1 **Association of *Prevotella* enterotype with polysomnographic data in obstructive**
2 **sleep apnea/hypopnea syndrome patients**

4 **Running Title: Various enterotypes in OSAHS**

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Abstract

Intermittent hypoxia and sleep fragmentation are critical pathophysiological processes involved in obstructive sleep apnea/hypopnea syndrome (OSAHS). These manifestation independently affect similar brain regions and contribute to OSAHS-related comorbidities that are known to be related to the host gut alteration microbiota. We hypothesized that microbiota disruption influences the pathophysiological processes of OSAHS through a microbiota–gut–brain axis. Thus, we aim to survey enterotypes and polysomnographic data of OSAHS patients. Subjects were diagnosed by polysomnography, from whom fecal samples were obtained and analyzed for the microbiome composition by variable regions 3–4 of 16S rRNA pyrosequencing and bioinformatic analyses. We examined blood cytokines level of all subjects. Three enterotypes *Bacteroides* (n=73), *Ruminococcus* (n=14), and *Prevotella* (n=26) were identified. Central apnea indices, mixed apnea indices, N1 sleep stage, mean apnea–hypopnea duration, and arousal indices were increased in apnea–hypopnea indices (AHI) ≥ 15 patients with the *Prevotella* enterotype. However, for AHI<15 subjects, obstructive apnea indices and systolic blood pressure were significantly observed in *Ruminococcus* and *Prevotella* enterotypes, respectively. The present study indicates the possibility of pathophysiological interplay between enterotypes and sleep structure disruption in sleep apnea through a microbiota–gut–brain axis and offers some new insight toward the pathogenesis of OSAHS.

Key Words: central apnea indices, enterotypes, microbiota, polysomnography,

49 obstructive sleep apnea/hypopnea syndrome

50 **Importance**

51 Intermittent hypoxia (IH) and sleep fragmentation (SF) are hallmarks of are the
 52 predominant mechanism underlying obstructive sleep apnea/hypopnea syndrome
 53 (OSAHS). Moreover, IH and SF of pathophysiological roles in the gut microbiota
 54 dysbiosis in OSAHS have been demonstrated. We hypothesized that gut microbiota
 55 disruption may cross-talk the brain function via microbiota–gut–brain axis. Indeed,
 56 we observed central apnea indices and other parameters of disturbances during sleep
 57 were significantly elevated in $AHI \geq 15$ patients with the *Prevotella* enterotype. This
 58 enterotype prone to endotoxin production, driving systemic inflammation, ultimately
 59 contributes to OSAHS-linked comorbidities. Vice versa, increasing the arousal index
 60 leads to systemic inflammatory changes and accompanies metabolic dysfunction. We
 61 highlight that the possibility that the microbiota–gut–brain axis operates a
 62 bidirectional effect on the development of OSAHS pathology.

Introduction

Intermittent hypoxia (IH) and sleep fragmentation (SF) are hallmarks of obstructive sleep apnea/hypopnea syndrome (OSAHS) [1-3]. IH plays a critical pathophysiological role in OSAHS, often accompanied by reduced oxygen saturation, increased systemic pressure and bloodstream, excessive sympathetic neural activity, impairment of autonomic function and apnea episodes end with an arousal of the central nervous system (CNS), ultimately result in vascular endothelial dysfunction and multi-organ morbid consequences. The underlying mechanism involves inflammation and oxidative stress cascades [4,5].

Contrastingly, sleep structure disruption is another risk factor for the pathophysiology of OSAHS, causing major end-organ morbidity independent of IH [6,7]. Repeated arousals disturbing different stages of sleep are the predominant mechanism underlying OSAHS-induced brain injury wherein results from disruptions of rapid eye movement (REM) and non-REM (NREM) [7]. Even disturbances in sleep continuity are associated with emotional disorders [8]. SF promotes obesity and metabolic abnormalities and may be mediated by concurrent alterations of the host gut microbiota and concurrent systemic and adipose tissue inflammatory alterations accompanied by insulin resistance [3,9]. Prolongation of the N1 stage and shortening of REM times were observed in OSAHS-induced hypertension patients. Reportedly, prolongation of the N1 sleep stage causes elevation of fasting blood glucose [10]. Elevated serum lipopolysaccharide (LPS)-binding protein levels might prolong the N1 stage and increase SF, which may be related to increased nighttime respiratory events

and arousals [10]. Interestingly, the disturbance of sleep structure also contributes to mild cognitive decline in OSAHS [7]. However, treating OSAHS patients with continuous positive airway pressure (CPAP) has protective effects on neurocognition, and it has been postulated that the microbiota can be modulated during CPAP treatment [11], implying that the microbiota might participate in the pathophysiological developed mechanism.

Emerging evidence suggests that the gut microbiota play a crucial role in modulating the risk of several chronic diseases and maintaining intestinal immunity and whole body homeostasis. These effects have important implications for diseases such as obesity, cardiometabolic abnormalities, inflammatory bowel disease (IBD), and mental illness [12]. Additionally, the gut microbiota alterations manifested in IH and FS mimic in OSAHS animal models [1,3]. However, some of the underlying mechanisms of OSAHS-related comorbidities remain unclear. Enterotype analysis has been proposed as a useful method to understand human gut microbial communities, including *Bacteroides*, *Ruminococcus*, and *Prevotella* enterotypes, irrespective of ethnicity, gender, age or body mass index (BMI) [13]. Moreover, enterotypes subdivision provides an attractive framework for linking human disease. For example, *Bacteroides* enterotype has been reported to pose an increased risk for IBD [14-16].

