Sleep, circadian rhythm and gut microbiota: alterations in Alzheimer’s disease and their potential links in the pathogenesis

Yi Li*, Lingzhan Shaoa, Yang Moub, Yan Zhangb, and Yong Pingb, c

ABSTRACT

In recent years, emerging studies have observed gut microbiota (GM) alterations in Alzheimer’s disease (AD), even in individuals with mild cognitive impairment (MCI). Further, impaired sleep and circadian patterns are common symptoms of AD, while sleep and circadian rhythm disruption (SCRD) is associated with greater β-amyloid (Aβ) burden and AD risk, sometimes years before the clinical onset of AD. Moreover, reports have demonstrated that GM and its metabolites exhibit diurnal rhythmicity and the role of SCRD in dampening the GM rhythmicity and eubiosis. This review will provide an evaluation of clinical and animal studies describing GM alterations in distinct conditions, including AD, sleep and circadian disruption. It aims to identify the overlapping and distinctive GM alterations in these conditions and their contributions to pathophysiology. Although most studies are observational and use different methodologies, data indicate partial commonalities in GM alterations and unanimity at functional level. Finally, we discuss the possible interactions between SCRD and GM in AD pathogenesis, as well as several methodological improvements that are necessary for future research.

Introduction

Alzheimer’s disease (AD) is a degenerative central nervous system (CNS) disorder, characterized by a progressive onset of neurocognitive symptoms, including amnesia, aphasia, disorientation, etc.1 While the etiology of AD remains largely unknown, AD is generally featured by the deposition of β-amyloid (Aβ) and the formation of neurofibrillary tangles of tau protein in CNS.

The human body harbors a large variety of microorganism communities which intensively interact with host and each other through direct contacts or metabolites.2 It has long been postulated that human gut microbiota (GM), the collection of all microorganism communities in the human digestive tract, holds great significance to human health and disease.3, 4 However, not until recently have we been able to investigate their composition and function with the advances in DNA sequencing and metagenomic analysis techniques.5 Moreover, brain-gut-axis (BGA), which studies the interactions between GM and CNS, has gained significant attention in recent years. There is much evidence showing altered GM composition in several neurological diseases, including Parkinson’s disease (PD) and autism spectrum disorder (ASD).6–8 Changes in GM composition and richness have also been observed in AD patients and individuals with mild cognitive impairment (MCI),9, 10 suggesting a potential role of GM dysbiosis in AD pathogenesis.

Several neurodegenerative diseases including AD, PD and Huntington disease (HD) have been implicated with sleep disturbance and circadian rhythm dysfunction.11 While sleep and circadian rhythm disruption (SCRD) are usually recognized as the consequences of these diseases, studies have reported the existence of sleep disorders long before the onset of AD and PD, even by decades.12–15 Moreover, growing evidence indicates that sleep disturbance and circadian rhythm misalignment may contribute to neuroinflammation, low Aβ clearance efficacy,
increased concentration of reactive oxygen species (ROS), compromised blood-brain-barrier (BBB) and GM dysbiosis.\textsuperscript{16–18} However, the present work revealed the correlation between SCRD and AD, but not causality, and further work is needed to resolve this issue.

Studies in the last few decades have long examined common determinants of the human GM, including diet, medicine and stress.\textsuperscript{19,20} Recent findings suggest a novel role of sleep and circadian rhythm in shaping and modulating the composition of GM.\textsuperscript{21} However, to the best of our knowledge, no reviews to date have considered the possible contributions of synergistic interactions between SCRD and GM dysbiosis to the pathogenesis of AD. In this review, we first present recent studies that examined the GM alterations in AD and SCRD. We summarize those findings and compare the GM changes at both compositional and functional levels across studies. We observe commonalities in GM alterations of individual bacteria and unanimous changes at functional level between AD and SCRD conditions. Therefore, we discuss possible interactions between SCRD and GM, which contribute to AD onset by inducing peripheral and central inflammation (Figure 1). We reason that this is achieved through various pathways including disrupted gut barrier integrity, compromised blood-brain barrier (BBB), decreased short-chain fatty acids (SCFAs) production and increased pro-inflammatory metabolites.

**GM and AD**

The role of microorganisms in the pathogenesis of AD was initially proposed by Alois Alzheimer, the first describer of this progressive neurodegenerative disorder.\textsuperscript{22} After decades of insufficient research, there has been a resurgence of interests in this hypothesis, largely owing to a growing body of evidence from clinical and animal tests. Several kinds of infectious agents such as bacteria, fungi, virus and protozoa that are highly associated with AD have been reviewed elsewhere.\textsuperscript{1,23–25} In this part, we focus on GM alterations, probiotic and antibiotic treatments, and fecal microbiota transplantation (FMT) in both AD patients and models.
Table 1. Summary of studies investigating GM alteration in AD.

| Reference | Participant/animal model | GM profiling method | Higher or lower bacterial taxa in AD patients/AD animal models | Other major findings |
|-----------|--------------------------|---------------------|---------------------------------------------------------------|---------------------|
| **Human study** | | | | |
| 26 | 43 AD patients and 43 age- and gender-matched HC | 16S rRNA gene seq V3-V4 region | ↑ Family: Enterococcaceae, Lactobacillaceae Genus: Subdoligranulum Species: Ruminococcus gravis ↓ Family: Lachnospiraceae, Bacteroidaceae, Veillonellaceae Genus: Lachnoclostridium, Bacteroides | - Similar alteration of gut and blood microbiota in AD and MCI - Increased blood Staphylococcus, Pseudomonas, and Escherichia in AD and MCI vs. HC - Dorea, Blautia, and Escherichia as risk factors for AD |
| 9 | 30 AD patients, 30 MCI patients, and 30 age- and gender-matched HC | 16S rRNA gene seq V3-V4 region | ↑ Family: Lachnospiraceae, Streptococcaceae, Erysipelotrichaceae, Coriobacteriaceae, Lactobacillaceae, Bifidobacteriaceae Genus: Akkermansia, Blautia, Dorea, Eggerthella, Streptococcus, Bifidobacterium, Lactobacillus ↓ Family: Alistipes, Bacteroides, Butyricimonas, Haemophilus, Parabacteroides | - Progressive enrichment of Enterobacteriaceae distinguishes AD from aMCI and HC - Elevated bacterial secretion system and LPS biosynthesis |
| 10 | 33 AD patients, 32 aMCI patients, and 32 age- and gender-matched HC | 16S rRNA gene seq V3-V4 region | ↑ Family: Enterobacteriaceae, Veillonellaceae ↓ Family: Clostridiaceae, Lachnospiraceae, Ruminococcaceae Genus: Blautia, Ruminococcus | - Progressive GM shift in AD mice at 3 months |
| 27 | 25 AD patients and 25 age- and gender-matched HC | 16S rRNA gene seq V4 region | ↑ Family: Bacteroidaceae, Rikenellaceae, Gemellaceae Genus: Blautia, Bacteroides, Alistipes, Bilophila, Gemella, Phascolarctobacterium ↓ Family: Ruminococcaceae, Bifidobacteriaceae, Clostridiaceae, Peptostreptococcaceae, Mogibacteriaceae, Turicibacteriaceae Genus: Bifidobacterium, Dialister, Clostridium, Turibacter, Adlercreutzia | - Escherichia and Shigella correlate with pro-inflammatory IL-1β, NLRP3 and CXCL2 - Eubacterium rectale correlates with anti-inflammatory IL-10 |
| 28 | 40 Amy+ patients, 33 Amy- patients, and 10 HC | Microbial DNA qPCR Assay Kit | Amy+ vs. HC Species: Eubacterium rectale, Bacteroides fragilis | - - |
| **Animal study** | | | | |
| 29 | Female APP/PS1 mice Control: female WT mice Age: 3, 6 and 24 months | 16S rRNA gene seq V1-V3 region | ↑ Family: Erysipelotrichaceae Genus: Sutterella ↓ Family: Rikenellaceae | - Progressive GM structure with decreased fermentation capacity - Dysregulated lipid, carbon and pyruvate metabolism |
| 30 | Male SAMP8 mice Control: male SAMP1 mice Age: 6 months | 16S rRNA gene seq V3-V4 region | ↑ Genus: Alistipes, Akkermansia, norank_f__Lachnospiraceae, Odoribacter, Streptococcus, Rikenella, Butyricicoccus Genus: Prevotella, Parasutterella, Butyrivibrio, Eubacterium, Ruminococcus, norank_f__S24_7, 7, Prevotellaceae, Enterococcaceae Genus: Faecalibaculum, Ruminococcaceae UCG-01, Alloprevotella, Enterococcus | - Alleviated AD pathology in AD mice after FMT from WT mice - Increased level of butyrate in FMT-treated AD mice |
| 31 | Male APP/PS1 mice Control: male WT mice Age: 6 months | 16S rRNA gene seq V3-V4 region | ↑ Family: Verrucomicrobiaceae, Desulfuviromonaceae, Staphylococcaceae, Corynebacteriaceae Genus: Akkermansia, Staphylococcus, Desulfuviromonas, unclassified_f__Erysipelotrichaceae, Genus: S24_7, Prevotellaceae, Enterococcaceae Genus: Faecalibaculum, Ruminococcaceae UCG-01, Alloprevotella, Enterococcus | - Decreased spatial learning and memory function in WT pseudo GF mice after FMT from AD mice |
| 32 | Male SAMP8 mice Control: male SAMP1 mice Age: 7 months | 16S rRNA gene seq V3-V5 region | ↑ Genus: uncultured Bacteroidales bacterium ↓ Family: Clostridiales vadinBB60 group, Family XIII, Christensenellaceae, Ruminococcaceae, Desulfuviromonaceae, Deferribacteraceae Genus: Mucipirillum, Seratia, Subdoligranulum, Ruminoclostridium, Coprococcus, Oscillibacter | - Lower level of SCFAs in feces and brain of AD mice |
| 33 | Male APP/PS1 mice Control: male WT mice Age: 1, 3, 5–6, 8–12 months | 16S rRNA gene seq V3-V4 region | ↑ Family: Erysipelotrichaceae, Verrucomicrobiaceae Species: Desulfuvirobirch C21_c20 Genus: Ruminococcus, Butyricicoccus Species: Butyricicoccus pullicaceorum | - Disrupted intestinal structure |
| 34 | Male APP/PS1 mice Control: male WT mice Age: 3, 6 and 8 months | 16S rRNA gene seq V3-V4 region | ↑ Family: Helicobacteraceae, Desulfuviromonaceae, Coriobacteriaceae Genus: Odoribacter, Helicobacter Genus: Prevotella, Ruminococcus | - Impaired spatial learning and increased Aβ burden in AD mice | (Continued)
**GM alterations in AD: from clinical and animal literature**

Recent clinical observations have found significant GM alterations in both AD and MCI patients. Here, we summarize the alterations of GM composition in AD patients compared to controls in Table 1 (top). In addition, animal models are also used in other studies, and the relevant findings are summarized in Table 1 (bottom).

