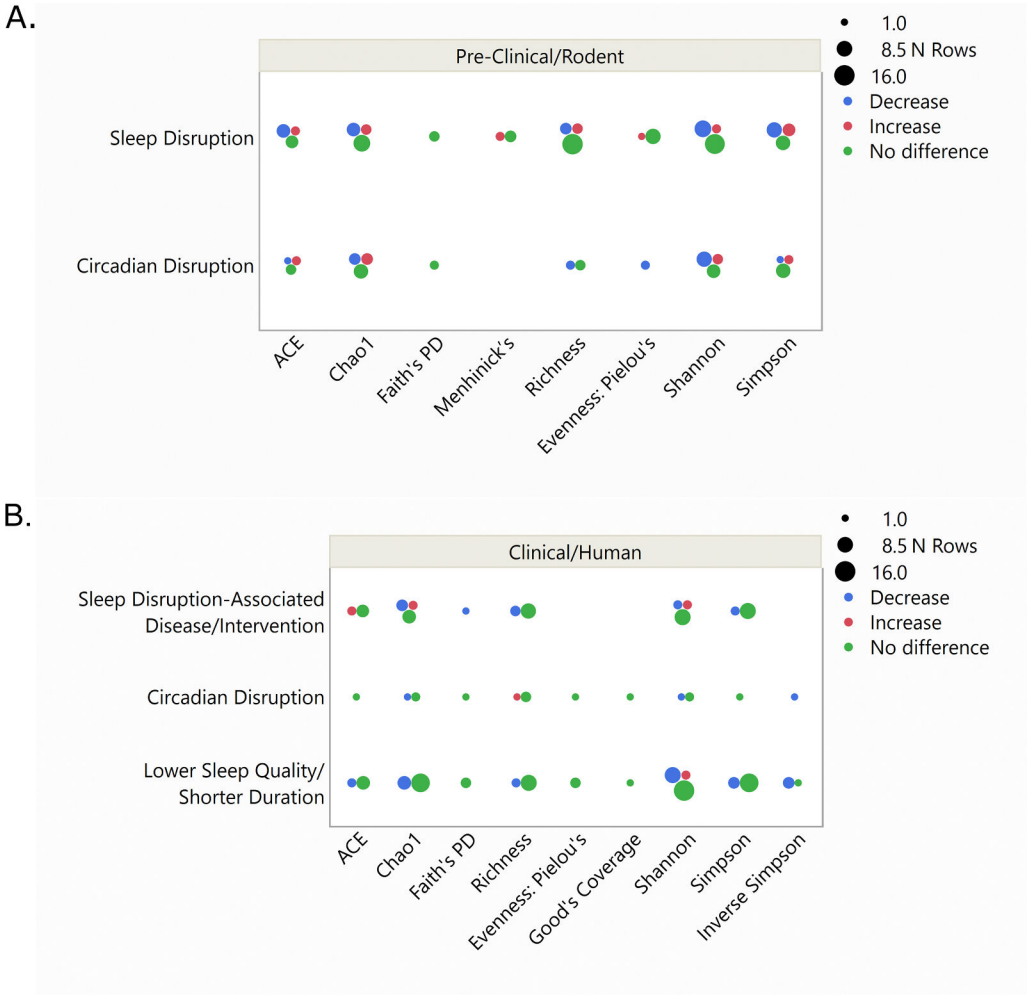

Fig. 2.

Relationships between Gut Microbiome Alpha Diversity and Altered Sleep Characteristics or Models. Legend. Alpha Diversity Associations with Sleep Characteristics and Sleep Disruption Model Systems. A. Rodent/Preclinical model systems were grouped based on their method of sleep disruption and results compared across different alpha diversity metrics. B. Human/Clinical studies were grouped based on the sleep pathology diagnosis or sleep characteristics and results were compared across different alpha diversity metrics. Measures of bacterial richness include abundance-based coverage estimator (ACE), Chao1, Faith's Phylogenetic Diversity (PD), and 'richness' (encompassing observed operational taxonomic units or amplicon sequence variants and observed species) metrics. Measures of bacterial evenness include Pielou's index, and estimation of sampling completeness is measured through Good's coverage index. Measures of bacterial richness and evenness include Shannon, Simpson, and inverse Simpson indices. Red circles indicate a significant increase in alpha diversity, blue indicate a significantly decreased alpha diversity and green circles indicate no significant differences in alpha diversity. The size of the circle is scaled so metrics that are more frequently mentioned appear larger. Fecal samples were collected noninvasively, while jejunal, colon, and cecal samples were collected invasively by study investigators. For illustration and comparison purposes, sleep characteristics categories were

