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Original Research

The Interaction of Severe Obstructive Sleep Apnea Hypopnea Syndrome and Abdominal Obesity on Cognitive Function

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Abstract

Background: Both obstructive sleep apnea-hypopnea syndrome (OSAHS) and obesity are related to cognitive deficits, but the interaction effects of OSAHS and abdominal obesity on cognitive function are unclear. Thus, we performed this study to investigate this issue. **Methods**: We recruited subjects who received polysomnography test, anthropometric measurements and cognitive function assessment and/or blood protein test. Correlations between apnea-hypopnea index (AHI) and cognitive function were assessed. Analysis of covariance was used to compare the differences in cognitive function between groups and detect the interactions of OSAHS and obesity on cognitive function. Multiple linear regression models were used to determine the associations between OSAHS and cognitive function. **Results**: In total, 196 subjects with Montreal Cognitive Assessment (MoCA), 161 subjects with Symbol Digit Modalities Test (SDMT) and Trail making test, and 44 subjects with blood protein test were enrolled. Significant negative correlations between AHI and visuospatial and executive, language, delayed recall and total score of MoCA were observed. After adjusting for multiple confounding factors, subjects with severe OSAHS had significant lower delayed recall score and total score of MoCA, SDMT index, and Aβ40 protein level than those with non-severe OSAHS group. Severe OSAHS was independently negatively associated with delayed recall score and total score of MoCA, SDMT index, and Aβ40 protein level. An interactive effect of severe OSAHS and abdominal obesity on language score of MoCA was found. **Conclusions**: Severe OSAHS increased the risk of cognitive deficits. Interaction effect of severe OSAHS and abdominal obesity on language was seen.

Keywords: obstructive sleep apnea-hypopnea syndrome; abdominal obesity; cognitive function; interactive effects

1. Introduction

Obstructive sleep apnea-hypopnea syndrome (OSAHS) is a highly prevalent disease. It is been reported that approximately 25% of men and 13% of women worldwide suffer from OSAHS [1]. Recent evidence showed an significant positive association between OSAHS and cognitive deficits [2]. Compared with patients without OSAHS, those with OSAHS exhibited significant impaired cognitive function, including impaired vigilance and executive function, declined memory and motor coordination deficits, and the degree of cognitive deficits elevated with the severity of OSAHS [3]. A recent meta-analysis showed that the risk of cognitive deficits in patients with OSAHS increased by 26% [4]. The cognitive deficits associated with OSAHS affect the quality of life of patients and lead to frequent occurrence of malignant accidents at work and traffic, which severely damage national health [3]. Thus, more attention should be attached to cognitive deficits in patients with OSAHS.

Although a robust association between OSAHS and cognitive deficits is established by previous studies, Kilpinen *et al.* [5] pointed out that future studies were needed to further clarify the joint effects of OSAHS and other comorbidities including obesity on cognitive function. Obesity often coexists with OSAHS. Obesity can not only increase the risk of OSAHS, but also have a negative impact on cognitive function [6]. Studies have shown that obesity itself can lead to cognitive dysfunction [7,8]. A variety of obesity indexes, including body mass index (BMI), Waist to hip ratio (WHR) and waist circumference (WC) have been shown to hold a negative impact on learning, memory and language ability [9]. Meanwhile, in children and adolescents, obesity and OSAHS have been shown to exert a synergistic effect on cognitive deficits [10–12]. However, the joint effects of OSAHS and obesity on cognitive function in adults are unclear.

A study found that in young people, compared with mild OSAHS and the control group, moderate to severe OSAHS is associated with increased total tau levels [13]. Another study found that in the middle-aged, the blood Aβ40, Aβ42, and phosphorylated tau levels of OSAHS subjects were significantly higher than those of the control group [14]. These studies all suggest a potential link between OSAHS and Aβ40, Aβ42 and tau protein levels.

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Thus, we performed this cross-sectional study to further verify the relationships between OSAHS and cognitive function, as well as the interactions of OSAHS and obesity on cognitive function. Except for that, we also explored the relationships between OSAHS and cognitive-related protein to provide more evidence.

2. Methods

2.1 Participants

The subjects were the patients admitted to the First Affiliated Hospital of Nanchang University and underwent polysomnography (PSG) between February 2019 and September 2020 due to snoring symptoms. All subjects received a questionnaire survey of basic information and past medical history before PSG. After completing these survey, the Epworth Sleepiness Scale (ESS) [15] was used to assess subjective sleepiness. This study was approved by the ethics committee of the First Affiliated Hospital of Nanchang University and was carried out following the Declaration of Helsinki. Subjects were informed of the general content of the study before taking the test, followed the principle of voluntariness, and signed the informed consent.

Inclusion criteria: (1) aged no less than 18 years old; (2) education years: no less than 5 years; (3) never underwent related surgery, ventilator, or related treatment (including various types of weight-loss measures, OSAHS treatment surgery, continuous positive airway pressure, etc.). Exclusion criteria: (1) serious systemic diseases (including heart failure, severe cerebral infarction, myocardial infarction, etc.); (2) a history of Mental or neurological diseases, or a history of psychotropic drug dependence; (3) taking drugs that affect nerve function or drinking alcoholic beverages within 24 hours before receiving relevant examinations; (4) a history of other sleep-related diseases; (5) unable to cooperate with the research due to various reasons; (6) missing or incomplete data.

2.2 Anthropometric Measurements

Height, weight, neck circumference (NC), WC, hip circumference (HC), and BMI are measured and assigned readings by the same professional researchers using the same measuring equipment (tape measure, automatic height and weight instrument), based on the WHO standard method. The criteria for determining abdominal obesity of Chinese adults: male WC $\geq$90 cm, female WC $\geq$85 cm [16].

2.3 PSG Test

Subjects are not allowed to drink tea, alcohol, or coffee within 24 hours before monitoring and must not have a history of taking sedatives and hypnotic drugs shortly. All subjects used a PSG based on a non-interference single laboratory to monitor and scored respiratory events. Simultaneously recorded electroencephalogrphy, electromyogram, electrooculogram, electrocardiogram, nasal cavity and oral airflow, Chest and abdominal cavity respiratory activity, snoring, pulse oximetry, and other data. All tests started before 10:00 at night and ended after 6:00 AM the next day.