Note that transgenic mice including APP/PS1, SAMP8, 5xFAD and their derivatives were the most frequently used AD models. Substances such as D-galactose, Aβ protein and lipopolysaccharide (LPS) were also used in several studies to induce AD pathology.

It has been suggested that α-diversity analysis and Firmicutes/Bacteroidetes (F/B) ratio, two frequently used criteria in microbiome analysis, are not reliable in investigating the association between GM alteration and PD. Interestingly, we also found inconsistent results of α-diversity, F/B ratio and GM changes at high phylogenetic rank (e.g., phylum, class and order level) in both AD and healthy controls.

![Figure 2: A diagram showing GM compositional changes in AD studies. Increased pro-inflammatory taxa like Erysipelotrichaceae and Enterobacteriaceae were observed in both AD patients and AD animal models. Escherichia and Shigella of Enterobacteriaceae, which have long been proposed to contribute to series of gastrointestinal diseases, could disrupt the integrity of epithelial cell and lead to leaky gut. Anti-inflammatory Eubacterium and SCFA-producing Ruminococcus were decreased in AD. Two probiotic taxa Lactobacillus and Bifidobacterium have been proven to restore cognitive function and ameliorate Aβ pathology in AD animals.](image-url)
SCRD studies. The findings showed better concordance at higher taxonomic resolution. Therefore, GM alterations at family, genus and species level are presented in the following tables (Tables 1–5). Generally, we have identified higher level of pathobionts and lower level of beneficial bacteria in both AD patients and animals (Figure 2).

The pro-inflammatory taxa *Escherichia* and *Shigella* of Enterobacteriaceae have long been proposed to contribute to series of gastrointestinal diseases. Increased level of *E. coli* LPS has also been detected in the postmortem brain samples of AD patients. The exotoxin of *Escherichia* and *Shigella* could disrupt the integrity of epithelial cell further leading to leaky gut and facilitates the translocation of bacteria into the blood. *E. coli* along with several gram-negative bacteria possess systems for producing bacterial Aβ which is able to penetrate intestinal barrier and BBB and initiate cross-seeding in the CNS. In addition to *Escherichia*, bacterial Aβ producing systems have also been found in *Staphylococcus*, highlighting its potential role in contributing to AD pathogenesis. Although *Staphylococcus* was not detected in human fecal sample, its higher abundance was found in the blood of AD patients. Studies have reported that strains of *Ruminococcus gnavus* which belong to the family Lachnospiraceae use terminal mucin glycans to degrade mucus layer of intestinal barrier. Increased level of *Ruminococcus gnavus* has been associated with inflammatory bowel disease, suggesting the potential role of *Ruminococcus gnavus* in promoting inflammation.

The two families Ruminococcaceae and Clostridiales, major SCFA-producing taxa in mammalian GM, have been reported to be decreased in various metabolic and neurodegenerative diseases. The relative abundance of Ruminococcaceae was found to be positively correlated with higher Mini-mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) scores, which indicates better cognitive functions. Lower level of anti-inflammatory taxa *Eubacterium rectale* and *Bacteroides fragilis* along with increased pro-inflammatory cytokines such as IL-1β, NLRP3 and CXCL2 have been also detected in AD patients. *Lactobacillus* and *Bifidobacterium* are two common probiotic taxa capable of producing neurotransmitter gamma-aminobutyrate (GABA) whose metabolism has been reported to be disrupted in AD patients. *Lactobacillus* and *Bifidobacterium* play an important role in protecting intestinal cells and inducing anti-inflammatory responses. Studies have shown that probiotic treatment using strains of *Lactobacillus* and *Bifidobacterium* was able to ameliorate symptoms associated with AD.

**GM interventions restore the progression of AD**

As stated above, most studies focusing on GM and AD presented correlations but not causal relationships. While it remains an open question in the field, several studies have begun to demonstrate how GM affect AD pathology by showing the beneficial effects through GM intervention in animal models, including probiotic supplement, antibiotic treatment, germ-free (GF) animals and fecal microbiota transplantation (FMT). These successful trials support the role of GM dysbiosis in contributing to AD pathogenesis and progression and suggest potential benefits of GM modulation for AD treatment (Table 2) (Figure 3).

**Sleep, circadian rhythm and GM**

Although human gut ecosystem maintains rather resilient, perturbation by antibiotics, high-fat food and stress could damage intestinal homeostasis. These key determinants of GM have been studied extensively over the past decades, but the role of sleep and circadian rhythm in regulating GM was underestimated. Recent studies have shown that human GM display diurnal oscillation at both compositional and functional levels. It has been suggested that SCRD may lead to GM dysbiosis through several indirect ways, including disrupting the rhythmic fluctuation of GM, activating the HPA axis, increasing food and energy intake, decreasing physical activity and damaging gut barrier integrity. In this part, we summarize recent progress regarding the correlation between SCRD and GM dysbiosis as well as how SCRD impacts GM (Table 3, 4). Like the findings in AD, increased pathobionts and decreased beneficial bacteria were identified in SCRD conditions in both human and animal models.
Table 2. Summary of studies investigating GM intervention and AD.

| Reference | Participant/animal model | Treatment | Main findings (Exp vs. Con) |
|-----------|--------------------------|-----------|-----------------------------|
| **Probiotic supplement** | | | |
| 51 | AD patients | | |
| Exp: AD patients + probiotic milk | Duration: 12 weeks | Probiotic milk contained *Lactobacillus acidophilus, Lactobacillus casei, Bifidobacterium bifidum, and Lactobacillus fermentum* | ↑ cognitive function |
| Con: AD patients + normal milk | | | ↑ insulin and lipid metabolism |
| 54 | AD patients | | |
| Exp: data after taking Omnibiotic Stress Repair | Duration: 4 weeks | Omnibiotic Stress Repair contained 9 strains from *Lactococcus, Lactobacillus, and Bifidobacterium* | ↑ Faecalibacterium prausnitzii |
| Con: baseline data before probiotic treatment | | | ↑ tryptophan metabolism and serum kynurenine |
| 55 | Female App<sup>NL-GF</sup> mice | | |
| Exp: AD mice + VSL#3 | Duration: 8 weeks | VSL#3 contained 8 strains of lactic acid-producing bacteria | ↓ intestinal inflammation and gut permeability |
| Con: AD mice + vehicle (water) | | | |
| 52 | Male 3xTg-AD mice | | |
| Exp: AD mice + SLAB51 | Duration: 4 months | SLAB51 contained 9 live probiotic strains | ↓ cognitive impairment |
| Con: AD mice + vehicle (water) | | | ↓ pro-inflammatory cytokines |
| 56 | Male ddY mice + intra-hippocampal Aβ injection | | |
| Exp: AD mice + probiotic supplement/acetate | Duration: starting 2 days before Aβ injection | Probiotic supplement: living, heat-killed or fragmented *Bifidobacterium breve* A1 | ↓ Aβ deposition in hippocampus |
| Con: AD mice + vehicle (water) | | | Partially attenuated behavioral deficit by non-viable *B. breve* A1 and acetate |
| 57 | Male Wistar rats + intra-hippocampal Aβ injection | | |
| Exp: AD rats + probiotic supplement | Duration: 8 weeks | Probiotic supplement: *Lactobacillus acidophilus, Lactobacillus fermentum, Bifidobacterium lactis,* and *Bifidobacterium longum* | ↓ spatial memory |
| Con: AD rats + vehicle (water) | | | ↓ Aβ deposition in brain |
| 58 | Male Sprague-Dawley rats | | |
| Exp: (1) rats + antibiotic, (2) rats + antibiotic + probiotic | Duration: 41 days | Antibiotic: ampicillin, Probiotic: *Lactobacillus fermentum* NS59 | Disrupted GM in (1) and normalized GM in (2) |
| Con: rats + vehicle (water) | | | ↓ colon inflammation in (2) vs. (1) |
| | | | ↓ spatial memory in (2) vs. (1) |
| **Antibiotic treatment** | | | |
| 59 | Male APP/PS1 mice | | |
| Exp: AD mice + ABX treatment | Duration: post-natal day 14 to day 21 | ABX contained 9 antibiotics | Altered GM composition |
| Con: AD mice + vehicle (water) | | | ↓ Aβ deposition in the brain |
| | | | ↓ glial reactivity at Aβ plaque |
| 60 | Male APP/PS1 mice | | |
| Exp: AD mice + ABX treatment | Duration: lifespan | ABX contained 9 antibiotics | Altered GM composition |
| Con: AD mice + vehicle (water) | | | ↓ neuroinflammation |
| 61 | SxFAD mice | | |
| Exp: AD mice + ABX treatment | Duration: 5 months | ABX contained ampicillin, streptomycin and colistin | Altered GM composition |
| Con: AD mice + vehicle (water) | | | ↓ GM abundance |
| | | | ↓ infiltration of pro-inflammatory TH1 cells and M1 cells into the brain |
| 62 | APPPS1-21 mice | | |
| Exp: (1) male + ABX, (2) female + ABX | Duration: lifespan | ABX contained kanamycin, gentamicin, colistin, metronidazole and vancomycin | Sex-specific gut microbiota alteration |
| Con: male/female + vehicle (water) | | | (1): ↑ anti-inflammatory cytokines, ↓ Aβ, and ↓ phagocytic microglial at Aβ |
| 63 | Male 5xFAD mice | | |
| Exp: AD mice + ABX treatment | Duration: 2 months | ABX contained vancomycin, cefoxitin, gentamicin, and metronidazole | ceca size and weight |
| Con: AD mice + vehicle (water) | | | ↓ level of hippocampal Aβ |
| | | | ↑ cognitive function |