Notably, the characteristics of IH and SF in OSAHS can trigger the inflammatory response, which then alters the intestinal microbial community composition [1,3,9]. Conversely, gut microbiomes can also respond to the brain via the microbiota–gut–brain axis, as has been reported in psychiatric disorders [17,18]. However, this

hypothesis has not been verified for OSAHS. Thus, the present study tested the hypothesis that the microbiota–gut–brain axis is involved in the pathogenesis of OSAHS. We examined whether impaired sleep architecture is associated with gut microbiota alteration by investigating sleep parameters of polysomnography (PSG) data and pro-inflammatory cytokines in various enterotypes of OSAHS subjects.

Results

Patient characteristics and enterotype distribution

We enrolled 113 patients (61, AHI<15; 52, AHI≥15). Patients were divided according to three enterotypes: *Bacteroides* (n=73), *Ruminococcus* (n=14), and *Prevotella* (n=26) (Figure 1). The ages of the *Ruminococcus* enterotype patients were significantly higher than those of the *Bacteroides* enterotype patients (Table 1). BMI and hip circumference of the *Prevotella* enterotype patients were significantly higher than those of the *Bacteroides* enterotype patients (Table 1).

PSG parameter analysis

Comparisons among patients with different enterotypes showed that central apnea times, mixed apnea index, and mixed apnea times were the highest in the *Prevotella* enterotype patients (Table 2).

Using 15 as the AHI cut-off, when AHI≥15, N1 sleep stage, arousal time in REM, arousal index in REM, arousal time in NREM, total sleep arousal times, total sleep arousal index, central apnea times, mixed apnea index, and mixed apnea times were

the highest in the *Prevotella* enterotype patients. Contrastingly, sleep latency and arousal time were the lowest in the *Prevotella* enterotype patients (Table 3). When AHI<15, obstructive apnea index and obstructive apnea times were the highest in the *Ruminococcus* enterotype subjects, the highest and average systolic BP were the highest in the *Prevotella* enterotype subjects (Table 4).

We used individual enterotypes for comparison due to the effects of *Ruminococcus* and *Prevotella* enterotypes on PSG. For *Ruminococcus* enterotype patients, AHI, apnea-hypopnea times, oxygen desaturation index, highest systolic blood pressure (BP), and average systolic BP were all significantly elevated in AHI≥15 patients (Table 5).

For *Prevotella* enterotype patients, N1 sleep stage, N3 sleep stage, arousal index in REM, arousal time in NREM, arousal index in NREM, total sleep arousal times, total sleep arousal index, AHI, apnea-hypopnea times, obstructive apnea index, obstructive apnea times, central apnea index, mixed apnea index, hypopnea index, hypopnea times, longest apnea time, mean apnea–hypopnea duration (MAD), longest hypopnea time, average hypopnea time, oxygen desaturation index, and mean heart rate were significantly elevated in AHI≥15 patients. However, sleep latency, arousal time, lowest oxygen saturation, and average oxygen saturation were significantly decreased in AHI≥15 patients (Table 6).

Cytokine analysis

There were not significantly different in IL- 6 and TNF-α among three

enterotypes patients (Figure 2).

Discussion

OSAHS is a systemic and comprehensive disorder associated with comorbidities, including cardiovascular disease, metabolic abnormalities, and neuropsychiatric and neurodegenerative disorders [4,5,7,9]. Thus, the IH mechanism alone is insufficient to interpret the complete pathogenesis of OSAHS because OSAHS is also affected by several other aspects, including the CNS. This study shows that central apnea indices are significantly elevated in $AHI \geq 15$ patients with the *Prevotella* enterotype, accompanied other parameters of disturbances in sleep. However, for $AHI < 15$ results, changes in obstructive apnea indices and systolic BP are the remarkable observations in *Ruminococcus* enterotype and *Prevotella* enterotype subjects, respectively.

Bacteroides enterotype is associated with Western-style diets, including consuming high amounts of protein and fat. *Prevotella* enterotype is associated with diets high in carbohydrates (fiber) and simple sugars, whereas *Ruminococcus* species enterotype is linked to non-digestible carbohydrates [14]. Despite the fact that the *Bacteroides* predominant enterotype seems to be more common in IBD patients, the *Prevotella* enterotype is more representative in healthy subjects [15,16]. Our findings show that *Bacteroides* enterotype patients are not susceptible to OSAHS, in contrast to the susceptibility of *Prevotella* and *Ruminococcus* enterotype patients.

IH-exposed mice mimic OSAHS, causing profound alterations in gut microbiota. Hypoxia/re-oxygenation is the most pronounced [1], inducing an alteration in

intestinal epithelial barrier markers and increasing intestinal permeability, leading to local and systemic inflammatory responses and consequent multi-organ morbidities [20,21]. However, only *Bacteroides* and *Prevotella* enterotypes can be classified in the rodent model, IH-exposed mice classify as the *Prevotella* enterotype [1], who is similar to our particularly OSAHS patients. It has also been shown that IH leads to gut microbiota alteration and accompanying endotoxin production [22]. It is that IH model creates an anoxic environment in the intestine, which is beneficial for obligate anaerobic bacterial growth, endogenous LPS production from gram-negative bacteria, and triggering inflammation. Notably, *Prevotella* is a genus of gram-negative anaerobic bacteria, and it tends to alter intestinal permeability [1,2]. Although this evidence only reveals the IH contribution to the pathogenesis, we speculated that SF is another principal contributor [3]. SF-induced mice manifest inflammation and enhanced production of endotoxins produced by gut microbiota, too [3]. In middle-aged nonobese males with OSAHS, disruption of the intestinal barrier and concurrent increased serum d-lactate levels possibly contribute to intestinal hyperpermeability and are significantly positively associated with IL-1 β , IL-6, and TNF- α in serum [19] in which TNF- α elevation in *Prevotella* enterotype subjects is similar with our results, but it did not reach statistically significant differences. Moreover, LPS may play a key role in driving systemic inflammation, it has been shown in IH and SF modeling OSAHS models [1-3].