After the monitoring, the professional and technical personnel will interpret and review according to the American Academy of Sleep Medicine (AASM) criteria and related event interpretation standards [17]. The apnea-hypopnea index (AHI) refers to the average number of apneas and hypopneas per hour during sleep [17,18]. Lowest oxygen saturation (LSpO2) refers to the lowest value of blood oxygen during sleep, in % [17,18]. Oxygen-desaturation index (ODI) refers to the number of times that blood oxygen drops by 4% or more from baseline per hour during sleep [17,18]. According to the standards established by the AASM, AHI $<$5 is defined as no OSAHS, AHI 5–15 is defined as mild OSAHS, AHI 15–30 is defined as moderate OSAHS, and AHI $\geq$30 is defined as severe OSAHS [17,18].

2.4 Cognitive Function Assessment

All MoCA scale evaluations are conducted under the same standard guidance by the professionally trained personnel. After completing the evaluation, the professional analyzed each field's scores and total scores according to the same standards.

(1) Chinese-Beijing Version of Montreal Cognitive Assessment (MoCA) [19]: MoCA is used to initially and quickly detect the overall cognitive level of patients, including 8 items, namely visuo-spatial and executive, naming, attention, language, abstraction, delayed recall, orientation and total score.

(2) Symbol Digit Modalities Test (SDMT) [20]: SDMT is a scale used to assess attention and processing speed. The subjects were asked to fill in the symbols corresponding to the numbers in the form within 90 seconds. The number of correctly completed within 90 seconds (correct number) is recorded as an analysis indicator.

(3) Trail making test-Part A (TMT) [21]: TMT is also a scale used to assess attention and processing speed. Record the time (in seconds) spent to complete all connections, the number of errors, and the number of pen strokes. The shorter the time, the better the performance.

2.5 Blood Collection, Processing, and Protein Level Determination

After receiving the PSG monitoring, we draw 5 mL of fasting blood from the subjects participating in the blood test. Use a centrifuge to separate the serum within 60 minutes at 3000 rpm and 10 minutes. After separation, use a cryotube to store and immediately freeze at –80 °C until determined in batch. Radioimmunoassay (RIA) was used to detect the levels of Aβ40, Aβ42, and tau protein. All protein kits were purchased from the Beijing Huaying Institute of Biotechnology. The detection operation steps are carried out in strict accordance with the requirements of the instructions.

2.6 Statistical Analysis

Data are presented as means ± SD, medians (interquartile range), and numbers (percentage) if they were normally distributed, skewed, or categorical, respectively. The correlation between the variables was confirmed by spearman correlation analysis. Differences in basic characteristic between the groups were examined by Mann-Whitney U test, *t* test, chi-square test or Fisher's exact test according to distribution. Differences in cognitive function assessments and protein levels between the groups were examined in an analysis of covariance (ANCOVA) with adjusting for multiple confounding factors. Multiple linear regression models were used to determine the influencing factors of each cognitive function assessment and protein levels. Interaction effects of OSAHS and abdominal obesity was examined with ANCOVA. SPSS 22.0 (SPSS Inc., Chicago, IL, USA) and R software version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria) were used to perform statistical analysis. A p value < 0.05 was considered to indicate statistical significance.

3. Results

In total, 196 subjects who completed (MoCA) test and 161 subjects who completed the SDMT and TMT were enrolled.

3.1 Basic Characteristics Stratified by Severe OSAHS

For subjects who completed MoCA, they were divided into subjects with severe OSAHS (n = 119) and subjects with non-severe OSAHS group (n = 77). Compared to subjects with non-severe OSAHS, those with severe OSAHS were more obese (exhibited by higher BMI, NC, WC and HC), and had significant higher ESS and more severe OSAHS (exhibited by higher AHI and ODI, and lower LSPO2) (all $p < 0.05$) (Table 1).

For subjects who completed SDMT and TMT, they were also divided into subjects with severe OSAHS (n = 98) and subjects with non-severe OSAHS group (n = 63). Compared to subjects with non-severe OSAHS, those with severe OSAHS were more obese, and had significant higher ESS, more alcohol consumption and more severe OSAHS (all $p < 0.05$) (Table 2).

For subjects who completed Aβ40, Aβ42, and tau protein levels test, they were divided into subjects with severe OSAHS (n = 19) and subjects with non-severe OSAHS group (n = 25). Compared to subjects with non-severe OSAHS, those with severe OSAHS had more severe OSAHS and significant higher NC (all $p < 0.05$) (Table 3).

3.2 Relationships between OSAHS and Cognitive Function

To explore the relationships between severe OSAHS and cognitive functions, we first ran a correlation analysis between AHI and MoCA. Significant negative correlations between visuo-spatial and executive, language, delayed recall and total score of MoCA and AHI have been observed ($p < 0.05$, Fig. 1), while no significant correlation between AHI and SDMT index, TMT index, Aβ40 protein level, Aβ42 protein level and tau protein levels was seen ($p \geq 0.05$, Figs. 2,3).

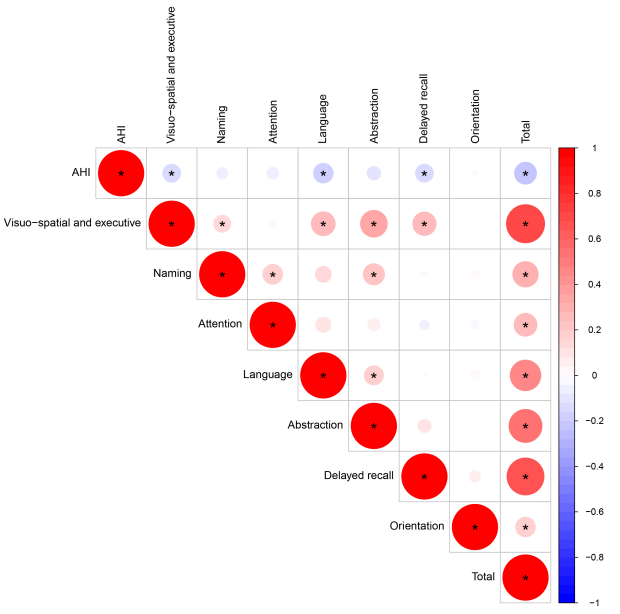

Fig. 1. The correlation between AHI and each score of the MoCA scale.