(Continued)
| Reference | Participant/animal model | Treatment | Main findings (Exp vs. Con) |
|-----------|--------------------------|-----------|----------------------------|
| 64        | Male APPS1-21 mice       | Duration: lifespan | ↑ ceca size and altered GM composition, ↑ Aβ deposition only in (1) |
|           | Exp: (1) AD mice + ABX, (2) AD mice + individual ABX, Con: AD mice + vehicle (water) | ABX contained kanamycin, gentamicin, colistin, metronidazole, and vancomycin | |
| 36        | APP/PS1 mice             | Duration: lifespan | ↑ Aβ level and Aβ deposition |
|           | Exp: GF AD mice          | GF mice: embryos were washed with Invitrogen and transferred to GF pseudo-pregnant mice | ↓ inflammatory |
|           | Con: conventionally raised AD mice | - ↑ Aβ-degrading enzyme |
| 65        | Female APP/PS1 mice      | Duration: lifespan | ↑ Altered GM composition in (1) vs. (3) |
|           | Exp: (1) SPF AD mice, (2) GF AD mice, (3) SPF WT mice, (4) GF WT mice | - ↑ cognitive function in (1) vs. WT |
|           | Con: (1) SPF AD mice, (2) GF AD mice, (3) SPF WT mice, (4) GF WT mice | - ↑ Aβ and inflammation in (1) vs. (2) and (3) |
| 63        | Male 5xFAD mice          | Duration: lifespan | ↑ ceca size and weight |
|           | Exp: GF AD mice          | GF mice were generated through embryo transfer | - ↑ Aβ and inflammation |
|           | Con: SPF AD mice         | - ↑ cognitive function |
|           |                          | - ↑ Aβ uptake by microglial |
| 35        | Female ADLPAVT mice      | Duration: 16 weeks | - ↓ cognitive impairment |
|           | Exp: AD mice + WT FMT    | FMT: oral gavage | - ↓ Aβ, tau pathology, and glial activity |
|           | Con: AD mice + vehicle (water) | | - ↓ expression of inflammation-related genes |
| 36        | GF APP/PS1 mice          | Duration: 16 weeks | ↑ overall Aβ level in (1) and (2) |
|           | Exp: (1) GF AD mice + AD FMT, (2) GF AD mice + WT FMT | - ↑ expression of increased brain Aβ42 in (1) vs. (2) |
|           | Con: GF AD mice + vehicle (water) | | |
| 61        | WT mice                  | Duration: 7 months | - ↓ discriminating learning |
|           | Exp: WT mice co-housed with AD mice | FMT: oral gavage | - Similar GM and cytokine expression to AD mice |
|           | Con: WT mice separately housed with AD mice | | - ↑ infiltrating Th1 cells into brain |
| 61        | (1) WT mice + Aβ injection + AD FMT | Duration: 7 months | - (1) ↑ Th1 cells and ↓ Th2 cells in brain |
|           | (2) AD mice + WT FMT     | FMT: oral gavage | - (2) ↓ Th1 cells in brain |
|           | (3) WT mice + Aβ injection + GV-971-treated AD FMT | | - (3) ↓ Th2 cells in brain |
| 31        | Male APP/PS1 mice        | Duration: 14 days | - ↑ neuroinflammation |
|           | Exp: AD mice + WT FMT    | FMT: oral gavage | - ↑ Aβ deposition and tau phosphorylation |
|           | Con: AD mice + vehicle (water) | | - ↑ GM dysbiosis and cognitive deficits |
| 32        | Male pseudo GF WT mice   | Duration: 14 days | - ↑ cognitive function in pseudo GF mice |
|           | Exp: (1) GF mice + SAMP8 FMT, (2) GF mice + SAMP1 FMT | FMT: oral gavage | - Restored GM composition in (2) not (1) |
|           | Con: GF WT mice + vehicle (water) | | - ↑ cognitive function in (2) not (1) |
| 62        | ABX-treated male APPS1-21 mice | Duration: lifespan | ↑ Aβ plaque burden |
|           | Exp: ABX-treated AD mice + AD FMT | FMT: oral gavage | - GM profile similar to AD mice |
|           | Con: ABX-treated AD mice + vehicle (water) | | - Microglial morphologies similar to AD mice |

Note: Exp = experimental group, Con = control group, ABX = antibiotic cocktail, GF = germ-free, SPF = specific pathogen-free, ↑ = increase, ↓ = decrease.
Figure 3. GM intervention studies in AD animal models. (a) Probiotic supplement study: AD mice feed with probiotic strains of Lactobacillus and Bifidobacterium showed reversed cognitive dysfunction, decreased Aβ deposition in brain and lower level of colon inflammation. (b) Antibiotic treatment and germ-free (GF) animal study: antibiotic treated embryo was transferred to pseudo-pregnant mice to generate GF mice. Both GF AD mice and AD mice feed with antibiotic display improved cognitive function, increased Aβ clearance and alleviated neuroinflammation. (c) Fecal microbiota transplantation (FMT) study: FMT from healthy wild-type (WT) donor could restore GM dysbiosis, ameliorate Aβ and tau pathology, and downregulate neuroinflammation in AD mice, whereas GF AD mice receiving FMT from AD mice show aggravated Aβ burden and GM profile similar as observed in AD mice.

**Sleep disturbance and GM alterations**

GM alterations in human and animal models caused by sleep disturbance or related to sleep quality are presented in Table 3 (top) and Table 3 (bottom), respectively. To date, only a few studies explored the effects of sleep impacting on GM in humans, restricting their focus on the association between specific bacterial taxa and sleep quality based on Pittsburgh sleep quality index (PSQI) or sleep physiology. Two studies compared the GM of individuals after short-term sleep deprivation with baseline data collected before deprivation. But their findings are largely inconsistent, likely owing to distinct experimental designs and several uncontrolled variables, including daily dietary and energy intake of the subjects. Therefore, few commonalities in GM changes can be concluded from human studies. In contrast, multiple animal-based experimental studies that focus on the impacts of long-term sleep deprivation and fragmentation on GM composition have been conducted, with largely identical results of GM alterations.

**Increased bacterial taxa by sleep disturbance**

In humans, partial sleep deprivation and poor sleep quality resulted in more abundant Ersiopelotrichaceae, Prevotellaceae and Coriobacteriaceae at family level (Table 3, top). Sleep deprivation and fragmentation in animals contributed to GM dysbiosis featured by increased Ruminococcaceae, Lachnospiraceae, Ersiopelotrichaceae, Enterobacteriaceae and Staphylococcaceae at family level, and *Ruminococcus, Prevotella, Escherichia* and *Shigella* at genus level (Table 3, bottom).

Prevotellaceae is also an immunogenic bacterial taxon highly coated by IgA. It has also been suggested that species of Prevotellaceae could induce intestinal inflammation, slow the
Table 3. Summary of studies examining the impact of sleep disturbance on GM and correlation between sleep quality and bacterial taxa.

| Reference | Participant/animal model | GM profiling method | GM alterations by sleep disturbance/correlated with poor sleep quality | Other major findings |
|-----------|--------------------------|---------------------|---------------------------------------------------------------------|---------------------|
| Human study | 71 9 healthy males Partial SD vs. NS Location: Sweden | 16S rRNA gene seq V4 region | † Family: Coriobacteriaceae, Erysipelotrichaceae | - Increased insulin resistance and fasting insulin level |
| 72 28 healthy adults PSQI for sleep measuring Location: USA | 16S rRNA gene seq V4 region | + Genus: Prevotella, Family: Lachnospiraceae, Genus: Blautia, Ruminococcus | - Better Stroop and Color-Word performance were associated with better sleep quality |
| 73 37 adults aging from 50 to 85 PSQI for sleep measuring Location: USA | 16S rRNA gene seq | - Phylum: Verrucomicrobia, Lentisphaerae | |
| Animal study | 74 22 healthy males Actiwatch for sleep measuring Location: USA | 16S rRNA gene seq V4 region | + Family: Lachnospiraceae Genus: Blautia, Lachnospiraceae UCG-004, Orchibacterium - Genus: Lachnospiraceae ND3007 | - Subtle GM alteration by short period of SD |
| 75 Male C57BL/6 J mice Chronic SF vs. NS | 16S rRNA gene seq V4 region | † Family: Lachnospiraceae, Ruminococcaceae | - Increased food intake, VWAT, inflammation, insulin resistance, and gut permeability - Enhanced inflammation in GF mice after FMT from SF mice |
| 76 Male C57BL/6 J mice Short SD vs. NS | 16S rRNA gene seq V3-V5 region | † Family: Lachnospiraceae Genus: Morrella Genus: Oxobacter | |
| 77 Male Wistar-Kyoto rats SF vs. NS | 16S rRNA gene seq V4 region | † Genus: Escherichia, Shigella, Enterococcus, Lachnospiraceae UCG-008 Genus: Butyribiota, Oscillospira, Eubacterium, Dorea Species: Eubacterium ruminantium | - Increased mean arterial pressure |
| 78 Male C57BL/6 N mice SD vs. NS | 16S rRNA gene seq V4 region | † Family: Bifidobacteriaceae, Lactobacillaceae, Turicibacteraceae Genus: Bifidobacterium, Lactobacillus, Turicibacter | - Reduced fecal bile acid and tetrarpenoids |
| 79 Sprague Dawley rats Acute SF (ASF) vs. NS Chronic SF (CSF) vs. NS | Distal ileum (D), cecum (C), and proximal colon (P) samples 16S rRNA gene seq | † Family: Enterobacteriaceae (D), S24-7 (D), Ruminococcaceae (C) Genus: Oscillospira (C), Bacteroides (C), Prevotella (C) † Family: Lactobacillaceae (D) Genus: Lactobacillus (P) CSF † Family: Staphylococcaceae (D), Clostridiaceae (D)(P), Erysipelotrichaceae (P), Ruminococcaceae (P) Genus: Prevotella (P), Clostridium (P) Family: Lactobacillaceae (D) | - Increased microbial invasion - Altered intestinal structure but not gut barrier integrity - Increased KC/GRO level |
| 80 Male Wistar rats Paradoxical SD vs. NS | 16S rRNA gene seq | † Genus: Parabacteroides, Ruminococcus, Aggregatibacter, Phascolarctobacterium Genus: Akkermansia, Oscillospira | - Depression-like behavior |

Note: NS = normal sleep, SD = sleep deprivation, SF = sleep fragmentation, PSQI = Pittsburgh Sleep Quality Index, FMT = fecal microbiota transplantation, GF = germ free, † = increase, ‡ = decrease, + = positively correlated, − = negatively correlated.
development of mucus layer and are involved in various intestinal diseases including IBD and colitis.\textsuperscript{83} Note that although sleep disturbance increased abundance of Ruminococcaceae and Lachnospiraceae in murine subjects, it is mainly due to increased food-intake as both families are highly fermentative bacteria utilizing the plant-derived fiber and polysaccharides in chow food.\textsuperscript{75}

**Decreased bacterial taxa by sleep disturbance**

In human studies, a decline in the relative abundance of *Ruminococcus* is correlated with poor sleep quality (Table 3, top). In animal subjects, Lactobacillaceae, Bifidobacteriaceae, Turicibacteraceae at both family and genus level, together with *Eubacterium* and *Akkermansia* at genus level, exhibited significant decrease after sleep deprivation (Table 3, bottom).