Prevotella enterotype patients with AHI $\geq$ 15 in our results, suggesting that LPS production triggers downstream signaling pathways, leading to the subsequent release

195 of pro-inflammatory IL-1 β , IL-6, and TNF- α cytokines [23]. Furthermore, the
 196 elevation of LPS-binding protein [19] is also verified in OSAHS, mimicking rodent
 197 models [3] and patients [19], particularly regarding in the higher d-lactate level of
 198 OSAHS patients. Inflammatory mediators can be produced by peripheral and central
 199 cells. Peripheral inflammatory mediators may invade the CNS by crossing the blood–
 200 brain barrier, affecting behaviors and causing metabolic problems and psychiatric
 201 disorders [24]. Here, our data suggest that the gut microbiota impact the brain in
 202 OSAHS patients by modulating inflammatory responses. Additionally, we should
 203 mention that the *Prevotella* enterotype is linked to diets rich in simple sugars. Simple
 204 carbohydrate consumption has been hypothesized to be related to elevated BP values
 205 and obesity [25], as shown in our data. *Prevotella* enterotype patients had a higher
 206 BMI and hip circumference than *Bacteriodes* enterotype patients. Monosaccharide
 207 intake induces inflammation in epithelial cells and contributes to hypertension [25],
 208 linking to LPS production, which can stimulate systemic inflammatory cascades [1].
 209 Inflammation mediates the pathogenesis of many physiological dysfunctions, such as
 210 metabolic syndrome and mental dysfunction [24], and thus might ultimately result in
 211 OSAHS-related metabolic comorbidities. Although *Ruminococcus* is associated with
 212 resistant starch, host health benefits from short chain fatty acids that have been
 213 demonstrated to regulate immune inflammatory responses [26]. The enriched bacteria
 214 *Ruminococcus* spp. and *Sutterella* spp. are found in autism spectrum disorder patients
 215 [27]. The abovementioned literature supports the hypothesis that microbiota

disruption influences the pathophysiological process of OSAHS through a microbiota–gut–brain axis.

Although OSAHS is one of the most common sleep apnea syndromes (SAS), other types are mixed sleep apnea (MSA) and central sleep apnea (CSA). The prevalences of OSAHS, complex SAS (CompSAS), and central SAS are 84.0%, 15.0%, and 0.4%, respectively [28]. MSA generally describes the mixture of both obstructive and central apnea events during diagnostic sleep, although many central apnea index occurrence is also identified as MSA, which is sometimes referred to as CompSAS [29]. Whereas CompSAS is a form of CAS wherein the persistence or emergence of central apneas or hypopneas have disappeared with CPAP, patients have predominately obstructive or mixed apneas occurring at ≥ 5 events/h [30]. Additionally, reportedly, there is a high prevalence of hypertension and heart disease in patients with CompSAS [31]. In our data, the central apnea index and mixed apnea index were significantly increased in *Prevotella* enterotype patients with $AHI \geq 15$. Thus, abnormalities in electrocardiography, electroencephalography, electromyography, and electro-oculography results should be of more concern.

Both IH and SF have been shown to independently affect similar CNS regions in animal research [7]. The N1 sleep stage is associated with the transition from wakefulness to other sleep stages or the following arousal during sleep. A higher N1 percentage might mean more events of wakefulness and/or arousal, SF (episodic arousal from sleep), and sympathetic overactivity during sleep [10]. REM sleep dysregulation significantly contributes to cognitive distortions and dysfunctions that

rely on emotion and memory functions are also affected [8]. Moreover, the effects of sleep deprivation on cognition have been investigated [32]. Thus, OSAHS patients have been found to have neurocognitive and emotional disorders, suggesting the modulation of various neurotransmitters during the sleep period [7]. Recently, a multicenter randomized controlled trial has been initiated evaluating the extent to which CPAP treatment improves neurocognitive dysfunction in OSAHS patients and examining the role of gut microbiota in this change [11]. Preliminary results suggest the viability of the hypothesis that microbiota modulate central nervous functions in OSAHS patients.

Although the neural mechanisms underlying SAS-induced brain injury have not been completely elucidated, repeated arousals enable the characterization of the different stages of sleep. In the present study, the N1 sleep stage, MAD, and arousal index were increased in *Prevotella* enterotype patients. BP was not significantly different among the three enterotype AHI $\geq$ 15 patient groups, but mean diastolic pressure during sleep was >80 mmHg, which was similar to that observed in a previous study [10]. MDA can act as an indicator of the levels of sleep parameters and blood oxygenation for the evaluation of severe OSAHS patients [33]. When MAD is elevated, sleep apnea appears to be more likely to cause respiratory arousal and might impair sleep stability, resulting in SF. This outcome might then be that the transition of the N2 sleep stage (the longest stage of sleep) to the N3 sleep stage is a vulnerable period, which is interrupted in OSAHS patients, and the overall sleep pattern becomes light sleep [33]. Additionally, chronic SF induction elevates fat mass, alters fecal

microbiota, promotes increased gut permeability, leads to systemic and adipose tissue inflammatory changes, and accompanies metabolic dysfunction [3]. These symptoms are known to be associated with OSAHS-related metabolic comorbidities, implying that the microbiota–gut–brain axis has a biaxial effect on the development of OSAHS pathology.

Contrastingly, evidence has shown that N1, N3, and REM sleep stages decrease and the N2 sleep stage increases in OSAHS patients [7]. However, a higher N1 percentage, a longer MAD, and a shortened REM sleep stage were revealed in AHI $\geq$ 15 patients with OSAHS-induced hypertension [10,33]. Our findings reveal that BP plays a vital role, particularly for SAS, where BP is comprehensively regulated by the peripheral and central systems. Hence, future studies should re-examine these questions in subgroups of hypertensive and normotensive OSAHS patients to assess their general applicability.