merged to a single category when possible (i.e., positive and negative alpha diversity metrics with PSQI scores were grouped to ‘Lower Subjective Sleep Quality’, with direction of association reflected in the figure). Please see Supplemental Fig. S2 for alpha diversity responses by sleep pathology group (defined in methods), Supplemental Table S2 & Supplemental Table S3 for original study results from included sources and Supplemental Table S4 for tabulated alpha diversity data used to make figures.

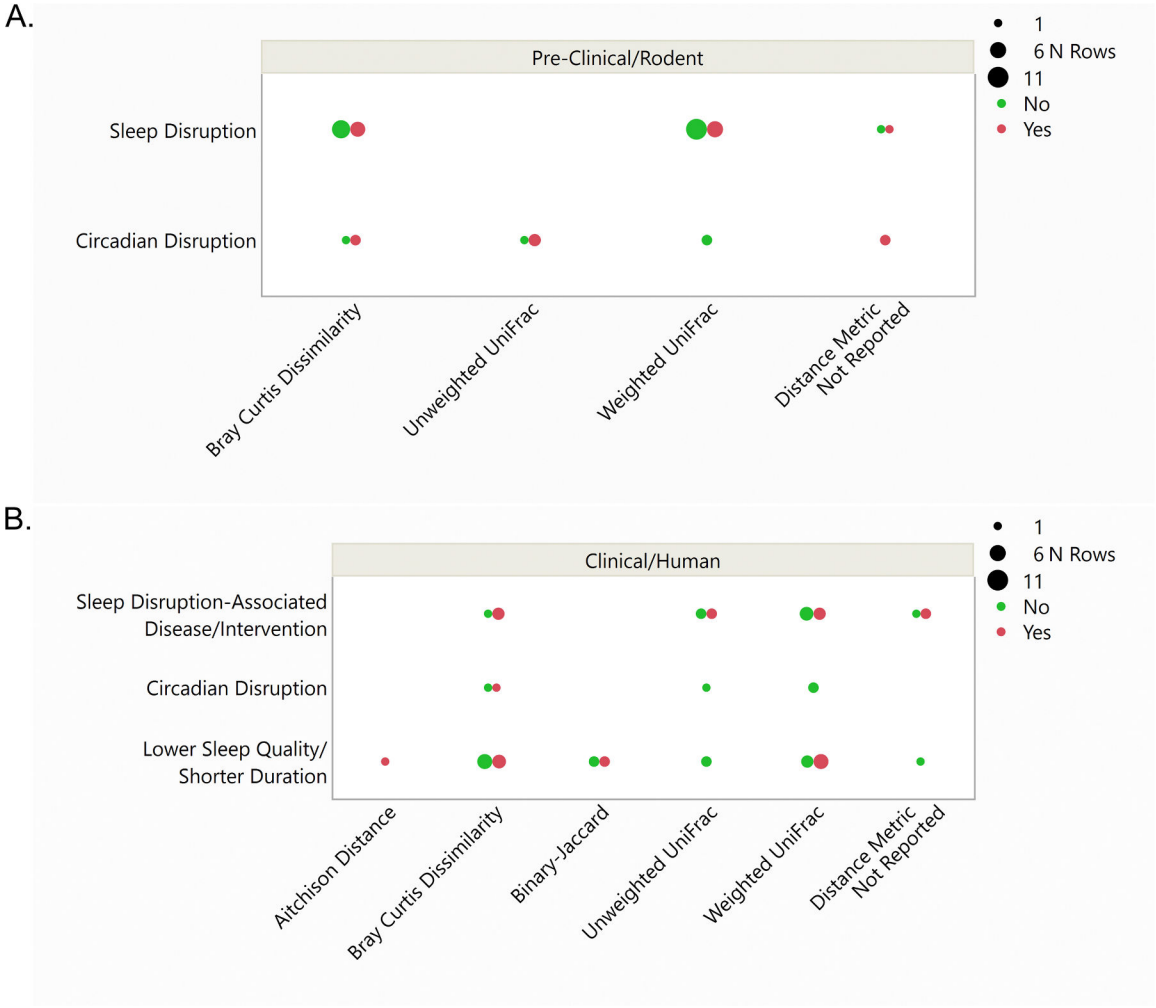

Fig. 3.

