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MISCELLANEOUS

# Biomarkers of Alzheimer's disease in severe obstructive sleep apnea–hypopnea syndrome in the Chinese population

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## Abstract

**Purpose** Patients with severe obstructive sleep apnea–hypopnea syndrome are often accompanied by symptoms such as decreased cognitive function and daytime sleepiness, while cognitive function is often associated with biomarkers of Alzheimer's disease. Therefore, this study aims to explore the level of Alzheimer's disease biomarkers in the plasma of obstructive sleep apnea–hypopnea syndrome patients as well as the relationship between cognitive function and daytime sleepiness.

**Methods** Between May and July 2019, 35 patients requiring hospitalization for severe obstructive sleep apnea–hypopnea syndrome and 16 normal control patients were selected from West China Hospital. Alzheimer's disease biomarkers (Aβ40, Aβ42, t-tau, p-tau) in plasma were detected by ELISA in all 51 subjects. The differences in Alzheimer's disease biomarkers between the two groups were compared. In addition, a correlation analysis of disease-related indicators and univariate analysis of the risk factors of obstructive sleep apnea–hypopnea syndrome was conducted using the logistic regression model.

**Results** The plasma levels of Alzheimer's disease biomarkers (Aβ40, t-tau, p-tau) in patients with severe obstructive sleep apnea–hypopnea syndrome were significantly higher than those in the control group ($29.24 \pm 32.52$, $13.18 \pm 10.78$, $p = 0.049$; $11.88 \pm 7.05$, $7.64 \pm 4.17$, $p = 0.037$; $26.31 \pm 14.41$, $17.34 \pm 9.12$, $p = 0.027$). Aβ42, Aβ40, t-tau, and p-tau were significantly negatively correlated with mean oxygen saturation, low oxygen saturation and Mini-Mental State examination scale scores, and positively correlated with oxygen desaturation index and Epworth Sleepiness Scale scores. T-tau and p-tau can be used as new risk factors for obstructive sleep apnea–hypopnea syndrome.

**Conclusion** Alzheimer's disease biomarkers in the plasma of obstructive sleep apnea–hypopnea syndrome patients are higher than those in the control group, and the mechanism of action may be related to sleep disorders and night hypoxia. The Alzheimer's disease biomarkers deposited in plasma may also cause the decline of patients' cognitive function, increased daytime sleepiness and accelerate the progression of obstructive sleep apnea–hypopnea syndrome.

**Keywords** Severe obstructive sleep apnea–hypopnea syndrome · Alzheimer's disease · Biomarkers

## Introduction

In recent years, many studies have shown that obstructive sleep apnea–hypopnea syndrome (OSAHS) is the cause of dementia [1]. The clinical manifestations of OSAHS include snoring, sleep architecture abnormalities, a frequent decrease in blood oxygen saturation, daytime drowsiness, and memory loss. OSAHS causes recurrent hypoxia and frequent nocturnal awakenings, resulting in impairment of neurological cognition and memory-function disorders [2, 3]. Some studies have analyzed the effects of OSAHS on cognitive function in terms of attention, situational memory, working memory, and executive function [4, 5]. A 5-year follow-up study in Taiwan showed that patients with OSAHS

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had 1.7 times higher risk of dementia within 5 years than non-OSAHS patients [6].

Alzheimer's disease (AD) is one of the most common causes of dementia, accounting for 60–70% of its occurrence [7]. In an East Boston study, the prevalence of AD in those older than 85 years of age was 47% [8]. OSAHS has been proven to cause progressive central nervous damage, which may lead to further cognitive decline or accelerate the progression of AD [9]. A recent longitudinal cohort study showed that sleep respiratory disorders were significantly associated with Mild Cognitive Impairment (MCI) and AD [10]. However, there is little literature about the relationship between OSAHS and AD biomarkers.

In the clinical setting, t-tau, p-tau, Aβ40, and Aβ42 are often analyzed in cerebrospinal fluid samples as key proteins in the process of AD [11]. However, in clinical practice, sampling cerebrospinal fluid from patients is risky, so peripheral blood is used instead for the identification of AD biomarkers [12].