After adjusting for gender, age, years of education, ESS score, abdominal obesity, smoking and alcohol consumption, compared to subjects with non-severe OSAHS, those with severe OSAHS had significant lower delayed recall score and total score of MoCA ($p = 0.012$, and $p = 0.002$, respectively) (Table 1 and Fig. 4). And subjects with severe OSAHS also had significant lower SDMT index ($p = 0.019$) (Table 2 and Fig. 5) and lower Aβ40 protein level ($p = 0.011$) (Table 3 and Fig. 6).

For those significant different cognitive function assessment between the groups including delayed recall, MoCA total score, SDMT index and Aβ40 protein, we ran multiple linear regression. After including severe OSAHS, gender, age, years of education, ESS score, abdominal obesity, smoking and alcohol consumption in the multiple linear regression, severe OSAHS was identified as an independent negative influencing factor of delayed recall (Beta = –0.178, $p = 0.012$), MoCA total score (Beta = –0.180, $p = 0.002$), SDMT index (Beta = –0.123, $p = 0.019$) and Aβ40 protein (Beta = –0.355, $p = 0.011$) (Table 4).

3.3 Interaction Effects of Severe OSAHS and Abdominal Obesity on Cognitive Function

Subjects were divided into four groups according to abdominal obesity and severe OSAHS. Strong main effects of severe OSAHS were detected on delayed recall ($F = 4.608$, $p^2 = 0.033$), total score of MoCA ($F = 10.758$, $p^2 =$

Table 1. Comparison of baseline characteristics, PSG, and MoCA score between the non-severe OSAHS and severe OSAHS groups.

Variable	Overall (n = 196)	Non-Severe OSAHS group (n = 77)	Severe OSAHS group (n = 119)	p^a	p^{1b}
BMI, Kg/m^2	26.45 (24.65, 29.02)	25.71 (23.88, 27.60)	26.81 (24.90, 29.76)	0.003	-
Age, years	41.00 (34.00, 52.00)	40.00 (32.00, 52.00)	43.00 (35.00, 52.00)	0.164	-
NC, cm	40.00 (38.00, 42.00)	38.50 (37.00, 41.00)	41.00 (39.00, 43.50)	<0.001	-
WC, cm	96.00 (90.88, 101.62)	94.00 (88.50, 97.00)	97.80 (92.25, 104.00)	<0.001	-
HC, cm	101.00 (97.00, 105.00)	100.00 (96.00, 103.50)	102.50 (98.00, 106.00)	0.025	-
ESS	10.00 (6.00, 14.00)	8.00 (4.00, 13.00)	12.00 (8.00, 15.00)	<0.001	-
Education level, years	11.00 (8.00, 15.00)	11.00 (8.00, 15.00)	11.00 (8.00, 14.00)	0.609	-
Male, N (%)	173 (88.3)	65 (84.4)	108 (90.8)	0.263	-
Abdominal Obesity, N (%)	156 (79.6)	56 (72.7)	100 (84.0)	0.082	-
Hypertension, N (%)	55 (28.1)	23 (29.9)	32 (26.9)	0.771	-
Diabetes, N (%)	7 (3.6)	3 (3.9)	4 (3.4)	1	-
Smoking, N (%)	93 (47.4)	32 (41.6)	61 (51.3)	0.237	-
Drinking, N (%)	96 (49.0)	32 (41.6)	64 (53.8)	0.127	-
PSG					
AHI	38.10 (19.42, 63.12)	12.70 (4.50, 21.30)	60.60 (44.60, 71.45)	<0.001	-
LSPO2	78.00 (65.75, 86.00)	87.00 (83.00, 90.00)	70.00 (61.00, 78.50)	<0.001	-
ODI	35.95 (14.88, 67.60)	9.80 (3.00, 18.10)	62.80 (39.00, 74.65)	<0.001	-
MoCA score					
Visuo-spatial and executive	4.00 (3.00, 5.00)	4.00 (4.00, 5.00)	4.00 (3.00, 5.00)	0.119	0.265
Naming	3.00 (3.00, 3.00)	3.00 (3.00, 3.00)	3.00 (3.00, 3.00)	0.383	0.355
Attention	6.00 (6.00, 6.00)	6.00 (6.00, 6.00)	6.00 (6.00, 6.00)	0.464	0.298
Language	2.00 (2.00, 3.00)	2.00 (2.00, 3.00)	2.00 (2.00, 2.00)	0.081	0.506
Abstraction	2.00 (1.00, 2.00)	2.00 (1.00, 2.00)	2.00 (1.00, 2.00)	0.201	0.278
Delayed recall	2.00 (1.75, 4.00)	3.00 (2.00, 4.00)	2.00 (1.00, 3.00)	0.007	0.012
Orientation	6.00 (6.00, 6.00)	6.00 (6.00, 6.00)	6.00 (6.00, 6.00)	0.844	0.965
Total score	25.00 (23.00, 27.00)	26.00 (24.00, 27.00)	25.00 (22.00, 26.00)	0.002	0.002

[a]: p: comparison of baseline characteristics, PSG indicators, and MoCA scores without adjustment. [b]: p^1: comparison of the various MoCA scores after adjusting for gender, age, years of education, ESS score, abdominal obesity, smoking and alcohol consumption. Continuous data are presented as medians (interquartile range). Abbreviations: BMI, body mass index; NC, neck circumference; HC, hip circumference; WC, waist Circumference; PSG, polysomnography; AHI, apnea-hypopnea index; LSPO2, lowest oxygen saturation; ODI, oxygen-desaturation index; MoCA, Chinese-Beijing Version of Montreal Cognitive Assessment.