Differences in Beta Diversity by Sleep Pathology or Sleep/Circadian Disruption Models. Legend. Beta Diversity Associations with Sleep Characteristics and Sleep Disruption Model Systems. A. Rodent/Preclinical model systems were grouped based on their method of sleep disruption and results compared across different beta diversity metrics. B. Human/ Clinical studies were grouped based on the sleep pathology diagnosis or sleep characteristics and results were compared across different beta diversity metrics. Red circles indicate a significant difference in beta diversity across groups, and green circles indicate no significant differences in beta diversity. The size of the circle is scaled so metrics that are more frequently mentioned appear larger. Fecal samples were collected noninvasively, while jejunal, colon, and cecal samples were collected invasively by study investigators. For illustration and comparison purposes, sleep characteristics categories were merged to a single category when possible (i.e., positive and negative alpha diversity metrics with PSQI scores were grouped to ‘Lower Subjective Sleep Quality’, with direction of association reflected in the figure). Please see Supplemental Fig. S3 for beta diversity responses by sleep pathology group (defined in methods), Supplemental Table S2 & Supplemental Table S3 for

original study results from included sources and Supplemental Table S5 for tabulated beta diversity data used to make figures.

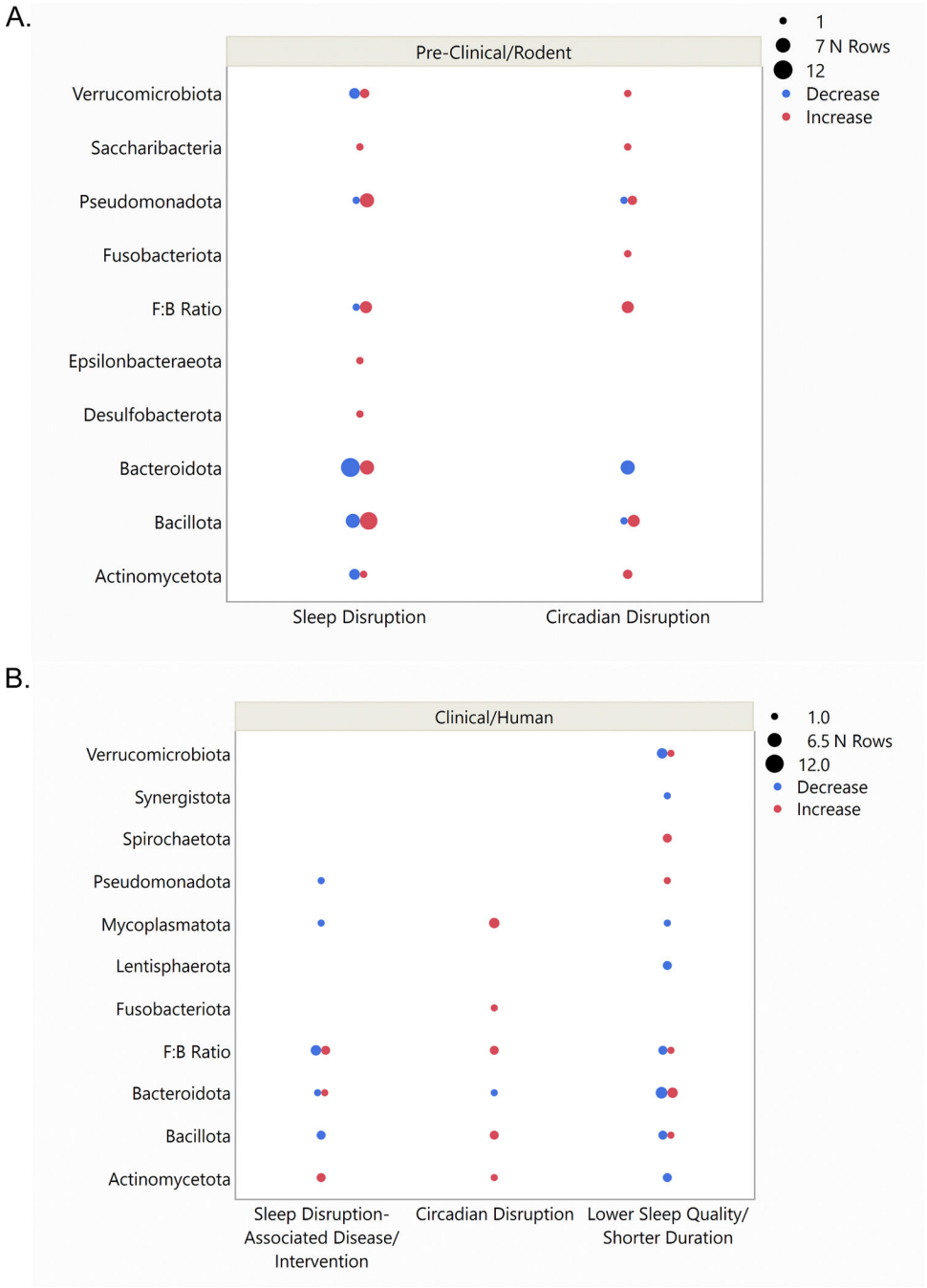

Fig. 4.

