

# Gait Characteristics and Neuroanatomical Alterations in Obstructive Sleep Apnea–Hypopnea Syndrome

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**Background:** Obstructive sleep apnea–hypopnea syndrome (OSAHS) affects over 936 million adults globally. Recently, it has been found to contribute to gait disorders, but there is limited information regarding how various indicators of OSAHS affect gait patterns.

**Methods:** A total of 136 subjects recruited from Nanjing Drum Tower Hospital were categorized based on apnea hypopnea index (AHI) and oxygen saturation (SpO<sub>2</sub>), respectively. All subjects underwent data collection regarding demographics, gait testing, sleep monitoring, multimodal magnetic resonance imaging (MRI), and a battery of clinical evaluations.

**Results:** Subjects with elevated AHI exhibited increased step width and decreased stride length in comparison to those with lower AHI. The nm (no or mild)-hypoxemia group demonstrated faster stride frequency than the ms (moderate to severe)-hypoxemia group. High-frequency obstructive sleep apnea–hypopnea resulted in cortical atrophy of the orbital part of right inferior frontal gyrus and upregulation of functional connectivity between the basal ganglia and left inferior temporal gyrus, basal ganglia and left insula, while the severity of hypoxemia led to functional alternations between right angular gyrus and left gyrus rectus, which manifested as respective alternations in gait. The area under the curve (AUC) for gait tests evaluating moderate-to-severe OSAHS was 0.842, using logistic regression models.

**Conclusion:** The frequency of respiratory events and the severity of hypoxemia caused different gait dysfunction and corresponding underlying mechanisms in patients with OSAHS. Gait testing might be a potential tool for rapidly screening OSAHS in the population.

**Keywords:** obstructive sleep apnea–hypopnea syndrome, gait, hypoxemia, magnetic resonance imaging

## Introduction

Obstructive sleep apnea–hypopnea syndrome (OSAHS) is a prevalent sleep disorder characterized by complete or partial collapse of the upper airways, represented by apneas (complete cessation of airflow) and hypopneas (partial reduction in airflow).<sup>1</sup> OSAHS, which can lead to the exacerbation of cardiovascular, metabolic, neurocognitive and other health issues, affects over 936 million adults aged 30–69 years worldwide.<sup>2,3</sup> Numerous studies suggest that sleep disturbance and intermittent hypoxia in OSAHS have a detrimental impact on the central nervous system,<sup>4,5</sup> such as the atrophy of frontoparietal cortices and hippocampus.<sup>6</sup> The severity of OSAHS is generally assessed based on apnea hypopnea index (AHI), which is evaluated by polysomnography (PSG) or out-of-center sleep testing (OCST).<sup>1</sup> Some have argued that relying solely on AHI is insufficient for a comprehensive assessment of its pathophysiological consequences.<sup>7</sup> AHI reflects only the frequency of sleep apnea–hypopnea, which may hardly capture the severity of hypoxemia. The frequency of respiratory events and the severity of hypoxemia may exert distinct effects on the brain,<sup>8,9</sup> which has been underestimated thus far. Hypoxic burden, a novel metric based on the area, provides a more comprehensive characterization of the depth and duration

of individual oxygen desaturation events.<sup>10</sup> Nevertheless, technical challenges exist in calculating this metric. According to Chinese guidelines,<sup>11</sup> both AHI and the nadir of oxygen saturation during sleep (SpO<sub>2</sub> nadir) should be utilized to assess the condition of OSAHS. Consequently, this study employed AHI and SpO<sub>2</sub> nadir as index to evaluate the severity of OSAHS and hypoxemia.

Falls have been the second leading cause of death among the elderly worldwide.<sup>12</sup> Gait dysfunction may result in instability, falls, and a decline in functional independence. Gait was traditionally viewed as an automated motor task dependent on muscle control, visual acuity and the vestibular system.<sup>13,14</sup> Recently, accumulating evidence demonstrates that gait is a cognitively-demanding activity<sup>15–17</sup> and emphasizes the importance of brain functional and structural integrity in gait control.<sup>18</sup> It was found gait speed could predict cognitive decline over the next decade,<sup>19</sup> suggesting that gait might be sensitive to alterations in the brain. Prior research proposed that individuals with OSAHS exhibited gait dysfunction,<sup>14,20</sup> but there has been limited focus on how various indicators of OSAHS affect gait and the underlying neuroimaging mechanisms.

Additionally, due to the high prevalence and significant negative effects of OSAHS, it is necessary to screen for OSAHS in the population. However, the diagnosis of OSAHS relies on sleep monitoring. Sleep monitoring requires professional equipment, long inspection time, and complex medical technology, which limits its promotion among the population. Several studies have investigated alternative approaches for the fast screening of OSAHS, including standardized questionnaires, measurement of SpO<sub>2</sub>, and ECG analysis. Gait indicators are low-cost, noninvasive, and easily accessible digital biomarkers with significant individual characteristics, can be assessed through one-minute gait tests. Conducting gait analysis is easier compared to gathering metrics for OSAHS through overnight sleep monitoring. It is demonstrated that gait indicators can recognize Alzheimer's disease and Parkinson's disease.<sup>21,22</sup> Gait tests may serve as a promising avenue for screening OSAHS in the population.

Therefore, we focused on the gait performance in OSAHS, aiming to (1) determine whether OSAHS and hypoxemia exert distinct effects on gait and identify specific gait indicators associated with these conditions; (2) explore the underlying neuroimaging mechanism of OSAHS affecting gait; and (3) identify the diagnostic ability of gait tests for OSAHS.

## Methods

### Subjects

This study was a cross-sectional study, involving 136 subjects (25 healthy people and 111 patients with OSAHS) who were recruited from Nanjing Drum Tower Hospital between 2021 and 2024. The study was approved by the Ethics Committee of Nanjing Drum Tower Hospital (Ethics Approval No: 2023–327-02) and conducted according to the Declaration of Helsinki principles. Written informed consent was obtained from all subjects. All subjects underwent demographic data collection, gait testing, OCST, multimodal magnetic resonance imaging (MRI), and clinical assessments.

The inclusion criteria for OSAHS subjects were as follows: (1) age  $\geq 40$  years and  $\leq 85$  years; (2) right-handedness; (3) ability to cooperate with all inspection tasks, and (4) mild to severe OSAHS (AHI  $\geq 5$  events/h). People without OSAHS matched for age served as healthy subjects. The exclusion criteria for subjects were as follows: (1) other sleep-related disorders, such as narcolepsy or central sleep apnea; (2) any medical condition considered to interfere with gait, such as limb weakness, orthopedic, rheumatologic, or other diseases; (3) other neurological and psychiatric diseases, such as Parkinson's disease, epilepsy, or schizophrenia; (4) any conditions using pharmacotherapies that impact the central nervous system or mental status within the last 3 months; (5) serious physical illnesses, such as cancer; and (6) limited capacity to comply with the study protocol, such as being blind, deaf, or physically disabled.

The sample size was calculated using the statistical software G\*Power version 3.1.9.7.<sup>23</sup> An anticipated effect size of 0.95 was taken, with a significance level of 0.05 and a study power set at 80%. Based on these parameters, it is calculated that the minimum number of subjects required for each group is 19, resulting in a total sample size of at least 38 subjects. Our sample size satisfied these requirements.

### OCST

The diagnosis of OSAHS was based on an overnight sleep study by OCST. The subjects underwent OCST using a portable PSG device (BMC PolyWatch YH-600B; BMC Medical Co. Ltd., Beijing, China) under the guidance of a trained sleep

technician. This portable PSG device has been validated to be highly consistent with PSG.<sup>24</sup> It consisted of an abdominal band, used to detect thoracic and abdominal excursion; a finger pulse oximetry, used to measure oxygen saturation; thermistors for nasal airflow, and body position and heart rate recordings. Before and after bedtime, the technician would conduct a video call to ensure proper usage of the device. According to international guidelines,<sup>1</sup> the scoring was conducted using an automated algorithm that performs an initial analysis, followed by a review of the results by a trained sleep specialist who rectifies any possible mis-scoring produced by the computer program. The assessments conducted by the two specialists had a high consistency, with a kappa coefficient of 0.82.