Eubacteriaceae along with Clostridiaceae, Lachnospiraceae and Ruminococcaceae are important SCFAs producers of mammalian GM.\textsuperscript{49} The SCFA butyrate plays an important role in maintaining gut barrier and regulating immune responses toward anti-inflammatory status.\textsuperscript{84} The genus *Eubacterium* makes significant contribution to butyrate production since *Eubacterium rectale* makes up about 13\% of the clostridial cluster XIVa.\textsuperscript{49} Therefore, loss of *Eubacterium* caused by sleep disturbances could lead to a decline in butyrate level and disrupt the integrity of gut barrier. It has been found that the SCFA-producing taxon *Akkermansia* can successfully mitigate the development of obesity and diabetes, protect gut barrier integrity and stimulate anti-inflammatory responses.\textsuperscript{85}

**Circadian rhythm disruption and GM alterations**

In addition to sleep loss, circadian rhythm disruption is also receiving increasing attention, given the increased prevalence of altered sleep-wake cycle and jet lag, which are largely due to working night shift and traveling across time zones. Aberrant light exposure, high fat diet, alcohol consumption and irregular eating behavior have been found to induce circadian misalignment.\textsuperscript{86} Numerous studies have indicated a link between circadian rhythm disruption with higher risk of pathological conditions including obesity, cardiovascular diseases and neurodegenerative diseases. The diurnal oscillation of human GM is partially controlled by central clock,\textsuperscript{68} indicating the regulatory roles of circadian rhythms in GM eubiosis. Thus, we summarized recent studies focusing on the effects of circadian rhythm disruption on GM components in Table 4.\textsuperscript{68,87–91}

**Increased bacterial taxa by circadian rhythm disruption**

The GM of human after undergoing shift work or jet lag exhibited increased abundance of Erysipelotrichaceae, Prevotellaceae and Lachnospiraceae at family level, *Dorea* at genus level, and *Ruminococcus torques* and *Ruminococcus gauvreauii* at species level (Table 4, top). In murine models, circadian rhythm disruption (mainly achieved by altering light-dark cycles) resulted in an increase of Erysipelotrichaceae and Prevotellaceae at family level, *Prevotella* at genus level and *Ruminococcus torques* at species level, largely consistent with observations in humans (Table 4, bottom).

*Dorea, Ruminococcus torques* and *Ruminococcus gauvreauii* utilize glycoside hydrolases to breakdown mucus layer and produce propionate.\textsuperscript{92} Despite their SCFA-producing capacity, increased abundance of mucolytic bacteria has been associated with disrupted gut barrier and inflammatory bowel diseases.\textsuperscript{93} Studies have suggested the role of *Dorea* spp. in inflammation through the promotion of IFNγ production and mucin degradation.\textsuperscript{84,94} Significantly abundant pathobiont *Ruminococcus torques* has been found in patients with ulcerative colitis (UC) and CD.\textsuperscript{93} *Ruminococcus gauvreauii* has been found to be positively correlated with pro-inflammatory parameters in rats with fatty liver.\textsuperscript{95}

**Decreased bacterial taxa by circadian rhythm disruption**

In human studies, circadian disruption led to decreased levels of genus *Faecalibacterium* and species *Faecalibacterium prausnitzii* (Table 4, top). Ruminococcaceae at both family and genus level, *Turicibacter* at genus level and *Eubacterium plexicaudatum* at species level were decreased in animal studies after the disruption of light-dark cycles (Table 4, bottom).
Faecalibacterium was the only diminished bacterial taxa caused by circadian rhythm disruption at genus level. Faecalibacterium prausnitzii, the sole species of genus Faecalibacterium, is one of the most abundant bacteria in human GM representing more than 5% of bacterial population in intestine. It acts as an important SCFA butyrate producing taxon, similar to other members in Ruminococaceae family. Moreover, studies have reported a negative association of Faecalibacterium prausnitzii with various inflammatory bowel diseases including UC and CD, suggesting that it could be a health indicator.

**Linking GM, sleep, circadian and AD**

**GM and AD – causal or coincidental?**

What is the role of GM dysbiosis in AD? It remains debatable whether GM dysbiosis plays...
as causal or merely consequential role in AD. Recently, studies have started to support the idea that GM dysbiosis precedes the onset of AD and even contributes to AD pathogenesis. Li et al. found that AD and MCI groups had distinct GM compositions from healthy controls in both fecal and blood samples, largely consistent with a previous report by another group.9,10 These findings provide a new perspective that GM dysbiosis starting at early MCI is a developing process with the cumulation and depletion of specific bacterial taxa. Studies of GM intervention in AD including probiotic supplement, antibiotic treatment, germ-free animals and FMT further reinforced the causal role of GM dysbiosis in AD pathogenesis.

What causes GM dysbiosis before the onset of AD? Human GM is determined by multiple factors including early life exposure, medical intervention, diet, stress, sleep and circadian rhythm.21 Many studies have associated these factors with GM eubiosis, and their potential impacts on AD pathogenesis. A recent paper proposed a perspective that diet-induced GM dysbiosis plays a role in the pathogenesis of AD.44 Multiple reviews summarized GM alterations in AD and SCRD, respectively, but no reviews to date have systematically analyzed the patterns of GM changes in AD and SCRD simultaneously, or made a hypothesis linking SCRD, GM dysbiosis and AD.

**Linking SCRD to AD through GM dysbiosis**

As shown in the previous parts, GM alterations were observed in AD, sleep and circadian disruption, respectively. Reports have also indicated that GM alterations might contribute to AD pathogenesis.98,99 Studies which have been reviewed elsewhere have shown that SCRD was associated with greater Aβ burden and AD risk, sometimes decades before the clinical onset of AD.16 Therefore, we hypothesize that the interactions between SCRD and GM lead to GM dysbiosis indirectly; as a consequence, chronic systematic and neuro-inflammation and Aβ deposition occur, together with a plethora of metabolic and immunogenic responses that may finally contribute to the onset of AD (Figure 4).

First, we check the uniformity in GM alterations and their potential contributions to health and disease under AD and SCRD conditions. We compared the GM alterations and their potential roles (beneficial bacteria, pathobionts or controversial taxa) in a taxonomic view under distinct conditions: AD, sleep and circadian disruption (Table 5). We observe higher abundance of highly immunogenic Erysipelotrichaceae at family level in both human and rodents in each condition, but most other changes in individual bacteria were inconsistent between human and rodent (Table 5), which may be caused by the differences in GM components between these two species.100 Thus,

![Figure 4](image-url) **Figure 4.** Time-line for the development of AD via SCRD-induced GM dysbiosis. Long-term SCRD (e.g., insomnia, fragmented sleep, night shift work and frequent traveling between time zones) leads to chronic alteration of GM with overabundant pathobionts and reduced beneficial bacteria. GM dysbiosis disrupts gut barrier integrity and facilitates the invasion of pathogens and their metabolite (e.g., LPS, exotoxins and bacterial Aβ). These pro-inflammatory agents induce inflammation responses and compromise BBB structure, leading to neuro-inflammation and the onset of early MCI. As MCI develops, progressive enrichment of pathobionts such as Enterobacteriaceae further exacerbate neuro-inflammation, cognitive dysfunction and Aβ burden, which in the end contribute to the pathogenesis of AD.
| Implication in health and disease | Family | Genus/Species | Taxonomic level | Trend of GM alteration |
|----------------------------------|--------|---------------|----------------|------------------------|
| Human study                      |        |               |                |                        |
| Beneficial bacteria              |        |               |                |                        |
| Producing SCFAs                  | Akkermansiaceae | Akkermansia | //              | N/A                    | N/A                    |
| Promoting mucin expression       |        |               |                |                        |
| Anti-inflammatory                |        |               |                |                        |
| Inhibiting inflammation and infection | Bacteroidaceae | Bacteroides fragilis (NTBF) | ↓ (S*)         | N/A                    | N/A                    |
| Producing GABA, acetate, and lactate | Bifidobacteriaceae | Bifidobacterium | //            | N/A                    | N/A                    |
| Producing SCFAs                  | Clostridiales       | Clostridium | //              | N/A                    | N/A                    |
| Producing butyrate               | Eubacteriaceae     | Eubacterium rectale | ↓ (S*)         | N/A                    | N/A                    |
| Anti-inflammatory                |        |               |                |                        |
| Producing SCFAs                  |        |               |                |                        |
| Producing GABA, lactate, and amino acid | Lachnospiraceae | Lachnospira | //              | N/A                    |                        |
| Producing GABA, lactate, and amino acid | Enterobacteriaceae | Escherichia | ↑ (F*)         | N/A                    | ↑ (G*)                 |
| Producing butyrate               |        |               |                |                        |
| Anti-inflammatory                |        |               |                |                        |
| Producing SCFAs                  |        |               |                |                        |
| Producing GABA, lactate, and amino acid | Ruminococcaceae | Ruminococcus | ↓ (G*)         | N/A                    |                        |
| Producing GABA, lactate, and amino acid | Enterobacteriaceae | Enterobacter | ↑ (G*)         | N/A                    | ↑ (F*)                 |
| Producing butyrate               | Lactobacillaceae   | Lactobacillus | ↑ //           | N/A                    | ↑ (G*)                 |
| Anti-inflammatory                |        |               |                |                        |
| Producing SCFAs                  |        |               |                |                        |
| Controversial taxa               |        |               |                |                        |
| Producing propionate             | Lachnospiraceae    | Lachnospira | ↑ (G*)         | N/A                    | ↑ (F*, G*)             |
| Degradation mucin                |        |               |                |                        |
| Increasing gut permeability      | Enterobacteriaceae | Ruminococcus gauveaui | ↑ (S*)         | N/A                    | ↑ (F*, S*)             |
| Pathobionts                      |        |               |                |                        |
| Positively correlated with IBD   | Coriobacteriaceae  | Coriobacter | ↑ (F*)         | N/A                    | ↑ (F*)                 |
| Producing LPS, bacteria Aβ, and exotoxin | Enterobacteriaceae | Escherichia | ↑ (F*, G*) | N/A                    | ↑ (G*)                 |
| Damaging gut barrier             |        |               |                |                        |
| Highly immunogenic               | Erysipelaotrichaceae | Erysipelaota | ↑ (F*)         | ↑ (F*)                 |                        |
| Pro-inflammatory                 |        |               |                |                        |
| Animal study                     |        |               |                |                        |
| Beneficial bacteria              |        |               |                |                        |
| Producing SCFAs                  | Akkermansiaceae | Akkermansia | //              | ↓ (G*)                 | N/A                    |
| Promoting mucin expression       |        |               |                |                        |
| Anti-inflammatory                |        |               |                |                        |
| Inhibiting inflammation and infection | Bifidobacteriaceae | Bifidobacterium | ↓ (G*)         | ↑ (F**, G*)             | N/A                    |
| Producing butyrate               | Eubacteriaceae     | Eubacterium plexicaudatum | ↓ (G*)         | N/A                    | ↓ (S)                 |
| Anti-inflammatory                |        |               |                |                        |
| Producing SCFAs                  |        |               |                |                        |
| Producing GABA, acetate, and lactate | Lachnospiraceae | Lachnospira | //              | N/A                    |                        |
| Producing butyrate               |        |               |                |                        |
| Anti-inflammatory                |        |               |                |                        |
| Producing SCFAs                  |        |               |                |                        |
| Producing GABA, lactate, and amino acid | Lactobacillaceae | Lactobacillus | ↓ (G*)         | ↑ (F*)                 |                        |
| Producing GABA, lactate, and amino acid | Enterobacteriaceae | Enterobacter | ↑ (G*)         | ↑ (F**, G***)           |                        |
| Producing butyrate               |        |               |                |                        |
| Anti-inflammatory                |        |               |                |                        |
| Producing SCFAs                  |        |               |                |                        |
| Controversial taxa               |        |               |                |                        |
| Producing propionate             | Lachnospiraceae    | Lachnospira | ↑ (G**)        | N/A                    | ↑ (F**, G**)           |
| Degradation mucin                |        |               |                |                        |
| Increasing gut permeability      | Enterobacteriaceae | Enterobacter | ↑ (S)          | N/A                    |                        |
| Pathobionts                      |        |               |                |                        |
| Producing LPS, bacteria Aβ, and exotoxin | Enterobacteriaceae | Escherichia | ↑ (F*)         | ↑ (F*)                 |                        |
| Damaging gut barrier             |        |               |                |                        |
| Highly immunogenic               | Erysipelaotrichaceae | Erysipelaota | ↑ (F*)         | ↑ (F*)                 |                        |
| Pro-inflammatory                 |        |               |                |                        |
| Producing bacterial Aβ and toxin | Staphylococcaceae  | Staphylococcus | ↑ (F**, G**)  | ↑ (F*)                 |                        |