This paper aims to explore the relationship between plasma AD biomarkers and OSAHS: (1) The difference between AD biomarker content in the plasma of OSAHS patients and the control group; (2) The correlation between sleep monitoring indicators and AD biomarkers; (3) The correlation between cognitive function, sleepiness, and AD biomarkers; (4) Whether or not AD biomarkers are one of the risk factors for OSAHS.

## Methods

### Participant recruitment

The study involved the prospective and continuous inclusion of 35 patients admitted to West China Hospital for severe OSAHS from May to July 2019 as the OSAHS group. The variables that we obtained for our database included patient age, sex, height, weight, blood pressure, smoking history, drinking history, medication history, special disease history, surgical history, Body Mass Index (BMI), blood routine, blood biochemistry, coagulation function, arterial blood gas, lung function tests, Mini-Mental State examination scale (MMSE) scores, and Epworth Sleepiness Scale (ESS). The control group consisted of 16 patients found to have normal sleep patterns by polysomnography (PSG); the age and gender of the control group were matched to those of the OSAHS group. The plasma of the OSAHS group and control group was taken to detect biomarkers of AD: Aβ40, Aβ42, t-tau, p-tau.

Inclusion criteria in the experimental group were as follows: (1) The patients were diagnosed as OSAHS by polysomnography (PSG); (2) The length of time from diagnosis to admission was less than 1 month and these patients had never received continuous positive airway pressure (CPAP) treatment; (3) OSAHS was classified as severe (AHI > 30); (4) After examination (imaging, laryngoscope), patients clearly conformed with Uvulopalatopharyngoplasty (UPPP) treatment guidelines.

The control group exclusion criteria were as follows: (1) family history of dementia; (2) neurological diseases (such as Parkinson's disease) that may damage cognitive function; (3) malignant tumors or serious heart, lung, kidney, or liver diseases; (4) psychiatric patients; (5) long-term use of antidepressants, sedatives or hypnotic drugs.

All subjects provided written informed consent, and the research was approved by the ethics approval committee at West China Hospital.

### Polysomnography respiratory monitoring

All patients used Alice 5 (Philips Welcome, USA) PSG polysomnography, including six electroencephalogram electrodes, two electrooculogram electrodes, three mentalis electromyography electrodes, four lower limb electromyography electrodes, three electrocardio electrodes, an oronasal airflow thermal sensor, nasal pressure tube, chest and abdomen strap, snoring monitor, blood oxygen saturation monitor, etc. Data collection included: total sleep time (TST), Rapid Eye Movement (REM), N3 stage sleep time, apnea–hypopnea index (AHI), mean oxygen saturation (MSaO2), low oxygen saturation (LSaO2), and oxygen desaturation index (ODI). Meanwhile, hypopnea referred to more than 4% decrease in blood oxygen desaturation or arousal.

### AD biomarkers test

Fasting blood was collected from the OSAHS group the day prior to the UPPP operation. Fasting blood was collected from the control group the day after PSG. All blood samples were centrifuged, and the supernatant was stored at − 80 °C. To detect the levels of Aβ40 and Aβ42 in plasma, a human β amyloid enzyme-linked immunosorbent assay (ELISA) kit was used, while plasma t-tau and p-tau were determined by a human tau protein ELISA kit. All ELISA tests were carried out in strict accordance with the manufacturer's instructions. Each sample was measured at least three times according to the standard and the average value was taken for statistical analysis.

### Statistical analysis

Descriptive statistics were provided with mean and standard deviation (SD) for continuous variables and frequencies and percentages for categorical variables. We conducted a power analysis to assess the main biomarker difference between the OSAHS group and control group.

To test the significant differences of the biomarker between the two groups, our study with 35 patients and 16 control group would have at least 90% power. The power analysis was based on a two-sided test with a significant level of 0.05 and an effect size of mean difference of 1.0 standard deviation (SD). Demographics and clinical characteristics were compared with the Wilcoxon's rank-sum test for continuous variables and Chi-squared test or Fisher's exact tests for categorical variables. For the correlation analysis, Spearman correlation analyses were conducted. Univariate and multivariable logistic regression models were used to analyze the risk factors of OSAHS. For all comparisons, two-sided tests were applied with $p \leq 0.05$ considered as the statistical significance. All statistical analyses and figures were conducted in R-studio 7.0 software and Prism 8.0.