According to the AASM guidelines,<sup>1</sup> an apnea was defined as the complete cessation or a reduction of at least 90% of airflow for at least 10s. On the basis of the abdominal band signal and the shape of the respiratory pressure curve, apnea was defined as obstructive or other types. Hypopnea was defined as a reduction of at least 30% in the nasal pressure signal, accompanied by an oxygen desaturation of at least 3%. AHI was calculated as the sum of the mean number of apneas and hypopneas per hour. The lowest oxygen saturation level during sleep, referred to as the SpO<sub>2</sub> nadir, was recorded. The oxygen desaturation index (ODI) was determined as the number of desaturations >3% divided by total sleep time. TS90 represented the percent of the total sleep time below 90% oxygen saturation. Patients with OSAHS were identified based on criteria including an AHI  $\geq 5$  events per hour and the presence of obstructive apneas. Hypoxemia was defined as having an SpO<sub>2</sub> nadir at night of less than 90%.<sup>11</sup>

In addition, considering that sleep fragmentation in severe OSAHS patients and too short sleep duration make the results unreliable, we excluded subjects with total sleep time of fewer than 4 hours. The device is integrated with automated analysis software capable of evaluating the collected signals. When the signal is missing or poor quality, it will be marked as an artifact, which needs to be further confirmed by manual analysis to ensure the accuracy of the diagnostic results. Following a data quality assessment, periods of invalid recording such as equipment malfunction, poor signal quality, and disconnects were removed. The technically effective recording time for each subject is at least 4 hours. The classification criteria for OSAHS were as follows: mild OSAHS: AHI  $\geq 5$  times per hour and  $< 15$  times per hour; moderate OSAHS: AHI  $\geq 15$  times per hour and  $< 30$  times per hour; and severe OSAHS: AHI  $\geq 30$  times per hour. AHI of less than 5 times per hour was defined as not having OSAHS. The classification criteria<sup>11</sup> for hypoxemia were as follows: mild hypoxemia: SpO<sub>2</sub> nadir  $< 90\%$  and  $\geq 85\%$ ; moderate hypoxemia: SpO<sub>2</sub> nadir  $< 85\%$  and  $\geq 80\%$ ; and severe hypoxemia: SpO<sub>2</sub> nadir  $< 80\%$ . SpO<sub>2</sub> nadir of more than 90% was defined as not having hypoxemia. Based on the Chinese national guideline classification standard<sup>11</sup> and their clinical significance, we categorized the subjects into two groups based on their AHI and SpO<sub>2</sub> nadir, utilizing thresholds of 15 and 85, respectively. According to AHI, the subjects were categorized into two groups: the nm-OSAHS group (no or mild OSAHS, AHI  $< 15$  events per hour) and the ms-OSAHS group (moderate or severe OSAHS, AHI  $\geq 15$  events per hour). On the basis of their SpO<sub>2</sub> nadir, the subjects were categorized into two groups: the nm-hypoxemia group (no or mild hypoxemia, SpO<sub>2</sub> nadir  $\geq 85\%$ ) and the ms-hypoxemia group (moderate or severe hypoxemia, SpO<sub>2</sub> nadir  $< 85\%$ ).

## Gait Tests

A three-dimensional motion balance testing system (ReadyGo, Beijing CAS-Ruiyi Information Technology Co., Ltd).<sup>25–29</sup> was utilized to conduct gait testing. The system uses a unified camera setup, comprising an RGB camera and a depth camera. Notably, the system's compact design, occupying less than 1 m<sup>2</sup>, obviates the need for a dedicated testing room, as it operates efficiently within a 1  $\times$  5 m<sup>2</sup> area directly in front of the camera, free from obstructions. This device is capable of both observing and estimating 3D joints and landmarks through advanced visual perception, uniquely tracking multiple skeletons without requiring subjects to wear any sensors. In our study, subjects were instructed to walk at their customary pace on a level surface defined by two rectangles measuring 3 meters in length and 0.5 meters in width, while making turns within the rectangle. They wore comfortable footwear and did not use any assistive walking devices. Individuals with any medical conditions considered to affect gait, such as limb weakness, orthopedic disorders, rheumatologic conditions, or other relevant diseases, were excluded.

Artificial intelligence in the ReadyGo three-dimensional motion balance testing system and manual correction were utilized to annotate actions such as lifting, landing, swinging, standing and turning during walking. The ReadyGo system also automatically calculates gait indicators temporally, spatially, and spatiotemporally. The gait indicators included gait

velocity, stride length, step height, step width, stride frequency, stance phase, swing phase, and double-support time, with their maximum, minimum and median presented. This system has received approval from China's National Medical Device Registration Certificate (ID: 20242109713) and was extensively utilized in scientific studies, indicating excellent internal and external consistency.<sup>25–29</sup>

## Demographic Data Collection

Through face-to-face interviews, subjects reported their information including gender, age, level of education, body mass index (BMI) and vascular risk factors. The vascular risk factors included hypertension, diabetes, hyperlipidemia, smoking and drinking.

## Neuropsychological Evaluation

Each subject underwent a neuropsychological evaluation conducted by a trained neurologist. The mental state of subjects was assessed according to the Hamilton Depression Scale (HAMD), and the Hamilton Anxiety Scale (HAMA). Overall cognitive function was evaluated using the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA).

## Multimodal MRI Data Acquisition

The subjects underwent multimodal MRI scanning, including high-resolution T1-weighted turbo gradient echo sequence, blood oxygen level-dependent resting-state functional magnetic resonance imaging sequence (BOLD), T2-weighted fluid attenuated inversion recovery (FLAIR) sequence, T2-weighted imaging (SWI), magnetic resonance angiography (MRA) and diffusion-weighted imaging (DWI) at Nanjing Drum Tower Hospital using a Philips 3.0-T scanner (Philips Medical Systems, Andover, MA, USA). Subjects were instructed to remain awake, stay still in a relaxed manner, and avoid moving their head. The image processing involved the high-resolution T1-weighted turbo gradient echo sequence, BOLD, and T2-weighted FLAIR sequences.

Scanning parameters for the high-resolution T1-weighted turbo gradient echo sequence were as follows: repetition time (TR) of 8.2 ms, echo time (TE) of 3.8 ms, flip angle (FA) of 8°, slice number of 192, acquisition matrix size of 256 × 256, and layer thickness of 1.0 mm. For T2-weighted FLAIR sequence scanning, the parameters comprised a TR value of 4500 ms, TE value of 333 ms, inversion time (TI) of 1600 ms, slice number set at 200 with voxel size measuring 0.95 mm × 0.95 mm × 0.95 mm and an acquisition matrix size equal to 270 × 260.

## MRI Data Processing

### Structural Analysis

Lacunae and cerebral microbleeds were assessed based on multimodal MRI by two trained investigators.<sup>30</sup> The lesion segmentation tool (LST), a toolbox based on the statistical parametric mapping software package (SPM; [www.fil.ion.ucl.ac.uk/spm](http://www.fil.ion.ucl.ac.uk/spm)) 12, was utilized to quantify white matter lesions. This involved analyzing T2-weighted FLAIR sequences and high-resolution T1-weighted turbo gradient echo sequences with specific parameters: an initial threshold of 0.15, a Markov random field parameter of 1, and a maximum number of iterations of 50. The output from the LST provided measurements of white matter hyperintensity (WMH) volume. To assess white matter, we employed the voxel-based morphometry toolbox for SPM8 (VBM8), another toolbox based on SPM8. Total intracranial volume (TIV) was calculated by summing up the volumes of gray matter, white matter, and cerebrospinal fluid.

The Voxel-based Morphometry Toolbox for SPM8 (VBM8), which operates on the SPM8 platform, was utilized to analyze cerebral gray matter volume using high-resolution T1-weighted turbo gradient echo sequences. The processing steps included 1) cropping; 2) reorientation; 3) segmentation and normalization; and 4) applying an 8-mm FWHM Gaussian spatial kernel for image smoothing. The region exhibiting significant differences in a two-sample *t*-test (multiple comparison corrections: Gaussian random field (GRF)-corrected threshold of  $p < 0.001$  at the voxel level and  $p < 0.05$  at the cluster level) was extracted using Data Processing & Analysis for Brain Imaging (DPABI).<sup>31</sup>

## Functional Analysis

The fMRI analysis was based on the BOLD sequence. DPARSF, a toolbox based on the Resting-State Functional MR Imaging Toolkit (<http://www.restfmri.net>) and SPM12 was used for fMRI data analysis. The preprocessing steps included removing the first ten volumes of data, slice timing correction, realignment (note that those with head motion greater than 3.0 mm in any direction or rotation exceeding 3.0 degrees in any angular dimension were excluded), reorientation, co-registration of T1 images to functional images; image segmentation for the high-resolution T1-weighted turbo gradient echo sequence and the BOLD sequence by DARTEL, nuisance covariates regression (including linear detrending, Friston 24 head motion parameters, white matter signal, cerebrospinal fluid signal, and global signal), normalization using a 12-parameter nonlinear transformation to the standard Montreal Neurological Institute (MNI) space ( $3 \times 3 \times 3 \text{ mm}^3$ ), smoothing functional images with a 6-mm FWHM Gaussian spatial kernel, and band-pass filtering (0.01–0.08Hz).