Differences in RA of Phylum-Level Bacteria in Sleep and Circadian Disruption. Legend. Phylum-Level Associations with Sleep Characteristics and Sleep Disruption Model Systems. Differential abundance of bacterial phyla in A. Preclinical models of sleep or circadian disruption and B. Human/translational models of sleep or circadian disruption and sleep-associated disease. Red circles indicate a significant increase in relative abundance, and blue indicate a significantly decreased relative abundance. The size of the circle is scaled so taxa that are more frequently mentioned appear larger. Bacteria were classified according to the

International Committee on Systematics of Prokaryotes current nomenclature for consensus across studies (Oren et al#, 2023). Bacteroidetes were reclassified as Bacteroidota, Verrucomicrobia as Verrucomicrobiota, Lentisphaerae as Lentisphaerota, Proteobacteria as Pseudomonadota, Firmicutes as Bacillota, TM7 as Saccharibacteria, Actinobacteria as Actinomycetota, Tenericutes as Mycoplasmatota, Fusobacteria as Fusobacteriota, Spirochaetae as Spirochaetota, and Synergistetes as Synergistota. Abbreviations. F: B Ratio= Firmicutes: Bacteroidetes (or Bacillota: Bacteroidota) Ratio. Fecal samples were collected noninvasively, while jejunal, colon, and cecal samples were collected invasively by study investigators. Please see Supplemental Fig. S4 for phylum differential abundance responses by sleep pathology group (defined in methods), Supplemental Table S2 & Supplemental Table S3 for original study results from included sources and Supplemental Table S6 for tabulated phylum differential abundance data used to make figures.