## Results

There were 35 OSAHS patients in this study, including 30 males (85.8%) and five females (14.2%). There were 16 participants in the control group, including 14 males (87.5%) and two females (12.5%). All subjects were between 24 and 60 years of age. There were no statistical differences in age, gender, smoking history, drinking history, systolic pressure, diastolic pressure, diabetes history, or cardiovascular disease history between the OSAHS group and the control group; there was a significantly higher mean BMI, MMSE, and ESS in OSAHS group (25.65 vs 23.02, $p=0.003$; 27.14 vs 29.19, $p<0.001$; 11.91 vs 5.56, $p<0.001$, respectively) (Table 1).

There was no statistical difference in the plasma Aβ42 content between the OSAHS group and the control group ($p=0.631$). Plasma Aβ40, t-tau, and p-tau were significantly

**Table 1** Characteristics of the study population

| | OSAHS group ($n=35$) | Control group ($n=16$) | $p$ |
|---|---|---|---|
| Age (years) | 39.18 ± 9.22 | 42.43 ± 9.79 | 0.26 |
| Gender | | | |
| Male | 30 (85.8%) | 14 (87.5%) | 0.84 |
| Female | 5 (14.2%) | 2 (12.5%) | |
| BMI (kg/m$^2$) | 25.65 ± 2.78 | 23.02 ± 2.70 | **0.003** |
| Smokers | | | |
| Yes | 12 (34.3%) | 6 (37.5%) | 0.82 |
| No | 23 (65.7%) | 10 (62.5%) | |
| Drinkers | | | |
| Yes | 14 (40%) | 3 (18.75%) | 0.14 |
| No | 21 (60%) | 13 (81.25%) | |
| Hypertensio | | | |
| Yes | 14 (40%) | 6 (37.5%) | 0.87 |
| No | 21 (60%) | 10 (62.5%) | |
| Systolic pressure | 126.43 ± 16.24 | 125.81 ± 14.45 | 0.90 |
| Diastolic pressure | 89.54 ± 11.47 | 84.5 ± 9.22 | 0.13 |
| Diabetes | | | |
| Yes | 1 (1%) | 0 (0%) | 1.00 |
| No | 34 (99%) | 16 (100%) | |
| Cardiovascular | | | |
| Yes | 1 (1%) | 0 (0%) | 1.00 |
| No | 34 (99%) | 16 (100%) | |
| N3 | 6.83 ± 8.99 | 4.84 ± 6.62 | 0.38 |
| AHI | 63.92 ± 23.65 | 2.62 ± 1.93 | **< 0.0001** |
| MSaO2 (%) | 91.43 ± 3.4 | 95.29 ± 0.99 | **< 0.0001** |
| LSaO2 (%) | 71.91 ± 13.71 | 87.25 ± 6.93 | **0.008** |
| ODI (/h) | 64.57 ± 26.82 | 2.81 ± 2.25 | **< 0.0001** |
| REM (min, SD) | 63.28 ± 36.5 | 102.3 ± 104.6 | **0.042** |
| MMSE (score, SD) | 27.14 ± 1.65 | 29.19 ± 0.83 | **< 0.01** |
| ESS (score, SD) | 11.91 ± 4.84 | 5.56 ± 1.9 | **< 0.01** |

$p < 0.05$ are in bold

higher in the OSAHS group than in the control group (Table 2).

Aβ42, Aβ40, t-tau, and p-tau were significantly negatively correlated with MSaO2 and LSaO2, positively correlated with ODI, and not significantly correlated with AHI. Aβ42, Aβ40, t-tau were negatively correlated with N3 (Fig. 1). Aβ42, Aβ40, t-tau, and p-tau were significantly negatively correlated with MMSE and positively correlated with ESS ($p < 0.05$) (Fig. 2).

**Table 2** Differences in Aβ42, Aβ40, t-tau, p-tau in two groups

| | OSAHS group ($n = 35$) | Control group ($n = 16$) | $p$ |
|---|---|---|---|
| Aβ42 | 0.23 ± 0.17 | 0.26 ± 0.22 | 0.631 |
| Aβ40 | 29.24 ± 32.52 | 13.18 ± 10.78 | **0.049** |
| t-tau | 11.88 ± 7.05 | 7.64 ± 4.17 | **0.037** |
| p-tau | 26.31 ± 14.41 | 17.34 ± 9.12 | **0.027** |

$p < 0.05$ are in bold

The average oxygen saturation had a strong positive correlation with the minimum oxygen saturation, the average oxygen saturation had a strong negative correlation with sleepiness, and the minimum oxygen saturation had a strong negative correlation with oxygen reduction index. Aβ42 was strongly positively correlated with Aβ40; P-tau was strongly positively correlated with Aβ42, Aβ40, and t-tau; Aβ40 was strongly positively correlated with ESS (Fig. 3).