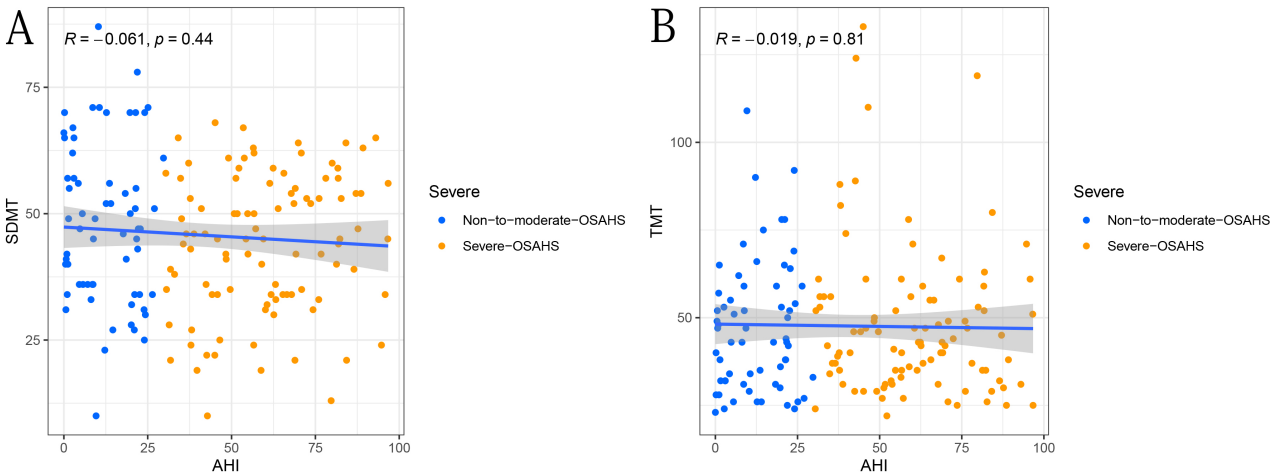

Fig. 2. The correlation between AHI and SDMT and TMT-A indexes. (A) SDMT. (B) TMT-A.

Table 2. Comparison of baseline characteristics, PSG, SDMT and TMT index between the non-severe OSAHS and severe OSAHS groups.

Variable	Overall (n = 161)	Non-Severe OSAHS group (n = 63)	Severe OSAHS group (n = 98)	p^a	p^{1b}
BMI, Kg/m^2	26.06 (24.22, 28.96)	25.31 (23.61, 27.52)	26.45 (24.78, 30.06)	0.01	-
Age, years	43.00 (34.00, 51.00)	40.00 (30.50, 51.00)	44.50 (34.25, 51.00)	0.16	-
NC, cm	40.00 (38.00, 42.00)	38.00 (37.00, 40.25)	41.00 (39.00, 43.00)	<0.001	-
WC, cm	96.00 (90.00, 101.00)	93.00 (87.50, 97.00)	96.50 (92.62, 104.00)	0.001	-
HC, cm	101.00 (96.00, 105.00)	101.00 (94.75, 104.00)	101.25 (97.25, 106.00)	0.066	-
ESS	10.00 (7.00, 14.00)	9.00 (4.00, 13.00)	11.00 (8.00, 15.00)	0.001	-
Education level, years	8.00 (8.00, 14.00)	8.00 (8.00, 14.00)	11.00 (8.00, 14.00)	0.384	-
Male, N (%)	141 (87.6)	53 (84.1)	88 (89.8)	0.412	-
Abdominal Obesity, N (%)	126 (78.3)	45 (71.4)	81 (82.7)	0.136	-
Hypertension, N (%)	31 (19.3)	11 (17.5)	20 (20.4)	0.796	-
Diabetes, N (%)	2 (1.2)	1 (1.6)	1 (1.0)	1	-
Smoking, N (%)	86 (53.4)	29 (46.0)	57 (58.2)	0.179	-
Drinking, N (%)	70 (43.5)	20 (31.7)	50 (51.0)	0.025	-
PSG					
AHI	39.70 (19.70, 63.20)	12.20 (3.65, 21.35)	59.25 (45.02, 74.12)	<0.001	-
LSPO2	78.00 (66.00, 87.00)	88.00 (83.00, 90.00)	69.00 (61.00, 76.00)	<0.001	-
ODI	37.40 (11.40, 66.00)	7.90 (2.10, 16.80)	56.10 (41.02, 79.70)	<0.001	-
Attention and processing speed					
SDMT	46.00 (34.00, 57.00)	47.00 (36.00, 59.00)	45.00 (34.00, 55.75)	0.154	0.019
TMT	43.00 (32.00, 56.00)	43.00 (32.00, 58.00)	43.00 (34.25, 55.75)	0.981	0.48

^{a}: p: comparison of baseline characteristics, PSG, SDMT, and TMT index without adjustment. ^{b}: p^1: comparison of PSG, SDMT and TMT index after adjusting for gender, age, years of education, ESS score, abdominal obesity, smoking and alcohol consumption. Continuous data are presented as medians (interquartile range). Abbreviations: BMI, body mass index; NC, neck circumference; HC, hip circumference; WC, waist Circumference; PSG, polysomnography; AHI, apnea-hypopnea index; LSPO2, lowest oxygen saturation; ODI, oxygen-desaturation index; SDMT, Symbol Digit Modalities Test; TMT, Trail making test.

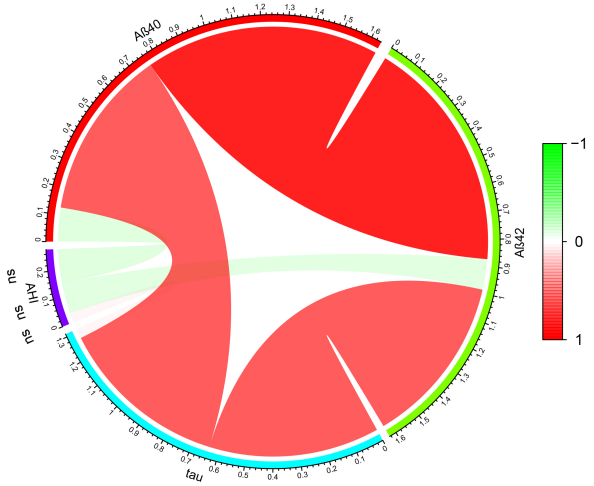

Fig. 3. The correlation between Aβ40, Aβ42 and tau protein, and AHI. The legend on the right of the circle graph shows the correlation coefficients corresponding to different colors. Above the circle: ns: no significance.