The current study initiates a new approach to the study of sleep apnea through a combination of polysomnographic measurements with analysis of gut microbiota. Central apnea index, mixed apnea index, N1 sleep stage, MAD, and arousal indices were all increased in AHI $\geq$ 15 patients with the *Prevotella* enterotype. Our results raise the possibility that the microbiota–gut–brain axis operates bidirectionally, with significant impact on the pathogenesis of OSAHS including functions of the gut and brain that eventually contribute to multiple end-organ morbidities.

Materials and Methods

Subjects

In total, 113 subjects were recruited and examined during a full night of PSG (SOMNOscreen™ plus PSG⁺; SOMNOmedics GmbH, Randersacker, Germany) by technologists in a sleep laboratory from 10 PM to 8 AM at the Department of Pulmonary and Critical Care Medicine. Fecal samples were collected the following morning. The Institutional Review Board of the Second Affiliated Hospital of Fujian Medical University approved this study (IRB No. 2017-78).

OSAHS evaluation

All the subjects underwent PSG with a computerized polysomnographic system, simultaneously including electrocardiography, electroencephalography, electromyography, and electrooculography. After one night of examination, AHI were calculated as the total number of episodes of apnea (continuous cessation of airflow for at least 10 s) and hypopnea (reduction in airflow for ≥ 10 s with oxygen desaturation $\geq 4\%$) by dividing the total sleep by events, according to the diagnostic criteria of the American Academy of Sleep Medicine. AHI <15 events/h was defined as non-OSAHS and AHI ≥ 15 events/h as OSAHS in this study, as reported previously [10,19].

Cytokine analysis

IL-6 and TNF- α were assayed by BD Human Enhanced Sensitivity Cytometric Bead Array Kit (BD Biosciences, New Jersey, USA) as described previously [18]. The standard coefficient of determination (r^2) was greater than 0.995.

Sampling, DNA extraction, and 16S rRNA gene amplification sequencing

Samples were collected and stored in a Microbiome Test Kit (G-BIO Biotech, Inc., Hangzhou, China). Magnetic bead isolation was performed to extract genomic DNA using a TIANamp stool DNA kit (TIANGEN Biotech Co., Ltd., Beijing, China), according to the manufacturer's instructions. The concentration of extracted DNA was determined by a Nanodrop ND-1000 spectrophotometer (Thermo Electron Corporation, USA), and DNA quality was confirmed using 1.0% agarose gel electrophoresis with 0.5 mg/mL ethidium bromide.

Isolated fecal DNA was used as a template to amplify the V3 and V4 hypervariable regions of the bacterial 16S ribosomal RNA gene. The V3 and V4 regions were PCR-amplified (forward primer, 5'-ACTCCTACGGGAGGCAGCAG-3'; reverse primer, 5'-GGACTACHVGGGTWTCTAAT-3'). The 16S target-specific sequence contained adaptor sequences permitting uniform amplification of a highly complex library ready for downstream next-generation sequencing on Illumina MiSeq (Illumina, USA). Negative DNA extraction controls (lysis buffer and kit reagents only) were amplified and sequenced as contamination controls. The amplicons were normalized, pooled, and sequenced on the Illumina MiSeq platform using a V3 reagent kit with 2×300 cycles per sample and with imported and prepared routine

data (samsheet) run in the MiSeq sequence program. After sequencing, Q30 scores were $\geq 70\%$, the percentage of clusters passing filter (i.e., cluster PF) was $\geq 80\%$, and there were at least 30,000 clean tags. Finally, image analysis and base calling were conducted with MiSeq Control Software.

Bioinformatic, predictive function and statistical analyses

Based on the Quantitative Insights into Microbial Ecology bio-informatic pipeline for performing taxonomy assignment by the operational taxonomic unit method, we used data of 113 sequences to analyze the fecal microbiota taxa. We analyzed differences in gut microbiota using the Wilcoxon test, as appropriate, and performed principal coordinate analysis on the basis of the Bray–Curtis distance function, using R statistics. We performed other analyses using statistically with SPSS version 19.0 (SPSS Inc., Chicago, IL, USA); data were analyzed by *t*-test or one-way ANOVA, followed by Scheffe post hoc analyses. We considered a two-sided *p* value of <0.05 to be statistically significant.

Declarations

Conflict of interest

The authors declare that they have no financial and personal relationships with others that may inappropriately influence the results and interpretation in this manuscript.

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Conception and design: CYK, HPZ, YMZ

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Figures and tables captions

Figure 1. The faecal taxa of non-obstructive sleep apnoea–hypopnea syndrome (OSAHS) and OSAHS subjects of three enterotypes.

Apnoea–hypopnea indices (AHI) < 15 as non-OSAHS, AHI ≥ 15 as OSAHS.

Enterotype 1: *Bacteroides*, Enterotype 2: *Ruminococcus*, Enterotype 3: *Prevotella*.

Figure 2. Cytokines levels analysis in three enterotypes subjects.

IL: interleukin, TNF: tumor necrosis factor.

Table 1. Participant characteristics.

Table 2. Polysomnographic data analysis in three enterotypes subjects.

Table 3. Polysomnographic data analysis in three enterotypes of apnoea–hypopnea indices ≥ 15 patients.

Table 4. Polysomnographic data analysis in enterotypes of apnoea–hypopnea indices < 15 subjects.

Table 5. Polysomnographic data analysis in *Ruminococcus* enterotype subjects.

AHI: apnoea–hypopnea indices. * p<0.05, ** p<0.01 compared with AHI<15 subjects.

505

506 **Table 6. Polysomnographic data analysis in *Prevotella* enterotype subjects.**

507 AHI: apnoea–hypopnea indices. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ compared with

508 AHI<15 subjects.

509

Table 1.