According to previous studies, bilateral angular gyrus (Anatomical Automatic Labeling (AAL) 65, AAL66), bilateral caudate nucleus (AAL71, AAL72), bilateral lenticular nucleus, putamen (AAL73, AAL74), bilateral lenticular nucleus, pallidum (AAL75, AAL76), bilateral thalamus (AAL77, AAL78) were set as regions of interest (ROIs) in functional connectivity (FC) analysis. The mean time series of the ROI was extracted, and the strengths of FC were calculated as Pearson's correlations between the averaged time series of the ROI and voxels in the remaining brain regions. Then, Pearson's correlation coefficients were normalized to a z-score matrix by using a Fisher r-to-z transformation, and the FC map was created between the ROI and the remaining brain regions. The region exhibiting significant differences in a two-sample *t*-test (multiple comparison corrections: GRF-corrected threshold of  $p < 0.001$  at the voxel level and  $p < 0.05$  at the cluster level) was extracted using Data Processing & Analysis for Brain Imaging (DPABI).<sup>31</sup>

## Quality Control Procedures

To ensure the integrity and reliability of our data, we implemented a series of quality control procedures. During the data collection phase, all data were gathered by trained investigators who had completed rigorous training programs. Regular calibration of measurement instruments was conducted by engineers to maintain accuracy. During the data entry phase, data were entered into a secure database by a data entry investigator and subsequently checked by another independent researcher. In the data analysis phase, we conducted multiple checks for outliers and missing values. Subjects with missing data for key OSAHS metrics, such as AHI and SpO<sub>2</sub> nadir, or demographic information were excluded from the analysis. For gait indicators exhibiting extreme values, defined as those exceeding three standard deviations from the mean, we substituted the median value to mitigate the influence of outliers.

## Statistical Analysis

Statistical analyses were performed via SPSS 27.0 (IBM SPSS Statistics for Windows, Armonk, NY, USA) and R version 4.4.2 (RStudio, Boston, MA). For continuous variables, the normality of the distribution was confirmed using the P–P plot before comparison. Continuous variables that were normally distributed were compared using an independent sample *t*-test. Continuous variables not conforming to a normal distribution were compared using the Mann–Whitney *U*-test. The chi-square test was used to compare categorical variables. Spearman correlation was employed to conduct correlation analysis. Crude and adjusted ordinal regression models were applied to assess the relationship between OSAHS metrics and gait indicators. The median values of gait indicators from both the left and right sides were combined to facilitate correlation analysis and ordinal logistic regression analysis. A logistic regression model including gait indicators and other factors was developed to predict the severity of OSAHS. Eighty percent of the subjects were randomly selected for the training set and 20% for the validation set. A value of  $p < 0.05$  was considered statistically significant.

## Results

### Clinical Assessments

A total of 136 subjects were recruited for this study. The mean age of the subjects was 67.3 years, comprising 81 female and 55 male subjects. The average duration of education was 12 years. Based on AHI, there were 68 subjects in the nm-OSAHS group (AHI < 15) and 68 subjects in the ms-OSAHS group (AHI ≥ 15). There was a significant difference in BMI and hypertension prevalence between the two groups, but no significant differences were found in age, education or other vascular risk factors

( $p > 0.05$ ). There were no marked differences between the two groups in neuropsychological tests. Significant differences were found in multiple OSAHS metrics. In the ms-OSAHS group, AHI ( $p < 0.001$ ), TS90 ( $p < 0.001$ ) and ODI ( $p < 0.001$ ) were all significantly higher than those in the nm-OSAHS group. SpO<sub>2</sub> nadir ( $p < 0.001$ ) and mean nocturnal SpO<sub>2</sub> ( $p = 0.003$ ) in the ms-OSAHS group were significantly lower than those in the nm-OSAHS group.

To further explore the effect of the severity of nocturnal hypoxia on gait, we divided the subjects based on the SpO<sub>2</sub> nadir. There were 67 subjects in the nm-hypoxemia category (SpO<sub>2</sub> nadir  $\geq 85\%$ ) and 69 subjects in the ms-hypoxemia category (SpO<sub>2</sub> nadir  $< 85\%$ ). The two groups differed significantly in BMI and hypertension incidence. No significant differences were observed in other demographic data or neuropsychological tests. In terms of OSAHS metrics, the ms-hypoxemia group exhibited high scores in AHI ( $p < 0.001$ ), TS90 ( $p < 0.001$ ) and ODI ( $p < 0.001$ ) and lower scores in SpO<sub>2</sub> nadir ( $p < 0.001$ ) and mean nocturnal SpO<sub>2</sub> ( $p < 0.001$ ), compared with the nm-hypoxemia group (detailed information is provided in Table 1).

## Gait Indicators

Gait indicators conforming to normal distribution were compared by independent sample *t* test. Mann–Whitney *U*-test was applied to analyze gait indicators that showed a skewed distribution. Step width of ms-OSAHS group was significantly wider than that of nm-OSAHS group ( $p < 0.01$ ). Stride length–median–right presented shorter in the ms-OSAHS group compared with the nm-OSAHS group, though this difference did not reach statistical significance ( $p = 0.064$ ). No statistically significant differences were found in other gait indicators. Next, gait indicators in the nm-hypoxemia group and the ms-hypoxemia group were compared, and patients with moderate-to-severe hypoxemia showed faster stride frequency ( $p < 0.05$ ). No significant differences were found in other gait indicators (Table 2, detailed comparison of other gait indicators is provided in Supplementary Table 1).

**Table 1** Results of Clinical Assessments

	Subjects (n = 136)	nm-OSAHS group (n = 68)	ms-OSAHS group (n = 68)	p value <sup>d</sup>	nm-hypoxemia (n = 67)	ms-hypoxemia (n = 69)	p value <sup>e</sup>
<b>Demographic Data</b>							
Age, years	67.3 ± 8.0	66.0 ± 8.0	68.6 ± 7.7	0.058 <sup>a</sup>	67.1 ± 7.7	67.4 ± 8.3	0.835 <sup>a</sup>
Education, years	12.0 (9.0, 16.0)	12.0 (9.0, 16.0)	12.0 (9.0, 16.0)	0.677 <sup>b</sup>	12.0 (9.0, 16.0)	11.0 (12.0, 16.0)	0.202 <sup>b</sup>
BMI, kg/m <sup>2</sup>	23.7 ± 3.2	22.6 ± 2.6	24.8 ± 3.4	<0.001 <sup>a</sup>	22.8 ± 3.1	24.6 ± 3.1	0.001 <sup>a</sup>
Female, %	59.6	64.7	54.4	0.221 <sup>c</sup>	55.2	63.8	0.310 <sup>c</sup>
Hypertension, %	41.2	29.4	52.9	0.005 <sup>c</sup>	26.9	55.1	<0.001 <sup>c</sup>
Diabetes, %	16.2	13.2	19.1	0.352 <sup>c</sup>	17.9	14.5	0.588 <sup>c</sup>
Hyperlipidemia, %	39.7	36.8	42.6	0.483 <sup>c</sup>	32.8	46.4	0.107 <sup>c</sup>
Smoking, %	14.7	11.8	17.6	0.333 <sup>c</sup>	16.4	13.0	0.579 <sup>c</sup>
Drinking, %	12.5	10.3	14.7	0.437 <sup>c</sup>	10.4	14.5	0.476 <sup>c</sup>
<b>Neuropsychological tests</b>							
HAMD	3.5 (1.0 ± 6.0)	4.0 (1.0, 7.0)	3.0 (1.5, 6.0)	0.958 <sup>b</sup>	3.0 (1.0, 5.5)	4.0 (1.0, 7.0)	0.712 <sup>b</sup>
HAMA	3.0 (1.0 ± 6.0)	3.0 (1.0, 6.0)	3.0 (1.5, 8.0)	0.559 <sup>b</sup>	3.0 (1.0, 5.5)	3.0 (2.0, 8.0)	0.353 <sup>b</sup>
MMSE	28.0 (26.0, 29.0)	28.0 (26.0, 29.0)	28.0 (26.0, 29.0)	0.821 <sup>b</sup>	28.0 (26.0, 29.0)	28.0 (26.0, 29.0)	0.718 <sup>b</sup>
MoCA	20.0 (23.0, 26.0)	23.5 (19.3, 26.0)	23.0 (21.0, 25.0)	0.709 <sup>b</sup>	23.0 (19.0, 26.0)	21.0 (23.0, 25.0)	0.717 <sup>b</sup>
<b>OSAHS metrics</b>							
AHI, events/h	14.9 (6.9, 26.9)	7.0 (3.9, 10.3)	26.9 (21.0, 36.0)	<0.001 <sup>b</sup>	7.9 (4.7, 18.4)	23.8 (13.4, 34.1)	<0.001 <sup>b</sup>
SpO <sub>2</sub> nadir, %	84.0 (80.0, 88.8)	88.0 (84.0, 90.0)	81.0 (76.3, 85.0)	<0.001 <sup>b</sup>	89.0 (87.0, 90.0)	80.0 (74.5, 83.0)	<0.001 <sup>b</sup>
TS90, %	0.2 (0.0, 1.3)	0.0 (0.0, 0.2)	1.1 (0.4, 2.7)	<0.001 <sup>b</sup>	0.0 (0.0, 0.1)	1.1 (0.4, 3.3)	<0.001 <sup>b</sup>
ODI, events/h	16.4 ± 12.7	5.9 (3.8, 9.8)	24.9 (17.4, 31.8)	<0.001 <sup>b</sup>	6.8 (3.9, 15.9)	19.5 (12.0, 31.6)	<0.001 <sup>b</sup>
Mean nocturnal SpO <sub>2</sub> , %	95.2 (94.0, 96.0)	95.6 (94.7, 96.4)	95.0 (93.8, 95.8)	0.003 <sup>b</sup>	95.6 (95.0, 96.3)	94.7 (93.9, 95.8)	<0.001 <sup>b</sup>
Mean pulse, times/min	61.2 ± 7.1	61.0 (56.0, 65.0)	59.5 (56.0, 65.8)	0.976 <sup>b</sup>	61.0 ± 7.0	61.5 ± 7.3	0.680 <sup>a</sup>