The univariate logistic regression analysis on BMI, smokers, drinkers, blood pressure, MSaO2, LSaO2, Aβ42, Aβ40, t-tau, and p-tau showed that BMI, AHI, ODI, MSaO2, LSaO2, t-tau, and p-tau were significant risk factors for OSAHS. Then, we used binary logistic to carry out a multivariate regression analysis on the significant variables, and finally, the BMI, MSaO2, LSaO2, t-tau, and p-tau

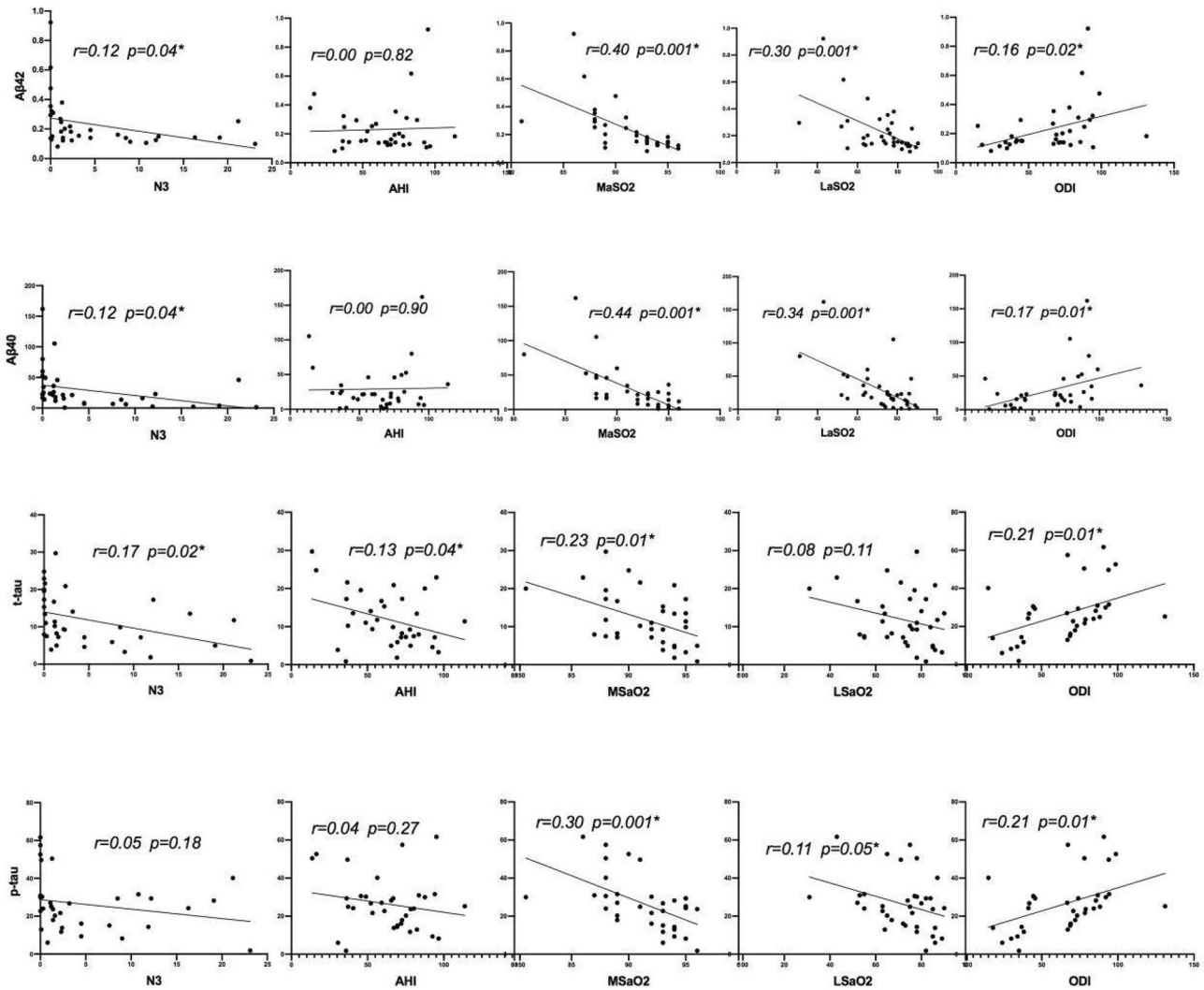


**Fig. 1** Correlation between the sleep indexes and the levels of Aβ42, Aβ40, t-tau, and p-tau

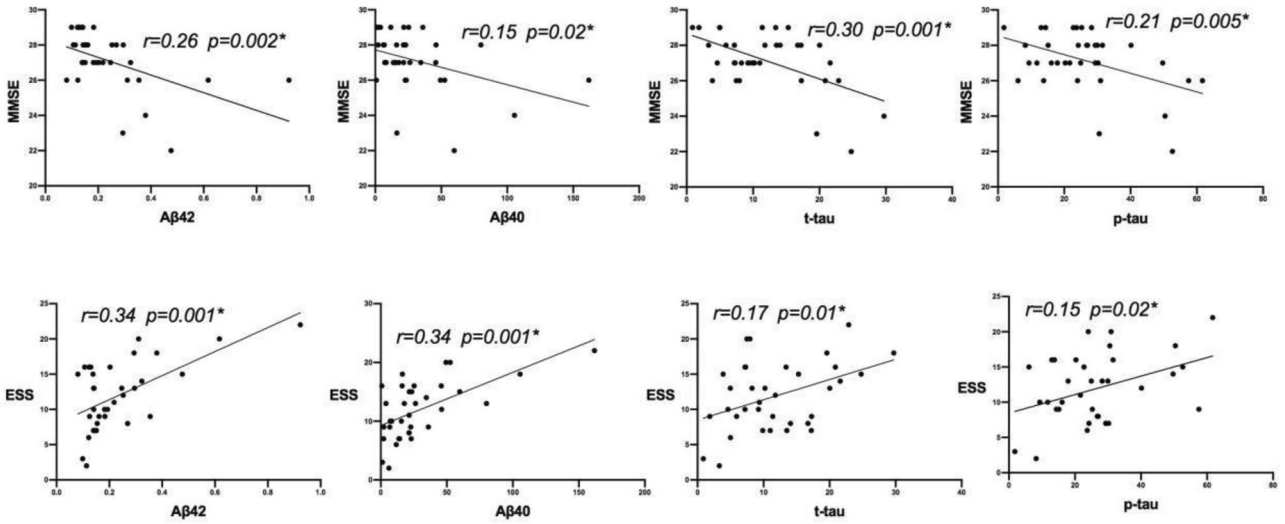