Note: ↑ = increase, ↓ = decrease, // = both increase and decreased were reported, N/A = not reported, F = family level, G = genus level, S = species level, * = number of study.

when analyzing the overlapping of GM alterations in different conditions, we conduct separate evaluations in humans and rodents. In humans, SCFAs-producing Ruminococcaceae at family or genus level is shown to be significantly lower in either condition, whereas highly immunogenic bacteria including Erysipelaotrichaceae and Coriobacteriaceae at family level are shown to be significantly higher in each condition. Most other GM components are inconsistent between different conditions, sometimes due to no relevant data available at present (Table 5). In animal models, similar trends are observed in several bacteria individuals between different conditions. For example, beneficial bacteria including Lactobacillaceae, Bifidobacteriaceae, Turicibacteraceae and
Lachnospiraceae at family and/or genus level are significantly decreased in AD, sleep disturbance and/or circadian disruption, and other parts of pathobionts are uniformly increased, with the exception of Ruminococcaceae. As stated above, the increase in Ruminococcaceae during sleep disturbance was probably due to aberrant food intake.

Next, we elucidate the potential role of GM dysbiosis in the development of AD by providing the evidence of how GM interventions, including probiotics, antibiotics, germ-free treatment and FMT, restore cognitive functions and alleviate AD pathology (Table 2) (Figure 3). Although various factors modulate GM composition, emerging evidence has indicated that SCRD could disturb GM and lead to GM dysbiosis. Most human studies merely investigated the correlation between SCRD and GM dysbiosis, while animal studies provided more insights into GM alterations under different SCRD conditions such as sleep deprivation, sleep fragmentation and circadian rhythm reversal. Studies have also revealed several possible mechanisms underlying how SCRD contributes to GM dysbiosis, including increased food intake, decreased physical activity, activation of HPA axis and compromised gut barrier integrity, and this topic has been reviewed elsewhere.21,101

Finally, we evaluate the specific roles of each individual bacteria and its potential contributions to health and disease. Intriguingly, dysfunctions mediated by the GM alterations are ideally unanimous in AD and SCRD conditions. Both AD and SCRD are associated with more abundant pathobionts leading to pro-inflammation and lower SCFAs, and less level of anti-inflammatory, SCFA-producing, and gut barrier-protecting bacteria (beneficial bacteria) (Table 5). These analyses demonstrate that GM dysbiosis caused by SCRD is largely consistent with the ones in AD, supporting our hypothesis that SCRD may contribute to AD partially by impacting on GM (Figure 5).

**Future directions**

In this review, we intend to summarize and evaluate the commonalities and distinctiveness of GM alterations in different conditions including AD, sleep disruption and circadian rhythm misalignment. Although data implied commonalities in these conditions, there were also condition-

---

**Figure 5.** Schematic diagram of how SCRD contributes to AD pathogenesis through GM dysbiosis. SCRD, such as sleep deprivation, sleep fragmentation and jet lag, disrupts gut homeostasis with increased pathobionts (e.g., Enterobacteriaceae, Erysipelotrichaceae and Prevotellaceae) and decreased beneficial bacteria (e.g., Eubacteriaceae, Ruminococcaceae and other SCFA-producing taxa). On one hand, pathobionts could damage gut barrier and cause leaky gut through the degradation of mucus layer. Pathogens and their metabolites induce pro-inflammatory responses and lead to increased BBB permeability. Bacteria-derived Aβ and LPS invade CNS and are associated with neuroinflammation and Aβ pathology. On the other hand, the compromised functions of beneficial bacteria (e.g., inhibiting infection, promoting mucus expression, producing neuromodulators and anti-inflammation SCFAs) are overwhelmed by overabundant pathobionts. Thus, the elevated neuroinflammation and aggravated Aβ burden facilitate the onset of AD.
specific changes in certain species. Significantly, heterogeneity of methodologies applied for genetic material extraction, DNA sequencing, the lifestyle of subjects and methods for data analysis could compromise the results among different studies and lead to inconsistency, which could be expected in human studies. We suggest that further work is needed to specify the alteration of GM at species and even strain level, and incorporate metabolic and functional analysis to reveal possible mechanisms linking GM dysbiosis and diseases using standardized experimental design and data analysis.

**Phylogenetic analysis of GM needs to be conducted at a high taxonomic resolution**

Studies have implicated that GM can be altered at lower taxonomic level without achieving alteration at high taxonomic level.\(^{39}\) For example, Firmicutes and Bacteroidetes are the two largest bacterial phyla of the mammalian gastrointestinal tract, and their ratio (F/B) was commonly used in GM analysis.\(^{102}\) However, reviews have reported inconsistent changes in F/B ratio across a series of neurodegenerative diseases and metabolic disorders, making F/B ratio a debatable and controversial criterion.\(^{6,99,103,104}\) In agreement with our findings, one review summarizing the GM alterations in patients with PD found that, at high taxonomic ranks like phylum and class level, the changes in bacterial taxa are neither disease-specific nor consistent among different studies, but a more concordant trend was observed at family and genus level.\(^{39}\)

Additionally, \(\alpha\)-diversity was thought to be a good indicator of health and diseases, and has been frequently investigated in GM analysis.\(^{105}\) However, we found that neither AD studies nor SCRD studies showed concordant variation of GM \(\alpha\)-diversity. And \(\alpha\)-diversity analysis was not included in several studies. This is supported by another review which examines the association between GM and PD. They found that the confounding results of \(\alpha\)-diversity alteration reported by different studies did not substantiate the role of \(\alpha\)-diversity analysis as reliable methods for identifying PD and its progression, suggesting that higher \(\alpha\)-diversity was not necessarily a predictor of better health.\(^6\)

**Future studies need to focus more on metabolic and functional analysis**

Most studies examining GM alterations in AD or SCRD only evaluated compositional changes of GM, and few conducted function-related analyses such as Kyoto Encyclopedia of Genes and Genomes (KEGG) test or metabolite screening. However, reviews have indicated that two taxonomically distinct bacterial taxa could share similar functions, while two closely related taxa may act antagonistically.\(^{92,106}\) This suggests that phylogenetic analysis which is based on the hypervariable regions of bacterial 16s RNA gene cannot alone represent GM alterations at both taxonomic and functional level. It is possible that an increase of one genus could be neutralized or even reversed by a decrease of predominant genus in the same family. Thus, it would be confusing and misleading to simply conduct compositional analysis in discussing GM alterations. Moreover, metabolic and functional analysis have provided some important molecular and signaling pathways including possible interaction mechanisms between SCRD and GM and how GM dysbiosis could contribute to AD development.\(^{10,28,30,33}\)

**Controversial roles of specific bacterial taxa**

Lachnospiraceae and Akkermansia muciniphila, two taxa frequently investigated by the abovementioned studies, still remain controversial in their functions. As a core component of mammalian GM, Lachnospiraceae acts as a double-edged sword in health and disease.\(^{92}\) On the one hand, several members of Lachnospiraceae like Blautia, Coprococcus and Roseburlia are crucial producers of butyrate and acetate, which induce anti-inflammatory responses, modulate insulin and lipid metabolism, and serve as the main nutrition source for colonic epithelial cells.\(^{107–109}\) But on the other hand, other members, especially those capable of both producing propionate and degrading mucin, such as Dorea spp, Ruminococcus gnavus and Ruminococcus torques, have been associated with series of inflammation–related disorders and increased gut barrier permeability.\(^{93,94}\) Unfortunately, the phylogenetic analyses in most studies were limited to the family level, possibly
leading to the inconsistent data regarding the role of Lachnospiraceae in health and disease.