	<i>Bacteroides</i> enterotype (n=73)	<i>Ruminococcus</i> enterotype (n=14)	<i>Prevotella</i> enterotype (n=26)
Gender (male/female)	61/12	11/3	20/6
Age (years, mean $\pm$ SD)	40.89$\pm$10.56b	53.14$\pm$14.37a	44.58$\pm$13.51ab
Height (cm)	166.28 $\pm$ 6.90a	164.61 $\pm$ 7.30a	166.83 $\pm$ 8.83a
Weight (kg)	72.51 $\pm$ 14.31a	71.62 $\pm$ 14.25a	79.41 $\pm$ 13.70a
Body mass index (kg m ⁻²)	26.11$\pm$3.87b	26.44$\pm$5.50ab	28.73$\pm$5.27a
Waist circumference (cm)	90.77 $\pm$ 9.87a	91.21 $\pm$ 13.33a	96.54 $\pm$ 12.27a
Hip circumference (cm)	96.95$\pm$6.03b	97.75$\pm$10.42ab	103.21$\pm$8.97a
Waist-to-hip ratio	0.94 $\pm$ 0.07a	0.93 $\pm$ 0.06a	0.93 $\pm$ 0.06a

Table

■ 2.

	<i>Bacteroides</i> enterotype (n=73)	<i>Ruminococcus</i> enterotype (n=14)	<i>Prevotella</i> enterotype (n=26)
Total sleep time (min)	389.01±99.14a	362.77±120.12a	429.64±119.1a
N1 sleep stage (min)	138.56±66.92a	152.04±82.37a	171.62±96.22a
N1 sleep stage (%)	36.10±15.90a	42.19±14.54a	39.76±17.28a
N2 sleep stage (min)	111.30±60.67a	85.85±44.25a	111.94±57.67a
N2 sleep stage (%)	28.10±11.99a	24.45±9.62a	25.86±10.48a
N3 sleep stage (min)	71.91±36.85a	57.71±45.99a	66.44±41.66a
N3 sleep stage (%)	18.33±8.29a	15.95±10.23a	16.25±9.79a
Non-rapid-eye movement (NREM) (min)	321.79±87.88a	295.60±96.74a	350.01±98.5a
NREM (%)	82.56±10.84a	82.57±7.62a	81.87±9.88a
Rapid-eye movement (REM) (min)	67.21±43.27a	67.17±37.26a	79.63±44.02a
REM (%)	17.43±10.84a	17.42±7.62a	18.12±9.88a
Sleep efficiency (%)	70.40±14.99a	64.62±21.45a	75.92±18.36a
Sleep latency	31.0±29.96a	31.70±29.97a	18.93±20.36a
Wake after sleep onset	129.91±71.69a	174.76±116.12a	110.50±98.33a
Arousal time (min)	157.64±78.71a	202.23±131.03a	128.14±100.46a
Arousal times	20.35±11.57a	19.64±12.70a	14.50±9.36a
Arousal index (events/h)	3.34±2.06a	3.86±3.19a	2.30±1.68a
Arousal time in REM	39.93±38.94a	39.42±34.74a	52.00±36.13a
Arousal index in REM	32.25±16.44a	29.52±17.66a	38.96±16.29a
Arousal time in NREM	210.15±126.03a	209.57±148.79a	288.19±226.67a
Arousal index in NREM	38.17±15.54a	39.98±16.20a	45.76±26.09a
Total sleep arousal times	250.08±136.58a	249.00±166.24a	340.19±249.89a
Total sleep arousal index	38.06±15.18a	38.75±15.83a	44.64±24.15a
Apnea-hypopnea index (events/h)	19.63±21.42a	27.90±22.63a	27.41±30.96a
Apnea-hypopnea times	132.19±170.66a	180.50±176.90a	221.34±278.37a
Obstructive apnea index (events/h)	8.85±15.04a	10.88±12.44a	10.62±16.09a
Obstructive apnea times	62.78±120.68a	71.28±102.99a	85.26±134.75a
Central apnea index (events/h)	0.46±1.29a	2.75±8.64a	1.92±4.04a
Central apnea times	3.39±9.45b	11.78±31.62ab	17.5±40.21a
Mixed apnea index (events/h)	0.59±1.52b	1.61±3.80ab	2.88±6.79a
Mixed apnea times	4.56±13.25b	10.5±27.95ab	25.73±64.8a
Hypopnea index (events/h)	9.71±8.95a	12.63±17.71a	11.98±14.29a
Hypopnea times	61.45±55.31a	86.92±136.55a	92.84±125.09a
Longest apnea time (s)	37.80±23.24a	46.64±27.65a	45.26±38.39a
Mean apnea-hypopnea duration (s)	19.55±8.98a	20.25±8.28a	20.01±9.78a
Longest hypopnea time (s)	68.26±33.06a	66.85±27.29a	78.50±32.89a
Average hypopnea time (s)	28.30±9.95a	29.75±12.62a	31.52±8.38a
Oxygen desaturation index (events/h)	18.72±20.79a	25.22±23.56a	25.9±29.82a
Lowest oxygen saturation (%)	82.26±8.81a	79.35±9.34a	82.23±10.88a
Average oxygen saturation (%)	94.34±2.04a	93.92±3.34a	94.15±2.66a

Longest oxygen desaturation (s)	109.16±42.98a	95.17±28.61a	99.51±40.54a
Mean heart rate	65.95±10.32a	65.00±7.93a	63.73±9.55a
Arrhythmia index (events/h)	12.89±54.36a	38.04±134.47a	4.23±8.19a
Maximum heart rate	99.41±15.06a	97.28±12.19a	96.92±16.70a
Minimum heart rate	51.67±8.97a	53.28±5.21a	51.53±6.68a
Blood pressure elevation index (events/h)	13.22±15.21a	16.43±15.52a	16.58±22.43a
The highest systolic blood pressure (mmHg)	157.98±39.08a	148.57±58.14a	158.80±45.51a
Average systolic blood pressure (mmHg)	120.41±25.98a	113.78±42.26a	118.19±28.64a
Average diastolic blood pressure (mmHg)	81.80±16.05a	77.21±24.46a	82.92±21.59a

Table

3.