0.001), and SDMT index (F = 5.950, p^2 = 0.016) after adjusting for gender, age, years of education, ESS, smoking, and alcohol consumption (Tables 5,6). Strong main effects of abdominal obesity were detected on visuo-spatial and executive (F = 7.095, p^2 = 0.008), and language (F = 8.961, p^2 = 0.003) (Tables 5,6).

An interaction of severe OSAHS and abdominal obesity was found for language (F = 6.252, p^3 = 0.013) (Table 5 and Fig. 7). In a simple effect analysis of further interactions, it was found that at the non-abdominal obesity category, severe OSAHS had a significant effect on language scores (p = 0.005). At abdominal obesity category, severe OSAHS had no significant impact on language scores (p = 0.944). At the non-severe OSAHS category, abdominal obesity had a significant impact on language scores (p < 0.001). At the severe OSAHS category, abdominal obesity had no significant impact on language scores (p = 0.492).

4. Discussion

In this study, we found that significant negative correlations between AHI and visuo-spatial and executive, language, delayed recall and total score of MoCA. Subjects with severe OSAHS had significant lower delayed recall score and total score of MoCA, SDMT index, and Aβ40 protein level than those with non-severe OSAHS group after adjusting for multiple confounding factors. Severe OSAHS was an independent negative influencing factor of de-

Table 3. Comparison of baseline characteristics, PSG, Aβ40, Aβ42 and tau protein between the non-severe OSAHS and severe OSAHS groups.

Variable	Overall (n = 44)	Non-Severe OSAHS group (n = 25)	Severe OSAHS group (n = 19)	p^a	p^{1b}
BMI, Kg/m^2	27.39 (24.47, 30.57)	25.95 (23.71, 29.41)	27.74 (26.06, 31.12)	0.09	-
Age, years	42.50 (32.25, 52.25)	46.00 (38.00, 57.00)	36.00 (30.50, 51.00)	0.148	-
NC, cm	39.75 (36.88, 42.12)	38.00 (35.00, 40.00)	41.00 (39.50, 43.50)	0.004	-
WC, cm	94.50 (87.75, 101.00)	92.00 (87.00, 96.00)	100.00 (93.00, 104.50)	0.063	-
HC, cm	102.00 (94.38, 107.00)	99.00 (92.00, 106.00)	104.00 (99.50, 108.50)	0.061	-
ESS	11.00 (7.75, 13.25)	12.00 (7.00, 13.00)	9.00 (8.00, 14.00)	0.695	-
Education level, years	8.00 (8.00, 11.00)	8.00 (5.00, 11.00)	11.00 (8.00, 11.50)	0.066	-
Male, N (%)	33 (75.0)	16 (64.0)	17 (89.5)	0.114	-
Abdominal Obesity, N (%)	32 (72.7)	17 (68.0)	15 (78.9)	0.641	-
Hypertension, N (%)	7 (15.9)	3 (12.0)	4 (21.1)	0.691	-
Diabetes, N (%)	0 (0.0)	0 (0.0)	0 (0.0)	1	-
Smoking, N (%)	20 (45.5)	11 (44.0)	9 (47.4)	-	-
Drinking, N (%)	18 (40.9)	12 (48.0)	6 (31.6)	0.431	-
PSG					
AHI	21.05 (4.50, 53.08)	5.80 (1.60, 17.00)	58.80 (48.55, 73.75)	<0.001	-
LSPO2	83.50 (65.00, 87.50)	87.00 (86.00, 90.00)	61.00 (55.00, 71.00)	<0.001	-
ODI	20.55 (4.38, 56.60)	4.60 (0.80, 12.40)	65.30 (43.80, 82.00)	<0.001	-
Attention and processing speed					
Aβ40	242.39 (159.80, 334.49)	278.22 (151.54, 339.04)	215.48 (164.53, 293.94)	0.32	0.011
Aβ42	185.93 (125.02, 243.24)	189.51 (126.22, 241.82)	169.17 (116.00, 228.21)	0.53	0.176
tau	27.78 (16.21, 42.73)	30.50 (16.31, 41.40)	27.64 (16.41, 45.79)	0.972	0.547

[a]: p: comparison of baseline characteristics, PSG, Aβ40, Aβ42, and tau protein levels without adjustment. [b]: p^1: comparison of protein levels after adjusting for gender, age, years of education, ESS score, abdominal obesity, smoking and alcohol consumption. Continuous data are presented as medians (interquartile range). Abbreviations: BMI, body mass index; NC, neck circumference; HC, hip circumference; WC, waist Circumference; PSG, polysomnography; AHI, apnea-hypopnea index; LSPO2, lowest oxygen saturation; ODI, oxygen-desaturation index.

Table 4. Identification of Influencing factors of delayed recall, MoCA total score, SDMT, and Aβ40 levels.

		Severe OSAHS	Abdominal obesity	Gender	Age	ESS	Smoking	Alcohol intake	Education
Delayed recall	Beta	–0.178	0.101	0.012	–0.209	0.038	–0.117	–0.019	0.247
	p	0.012	0.136	0.869	0.003	0.592	0.137	0.804	0.001
MoCA total score	Beta	–0.180	–0.050	–0.073	–0.261	–0.044	–0.047	–0.040	0.454
	p	0.002	0.374	0.225	<0.001	0.462	0.471	0.537	<0.001
SDMT	Beta	–0.123	0.012	0.025	–0.574	0.064	–0.013	0.012	0.397
	p	0.019	0.808	0.634	<0.001	0.217	0.828	0.839	<0.001
Aβ40	Beta	–0.355	0.481	–0.316	0.149	–0.149	0.343	–0.430	–0.074
	p	0.011	0.001	0.060	0.294	0.279	0.058	0.013	0.621

MoCA, Montreal Cognitive Assessment; SDMT, Symbol Digit Modalities Test; OSAHS, Obstructive sleep apnea-hypopnea syndrome; ESS, Epworth Sleepiness Scale.

layed recall score and total score of MoCA, SDMT index, and Aβ40 protein level. And an interactive effect of severe OSAHS and abdominal obesity on language score of MoCA was found.