Akkermansia muciniphila (A. muciniphila) is another important SCFA-producer that utilizes mucin as carbon source.\textsuperscript{110} However, reduced abundance of A. muciniphila has been associated with inflammatory bowel diseases and elevated inflammation.\textsuperscript{85} Several reviews have also suggested A. muciniphila as a promising probiotic in treating metabolic disorders and modulating immune responses.\textsuperscript{111,112} Different from other mucin-degrading taxa, A. muciniphila was also found to promote mucin production, despite its ability to breakdown mucus layer.\textsuperscript{113} Nevertheless, increased level of A. muciniphila was found in PD patients and some opposite effects have been reported.\textsuperscript{6,85}

**Controlling variables in human studies**

At compositional level, a weak connection of GM changes between human and animal studies can be established since human and murine harbor similar yet distinct microorganisms, although a shared trend of GM alterations was observed at functional level. However, compared to human, animal models exhibited more consistent GM alterations in both AD and SCRD studies. This discrepancy is mainly due to the limited studies available, heterogeneous samples and different methodologies applied in human studies.

In animal studies, mice and rats were born with identical genetic background, housed in constant environment and fed with unified food, and variables that could compromise the study have been carefully controlled as possible. Whereas in human studies, multiple factors including race, nationality, culture background and education may have substantial impacts on the lifestyle, daily diet and eating habit of participants, which directly affect GM composition.\textsuperscript{114} For example, participants of the five AD patients studies we have discussed above were from three continents with diverse culture background. It has been reported that diet plays a fundamental role in health and is a key determinant of GM.\textsuperscript{115,116} Western-style diet, high in animal protein, sugar and fat and low in vegetables, favors the growth of Bacteroidetes, especially Prevotella, which has been associated with colon cancer and several bowel diseases.\textsuperscript{117} Mediterranean diet, featured by fruit, plant fiber and unsaturated fat, shifts GM toward more abundant Akkermansia, Bifidobacterium and Lactobacillus.\textsuperscript{117} Also, food rich in dietary fiber and carbohydrates promotes the growth of highly fermentative bacteria such as Lachnospiraceae, Lactobacillaceae and Ruminococcaceae in the phylum Firmicutes.\textsuperscript{92} Thus, the diverse dietary could contribute to the discrepant GM alterations in AD patients from different countries. Moreover, the varied experimental designs and heterogeneous methods, including fecal sample acquirement, DNA extraction and sequencing, as well as the criteria in determining cognitive function and sleep quality, make it difficult to conclude a consistent trend of GM alterations from different studies.

Therefore, it seems improper to compare GM alterations in human studies solely based on low-level phylogenetic analysis, which can be easily affected by the abovementioned factors. However, we observed a coherent trend by taking the perspective of metabolism and functions (Table 5, Figure 4).

**Conclusion**

Based on the evaluations from different studies on GM at both compositional and functional levels, this review suggests a possible link between SCRD and AD by GM. We propose that long-term SCRD may indirectly lead to chronic GM dysbiosis by altering eating habit, lifestyle, metabolism, etc. SCRD and GM dysbiosis could work synergistically to contribute to the onset and progression of AD (Figure 5). However, the contribution of this alternative pathway in the development of AD remains unclear and requires further elucidation, since the etiology of sporadic AD varies from person to person.\textsuperscript{118} Also, more studies are needed to further demonstrate the specific mechanisms of how SCRD leads to GM dysbiosis and how probiotic and antibiotic treatment ameliorate AD pathology, as well as the potential implications of pathobionts such as Erysipelotrichaceae and Coriobacteriaceae in health and disease.

**Disclosure statement**

No potential conflict of interest was reported by the authors.
References

1. Ashraf GM, Tarasov VV, Chubarev MACA, Avila-Rodriguez VN, Bachurin M, Aliev G SO. The possibility of an infectious etiology of alzheimer disease. Mol Neurobiol. 2019;56(6):4479–4491. doi:10.1007/s12035-018-1388-y.

2. Sender R, Fuchs S, Milo R. Revised estimates for the number of human and bacteria cells in the body. PLoS Biol. 2016;14(8):e1002533. doi:10.1371/journal.pbio.1002533.

3. Lozupone CA, Stombaugh JI, Gordon JI, Jansson JK, Knight R. Diversity, stability and resilience of the human gut microbiota. Nature. 2012;489 (7415):220–230. doi:10.1038/nature11550.

4. Hornef M. Pathogens, commensal symbionts, and pathobionts: discovery and functional effects on the host. ILAR J. 2015;56(2):159–162. doi:10.1093/ilar/ilv007.

5. Gauld AL, Zhang V, Lamberti L, Jones EW, Obadia B, Korasidis N, Gavryushkin A, Carlson JM, Beerenwinkel N, Ludington WB. Microbiome interactions shape host fitness. Proc Natl Acad Sci U S A. 2018;115(51):E11951–E160. doi:10.1073/pnas.1809349115.

6. Nuzum ND, Loughman A, Szymlek-Gay EA, Hendy A, Teo WP, Macpherson H. Gut microbiota differences between healthy older adults and individuals with Parkinson’s disease: a systematic review. Neurosci Biobehav Rev. 2020;112:227–241. doi:10.1016/j.neubiorev.2020.02.003.

7. Fattoruso A, Di Genova L, Dell’Isola GB, Mencaroni E, Esposito S. Autism spectrum disorders and the gut microbiota. Nutrients. 2019;11: doi:10.3390/nu11030521.

8. Sun MF, Shen YQ. Dysbiosis of gut microbiota and microbial metabolites in Parkinson’s disease. Ageing Res Rev. 2018;45:53–61. doi:10.1016/j.arr.2018.04.004.

9. Li BY, He YX, Ma JF, Huang P, Du JJ, Cao L, Wang Y, Xiao Q, Tang HD, Chen SD. Mild cognitive impairment has similar alterations as Alzheimer’s disease in gut microbiota. Alzheimers Dement. 2019;15 (10):1357–1366. doi:10.1016/j.jalz.2019.07.002.

10. Liu P, Wu L, Peng GP, Han YQ, Tang RQ, Ge JP, Zhang LJ, Jia LF, Yue SQ, Zhou K, et al. Altered microbiomes distinguish Alzheimer’s disease from amnestic mild cognitive impairment and health in a Chinese cohort. Brain Behav Immun. 2019;80:633–643. doi:10.1016/j.bbi.2019.05.008.

11. Holth J, Patel T, Holtzman DM. Sleep in Alzheimer’s disease - beyond Amyloid. Neurobiol Sleep Circadian Rhythms. 2017;2:4–14. doi:10.1016/j.nbscr.2016.08.002.

12. Wang CN, Holtzman DM. Bidirectional relationship between sleep and Alzheimer’s disease: role of amyloid, tau, and other factors. Neuropsychopharmacol. 2020;45:104–120. doi:10.1038/s41386-019-0478-5.

13. Ju YES, Lucey BP, Holtzman DM. Sleep and Alzheimer disease pathology-a bidirectional relationship. Nat Rev Neurol. 2014;10(2):115–119. doi:10.1038/nnr.2013.269.

14. Sterniczuk R, Theou O, Rusak B, Rockwood K. Sleep disturbance is associated with incident dementia and mortality. Curr Alzheimer Res. 2013;10(7):767–775. doi:10.2174/15672050113109990134.

15. Lim ASP, Kowgier M, Yu L, Buchman AS, Bennett DA. Sleep fragmentation and the risk of incident Alzheimer’s disease and cognitive decline in older persons. Sleep. 2013;36(7):1027–1032. doi:10.1066/j.sleep.2012.08.001.

16. Musiek ES, Holtzman DM. Mechanisms linking circadian clocks, sleep, and neurodegeneration. Science. 2016;354(6315):1004–1008. doi:10.1126/science.aah4968.

17. Cuddapah VA, Zhang SL, Sehgal A. Regulation of the blood-brain barrier by circadian rhythms and sleep. Trends Neurosci. 2019;42(7):500–510. doi:10.1016/j.tins.2019.05.001.

18. Uddin MS, Tewari D, Al Mamun A, Kabir T, Niaz K, Wahed MII, Barreto GE, Ashraf GM. Circadian and sleep dysfunction in Alzheimer’s disease. Ageing Res Rev. 2020. doi:10.1016/j.arr.2020.101046.

19. La D, Cf M, Rn C, Db G, JE B, Be W, Av L, As D, Varma Y, Ma F, et al. Diet rapidly and reproducibly alters the human gut microbiome. Nature. 2014;505 (7484):559–+. doi:10.1038/nature12820.

20. Cryan JF, Dinan TG. Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. Nat Rev Neurosci. 2012;13(10):701–712. doi:10.1038/nrn3346.

21. Matenchuk BA, Mandhane PJ, Kozyrskyj AL. Sleep, circadian rhythm, and gut microbiota. Sleep Med Rev. 2020;53:101340. doi:10.1016/j.smrv.2020.101340.

22. Berchtold NC, Cotman CW. Evolution in the conceptualization of dementia and Alzheimer’s disease: greco-Roman period to the 1960s. Neurobiol Aging. 1998;19 (3):173–189. doi:10.1016/S0197-4580(98)00052-9.

23. Long JM, Holtzman DM. Alzheimer disease: an update on pathobiology and treatment strategies. Cell. 2019;179:312–339. doi:10.1016/j.cell.2019.09.001.

24. Devanand DP, Hypothesis V. Antiviral treatment in Alzheimer’s disease. Curr Neuro Neurosci. 2018;18. doi:10.1007/s11910-018-0863-1.

25. Sochocka M, Zvolinska K, Leszek J. The infectious etiology of Alzheimer’s disease. Curr Neuropharmacol. 2017;15 (7):996–1009. doi:10.2174/1570159X1566617031212937.

26. Zhuang ZQ, Shen LL, Li WW, Fu X, Zeng F, Gui L, Lu Y, Cai M, ZHU C, Tan YL, et al. Gut microbiota is altered in patients with Alzheimer’s disease. J Alzheimers Dis. 2018;63(4):1337–1346. doi:10.3233/jad-180176.

27. Vogt NM, Kerby RL, Dill-mcfarland KA, Harding SJ, Merluzzi AP, Johnson SC, Carlsson GM, Asthana S,
Zetterberg H, Blennow K, et al. Gut microbiome alterations in Alzheimer’s disease. Sci Rep-UK. 2017;7. doi:10.1038/s41598-017-13601-y.