**Notes:** <sup>a</sup>Analyzed by independent sample *t* test, expressed as mean ± standard deviation. <sup>b</sup>Analyzed by Mann–Whitney test, expressed as median (1st quartile –3rd quartile). <sup>c</sup>Analyzed by chi-square test. <sup>d</sup>p value between the nm-OSAHS and ms-OSAHS groups. <sup>e</sup>p value between the nm-hypoxemia and ms-hypoxemia groups.

**Abbreviations:** BMI, body mass index; HAMA, Hamilton Anxiety Scale; HAMD, Hamilton Depression Scale; MMSE, Mini-mental state examination; MoCA, Montreal cognitive assessment; AHI, apnea–hypopnea index; SpO<sub>2</sub>, pulsed dioxygen saturation; TS90, the percent of the total sleep time below 90% oxygen saturation; ODI, oxygen desaturation index, defined as a drop in SpO<sub>2</sub> > 3% for at least 10s; nm-OSAHS, subjects with no or mild obstructive sleep apnea–hypopnea syndrome, apnea hypopnea index < 15 events per hour; ms-OSAHS, subjects with moderate to severe obstructive sleep apnea–hypopnea syndrome, apnea hypopnea index  $\geq 15$  events per hour; nm-hypoxemia, subjects with no or mild hypoxemia, lowest oxygen saturation at night  $\geq 85\%$ ; ms-hypoxemia, subjects with moderate to severe hypoxemia, lowest oxygen saturation at night < 85%.

**Table 2** Gait Indicators Between OSAHS and Hypoxemia Groups

	Subjects (n = 136)	nm-OSAHS group (n = 68)	ms-OSAHS group (n = 68)	Statistics	p value <sup>c</sup>	nm-hypoxemia (n = 67)	ms-hypoxemia (n = 69)	Statistics	p value <sup>d</sup>
Stride length-median-right, m	1.08 ± 0.14	1.10 ± 0.13	1.06 ± 0.14	3.49	0.064 <sup>a</sup>	1.08 ± 0.14	1.08 ± 0.13	0.02	0.884 <sup>a</sup>
Stride frequency-median-left, steps / min	105.88 (96.71, 112.50)	105.88 (94.74, 112.50)	105.88 (100.00, 112.50)	-0.02	0.981 <sup>b</sup>	102.94 (94.74, 112.50)	105.88 (100.00, 112.50)	-2.04	0.041 <sup>b</sup>
Stride frequency-minimum-left, steps / min	94.74 (85.71, 100.00)	94.74 (85.71, 100.00)	94.74 (88.93, 100.00)	-0.29	0.770 <sup>b</sup>	90.00 (83.77, 100.00)	94.74 (90.00, 100.00)	-2.13	0.033 <sup>b</sup>
Stride frequency-minimum-right, steps / min	94.74 (85.71, 100.00)	90.00 (85.71, 100.00)	94.74 (90.00, 100.00)	-1.01	0.314 <sup>b</sup>	90.00 (85.71, 100.00)	94.74 (90.00, 100.00)	-2.41	0.016 <sup>b</sup>
Step width-median, m	0.12 (0.11, 0.14)	0.11 (0.11, 0.13)	0.13 (0.11, 0.15)	-2.96	0.003 <sup>b</sup>	0.12 (0.11, 0.14)	0.12 (0.11, 0.14)	-1.28	0.200 <sup>b</sup>
Step width-maximum, m	0.13 (0.12, 0.16)	0.13 (0.12, 0.15)	0.15 (0.13, 0.17)	-3.70	< 0.001 <sup>b</sup>	0.13 (0.12, 0.16)	0.14 (0.12, 0.16)	-1.26	0.209 <sup>b</sup>
Step width-minimum, m	0.11 ± 0.02	0.10 ± 0.02	0.11 ± 0.02	14.32	< 0.001 <sup>a</sup>	0.11 ± 0.02	0.11 ± 0.02	0.52	0.474 <sup>a</sup>

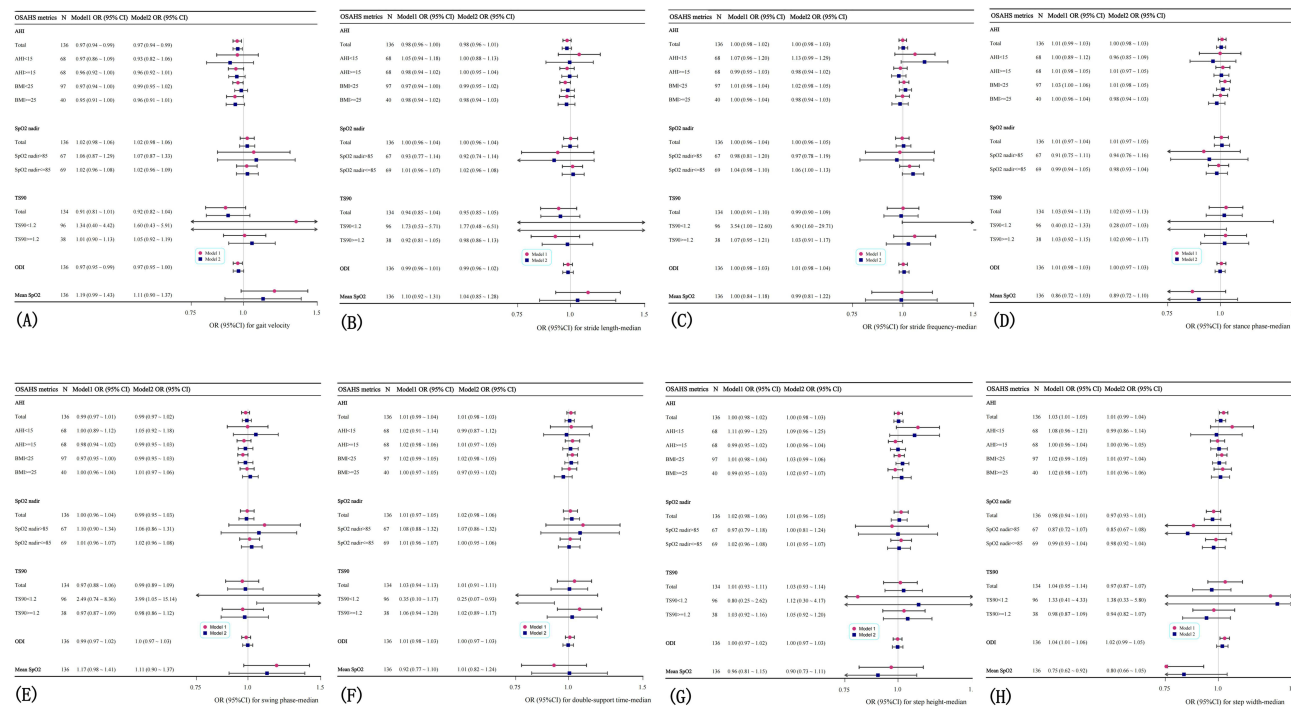
**Notes:** <sup>a</sup>Analyzed by independent sample *t* test, expressed as mean ± standard deviation. <sup>b</sup>Analyzed by Mann-Whitney *U*-test, expressed as median (1st quartile -3rd quartile). <sup>c</sup>*p* value between the nm-OSAHS and ms-OSAHS groups. <sup>d</sup>*p* value between the nm-hypoxemia and ms-hypoxemia groups.