	<i>Bacteroides</i> enterotype (n=32)	<i>Ruminococcus</i> enterotype (n=8)	<i>Prevotella</i> enterotype (n=12)
Total sleep time (min)	392.92±106.21a	387.61±116.85a	460.69±117.35a
N1 sleep stage (min)	162.46±71.21b	159.70±98.14ab	236.23±102.31a
N1 sleep stage (%)	41.93±15.78a	41.18±17.37a	50.03±16.75a
N2 sleep stage (min)	111.86±65.07a	95.24±48.56a	101.92±56.09a
N2 sleep stage (%)	27.65±11.46a	24.23±8.41a	22.03±9.76a
N3 sleep stage (min)	61.95±35.56a	63.06±55.27a	45.71±37.88a
N3 sleep stage (%)	15.61±7.96a	16.54±12.79a	9.90±7.97a
Non-rapid-eye movement (NREM) (min)	336.27±92.94a	318.00±102.04a	383.86±111.29a
NREM (%)	85.20±10.65a	81.94±5.83a	81.96±10.05a
Rapid-eye movement (REM) (min)	56.65±38.27a	69.61±33.06a	76.83±29.52a
REM (%)	14.80±10.65a	18.06±5.83a	18.04±10.05a
Sleep efficiency (%)	70.68±15.53a	68.66±19.05a	81.52±16.78a
Sleep latency	28.21±26.64a	26.26±15.89ab	7.93±5.48b
Wake after sleep onset	131.92±74.80a	156.49±119.11a	77.79±46.87a
Arousal time (min)	156.51±76.52a	177.55±118.32a	84.31±48.77b
Arousal times	19.34±12.06a	19.75±14.53a	12.50±10.70a
Arousal index (events/h)	3.35±2.52a	3.89±4.09a	1.89±1.83a
Arousal time in REM	34.81±29.91b	43.00±34.32ab	66.67±39.80a
Arousal index in REM	33.37±18.93b	34.26±17.70ab	50.00±13.49a
Arousal time in NREM	260.28±152.59b	262.13±178.51ab	433.25±262.42a
Arousal index in NREM	45.67±17.02a	46.20±18.56a	63.53±28.16a
Total sleep arousal times	295.09±160.4b	305.13±194.43ab	499.92±285.72a
Total sleep arousal index	44.99±16.94b	44.41±18.55b	61.68±25.41a
Apnea-hypopnea index (events/h)	36.39±22.86a	42.04±19.98a	52.53±29.78a
Apnea-hypopnea times	247.09±204.93a	278.88±176.82a	430.58±294.38a
Obstructive apnea index (events/h)	18.03±19.14a	14.43±15.52a	21.38±18.74a
Obstructive apnea times	129.47±159.54a	99.88±129.97a	173.25±159.52a
Central apnea index (events/h)	0.98±1.83a	4.81±11.28a	3.83±5.40a
Central apnea times	7.09±13.44b	20.63±40.61ab	35.50±54.65a
Mixed apnea index (events/h)	1.31±2.10b	2.78±4.81ab	6.19±9.08a
Mixed apnea times	10.13±18.71b	18.13±36.00ab	55.33±88.13a
Hypopnea index (events/h)	16.08±9.56a	19.99±20.79a	21.17±16.88a
Hypopnea times	100.41±57.37a	140.25±163.59a	166.50±155.08a
Longest apnea time (s)	50.31±19.59a	47.63±29.34a	69.08±38.55a
Mean apnea-hypopnea duration (s)	23.20±6.35a	20.30±6.90a	26.97±7.53a
Longest hypopnea time (s)	82.69±28.53a	70.25±25.97a	99.75±24.15a
Average hypopnea time (s)	31.29±6.58a	28.53±6.55a	35.74±8.24a
Oxygen desaturation index (events/h)	34.23±22.94a	38.98±22.58a	49.73±29.24a
Lowest oxygen saturation (%)	76.31±9.20a	76.00±10.01a	74.83±12.04a
Average oxygen saturation (%)	93.31±2.32a	93.13±4.09a	92.50±2.81a

Longest oxygen desaturation (s)	113.18±37.43a	103.39±23.54a	92.93±26.57a
Mean heart rate	66.56±10.38a	67.25±6.67a	67.83±10.83a
Arrhythmia index (events/h)	5.29±13.97a	65.06±177.85a	3.82±5.03a
Maximum heart rate	99.09±14.79a	99.75±15.64a	103.08±18.70a
Minimum heart rate	51.88±7.07a	54.50±4.44a	53.50±6.56a
Blood pressure elevation index (events/h)	20.91±18.96a	20.44±18.45a	26.09±27.79a
The highest systolic blood pressure (mmHg)	172.97±35.54a	180.75±38.26a	163.25±62.49a
Average systolic blood pressure (mmHg)	130.44±22.64a	138.50±22.91a	117.58±41.10a
Average diastolic blood pressure (mmHg)	87.28±13.38a	88.00±9.94a	84.25±29.45a

Table 4.