We have found that severe OSAHS increased the risk of cognitive deficits, evidenced by lower cognitive function assessments in subject with severe OSAHS and negative associations between severe OSAHS and cognitive function assessments, which are consistent with previous results. Systematic meta-analysis generally suggests that OSAHS can cause delayed long-term visual and language memory, impaired attention/alertness, declined visuospatial/structural ability and executive function deficits [22]. It is generally believed that language ability and psychomotor function are not affected by OSAHS, when OSAHS has ambiguous effects on working memory, short-term memory and overall cognitive function [22]. Not only that, the correlation of OSAHS with cognitive functioning (attention,

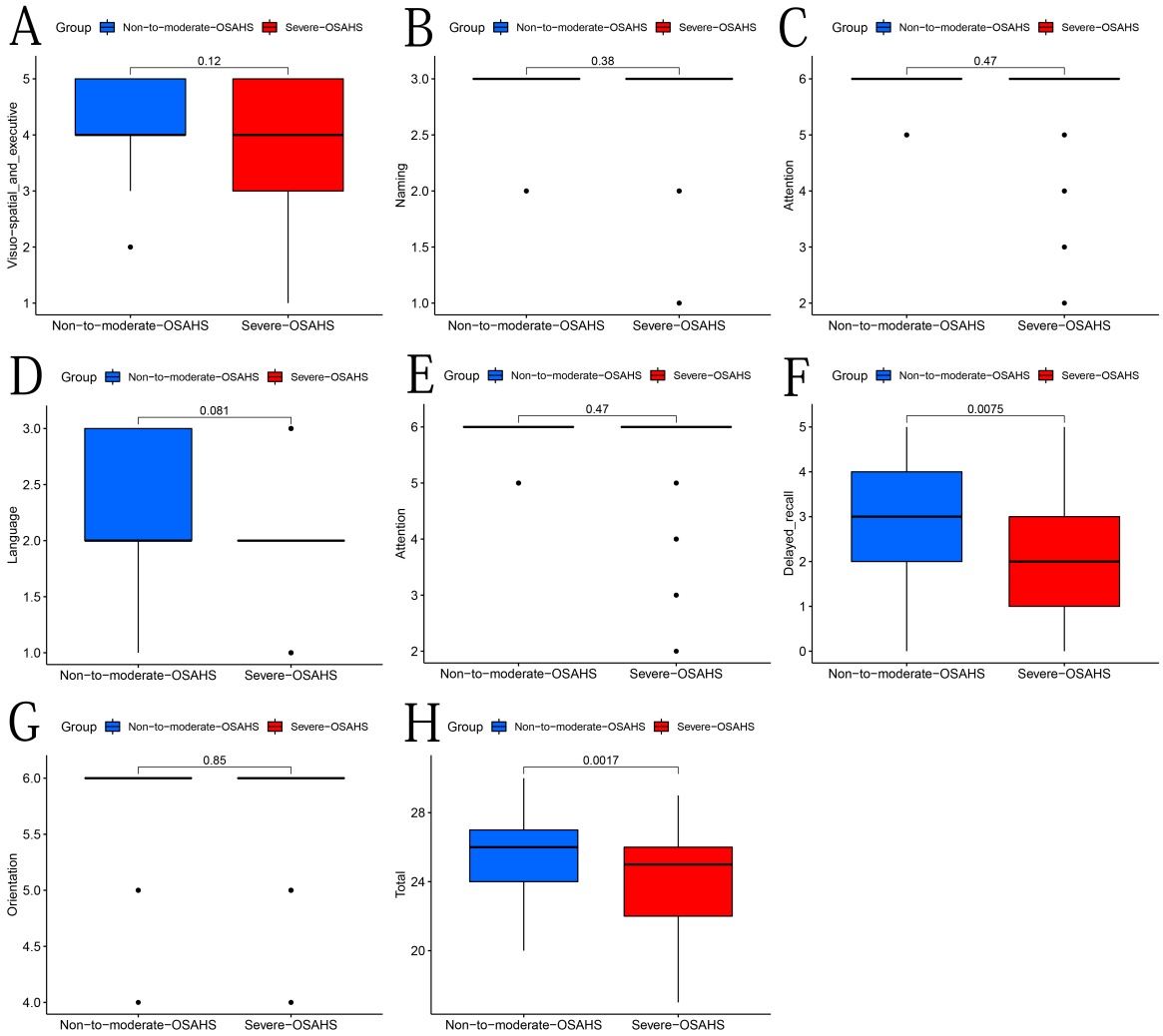

Fig. 4. Differences in each score of MoCA scale between severe OSAHS and non-severe OSAHS groups (That is non-to-moderate OSAHS in the figure). (A) Visuo-spatial and executive. (B) Naming. (C) Attention. (D) Language. (E) Abstraction. (F) Delayed recall. (G) Orientation. (H) Total score.

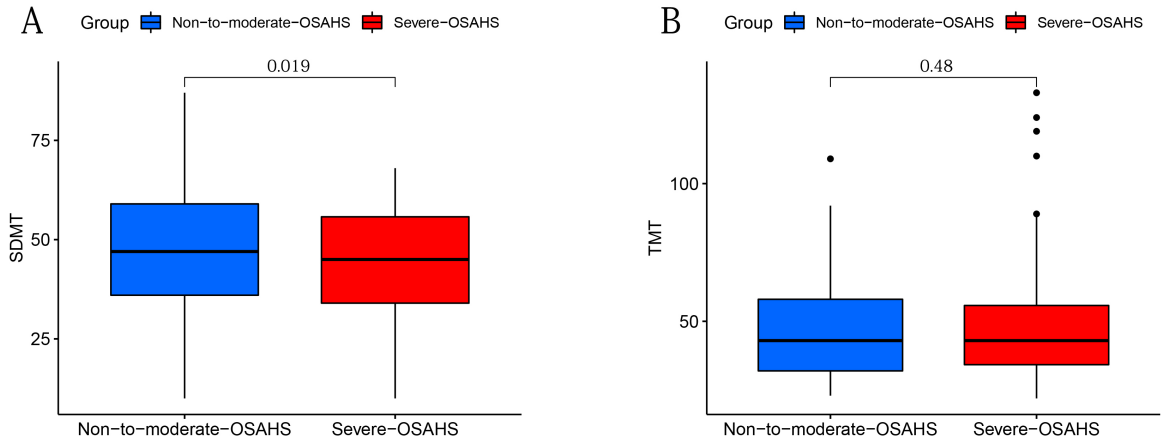

Fig. 5. Differences in them between severe OSAHS group and non-severe OSAHS group (That is non-to-moderate OSAHS in the figure). (A) SDMT. (B) TMT-A.