**Abbreviations:** nm-OSAHS, subjects with no or mild obstructive sleep apnea-hypopnea syndrome, apnea hypopnea index < 15 events per hour; ms-OSAHS, subjects with moderate to severe obstructive sleep apnea-hypopnea syndrome, apnea hypopnea index ≥ 15 events per hour; nm-hypoxemia, subjects with no or mild hypoxemia, lowest oxygen saturation at night ≥ 85%; ms-hypoxemia, subjects with moderate to severe hypoxemia, lowest oxygen saturation at night < 85%.

# Correlation Analysis and Ordinal Regression Analysis

Spearman correlation was used to analyze the correlation between OSAHS metrics and gait indicators. However, no correlation coefficients were greater than 0.3 (Supplementary Table 2). To further investigate the relationship between OSAHS, hypoxemia and gait dysfunction, both crude and adjusted ordinal linear regression analysis were applied (Figure 1). Independent variables were AHI, SpO<sub>2</sub> nadir, TS90, ODI and mean SpO<sub>2</sub>. Dependent variables included gait velocity, stride length-median, stride frequency-median, stance phase-median, swing phase-median, step height and step width, all categorized into tertiles. Model 1 was adjusted for no covariates, and model 2 was adjusted for age, body mass index, sex, smoking, drinking, hypertension and diabetes, which were chosen based on potential bias referred to previous studies.<sup>32,33</sup>

Our findings indicated that higher AHI negatively impacted gait velocity (OR 0.97, 95% CI 0.94–0.99) and stride length (OR 0.98, 95% CI 0.96–1.00), while it positively influenced step width (OR 1.03, 95% CI 1.01–1.05) (Figure 1A–H). The impact on gait velocity remained (OR 0.97, 95% CI 0.94–0.99) significant after accounting for covariates. Higher ODI significantly reduced gait velocity (OR 0.97, 95% CI 0.95–0.99), regardless of whether covariates were adjusted for (Figure 1A). In the ms-hypoxemia group, stride frequency is 1.06 times more likely to decrease with each 1% drop in SpO<sub>2</sub> nadir (95% CI 1.00–1.13), after considering covariables (Figure 1C). In subjects with TS90 less than 1.2, a 1% rise in TS90 resulted in a 3.54 times higher likelihood of stride frequency improvement (95% CI 1.00–12.60), increasing to 6.90 times after covariate adjustment (95% CI 1.60–29.71) (Figure 1C). In subjects with BMI ≥ 25 kg/m<sup>2</sup>, the crude ORs of AHI for gait velocity, stride length, swing phase and stance phase were 0.97 (95% CI 0.94–1.00), 0.97 (95% CI 0.94–1.00), 1.03 (95% CI 1.00–1.06) and 0.97 (95% CI 0.95–1.00), respectively (Figure 1A–E). It was suggested that obesity was important factors affecting gait dysfunction, and it was necessary to restrict BMI in follow-up studies.

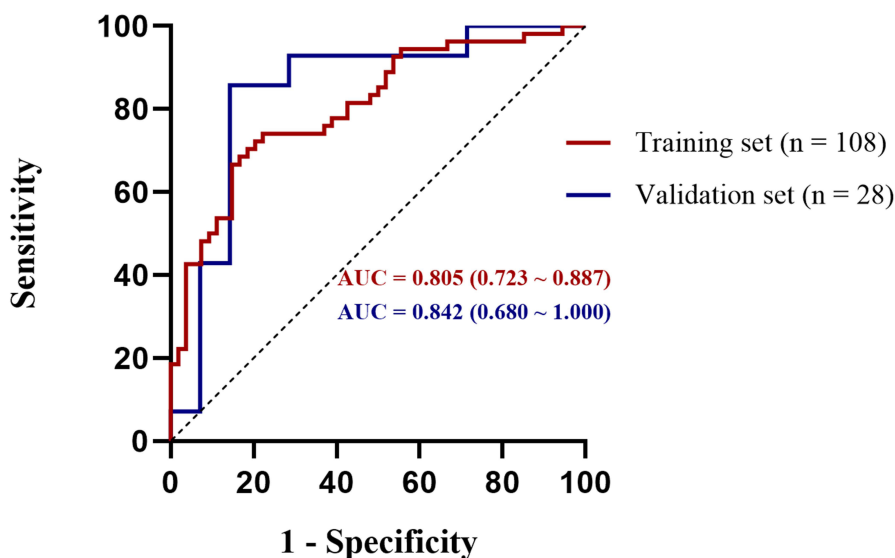


**Figure 1** Ordinal logistic regression analysis for gait indicators divided into tertiles.

**Notes:** Model 1 was adjusted for no variables. Model 2 was adjusted for age, body mass index, sex, smoking, drinking, hypertension and diabetes. (A) OR (95% CI) for higher gait velocity; (B) OR (95% CI) for higher stride length-median; (C) OR (95% CI) for higher stride frequency-median; (D) OR (95% CI) for higher stance phase-median; (E) OR (95% CI) for higher swing phase-median; (F) OR (95% CI) for higher double-support time-median; (G) OR (95% CI) for higher step height-median; (H) OR (95% CI) for higher step width-median.

**Abbreviations:** OSAHS, obstructive sleep apnea–hypopnea syndrome; OR, Odd ratio; CI, confidence interval; AHI, apnea–hypopnea index; SpO<sub>2</sub>, pulsed dioxygen saturation; TS90, the percent of the total sleep time below 90% oxygen saturation; ODI, oxygen desaturation index, defined as a drop in SpO<sub>2</sub> > 3% for at least 10s; BMI, body mass index.

## ROC curve used to predict moderate to severe OSAHS



**Figure 2** ROC curve for the prediction of moderate to severe OSAHS. The combination of stride length-median-right, step width-median, step width-maximum and step width-minimum, BMI and hypertension was used to determine moderate to severe OSAHS. The training set had an AUC of 0.805 (95% CI: 0.723–0.887), and the validation set had an AUC of 0.842 (95% CI: 0.680–1.000).

**Abbreviations:** OSAHS, obstructive sleep apnea–hypopnea syndrome; BMI, body mass index; ROC, receiver operating characteristic.

### Prediction Model for the Severity of OSAHS

We performed a logistic regression analysis to examine the potential of gait indicators in predicting moderate-to-severe OSAHS. Independent variables were selected based on observed differences between the nm-OSAHS and ms-OSAHS groups, including stride length-median-right, step width-median, step width-maximum, step width-minimum, BMI and hypertension. The dependent variable was the OSAHS group, with a value of 0 assigned to cases with no or mild symptoms and a value of 1 to those with moderate or severe symptoms. The dataset was randomly divided, with 80% ( $n = 108$ ) allocated to the training set and 20% ( $n = 28$ ) to the validation set. A receiver operating characteristic (ROC) curve was subsequently generated to calculate the area under the curve (AUC). The training set yielded an AUC of 0.805 (95% CI: 0.723–0.887) (Figure 2), with a sensitivity of 0.685 and specificity of 0.833 (Table 3). The validation set demonstrated an AUC of 0.842 (95% CI: 0.680–1.000) (Figure 2), with both sensitivity and specificity at 0.857 (Table 3). These findings indicated that the logistic regression model possesses excellent ability in predicting moderate-to-severe OSAHS.

### Neuroimaging Features of Lacunes, Cerebral Microbleeds, WMH Volume, White Matter Volume and Total Intracranial Volume

We assessed neuroimaging markers, including lacunes, cerebral microbleeds, WMH volume, total white matter volume, and total intracranial volume, in all subjects. No statistically significant differences were observed between the nm-OSAHS group

**Table 3** Stride Length, Step Width, BMI and Hypertension for Predicting Moderate to Severe OSAHS

Model	Area Under the ROC Curve	95% CI	Sensitivity	Specificity
Training set ( $n = 108$ )	0.805	0.723–0.887	0.685	0.833
Validation set ( $n = 28$ )	0.842	0.680–1.000	0.857	0.857

**Notes:** The combination of stride length-median-right, step width-median, step width-maximum, step width-minimum, BMI and hypertension was used to predict moderate to severe OSAHS.

**Abbreviations:** OSAHS, obstructive sleep apnea–hypopnea syndrome; BMI, body mass index; ROC, receiver operating characteristic.