	<i>Bacteroides</i> enterotype (n=41)	<i>Ruminococcus</i> enterotype (n=6)	<i>Prevotella</i> enterotype (n=14)
Total sleep time (min)	385.96±94.49a	329.65±126.87a	403.04±118.21a
N1 sleep stage (min)	119.91±57.60a	141.83±62.74a	116.25±42.34a
N1 sleep stage (%)	31.55±14.61a	43.55±11.10a	30.96±12.49a
N2 sleep stage (min)	110.88±57.82a	73.33±38.22a	120.54±59.68a
N2 sleep stage (%)	28.47±12.52a	24.77±11.88a	29.15±10.26a
N3 sleep stage (min)	79.70±36.37a	50.58±33.42a	84.21±37.23a
N3 sleep stage (%)	20.47±8.01a	15.17±6.46a	21.70±7.83a
Non-rapid-eye movement (NREM) (min)	310.49±83.12a	265.73±88.78a	321.00±78.85a
NREM (%)	80.51±10.68a	83.42±10.10a	81.80±10.11a
Rapid-eye movement (REM) (min)	75.47±45.56a	63.92±45.35a	82.04±54.54a
REM (%)	19.49±10.67a	16.58±10.10a	18.20±10.11a
Sleep efficiency (%)	70.20±14.75a	59.23±25.03a	71.13±18.87a
Sleep latency	33.20±32.47a	38.95±43.26a	28.36±23.75a
Wake after sleep onset	128.36±70.05a	199.13±118.10a	138.54±122.07a
Arousal time (min)	158.52±81.32a	235.15±150.88a	165.71±118.75a
Arousal times	21.15±11.26a	19.50±11.13a	16.21±8.06a
Arousal index (events/h)	3.35±1.66a	3.83±1.75a	2.66±1.52a
Arousal time in REM	43.93±44.70a	34.67±37.97a	39.43±28.30a
Arousal index in REM	31.39±14.39a	23.20±16.99a	29.50±12.13a
Arousal time in NREM	171.02±83.45a	139.50±51.31a	163.86±66.82a
Arousal index in NREM	32.33±11.41a	31.70±7.47a	30.54±9.82a
Total sleep arousal times	214.95±103.70a	174.17±84.67a	203.29±85.31a
Total sleep arousal index	32.66±11.13a	31.20±7.07a	30.04±8.81a
Apnea-hypopnea index (events/h)	6.56±4.54a	9.07±5.20a	5.88±3.43a
Apnea-hypopnea times	42.51±32.76a	49.33±38.24a	42.00±25.31a
Obstructive apnea index (events/h)	1.70±1.93b	6.17±4.27a	1.41±1.65b
Obstructive apnea times	10.73±12.29b	33.17±29.64a	9.86±10.79b
Central apnea index (events/h)	0.07±0.15a	0.00±0.00a	0.30±0.77a
Central apnea times	0.51±1.14a	0.00±0.00a	2.07±5.14a
Mixed apnea index (events/h)	0.03±0.11a	0.07±0.10a	0.05±0.09a
Mixed apnea times	0.22±0.72a	0.33±0.52a	0.36±0.63a
Hypopnea index (events/h)	4.75±3.94a	2.83±2.95a	4.11±2.65a
Hypopnea times	31.05±28.19a	15.83±20.05a	29.71±21.00a
Longest apnea time (s)	28.05±21.26a	45.33±27.91a	24.86±24.59a
Mean apnea-hypopnea duration (s)	16.70±9.74a	20.18±10.58a	14.06±7.29a
Longest hypopnea time (s)	57.00±32.26a	62.33±30.81a	60.29±28.51a
Average hypopnea time (s)	25.97±11.49a	31.40±18.67a	27.91±6.86a
Oxygen desaturation index (events/h)	6.63±5.30a	6.90±4.88a	5.48±3.66a
Lowest oxygen saturation (%)	86.9±4.88a	83.83±6.68a	88.57±3.34a

Average oxygen saturation (%)	95.15±1.35a	95.00±1.79a	95.57±1.51a
Longest oxygen desaturation (s)	106.03±47.08a	84.23±33.17a	105.15±49.88a
Mean heart rate	65.49±10.37a	62.00±9.08a	60.21±6.89a
Arrhythmia index (events/h)	18.83±71.31a	2.02±2.09a	4.60±10.36a
Maximum heart rate	99.66±15.44a	94.00±4.60a	91.64±13.25a
Minimum heart rate	51.51±10.30a	51.67±6.12a	49.86±6.54a
Blood pressure elevation index (events/h)	7.23±7.34a	11.10±9.49a	8.44±12.61a
The highest systolic blood pressure (mmHg)	146.29±38.09ab	105.67±53.6b	155.00±25.4a
Average systolic blood pressure (mmHg)	112.59±25.97a	80.83±40.36b	118.71±12.14a
Average diastolic blood pressure (mmHg)	77.54±16.80a	62.83±31.35a	81.79±12.63a

Table 5.