28. Cattaneo A, Cattane N, Galluzzi S, Provasi S, Lopizzo N, Festari C, Ferrari C, Guerra UP, Paghera B, Muscio C, et al. Association of brain amyloidosis with pro-inflammatory gut bacterial taxa and peripheral inflammation markers in cognitively impaired elderly. Neurobiol Aging. 2017;49:60–68. doi:10.1016/j.neurobiolaging.2016.08.019.

29. Bauerl C, Collado MC, Diaz Cuevas A, Vina J, Perez Martinez G. Shifts in gut microbiota composition in an APP/PSS1 transgenic mouse model of Alzheimer’s disease during lifespan. Lett Appl Microbiol. 2018;66 (6):464–471. doi:10.1111/lam.12882.

30. Peng W, Yi P, Yang J, Xu F, Wang Y, Zhang Z, Huang S, Wang Z, Zhang C. Association of gut microbiota composition and function with a senescence-accelerated mouse model of Alzheimer’s Disease using 16S rRNA gene and metagenomic sequencing analysis. Aging (Albany NY). 2018;10(12):4054–4065. doi:10.18632/aging.101693.

31. Sun J, JX X, Ling Y, Fy W, Ty G, Cw Y, Sq Y, Ky Y, Dh W, ZQ S, et al. Fecal microbiota transplantation alleviated Alzheimer’s disease-like pathogenesis in APP/PSS1 transgenic mice. Transl Psychiat. 2019;9. doi:10.1038/s41398-019-0525-3.

32. Zhan GF, Yang N, Li S, Huang NN, Fang X, Zhang J, Zhu B, Yang L, Yang C, Luo AL. Abnormal gut microbiota composition contributes to cognitive dysfunction in SAMP8 mice. Aging-Us. 2018;10(6):1257–1267. doi:10.18632/aging.101464.

33. Zhang L, Wang Y, Xia XY, Shi CH, Chen W, Song N, Fu XJ, Zhou R, Xu YF, Huang L, et al. Altered gut microbiota in a mouse model of Alzheimer’s disease. J Alzheimers Dis. 2017;60(4):1241–1257. doi:10.3233/JAD-170020.

34. Shen L, Liu L, Ji HF. Alzheimer’s disease histological and behavioral manifestations in transgenic mice correlate with specific gut microbiome state. J Alzheimers Dis. 2017;56(1):385–390. doi:10.3233/JAD-160884.

35. Kim MS, Kim Y, Choi H, Kim W, Park S, Lee D, Kim DK, Kim HJ, Choi H, Hyun DW, et al. Transfer of a healthy microbiota reduces amyloid and tau pathology in an Alzheimer’s disease animal model. Gut. 2020;69(2):283–294. doi:10.1136/gutjnl-2018-317431.

36. Harach T, Marungruang N, Duthilleul N, Cheatham V, Mc Coy KD, Frisoni G, Neher JI, Fak F, Jucker M, Lasser T, et al. Reduction of Abeta amyloid pathology in APPPS1 transgenic mice in the absence of gut microbiota. Sci Rep-UK. 2017;7. doi:10.1038/srep41802.

37. Kowalski K, Brain-Gut-Microbiota MA. Axis in Alzheimer’s disease. J Neurorogoastroenterol. 2019;25 (1):48–60. doi:10.5056/jnm18087.

38. Ticinesi A, Tana C, Nouvenne A, Prati B, Lauretani F, Meschi T. Gut microbiota, cognitive frailty and dementia in older individuals: a systematic review. Clin Interv Aging. 2018;13:1497–1511. doi:10.2147/Cia.S139163.

39. Gerhardt S, Mohajeri MH. Changes of colonic bacterial composition in Parkinson’s disease and other neurodegenerative diseases. Nutrients. 2018;10. doi:10.3390/nu10060708.

40. Zhao YH, Cong L, Jaber V, Lukiw WJ. Microbiome-derived lipopolysaccharide enriched in the peripheral region of Alzheimer’s disease’s brain. Front Immunol. 2017;8. doi:10.3389/fimmu.2017.01064.

41. Konig J, Wells J, Cani PD, Garcia-Rodenas CL, MacDonald T, Mercenier A, Whyte J, Troost F, Brummer RJ. Human intestinal barrier function in health and disease. Clin Transl Gastroen. 2016;7. doi:10.1038/ctg.2016.54.

42. Galloway S, Takechi R, MMS P-G, Dhaliwal SS, Mamo JCL. Amyloid-beta colocalizes with apolipoprotein B in absorptive cells of the small intestine. Lipids Health Dis. 2009;8. doi:10.1186/1476-511x-8-46.

43. Holmquist V, Chutna O, Bousset L, Aldrin-Kirk P, Li W, Bjorklund T, Wang ZY, Roybon L, Melki R, Li JY. Direct evidence of Parkinson pathology spread from the gastrointestinal tract to the brain in rats. Acta Neuropathol. 2014;128(6):805–820. doi:10.1007/s00401-014-1343-6.

44. Pistollato F, Cano SS, Elio I, Vergara MM, Giampieri F, Battino M. Role of gut microbiota and nutrients in amyloid formation and pathogenesis of Alzheimer disease. Nutr Rev. 2016;74(10):624–634. doi:10.1093/nutrit/nwu023.

45. Crost EH, Tailford LE, Monestier M, Swarbreck D, Henriissat B, Crossman LC, Juge N. The mucin-degradation strategy of Ruminococcus gravis: the importance of intracellular trans-sialidases. Gut Microbes. 2016;7(4):302–312. doi:10.1080/19490976.2016.1186334.

46. Schirmer M, Garner A, Vlamakis H, Xavier RJ. Microbial genes and pathways in inflammatory bowel disease. Nat Rev Microbiol. 2019;17(8):497–511. doi:10.1038/s41579-019-0213-6.

47. Nguyen TT, Hathaway H, Kosciolek T, Knight R, Jeste DV. Gut microbiome in serious mental illnesses: a systematic review and critical evaluation. Schizophr Res. 2019. doi:10.1016/j.schres.2019.08.026.

48. VDR D-P, Forlenza AS, Forlenza OV. Relevance of gutmicrobiota in cognition, behaviour and Alzheimers disease. Pharmacol Res. 2018;136:29–34. doi:10.1016/j.phrs.2018.07.007.

49. Riviere A, Selak M, Lantin D, Leroy F, De Vuyst L. Bifidobacteria and butyrate-producing colon bacteria: importance and strategies for their stimulation in the human gut. Front Microbiol. 2016;7:979. doi:10.3389/fmicb.2016.00979.

50. Kim YA, Keogh JB, Clifton PM. Probiotics, prebiotics, symbiotics and insulin sensitivity. Nutr Res Rev. 2018;31 (1):35–51. doi:10.1017/S095442421700018x.

51. Akbari E, Asemi Z, Daneshvar Kakhaki R, Bahmani F, Kouchaki E, Tamtaji OR, Hamidi GA, Salami M. Effect
of Probiotic supplementation on cognitive function and metabolic status in Alzheimer’s Disease: a randomized, double-blind and controlled trial. Front Aging Neurosci. 2016;8:256. doi:10.3389/fagi.2016.00256.

52. Bonfili L, Cecarini V, Berardi S, Scarpona S, Suchodolski JS, Nasuti C, Fiorini D, Boarelli MC, Rossi G, Eleuteri AM. Microbiota modulation counteracts Alzheimer’s disease progression influencing neuronal proteolysis and gut hormones plasma levels. Sci Rep. 2017;7(1):2426. doi:10.1038/s41598-017-02587-2.

53. Itzhaki RF, Golde TE, Heneka MT, Readhead B. Do infections have a role in the pathogenesis of Alzheimer disease? Nat Rev Neurol. 2020;16(4):193–197. doi:10.1038/s41582-020-0323-9.

54. Leblhuber F, Steiner K, Schuetz B, Fuchs D, Gostner JM. Probiotic supplementation in patients with Alzheimer’s dementia - an explorative intervention study. Curr Alzheimer Res. 2018;15(12):1106–1113. doi:10.2174/13892029166681013144834.

55. Kaur H, Nagamoto-Combs K, Golovko S, Golovko MY, Klug MG, Combs CK. Probiotics ameliorate intestinal pathophysiolo in a mouse model of Alzheimer’s disease. Neurobiol Aging. 2020;92:114–134. doi:10.1016/j.neurobiolaging.2020.04.009.

56. Kobayashi Y, Sugahara H, Shimada K, Mitsuyama E, Kuhara T, Yasuoka A, Kondo T, Abe K, Xiao JZ. Therapeutic potential of Bifidobacterium breve strain AI for preventing cognitive impairment in Alzheimer’s disease. Sci Rep-UK. 2017;7:10.1038/s41598-017-13368-2.

57. Azm SAN, Dizayyeri A, Safa M, Azami K, Ahmadvand B, Sabbaghiarani F, Sharifzadeh M, Vafa M. Lactobacillus and bifidobacteria ameliorate memory and learning deficits and oxidative stress in beta-amyloid (1-42) injected rats. Appl Physiol Nutr Me. 2018;43(7):718–726. doi:10.1139/apnm-2017-0648.

58. Wang T, Hu X, Liang S, Li W, Wu X, Wang L, Jin F. Lactobacillus fermentum NS9 restores the antibiotic induced physiological and psychological abnormalities in rats. Benef Microbes. 2015;6:707–717. doi:10.3920/Bm.2014.0177.

59. Minter MR, Hinterleitner R, Meisel M, Zhang C, Leone V, Zhang XQ, Oyler-Castrillo P, Zhang XL, Musch MW, Shen XU, et al. Antibiotic-induced perturbations in microbial diversity during post-natal development alters amyloid pathology in an aged APP(SWE)/PS1(Delta E9) murine model of Alzheimer’s disease. Sci Rep-UK. 2017;7:10.1038/s41598-017-11047-w.

60. Minter MR, Zhang C, Leone V, Ringus DL, Zhang XQ, Oyler-Castrillo P, Musch MW, Liao F, Ward JF, Holtzman DM, et al. Antibiotic-induced perturbations in gut microbial diversity influences neuro-inflammation and amyloidosis in a murine model of Alzheimer’s disease. Sci Rep-UK. 2016;6:10.1038/srep30028.