**Table 4** Neuroimaging Features of Lacunes, Cerebral Microbleeds, WMH Volume, White Matter Volume and Total Intracranial Volume

	Subjects (n = 136)	nm-OSAHS group (n = 68)	ms-OSAHS group (n = 68)	p value <sup>c</sup>	nm-hypoxemia (n = 67)	ms-hypoxemia (n = 69)	p value <sup>d</sup>
<b>Neuroimaging features</b>							
Lacunes, n	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.845 <sup>b</sup>	0.0 (0.0, 1.0)	0.0 (0.0, 0.0)	0.126 <sup>b</sup>
Cerebral microbleeds, n	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	0.576 <sup>b</sup>	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	0.920 <sup>b</sup>
WMH volume, mL	3.3 (1.3, 8.3)	3.1 (1.1, 9.4)	3.4 (1.5, 7.9)	0.858 <sup>b</sup>	3.9 (1.6, 10.6)	2.8 (1.1, 7.4)	0.198 <sup>b</sup>
White matter volume, mL	475.6 ± 1350.3	482.0 ± 59.3	469.2 ± 61.4	0.221 <sup>a</sup>	477.4 ± 58.2	473.9 ± 62.9	0.739 <sup>a</sup>
Total intracranial volume, mL	1350.3 ± 135.7	1357.8 ± 139.1	1342.8 ± 132.8	0.520 <sup>a</sup>	1364.3 ± 139.4	1336.7 ± 131.5	0.236 <sup>a</sup>

**Notes:** <sup>a</sup>Analyzed by independent sample t test, expressed as mean ± standard deviation. <sup>b</sup>Analyzed by Mann–Whitney test, expressed as median (1st quartile–3rd quartile). <sup>c</sup>p value between the nm-OSAHS and ms-OSAHS groups. <sup>d</sup>p value between the nm-hypoxemia and ms-hypoxemia groups.

**Abbreviations:** WMH, white matter hyperintensity; nm-OSAHS, subjects with no or mild obstructive sleep apnea–hypopnea syndrome, apnea hypopnea index < 15 events per hour; ms-OSAHS, subjects with moderate to severe obstructive sleep apnea–hypopnea syndrome, apnea hypopnea index ≥ 15 events per hour; nm-hypoxemia, subjects with no or mild hypoxemia, lowest oxygen saturation at night ≥ 85%; ms-hypoxemia, subjects with moderate to severe hypoxemia, lowest oxygen saturation at night < 85%.

and the ms-OSAHS group. Moreover, no differences in these parameters were detected between the nm-hypoxemia group and the ms-hypoxemia group (Table 4).

### Structural Analysis

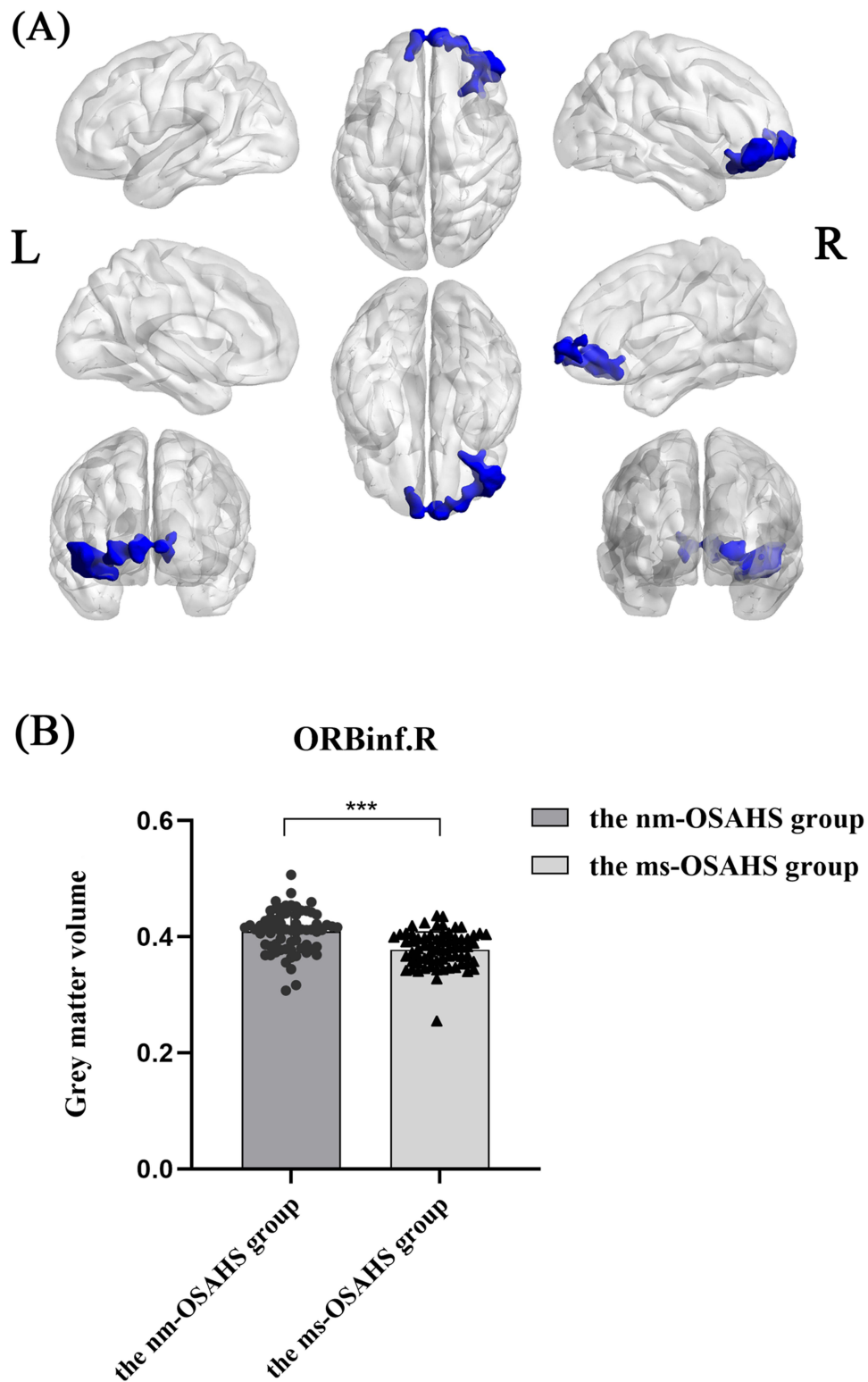
In the whole-brain VBM analysis, significant gray matter loss of ORBinf.R (the right inferior frontal gyrus and orbital part) was observed in the ms-OSAHS group compared with the nm-OSAHS group (Figure 3A and B). Figure 3B displays the mean and standard error of the gray matter volume in ORBinf.R. A negative correlation was identified among the AHI ( $r = -0.383$ ,  $p < 0.001$ ), ODI ( $r = -0.412$ ,  $p < 0.001$ ), and the gray matter volume in the ORBinf.R (Supplementary Table 3). Spearman correlation analysis revealed no significant relationship between the gray matter volume of ORBinf.R and the gait indicators of stride length and step width in the ms-OSAHS group. Furthermore, no differences in cerebral gray matter volume were detected between the nm-hypoxemia group and the ms-hypoxemia group.

### FC Analysis

The ms-OSAHS group presented increased FC between the left basal ganglia and left inferior temporal gyrus, the left pallidum and left insula, with this difference being statistically significant (GRF correction, voxel level  $P < 0.001$ , cluster level  $P < 0.05$ ) (Figure 4A–D). AHI and ODI were positively associated with FC values between the left basal ganglia and left inferior temporal gyrus, the left pallidum and left insula ( $r > 0.3$ ) (see Supplementary Table 3). Additionally, we observed increased FC between the right angular gyrus and left gyrus rectus in the ms-hypoxemia group compared with the nm-hypoxemia group (Figure 4A and E). FC between right angular gyrus and left gyrus rectus was positively correlated with the stride frequency–minimum–left ( $r = -0.303$ ,  $p = 0.011$ ) (Figure 5). A negative correlation between FC values of the right angular gyrus and the left gyrus rectus with SpO<sub>2</sub> nadir was also identified ( $r = -0.321$ ,  $p < 0.001$ ) (Supplementary Table 3). There were no significant differences in FC existed between the other seed regions.