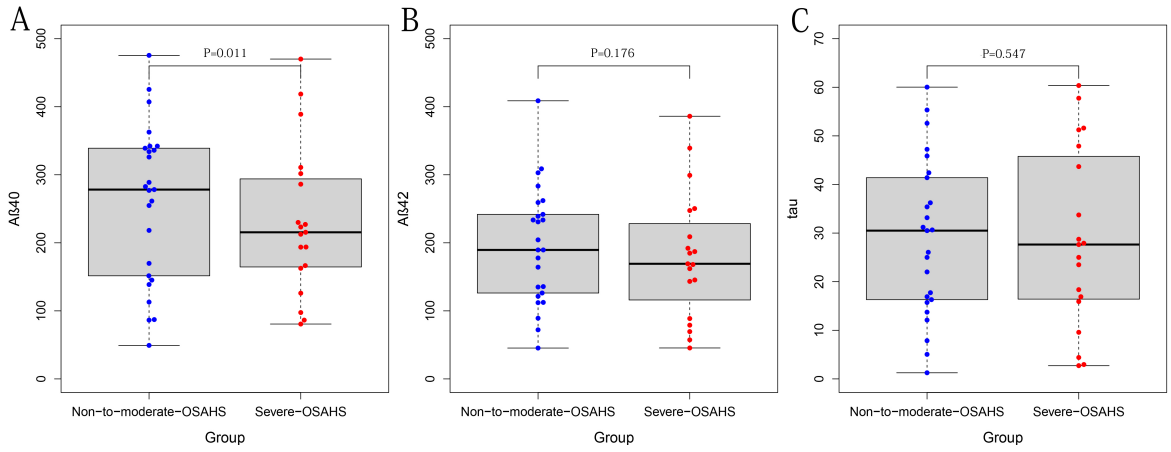

Fig. 6. Differences in Aβ40, Aβ42 and tau protein between severe OSAHS and non-severe OSAHS groups (That is non-to-moderate OSAHS in the figure). (A) Aβ40. (B) Aβ42. (C) tau.

Table 5. Analysis of the interaction effect of severe OSAHS and abdominal obesity on MoCA.

	Non-abdominal obesity		Abdominal obesity		p^{1a}	Main effect, p^{2b}		Interaction, p^{3c}
	Non-Severe OSAHS	Severe OSAHS	Non-Severe OSAHS	Severe OSAHS		Abdominal obesity	Severe OSAHS	
	(n = 21)	(n = 19)	(n = 56)	(n = 100)				
Visuo-spatial and executive	4.62 ± 0.59	4.26 ± 0.73	3.93 ± 0.93	3.80 ± 1.06	0.003	0.008	0.264	0.741
Naming	2.95 ± 0.22	2.84 ± 0.38	2.95 ± 0.23	2.91 ± 0.35	0.588	0.329	0.297	0.624
Attention	6.00 ± 0.00	5.74 ± 0.81	5.93 ± 0.26	5.85 ± 0.61	0.342	0.715	0.166	0.342
Language	2.71 ± 0.46	2.11 ± 0.74	1.98 ± 0.73	1.99 ± 0.66	<0.001	0.003	0.060	0.013
Abstraction	1.76 ± 0.54	1.47 ± 0.51	1.55 ± 0.66	1.46 ± 0.78	0.335	0.937	0.231	0.596
Delayed recall	2.81 ± 1.40	2.11 ± 1.37	2.91 ± 1.33	2.35 ± 1.48	0.046	0.138	0.033	0.998
Orientation	5.86 ± 0.36	5.95 ± 0.23	5.88 ± 0.38	5.84 ± 0.42	0.730	0.684	0.567	0.311
Total MoCA score	26.71 ± 1.93	24.47 ± 2.27	25.12 ± 2.41	24.20 ± 2.77	<0.001	0.358	0.001	0.216

[a]: p^1: the overall comparison p-value. [b]: p^2: p-value after adjusting for the factors of gender, age, years of education, ESS, smoking, and alcohol consumption. [c]: p^3: p value of the interaction analysis of the effects of severe OSAHS and abdominal obesity on each MoCA score. Continuous data are presented as means ± SD.

Table 6. Analysis of the interaction effect of severe OSAHS and abdominal obesity on SDMT and TMT index.

	Non-abdominal obesity		Abdominal obesity		p^{1a}	Main effect, p^{2b}		Interaction, p^{3c}
	Non-severe OSAHS	Severe OSAHS	Non-severe OSAHS	Severe OSAHS		Abdominal obesity	Severe OSAHS	
	(n = 18)	(n = 17)	(n = 45)	(n = 81)				
SDMT	52.00 ± 13.16	44.71 ± 11.18	46.87 ± 16.74	43.95 ± 14.41	0.190	0.837	0.016	0.446
TMT	41.17 ± 13.38	43.41 ± 13.66	49.42 ± 20.17	48.94 ± 22.57	0.358	0.469	0.543	0.998

[a]: p^1: the overall comparison p-value. [b]: p^2: p-value after adjusting for the factors of gender, age, years of education, ESS, smoking, and alcohol consumption. [c]: p^3: p value of the interaction analysis of the effects of severe OSAHS and abdominal obesity on SDMT and TMT indexes. Continuous data are presented as means ± SD.

memory, thinking, speech) observed in Berdina *et al*. [23]'s study also supports our results.