61. Wang XY, Sun GQ, Feng T, Zhang J, Huang X, Wang T, Xie ZQ, Chu XK, Yang J, Wang H, et al. Sodium oligomannate therapeutically remodels gut microbiota and suppresses gut bacterial amino acids-shaped neuroinflammation to inhibit Alzheimer’s disease progression. Cell Res. 2019;29(10):787–803. doi:10.1038/s41422-019-0216-x.

62. Dodiya HB, Kunzt T, Shaik SM, Baufeld C, Leibowitz J, Zhang XL, Gottel N, Zhang XQ, Butovsky O, Gilbert JA, et al. Sex-specific effects of microbiome perturbations on cerebral A beta amyloidosis and microglia phenotypes. J Exp Med. 2019;216(7):1542–1560. doi:10.1084/jem.20182386.

63. Mezo C, Dokalis N, Mossad O, Staszewski O, Neuber J, Yilmaz B, Schnepl D, De Aguerdo MG, Ganal-Vonarburg SC, Macpherson AJ, et al. Different effects of constitutive and induced microbiota modulation on microglia in a mouse model of Alzheimer’s disease. Acta Neuropathol Com. 2020;8:10.1186/s40478-020-00998-5.

64. Broadhead MJ, Bonthonc R, Arcinas L, BeS Z, Zhu F, Goff F, Nylk J, Dholakia K, Gunn-Moore F, Grant SGN, et al. Synergistic depletion of gut microbial consortia, but not individual antibiotics, reduces amyloidosis in APPPS1-21 Alzheimer’s transgenic mice. Sci Rep-UK. 2020;10:10.1038/s41598-020-64797-5.

65. Li Z, Zhu H, Guo YX, Du XP, Qin C. Gut microbiota regulate cognitive deficits and amyloid depositin in a model of Alzheimer’s disease. J Neurochem. 2020. doi:10.1111/jnca.15031.

66. Walker AW, Ince J, Duncan SH, Webster LM, Holtrop G, Ze XL, Brown D, Stares MD, Scott P, Bergerat A, et al. Dominant and diet-responsive groups of bacteria within the human colonic microbiota. Isme J. 2011;5(2):220–230. doi:10.1038/ismej.2010.118.

67. Liu XF, Cao SQ, Zhang XW. Modulation of gut microbiota brain axis by probiotics, prebiotics, and diet. J Agr Food Chem. 2015;63(36):7885–7895. doi:10.1021/acs.jafc.5b02404.

68. Thaiss CA, Zeedi D, Levy M, Zilberman-Schapira G, Suez J, Tengeler AC, Abramson L, Katz MN, Korem T, Zmora N, et al. Transkingdom control of microbiota diurnal oscillations promotes metabolic homeostasis. Cell. 2014;159(3):514–529. doi:10.1016/j.cell.2014.09.048.

69. Parkar SG, Kalsbeek A, Cheeseman JF. Potential role for the gut microbiota in modulating host circadian rhythms and metabolic health. Microorganisms. 2019;7:10.3390/microorganisms7020041.

70. Krueger JM, Opp MR. Sleep and microbics. Int Rev Neurobiol. 2016;131:207–225. doi:10.1016/bsn.2016.07.003.

71. Benedict C, Vogel H, Jonas W, Woting A, Blaut M, Schurmann A, Cedernaes J. Gut microbiota and glucometabolic alterations in response to recurrent partial sleep deprivaton in normal-weight young individuals. Mol Metab. 2016;5(12):1175–1186. doi:10.1016/j.molmet.2016.10.003.

72. Grosicki GJ, Riemann BL, Flatt AA, Valentino T, Lustgarten MS. Self-reported sleep quality is associated with gut microbiome composition in young, healthy individuals: a pilot study. Sleep Med. 2020;73:76–81. doi:10.1016/j.sleep.2020.04.013.
73. Anderson JR, Carroll I, Azcarate-Peril MA, Rochette AD, Heinberg IJ, Peat C, Steffen K, Manderino LM, Mitchell J, Gunstad J. A preliminary examination of gut microbiota, sleep, and cognitive flexibility in healthy older adults. Sleep Med. 2017;38:104–107. doi:10.1016/j.sleep.2017.07.018.

74. Smith RP, Easson C, Lyle SM, Kapoor R, Donnelly CP, Davidson EJ, Parikh E, Lopez JV, Tartar JL. Gut microbiome diversity is associated with sleep physiology in humans. Plos One. 2019;14. doi:10.1371/journal.pone.0222394.

75. Poroyko VA, Carreras A, Khalyfa A, Khalyfa AA, Leone V, Peris E, Almendros I, Gileles-Hillel A, Qiao Z, Hubert N, et al. Chronic sleep disruption alters gut microbiota, induces systemic and adipose tissue inflammation and insulin resistance in mice. Sci Rep. UK. 2016;6. doi:10.1038/srep35405.

76. El Aïdy S, Bolsius YG, Raven F, Havekes R. A brief period of sleep deprivation leads to subtle changes in mouse gut microbiota. J Sleep Res. 2019. doi:10.1111/jsr.12920.

77. Maki KA, Burke LA, Calik MW, Watanabe-Chailland M, Sweeney D, Romick-Rosendale LE, Green SJ, Fink AM. Sleep fragmentation increases blood pressure and is associated with alterations in the gut microbiome and fecal metabolome in rats. Physiol Genomics. 2020;52(7):280–292. doi:10.1152/physiolgenomics.00039.2020.

78. Bowers SJ, Vargas F, Gonzalez A, He SN, Jiang P, Dorrestein PC, Knight R, Wright KP, Lowry CA, Fleschner M, et al. Repeated sleep disruption in mice leads to persistent shifts in the fecal microbiome and metabolome. Plos One. 2020;15. doi:10.1371/journal.pone.0229001.

79. Triplet J, Ellis D, Braddock A, Roberts E, Ingram K, Perez E, Short A, Brown D, Hutzley V, Webb C, et al. Temporal and region–specific effects of sleep fragmentation on gut microbiota and intestinal morphology in Sprague Dawley rats. Gut Microbes. 2020;11(4):706–720. doi:10.1080/19490997.2019.1701352.

80. Ma W, Song J, Wang H, Shi F, Zhou N, Jiang J, Xu Y, Zhang L, Yang L, Zhou M. Chronic paradoxical sleep deprivation-induced depression-like behavior, energy metabolism and microbial changes in rats. Life Sci. 2019;225:88–97. doi:10.1016/j.lfs.2019.04.006.

81. Zhang SL, Bai L, Goel N, Bailey A, Jang CJ, Bushman FD, Meerro P, Dinges DF, Sehgal A. Human and rat gut microbiome composition is maintained following sleep restriction. P Natl Acad Sci USA. 2017;114(8):E1564–E71. doi:10.1073/pnas.1620673114.

82. Palm NW, de Zoete MR, Cullen TW, Barry NA, Stefanowski J, Hao LM, Degnan PH, Hu JZ, Peter I, Zhang W, et al. Immunoglobulin A coating identifies colitogenic bacteria in inflammatory bowel disease. Cell. 2014;158(5):1000–1010. doi:10.1016/j.cell.2014.08.006.

83. Jakobsson HE, Rodriguez-Pineiro AM, Schutte A, Ermund A, Boysen P, Bemark M, Sommer F, Backhed F, Hansson GC, Johansson MEV. The composition of the gut microbiota shapes the colon mucus barrier. Embo Rep. 2015;16(2):164–177. doi:10.15252/embr.201439263.

84. Schirmer M, Smeekens SP, Vlamakis H, Jaeger M, Oosting M, Franzosa EA, Ter Horst R, Jansen T, Jacobs L, MJ B, et al. Linking the human gut microbiome to inflammatory cytokine production capacity (vol 167, pg 1125, 2016). Cell. 2016;167(7):1897. doi:10.1016/j.cell.2016.11.046.

85. Derrien M, Belzer C, de Vos WM. Akkermansia muciniphila and its role in regulating host functions. Microb Pathogenesis. 2017;106:171–181. doi:10.1016/j.micpath.2016.02.005.

86. Voigt RM, Forsyth CB, Green SJ, Engen PA, Circadian KA. Rhythm and the gut microbiome. Int Rev Neurobiol. 2016;131:193–205. doi:10.1016/bs.irn.2016.07.002.

87. Mortas H, Bilici S, Karakan T. The circadian disruption of night work alters gut microbiota consistent with elevated risk for future metabolic and gastrointestinal pathology. Chronobiol Int. 2020. doi:10.1080/07420528.2020.1778717.

88. Liu Z, Wei ZY, Chen J, Chen K, Mao X, Liu Q, Sun Y, Zhang Z, Zhang Y, Dan Z, et al. Acute sleep–wake cycle shift results in community alteration of human gut microbiome. mSphere. 2020;5. doi:10.1128/mSphere.00914-19.

89. Khalyfa A, Poroyko VA, Qiao Z, Gileles-Hillel A, Khalyfa AA, Akbarpoure M, Almendros I, Farre R, Gozal D. Exosomes and metabolic function in mice exposed to alternating dark–light cycles mimicking night shift work schedules. Front Physiol. 2017;8:882. doi:10.3389/fphys.2017.00882.

90. Deaver JA, Eum SY, Toborek M. Circadian disruption changes gut microbiome taxa and functional gene composition. Front Microbiol. 2018;9:737. doi:10.3389/fmicb.2018.00737.

91. Klímova KM, Batotsy Enumeration EG, Yunes RA, Gilyaeva EH, Poluektova EU, Kostrova TA, Kudryavtseva AV, Odorskaya MV, Kashuro VA, Kasianov AS, et al. Effects of desynchronisation on the gut microbiota composition and physiological parameters of rats. Bmc Microbiol. 2019;19. doi:10.1186/s12866-019-1535-2.

92. Vaccar M, Celano G, Calabrese FM, Portincasa P, Gobbetti M, De Angelis M. The controversial role of human gut lachnospiraceae. Microorganisms. 2020;8. doi:10.3390/microorganisms8040573.

93. Png CW, Linden SK, Gilshenan KS, Zoetendal EG, McSweeney CS, Sly LI, McGuckin MA, Florin TH. Mucolytic bacteria with increased prevalence in IBD mucosa augment in vitro utilization of mucin by other bacteria. Am J Gastroenterol. 2010;105(11):2420–2428. doi:10.1038/aig.2010.281.

94. Crest EH, Tailford LE, Le Gall G, Fons M, Henrisat B, Juge N. Utilisation of mucin glycans by the human gut symbiont ruminococcus gnarus is strain-dependent. Plos One. 2013;8. doi:10.1371/journal.pone.0076341.