### Discussion

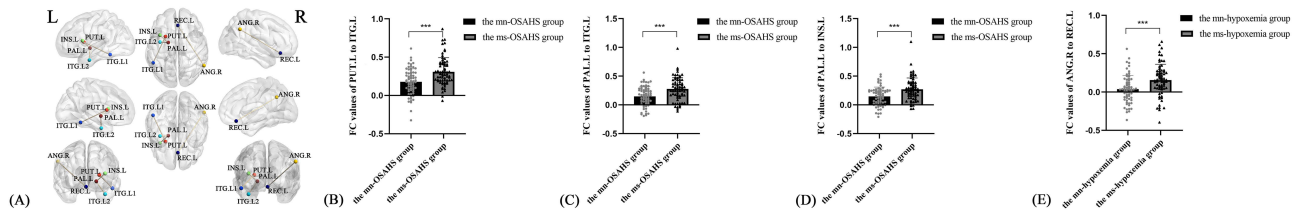
In this study, we focused on gait characteristics and their underlying neuroimaging mechanisms in patients with OSAHS. This is the first study to demonstrate that AHI and SpO<sub>2</sub> nadir correspond to different gait abnormalities in patients with OSAHS at the same cognitive level. High-frequency sleep apnea–hypopnea resulted in cortical atrophy of ORBinf.R and upregulation of FC between the basal ganglia and the left inferior temporal gyrus (ITG. L), basal ganglia and left insula (INS. L), whereas the severity of hypoxemia led to functional alternations between the right angular gyrus (ANG. R) and left gyrus rectus (REC. L), which manifested as respective alternations in gait. Furthermore, gait tests were able to evaluate the severity of AHI in OSAHS by logistic regression models. Our current findings contributed to a more comprehensive understanding of the impact of OSAHS on gait patterns and might provide an efficient method for OSAHS screening in the population.



**Figure 3** Difference in structural analysis between nm-OSAHS and ms-OSAHS groups **(A)** The blue-shaded area was the brain region with significant difference in the structural analysis between the nm-OSAHS and ms-OSAHS groups: ORBinf.R (Montreal Neurological Institute coordinates of peak voxel:  $x = 40.5, y = 39, z = -9$ , cluster size: 4090 voxels; Gaussian-Random-Field-Correction for multiple comparisons:  $P < 0.001$  at voxel level,  $P < 0.05$  at cluster level). **(B)** The gray matter volume of ORBinf.R in the nm-OSAHS ( $0.409 \pm 0.036$ ) and ms-OSAHS ( $0.378 \pm 0.030$ ) groups was significantly differed.

**Note:** \*\*\* $p < 0.001$ .

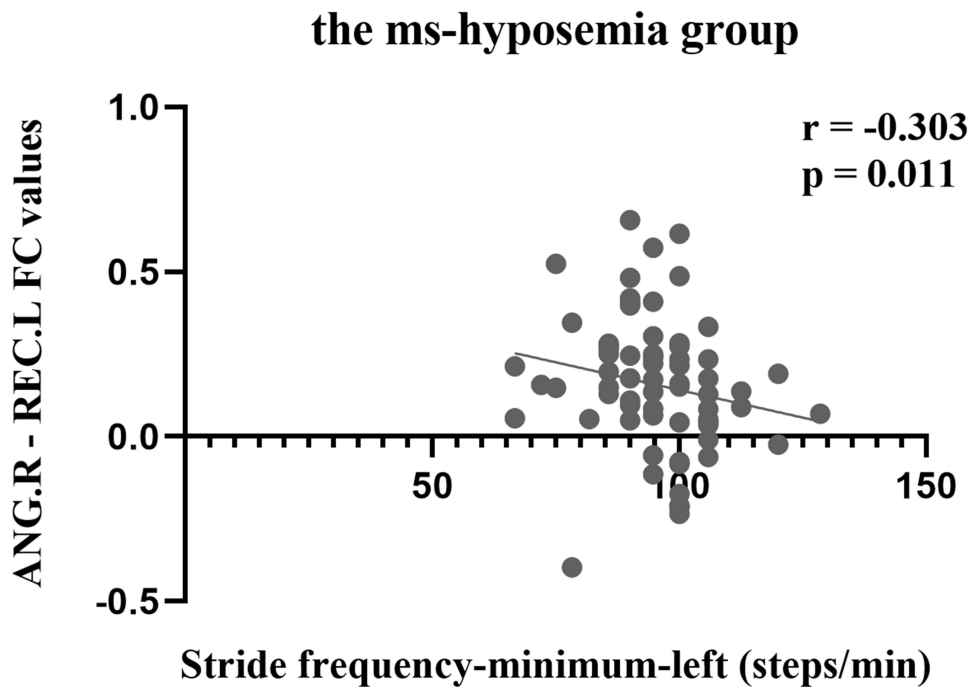
**Abbreviations:** ORBinf.R, the right inferior frontal gyrus, orbital part; nm-OSAHS, subjects with no or mild obstructive sleep apnea–hypopnea syndrome, apnea hypopnea index  $< 15$  events per hour; ms-OSAHS, subjects with moderate-to-severe obstructive sleep apnea–hypopnea syndrome, apnea hypopnea index  $\geq 15$  events per hour.



**Figure 4** Functional connectivity and differences in FC values of PUT, L, PAL, L and ANG. **(A)** Compared to the nm-OSAHS group, the ms-OSAHS group demonstrated strengthened FC between PUT, L and ITG, L1 (Montreal Neurological Institute coordinates of peak voxel:  $x = -51, y = -48, z = -18$ , cluster size: 71 voxels; Gaussian-Random-Field-Correction for multiple comparisons:  $P < 0.001$  at voxel level,  $P < 0.05$  at cluster level), PAL, L and ITG, L2 (Montreal Neurological Institute coordinates of peak voxel:  $x = -36, y = -3, z = -30$ , cluster size: 86 voxels; Gaussian-Random-Field-Correction for multiple comparisons:  $P < 0.001$  at voxel level,  $P < 0.05$  at cluster level). Compared to the nm-hypoxemia group, the ms-hypoxemia group demonstrated strengthened FC between ANG, R and REC, L (Montreal Neurological Institute coordinates of peak voxel:  $x = 3, y = 33, z = -15$ , cluster size: 65 voxels; Gaussian-Random-Field-Correction for multiple comparisons:  $P < 0.001$  at voxel level,  $P < 0.05$  at cluster level). **(B)** The FC of PUT, L to ITG, L was significantly differed between the nm-OSAHS ( $0.178 \pm 0.171$ ) and the ms-OSAHS ( $0.309 \pm 0.184$ ) groups. **(C)** The FC of PAL, L to ITG, L was significantly differed between the nm-OSAHS ( $0.149 \pm 0.170$ ) and the ms-OSAHS ( $0.278 \pm 0.201$ ) groups. **(D)** The FC of PAL, L to INS, L was significantly differed between the nm-OSAHS ( $0.150 \pm 0.161$ ) and the ms-OSAHS ( $0.272 \pm 0.197$ ) groups. **(E)** The FC of ANG, R to REC, L was significantly differed between the nm-hypoxemia group ( $0.038 \pm 0.179$ ) and the ms-hypoxemia ( $0.157 \pm 0.206$ ) groups.

**Note:**\*\*\* $p < 0.001$ .

**Abbreviations:** FC, functional connectivity; PUT, L, the left lenticular nucleus, putamen; ITG, L, the left inferior temporal gyrus; PAL, L, the left lenticular nucleus, pallidum; INS, L, the left insula; ANG, R, the right angular gyrus; REC, L, the left gyrus rectus; nm-OSAHS, subjects with no or mild obstructive sleep apnea-hypopnea syndrome, apnea hypopnea index  $< 15$  events per hour; ms-OSAHS, subjects with moderate-to-severe obstructive sleep apnea-hypnea syndrome, apnea hypopnea index  $\geq 15$  events per hour; nm-hypoxemia, subjects with no or mild hypoxemia, lowest oxygen saturation at night  $\geq 85\%$ ; ms-hypoxemia, subjects with moderate-to-severe hypoxemia, lowest oxygen saturation at night  $< 85\%$ .



**Figure 5** Correlation between stride frequency and FC of ANG, R to REC, L Spearman correlation analysis showed that FC of ANG, R to REC, L was negatively associated with stride frequency-minimum-left in the ms-hypoxemia group ( $r = -0.303, p = 0.011$ ).

**Abbreviations:** FC, functional connectivity; ANG, R, the right angular gyrus; REC, L, the left gyrus rectus; ms-hypoxemia, subjects with moderate-to-severe hypoxemia, lowest oxygen saturation at night  $< 85\%$ .