**Fig. 2** Correlation between MMSE and ESS, and the levels of Aβ42, Aβ40, t-tau, and p-tau. *MMSE* The Mini-Mental State Exam is a widely used test of cognitive function among the elderly, it includes tests of orientation, attention, memory, language and visual-spatial skills. *ESS* The Epworth sleepiness scale is a self-administered questionnaire that is routinely used by doctors to assess daytime sleepiness

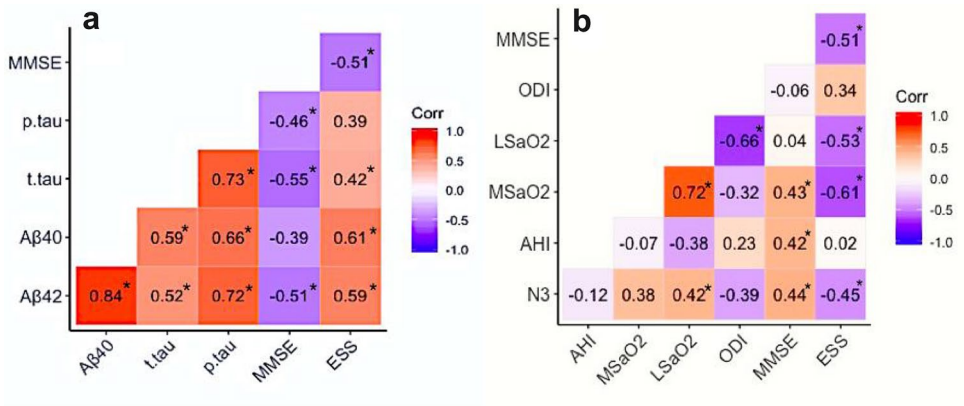


**Fig. 3** **a** Spearman correlation coefficient between the MMSE and ESS, and the levels of Aβ42, Aβ40, t-tau, and p-tau. **b** Spearman correlation coefficient between the MMSE and ESS, and ODI, LSaO2, MSaO2, AHI and N3. *$p < 0.05$