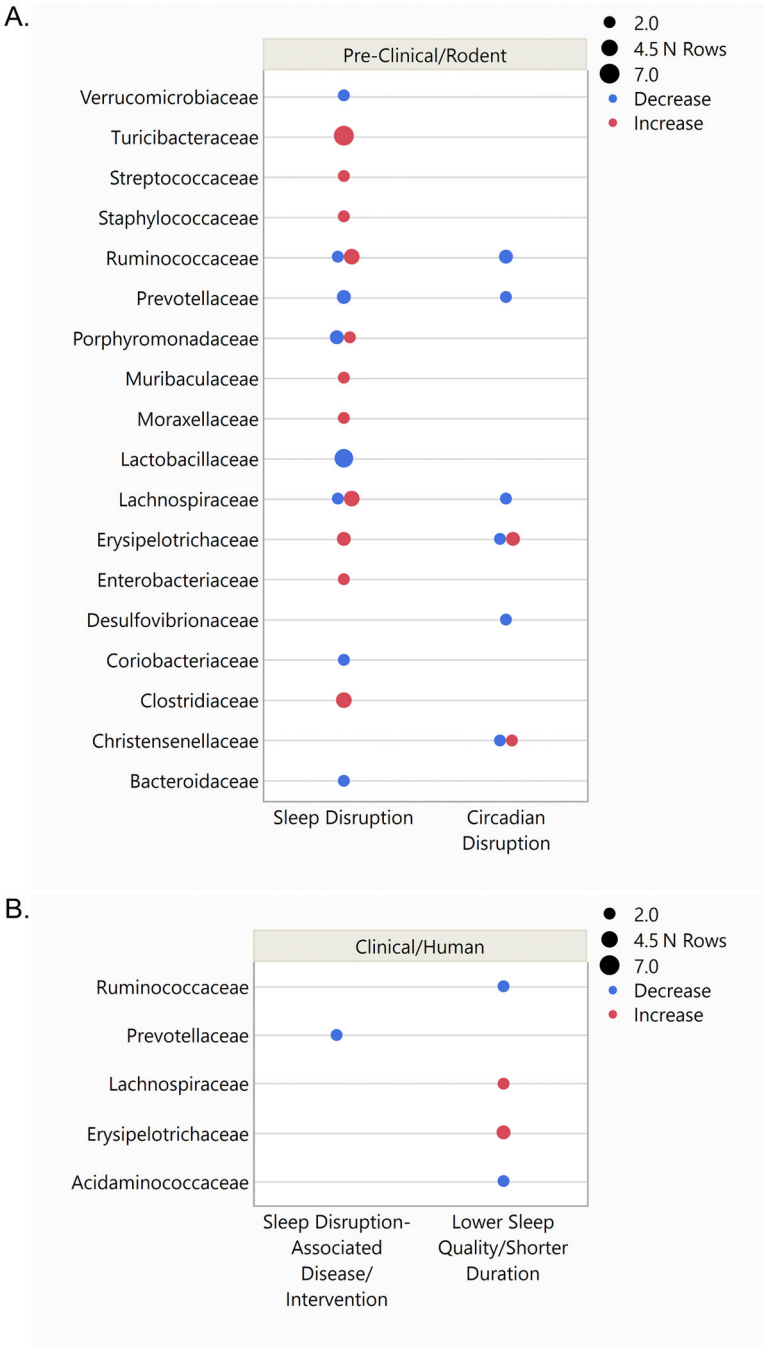

Fig. 5.

Differences in Relative Abundance of Family-Level Bacteria in Sleep and Circadian Disruption. Legend. Family-Level Associations with Sleep Characteristics and Sleep Disruption Model Systems. Differential abundance of bacteria at the taxonomic level of family in A. Preclinical models of sleep or circadian disruption and B. Human/translational models of sleep or circadian disruption and sleep-associated disease. Red circles indicate a significant increase in relative abundance, and blue indicate a significantly decreased relative abundance. The size of the circle is scaled so taxa that are more frequently mentioned appear

larger. Taxa were required to be reported at least twice to be included in the figure. Fecal samples were collected noninvasively, while jejunal, colon, and cecal samples were collected invasively by study investigators. Please see Supplemental Fig. S5 for family differential abundance responses by sleep pathology group (defined in methods), Supplemental Table S2 & Supplemental Table S3 for original study results from included sources and Supplemental Table S7 for tabulated family differential abundance data used to make figures.