At present, it is mainly believed that OSAHS especially impaired cognitive function through intermittent hypoxia and disrupted sleep architecture. Long-term intermittent hypoxia can cause cerebral vasoconstriction and changes in cerebral hemodynamics, which slows down the blood flow rate, further making the brain in a state of low perfusion for a long time, and ultimately aggravating neuronal hypoxia [24]. The cerebral cortex, hippocampus, and cerebellum are particularly sensitive to hypoxia and easy to be damaged to cause cognitive deficits [25]. Meanwhile, the inflammatory response and oxidative stress response triggered by intermittent hypoxia [26,27] will also lead to cognitive deficits, showing short-term decreased attention and vigilance, long-term memory, and decreased executive function [27]. Besides, sleep structure disturbances, manifesting as sleep fragmentation and total sleep time reduction caused by repeated arousals, prolonged light sleep, and shortened deep sleep, are also be shown to aggravate cog-

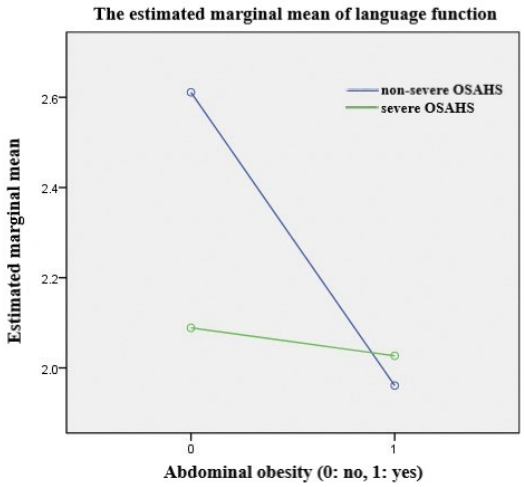

Fig. 7. Interaction plot between severe OSA and abdominal obesity on language function.

nitive deficits [28]. Sleep fragmentation damages the fine structures of the brain and destroy the integrity of axons extensively [29]. Long-term lack of sleep causes permanent neuronal degeneration, especially in memory-related brain regions such as the hippocampus, reduces the activation of the frontal and parietal networks and changes the internal functions of the thalamus [30].

Previous studies have found that the lack of sleep, disturbed sleep and intermittent hypoxia of OSAHS elevated the level of Aβ and tau protein in brain by increasing the production and decreasing the clearance rate of them, which caused the deposition of Aβ and tau protein in brain, forming amyloid plaques and neurofibrillary tangles, leading to neurodegeneration and cognitive deficits [31–34]. Thus, Aβ and tau protein play an important role in the OSAHS-related cognitive deficits. Thus, we also explored the relationships between these protein level and OSAHS to add more evidence. We found that Aβ40 protein levels of subjects with severe OSAHS group were significantly lower than those with non-severe OSAHS, and severe OSAHS was an independent negative influencing factor of Aβ40 protein level, which was inconsistent with previous study [14]. However, our results are consistent with those of Madaeva *et al*. [35]. Different levels of Aβ42 in the blood at different stages of the disease might explain the divergent results. At early stage, OSAHS induces increased production and decreased clearance of Aβ, resulting in an increase in its level [33]. Later, as the condition of OSAHS worsen, cognitive function further declines and the consumption of a large amount of Aβ to form the amyloid plaques occurs, which leads to a decrease of its level.

Obesity has been identified as a risk factor for OSAHS [36,37]. Weight gain reduces the size of the upper respiratory tract, thereby increasing the incidence of apnea events [38]. And the physiological component of obesity, including blood sugar control, insulin action, and leptin signaling, cause a greater reduction in the muscle tone of the pharyngeal dilator and increase the chance of obstruction during sleep [36]. Meanwhile, obesity is shown to have a negative impact on cognitive function [6–9]. In our study, we also found that abdominal obesity had strong main effects on visuo-spatial and executive ability and language ability (Table 5).

Although numerous studies have confirmed the negative effects of obesity and OSAHS on cognitive function alone, the joint effect of the two on cognitive function is still unclear. Thus, we tried to explore the interaction of abdominal obesity and severe OSAHS on cognitive function. After adjusting for confounding factors, the interaction of severe OSAHS and abdominal obesity on language score of MoCA was found. In a further simple effect analysis, in non-abdominal obesity and non-severe OSAHS levels, severe OSAHS and abdominal obesity had a significant negative impact on language scores. On the levels of abdominal obesity and severe OSAHS, respectively, severe OSAHS and abdominal obesity had no significant effect on language scores. This result suggests that severe OSAHS and abdominal obesity may have an antagonistic impact on language function, which is confusing and need to be further studied.

There are some limitations in this research. First of all, the cognitive domains evaluated in this study are limited, including only the metrics that cover cognitive domains and individual attention and information processing speed in MoCA. Secondly, although this study has a larger sample size than many previous single-center studies, it still failed to get more positive results, suggesting that such studies require larger sample size data to support. Therefore, the results of this study still need to be confirmed in large samples and in other populations in the future. Third, although we have adjusted some factors that may affect cognitive function, we cannot adjust the interference of other confounding factors that cannot be measured, such as APOE4 genotype and tester's skill level. Fourth, we have not been able to find a suitable mechanism to explain the interaction of abdominal obesity and severe OSAHS on language ability. Despite this, the sleep data and the relatively large sample size increased the credibility of our results.

5. Conclusions

We found that OSAHS increased the risk of cognitive deficits. And interaction effect of severe OSAHS and abdominal obesity was detected on language. More large-sample-size studies are required to further clarify the interaction of OSAHS and comorbidities on cognitive deficits.

Author Contributions

ZYZ and YYX designed the research; XF prepared the figures and drafted the manuscript; YYX, YPX and XF analyzed the data; XF contributed analytic tools and finalized

the manuscript; XF, YZ, LLZ and JQL participated in the writing of the manuscript. All authors have read and approved the final manuscript.

Ethics Approval and Consent to Participate

This study was approved by the ethics committee of the First Affiliated Hospital of Nanchang University (Approval No. 2019- 051) and was carried out following the Declaration of Helsinki. Subjects were informed of the general content of the study before taking the test.

Acknowledgment

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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