*:p<0.05

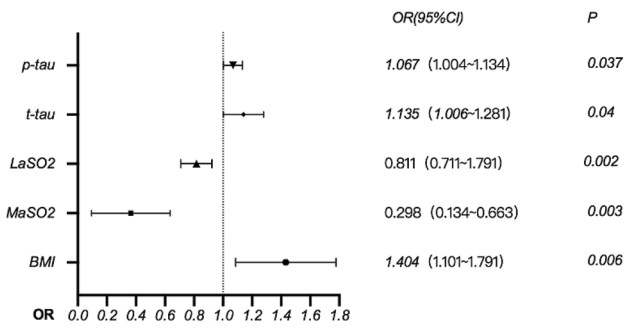


**Fig. 4** Significant risk factors for OSAHS

were found to be the significant independent risk factors for OSAHS. These results were summarized in a forest plot (Fig. 4).

## Discussion

OSAHS is closely related to cognitive dysfunction and its main mechanisms are nocturnal sleep structural disorder and hypoxemia [13, 14]. In this study, four AD biomarkers are significantly negatively correlated with MSaO2 and LSaO2 and positively correlated with ODI. Aβ42, Aβ40, and t-tau are negatively correlated with N3. In other words, the lower the oxygen saturation and the shorter the deep sleep time, the higher the plasma AD biomarker content. Hypoxia can also increase the expression of hypoxia-inducible factor 1α (HIF-1-α), enhancing the activity of β and γ secretase [15]; this results in an increase in Aβ content in mice [16]. In cases of hypoxia, the expression of ADAM10, a precursor protein of α secretagogue,

in nerve cells is reduced [17], resulting in the inhibition of Aβ protein production. On the other hand, hypoxia can down-regulate the level of Aβ-degrading enzymes, namely enkephalinase [18], resulting in a decrease in the Aβ clearance rate. Respiratory airflow interruption caused by collapse or obstruction of the upper airway occurs constantly in OSAHS patients during sleep, making it difficult to enter into a state of deep sleep. Short deep sleep time can affect the recovery of cerebral cortex function; it can also affect cognitive function, including decreases in alertness, attention, sensory perception, and memory ability [19]. In our study, the AD biomarker proteins Aβ40, t-tau, and p-tau in OSAHS patients were significantly increased compared to the control group. AD biomarkers may accumulate in the plasma of OSAHS patients with preclinical dementia due to hypoxia. Hypoxia may upregulate the shear activity of γ-secretase through the HIF-1α pathway, thus accelerating the abnormal metabolism and promoting the production of Aβ and Tau protein, similar to the findings of Ju et al. [15, 20].

MMSE is the preferred scale for dementia screening [21], which measures the following seven aspects: time orientation, place orientation, immediate memory, attention, calculation, delayed memory, language, and visual space. ESS mainly evaluates the degree of daytime sleepiness of patients under different daily life conditions [22]. This study found that MMSE score was negatively correlated with four AD biomarkers, suggesting that the more severe the cognitive impairment, the higher the content of AD biomarkers, which is similar to the previous results [23, 24]. The pathological mechanism of AD is the deposition of β-amyloid (Aβ) protein in nerve tissue, which causes the formation of senile plaque, and the hyperphosphorylation of microtubule-like tau-protein leads to neurofibrillary tangles (NFT). This results in the formation of paired spiral fiber, which causes nerve cell death [25]. In our study, ESS score is shown to be positively correlated with four AD biomarkers, suggesting that the more serious somnolence symptoms, the higher the serum AD biomarker content.