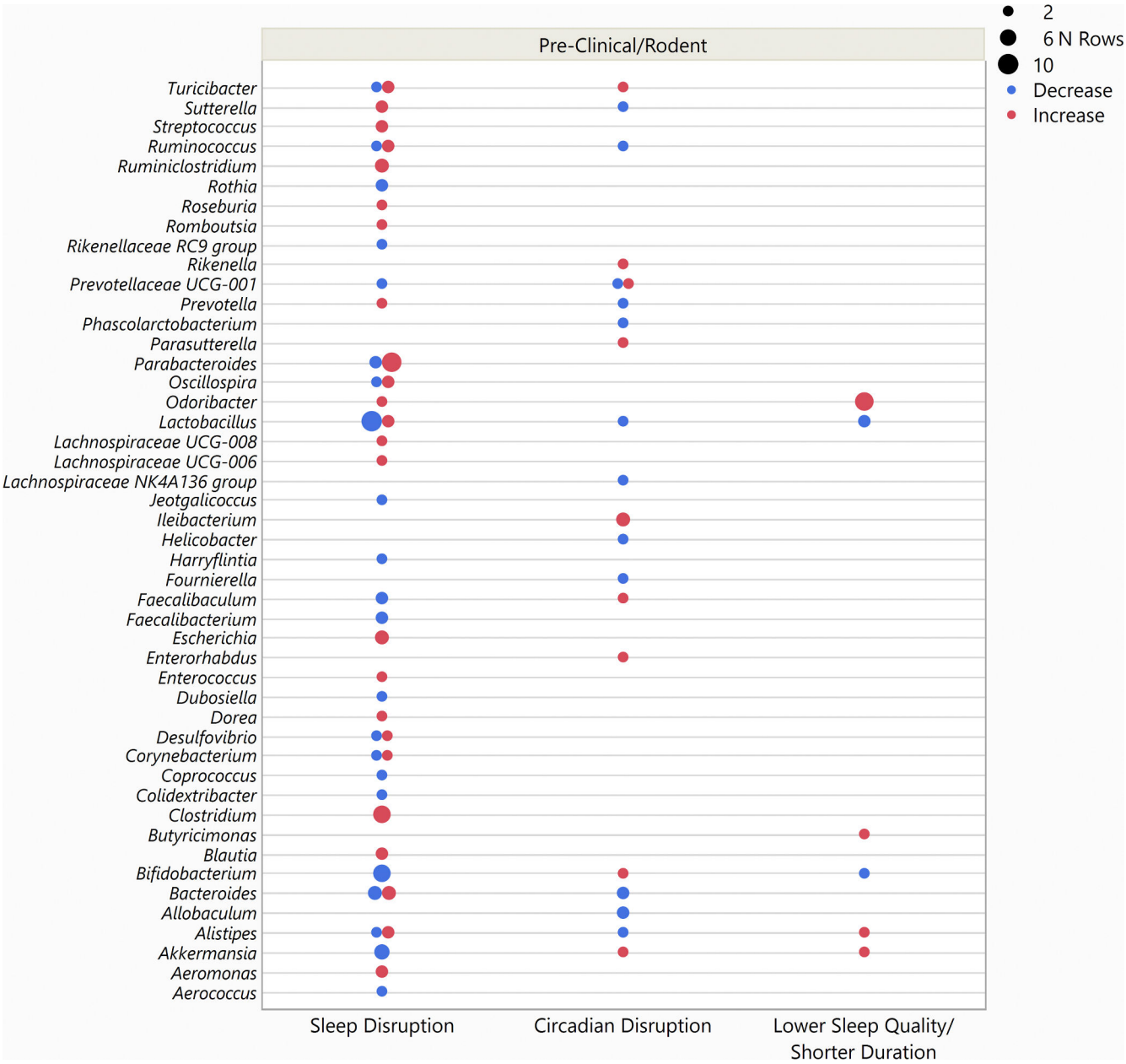

Fig. 6.

Differences in Relative Abundance of Genus-Level Bacteria in Sleep and Circadian Disruption: Preclinical Sources. Legend. Genus-Level Associations with Sleep Characteristics and Sleep Disruption Model Systems. Differential abundance of bacteria at the taxonomic level of genus in preclinical models of sleep or circadian disruption. Red circles indicate a significant increase in relative abundance, and blue indicate a significantly decreased relative abundance. The size of the circle is scaled so taxa that are more frequently mentioned appear larger. Taxa were collapsed to the level of genus (if species reported), and genera required to be reported at least twice to be included in the figure. Fecal samples were collected noninvasively, while jejunal, ileal, colon, and cecal samples were collected invasively by study investigators. Please see Supplemental Fig. S6 for genus differential

abundance responses by sleep pathology group (defined in methods), Supplemental Fig. S7 for species differential abundance responses, Supplemental Table S2 for original study results from included sources, and Supplemental Table S8 for tabulated genus and species differential abundance data used to make figures.