	AHI < 15	AHI ≥ 15
Total sleep time (min)	329.65±126.87	387.61±116.85
N1 sleep stage (min)	141.83±62.74	159.70±98.14
N1 sleep stage (%)	43.55±11.10	41.18±17.37
N2 sleep stage (min)	73.33±38.22	95.24±48.56
N2 sleep stage (%)	24.77±11.88	24.23±8.41
N3 sleep stage (min)	50.58±33.42	63.06±55.27
N3 sleep stage (%)	15.17±6.46	16.54±12.79
Non-rapid-eye movement (NREM) (min)	265.73±88.78	318.00±102.04
NREM (%)	83.42±10.10	81.94±5.83
Rapid-eye movement (REM) (min)	63.92±45.35	69.61±33.06
REM (%)	16.58±10.10	18.06±5.83
Sleep efficiency (%)	59.23±25.03	68.66±19.05
Sleep latency	38.95±43.26	26.26±15.89
Wake after sleep onset	199.13±118.10	156.49±119.11
Arousal time (min)	235.15±150.88	177.55±118.32
Arousal times	19.50±11.13	19.75±14.53
Arousal index (events/h)	3.83±1.75	3.89±4.09
Arousal time in REM	34.67±37.97	43.00±34.32
Arousal index in REM	23.20±16.99	34.26±17.70
Arousal time in NREM	139.50±51.31	262.13±178.51
Arousal index in NREM	31.70±7.47	46.20±18.56
Total sleep arousal times	174.17±84.67	305.13±194.43
Total sleep arousal index	31.20±7.07	44.41±18.55
Apnea-hypopnea index (events/h)	9.07±5.20	42.04±19.98**
Apnea-hypopnea times	49.33±38.24	278.88±176.82**
Obstructive apnea index (events/h)	6.17±4.27	14.43±15.52
Obstructive apnea times	33.17±29.64	99.88±129.97
Central apnea index (events/h)	0.00±0.00	4.81±11.28
Central apnea times	0.00±0.00	20.63±40.61
Mixed apnea index (events/h)	0.07±0.10	2.78±4.81
Mixed apnea times	0.33±0.52	18.13±36.00
Hypopnea index (events/h)	2.83±2.95	19.99±20.79
Hypopnea times	15.83±20.05	140.25±163.59
Longest apnea time (s)	45.33±27.90	47.63±29.34
Mean apnea-hypopnea duration (s)	20.18±10.58	20.30±6.90
Longest hypopnea time (s)	62.33±30.81	70.25±25.97
Average hypopnea time (s)	31.40±18.67	28.53±6.55
Oxygen desaturation index (events/h)	6.90±4.88	38.98±22.58**

Lowest oxygen saturation (%)	83.83±6.68	76.00±10.01
Average oxygen saturation (%)	95.00±1.79	93.13±4.09
Longest oxygen desaturation (s)	84.23±33.17	103.39±23.54
Mean heart rate	62.00±9.08	67.25±6.67
Arrhythmia index (events/h)	2.02±2.09	65.06±177.85
Maximum heart rate	94.00±4.60	99.75±15.64
Minimum heart rate	51.67±6.12	54.50±4.44
Blood pressure elevation index (events/h)	11.10±9.49	20.44±18.45
The highest systolic blood pressure (mmHg)	105.67±53.60	180.75±38.26*
Average systolic blood pressure (mmHg)	80.83±40.36	138.50±22.91**
Average diastolic blood pressure (mmHg)	62.83±31.35	88.00±9.94

Table 6.

	AHI < 15	AHI ≥ 15
Total sleep time (min)	403.04±118.21	460.69±117.35
N1 sleep stage (min)	116.25±42.34	236.23±102.31**
N1 sleep stage (%)	30.96±12.49	50.03±16.75**
N2 sleep stage (min)	120.54±59.68	101.92±56.09
N2 sleep stage (%)	29.15±10.26	22.03±9.76
N3 sleep stage (min)	84.21±37.23	45.71±37.88*
N3 sleep stage (%)	21.70±7.83	9.90±7.97**
Non-rapid-eye movement (NREM) (min)	321.00±78.85	383.86±111.29
NREM (%)	81.80±10.11	81.96±10.05
Rapid-eye movement (REM) (min)	82.04±54.54	76.83±29.52
REM (%)	18.20±10.11	18.04±10.05
Sleep efficiency (%)	71.13±18.87	81.52±16.78
Sleep latency	28.36±23.75	7.93±5.48**
Wake after sleep onset	138.54±122.07	77.79±46.87
Arousal time (min)	165.71±118.75	84.31±48.77*
Arousal times	16.21±8.06	12.50±10.70
Arousal index (events/h)	2.66±1.52	1.89±1.83
Arousal time in REM	39.43±28.30	66.67±39.80
Arousal index in REM	29.50±12.13	50.00±13.49***
Arousal time in NREM	163.86±66.82	433.25±262.42**
Arousal index in NREM	30.54±9.82	63.53±28.16**
Total sleep arousal times	203.29±85.31	499.92±285.72**
Total sleep arousal index	30.04±8.81	61.68±25.41**
Apnea-hypopnea index (events/h)	5.88±3.43	52.53±29.78***
Apnea-hypopnea times	42.00±25.31	430.58±294.38**
Obstructive apnea index (events/h)	1.41±1.65	21.38±18.74**
Obstructive apnea times	9.86±10.79	173.25±159.52**
Central apnea index (events/h)	0.30±0.77	3.83±5.40*
Central apnea times	2.07±5.14	35.50±54.65
Mixed apnea index (events/h)	0.05±0.09	6.19±9.08*
Mixed apnea times	0.36±0.63	55.33±88.13
Hypopnea index (events/h)	4.11±2.65	21.17±16.88**
Hypopnea times	29.71±21.00	166.50±155.08**
Longest apnea time (s)	24.86±24.59	69.08±38.55**
Mean apnea-hypopnea duration (s)	14.06±7.29	26.97±7.53***
Longest hypopnea time (s)	60.29±28.51	99.75±24.15**
Average hypopnea time (s)	27.91±6.86	35.74±8.24*
Oxygen desaturation index (events/h)	5.48±3.66	49.73±29.24***

Lowest oxygen saturation (%)	88.57±3.34	74.83±12.04***
Average oxygen saturation (%)	95.00±1.79	92.50±2.81**
Longest oxygen desaturation (s)	84.23±33.17	92.93±26.57
Mean heart rate	62.00±9.08	67.83±10.83*
Arrhythmia index (events/h)	2.02±2.09	3.82±5.03
Maximum heart rate	94.00±4.60	103.08±18.70
Minimum heart rate	51.67±6.12	53.50±6.56
Blood pressure elevation index (events/h)	11.10±9.49	26.09±27.79
The highest systolic blood pressure (mmHg)	105.67±53.60	163.25±62.49
Average systolic blood pressure (mmHg)	80.83±40.36	117.58±41.10
Average diastolic blood pressure (mmHg)	62.83±31.35	84.25±29.45