Alzheimer's disease is the most common type of dementia with 40–80% of AD patients suffering from sleep disorders [26]. Sleep disorders play an important role in the occurrence and development of AD. Sleep disorders and hypoxemia are the causes of amyloid plaque formation [27]. Soluble Aβ level is higher in the brain when awake, but lower during sleep, indicating that Aβ protein is cleared in the brain during sleep [28]. Recent studies also support that pathological process of Aβdeposition in the brain can lead to sleep and circadian rhythm disorder [29, 30].

Aβ proteins are produced by continuous proteolysis of the amyloid precursor protein (APP) by β secretase (BACE-1) and γ secretase [31]; soluble Aβ40 and insoluble Aβ42 are the two main types of Aβ proteins. At present, most clinical diagnoses of AD are made by measuring the level of Aβ in cerebrospinal fluid. However, as we were not able to obtain cerebrospinal fluid in this experiment, peripheral blood was used. In a study by Eisele [32], the relationship between peripheral blood Aβ42 and central nervous system Aβ42 maintained a dynamic balance. Increased Aβ protein in peripheral blood may cause the intracranial Aβ protein content to increase through the blood–brain barrier (BBB) [33, 34]. Moreover, an increase in peripheral Aβ could also hinder the central Aβ clearance pathway [35]. In this experiment, we also found that there is a synergistic effect among the four proteins, which jointly act on the cognitive function and sleep of patients. In the clinic, the accuracy rate of diagnosis of AD by Aβ42 and Aβ40 could reach 80–90%, and the sensitivity and specificity of pre-clinical AD diagnosis by combining p-tau and t-tau could reach 83% and 72%, respectively [36, 37].

Some studies have confirmed that the risk factors for OSAHS include BMI, AHI, LSaO2, ESS score, etc., but AD biomarkers have not yet been used as risk factors [38]. In this study, Aβ42, Aβ40, t-tau, p-tau were included in the risk factors for regression analysis. It was found that the tau proteins can be used as an independent factor for OSAHS, indicating an interaction between sleep disorder and AD protein deposition. A few studies have shown that AD biomarkers can be used as risk factors for Alzheimer's disease with OSAHS [39]. BMI is also an independent risk factor for OSAHS, which may also affect biomarkers of AD [13, 40]. A study involving 1423 subjects showed that obesity was related to male cognitive impairment [41]. Another Swedish 18-year follow-up study of 392 elderly participants showed that obese elderly women had an increased risk of developing dementia or AD when compared with persons of normal weight. For every 1.0 increase in BMI in subjects over 70 years of age, the risk of developing AD increases by 36% [42]. Other studies have shown that the cognitive function of obese children and adolescents is lower than that of persons of normal weight [43]. A study by Leila in 2016 found an increase in plasma AD biomarker proteins of obese children with OSAHS, suggesting that OSAHS may accelerate the pathological progress of AD in childhood [44]. Sleep architecture abnormalities and intermittent hypoxia may damage the function of the BBB in OSAHS patients and obesity may aggravate the BBB damage process. Thus, a higher Aβ concentration may be detected in the plasma of obese OSAHS children than in the plasma of OSAHS children of normal weight [45].

## Study limitations

First, the sample size was small and only included patients with severe OSAHS who required surgery. As a result, we cannot verify whether the plasma levels of Aβ42, Aβ40,

t-tau, and p-tau increase gradually with increasing OSAHS severity. Second, because sleep disorders are associated with AD biomarkers, the AD biomarkers in plasma of OSAHS patients without sleepiness may not be high. Therefore, to improve the research design, we should further compare OSAHS patients without sleepiness to those with sleepiness and a control group.

## Conclusion

The AD biomarkers (Aβ40, t-tau, p-tau) in the OSAHS group were significantly higher than those in the control group. Sleep disorder and hypoxia at night may lead to an increase of AD biomarker content in plasma, thus causing a decrease in cognitive function and an increase in daytime sleepiness. T-tau and p-tau could also be used as risk factors for OSAHS, which may indicate the interaction between sleep disorder and AD biomarkers. Weight control is still an important measure to control OSAHS, considering its correlation to BMI.

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**Author contributions** WK: design of the research, collection of data, writing up of article; HG and JW: collection of experiment data; YZ and WX: analysis of experiment data, revising the article. All authors read and approved the final manuscript.

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### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical permissions** All participants gave their informed consent including for the use of ELISA data. The West China Hospital Ethics Review Committees approved the study protocols. Approval number is 2019(485).

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