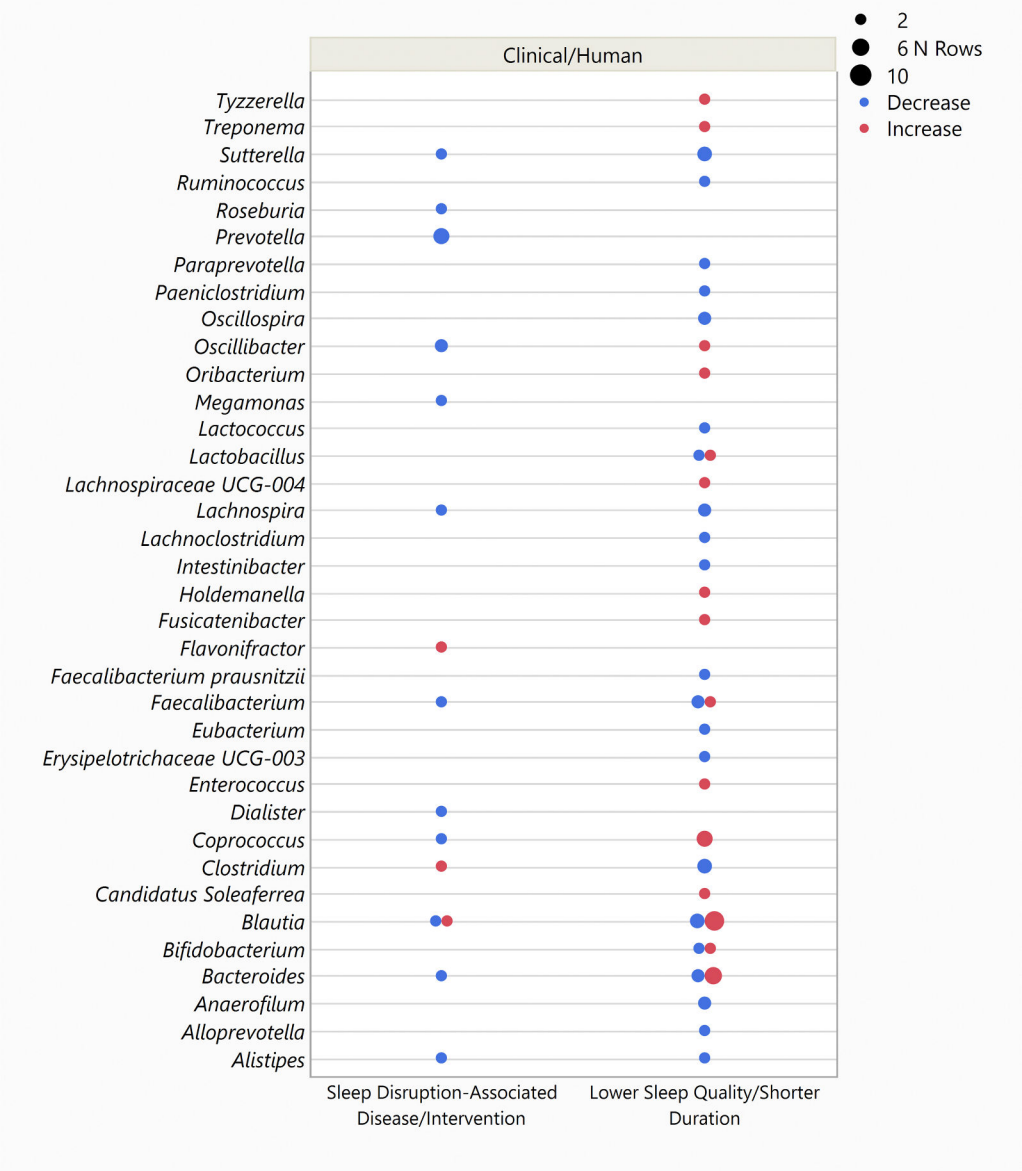

Fig. 7.

Differences in Relative Abundance of Genus-Level Bacteria in Sleep and Circadian Disruption: Human/Translational Sources. Legend. Differences in Relative Abundance of Genus-Level Bacteria by Sleep Pathology Group: Human/Translational Sources. Differential abundance of bacteria at the taxonomic level of genus in human sleep phenotypes, sleep disruption interventions or sleep-associated disease. Red circles indicate a significant increase in relative abundance, and blue indicate a significantly decreased relative abundance. The size of the circle is scaled so taxa that are more frequently mentioned appear larger. Taxa were collapsed to the level of genus (if species reported), and genera required to be reported at least twice to be included in the figure. Please see Supplemental Fig. S6 for genus differential abundance responses by sleep pathology group (defined in methods), Supplemental Fig. S7 for species differential abundance responses, Supplemental Table S3

for original study results from included sources, and Supplemental Table S8 for tabulated genus and species differential abundance data used to make figures.