Falls represent a primary cause of unintentional injuries, diminished quality of life, and reduced functional capacity among the elderly population.<sup>12</sup> Recent evidence suggested that prevalent sleep disorders, especially OSAHS, may constitute a significant modifiable risk factor for falls.<sup>14</sup> Considering the rising longevity of older adults and the prevalence of falls within this population, more needs to be done to reduce the risk of falls. Emerging research indicated that Continuous Positive Airway Pressure (CPAP) therapy for OSAHS might reduce the risk of falls in older adults.<sup>34,35</sup>

Two studies from the Outcomes of Sleep Disorders in Older Men cohort study identified hypoxemia, rather than AHI, was associated with an elevated risk of falls.<sup>36,37</sup> It is crucial to further delineate the mechanisms by which OSAHS influences gait and balance, thereby providing more comprehensive guidance for fall prevention strategies. In our study, we observed that higher AHI was correlated with increased step width and reduced stride length. Patients with moderate-to-severe hypoxemia had faster stride frequency. This finding was further verified in ordinal logistic regression. Although the 95% confidence intervals did not reach statistical significance following the adjustment for covariates, such as BMI, this might be attributable to the significant role of BMI as a variable influencing both OSAHS and gait. Furthermore, ODI, TS90 and mean SpO<sub>2</sub> nadir demonstrated associations with gait indicators. These metrics, however, capture only a singular dimension of hypoxemia, underscoring the necessity for employing more comprehensive measures, such as the hypoxemia burden, in future researches. The hypoxemia burden has been previously demonstrated to correlate with mortality outcomes.<sup>38</sup>

Baillieux et al proposed that patients with severe obstructive sleep apnea showed poor performance in step width.<sup>39</sup> In static postural stability tests, OSAHS patients also showed increased mediolateral distance.<sup>40,41</sup> However, previous studies did not consider cognitive differences between patients and controls. Cognition is an important factor affecting gait and was of great concern in our study. Ordinal logistic regression showed that AHI affected gait velocity, but no differences were found between nm-OSAHS and ms-OSAHS groups. This discrepancy might be attributed to the latter analysis accounting for cognitive function, which has been confirmed to be closely linked to gait velocity.<sup>42</sup> Decreased stride length, increased step width and faster stride frequency might be compensatory stepping strategies to recover from a forward loss of balance.<sup>43–46</sup>

Gait is a reflection of brain function.<sup>15,47,48</sup> Previous research proposed that different indicators of OSAHS might result in impairments of different cognitive dimensions<sup>49</sup> and brain structures.<sup>9</sup> Different alterations in gait may indicate different neuroimaging patterns in the brain. However, seldom does previous studies involve in underlying mechanisms of gait dysfunction caused by OSAHS. We took the lead in pinpointing gait-related neuroimaging features in patients with OSAHS. Respiratory events and hypoxemia exhibited different neuroimaging features. Structurally, high-frequency hypopnea and sleep apnea were more likely to cause cortical atrophy than hypoxemia was. Previous studies also reported cortical atrophy of the frontal lobe in patients with OSAHS.<sup>50,51</sup> Reduced grey matter volume in the prefrontal regions led to changes in gait patterns.<sup>52</sup> Functionally, high-frequency hypopnea and sleep apnea might cause behavioral modulation through the cortical–basal ganglia circuit, whereas hypoxemia may occur through altered functional interactions of the bilateral prefrontal cortex. The basal ganglia are important in motor control. Alexander reported that asymmetrical gait was evident in patients with injury to the putamen.<sup>53</sup> The discharge patterns of neurons in the pallidum are well related to visually guided gait modifications.<sup>54</sup> Gait is a product of senior cognitive processing, including cognitive control, attention and so on.<sup>55</sup> We identified the ITG. L was closely associated with AHI-related gait dysfunction. The ITG. L is responsible for visual perception.<sup>56</sup> It has been reported that spatiotemporal parameters (eg stride length) benefit from visual cues during walking.<sup>57,58</sup> In a study of gait adaptation, perturbations of the visual field could reduce stride length and expand step width.<sup>59</sup> Our previous study reported functional alteration in the left inferior temporal gyrus in subjects with Tinetti test scores <24.<sup>60</sup> Thus, visual processing might play an important role in the impact of OSAHS on stride length and step width.

With regard to hypoxemia, we found that decreased consistency of neuronal activity between the bilateral prefrontal cortices might be responsible for the increased stride frequency. Prefrontal cortices were great important in senior cognitive processing. It was demonstrated that the angular gyrus was the key neuroimaging node of attention<sup>61,62</sup> and spatial perception,<sup>63</sup> which were essential for maintaining balance during walking. The ANG. R was also reported to be functionally engaged in gait and balance dysfunction.<sup>60</sup> REC. L is a part of the prefrontal cortex. In a study of autism spectrum disorder, meta-analytic decoding of the left gyrus rectus annotated functional items related to social cognition.<sup>64</sup> In our previous study, the thickness of the REC. L was directly proportional to gait performance, while no significant correlation was found.<sup>65</sup> In subjects with ms-hypoxemia, the functional connectivity between the ANG. R and REC. L reduced and was significantly related to the stride frequency. We provided new evidence for the close association between ANG. R, REC. L and stride frequency. To summarize, we should fully consider the distinct gait and neuroimaging patterns of AHI and hypoxia in the diagnosis and treatment of OSAHS. Considering that CPAP therapy is only partially effective for OSAHS and its efficacy in improving gait dysfunction remains controversial,<sup>34,66</sup> ORBinf.R, ITG. L, ANG. R and REC. L might serve as potential targets for neural modulation in the treatment of OSAHS.

## Limitations

There remain certain limitations to this research. First, this study has a cross-sectional and single-center design, which limits the ability to infer causality. It remains unclear whether OSAHS precedes and contributes to neuroanatomical alterations and subsequent gait changes, or whether preexisting neuroanatomical vulnerabilities predispose individuals to OSAHS or exacerbate its progression. Similar to a previous study,<sup>67</sup> we also observed a mismatch between neuroimaging findings and gait indicators, which is worth further exploration. In the future, we plan to expand the research to multi-center settings and conduct longitudinal follow-up, with periodic evaluations of neuroimaging and gait indicators over multiple years to track temporal changes. Additionally, randomized controlled trials evaluating CPAP therapy on neuroanatomical and gait outcomes could help clarify the causal relationship involved.

Second, the clinical implementation of Readygo, a novel gait assessment system, remains in its nascent phase, requiring further specific validation data and test–retest reliability. In future research, we will prioritize obtaining these data in similar populations. Gait assessments could involve two consecutive measurements, with repeat measurements conducted on the second day during similar time periods to enhance the robustness and generalizability of findings.

Third, we employed SpO<sub>2</sub> nadir as a metric to evaluate hypoxemia severity, which represents a single point measurement that is susceptible to artifacts and neglects the frequency and duration of oxygen desaturation episodes. Future research should consider incorporating more comprehensive metrics of hypoxemia, such as hypoxic burden. Hypoxic burden better characterizes the overall pattern of oxygen desaturation and has been demonstrated to have significant implications for both cardiovascular<sup>38</sup> and cognitive health.<sup>68</sup>

Finally, due to the limitation of sample size, we chose the GRF correction method in the neuroimaging analyses. Our current discovered brain regions are relatively large, and more stringent multiple comparison correction methods may contribute to focusing on the key neural nodes in OSAHS.

In conclusion, patients with obstructive sleep apnea–hypopnea and hypoxemia had different gait dysfunction and corresponding underlying mechanisms in OSAHS. Higher frequency respiratory events affected stride width and stride length, while reduced oxygen saturation levels influenced stride frequency. Our findings provided a rationale for further mechanistic researches and found that the gait test might serve as a screening tool for OSAHS, thereby contributing to the overall enhancement of public health.

## Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## Ethics Approval Statement

This study was conducted according to the Declaration of Helsinki principles. Ethical approval for this study was obtained from the Ethics Committee of Nanjing Drum Tower Hospital (Ethics Approval No: 2023-327-02).

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## Author Contributions

Jialiu Jiang: conceptualization, data curation, investigation, methodology, formal analysis, writing – review and editing, writing – original draft; Yuting Mo: conceptualization, software, investigation, data curation, formal analysis, methodology, writing – review and editing, supervision; Zulalai Abuduwalli: writing – original draft, investigation; Chenglu Mao: data curation, writing – review and editing, investigation; Shuang Fang: data curation, investigation, writing – original

draft; Zhihong Ke, investigation, writing – original draft; Zheqi Hu: investigation, writing – original draft; Lili Huang: investigation, writing – original draft; Shuai Xu: investigation, writing – original draft; Dan Yang: investigation, writing – original draft; Ruozhu Xiong: investigation, writing – original draft; Pei Xie: investigation, writing – original draft; Xiaolei Zhu: writing – review and editing, supervision; Yun Xu: resources, writing – review and editing, funding acquisition, supervision.

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