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Research article

Association of obstructive sleep apnea with cognitive decline and age among non-demented older adults

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ABSTRACT

We aimed to investigate whether obstructive sleep apnea (OSA) status affects the relationship between cognitive decline and age among non-demented elderly people. A total of 1422 participants (493 normal cognition and 929 amnestic mild cognitive impairment) were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort. Based on the self-reported medical history of OSA, participants were categorized into two groups (OSA- and OSA +). Multiple linear regression models were performed to assess the effect of the OSA * Age interaction on MMSE, ADAS-cog11 and RAVLT immediate recall in non-demented group and in APOE ε4 carriers/non-carriers adjusting for gender and educational attainment. In the present study, the OSA + group demonstrated significant cognitive decline versus the OSA- group. In addition, in APOE ε4- group, our findings showed a significant OSA * age interaction for ADAS-cog11 and RVALT immediate recall, but not MMSE. No significant interaction was observed in the APOE ε4+ individuals. In conclusion, our findings implicate that OSA status may affect the association of age with cognitive impairment among non-demented older people.

1. Introduction

Obstructive sleep apnea (OSA) is recognized as the most common type of sleep apnea among older adults, and it affects at least 20 % of people who are older than 65 [1,2]. The OSA is associated with various of factors including age, gender and body mass index (BMI) [3]. Clinically, OSA is a risk for many clinical consequences, including systemic hypertension [4], cardiovascular disease [5], stroke, and abnormal glucose metabolism [6]. Chronic intermittent hypoxia and sleep fragmentation were suggested to be the possible mechanistic links between OSA and Alzheimer's disease (AD) [7–11]. Another study had demonstrated that OSA was associated with global cognitive decline at early age [12,13]. In addition, compared to the control group, the OSA group was showed a lower MMSE score at baseline in a cohort study [13]. Indeed, compared to healthy controls, individuals with OSA are impaired on verbal episodic memory and visuo-spatial episodic memory [14], but not visual memory [15]. Moreover, an association was found between OSA and early AD clinical and neuropathological biomarkers changes [16]. A longitudinal study showed that subjects with OSA experienced a faster increase in brain amyloid deposition and tau aggregates [17].

Aging is recognized as population characteristics of western societies, and it is assessed that over 20 % of the population will be over 65 years old by 2050 [18,19]. Age is a critical risk factor of cognitive decline, and results in increasing impact in terms of years of disability and high healthcare costs in many countries [20,21]. A study showed that age is associated with greater cognitive deficits, in which middle-aged individuals with severe OSA are more likely to have cognitive impairment than younger people with the same severity of OSA [22].

However, it is unknown whether the OSA has negative effects on cognitive decline would vary by age in non-demented subjects. Our

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[2] Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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primary aim was to identify whether OSA modulates the relationship between age and cognitive performance in subjects with NC and MCI from Alzheimer's disease neuroimaging initiative (ADNI) dataset. The secondary goal was to examine the disadvantages of OSA by age interaction for memory and cognition across the APOE ε4 carriers and non-carriers in this group.

2. Methods

2.1. Data source and participants

Cross-sectional data used in this study were extracted from ADNI (Alzheimer's Disease Neuroimaging) database in November 2019. ADNI is a longitudinal, multisite cohort study that began in 2004. ADNI recruited healthy older people, early or late MCI and early AD. The procedures of recruitment and eligibility criteria can be found at www.adniinfo.org.

Non-demented participants (NC and MCI) were included in this study. Briefly, an aMCI diagnosis in ADNI required an the mini-mental state examination (MMSE) score between 24 and 30, the Clinical Dementia Rating (CDR) of 0.5, a subjective memory complaint, and objective memory loss as measured by education-adjusted scores on the Wechsler Memory Scale Logical Memory II Delayed Recall, but without significant impairment in non-memory cognitive domains or functional impairment. The NC group had an MMSE score between 24 and 30, CDR of 0.

A total of 1437 participants had concurrent diagnostic, medical history, RAVLT immediate recall and APOE 4 from baseline as required for this study. Among the 1437 participants, 15 individuals had been excluded, including 12 individuals missing age value, 1 individual missing ADAS11, 10 individuals missing FAQ, and 2 individuals missing Rey Auditory Verbal Learning Test (RAVLT) immediate recall. Our final sample included 1422 people (493 NC and 929 MCI).

2.2. Neuropsychological outcomes

The MMSE, ADAS-cog11 and Rey Auditory Verbal Learning Test (RAVLT) was applied to measure global cognitive function and verbal memory [23,24]. RAVLT is a serial word list-learning test (Immediate Recall score, range: 0–75). Our primary outcome was the Immediate Recall scores. The CDR were used to access dementia severity.

2.3. APOE ε4 genotyping

Further information about the data of APOE ε4 genotypes of this study can be found at: adni.loni.usc.edu. In this study, our sample were classified as APOE ε4 negative (APOE ε4-, without APOE ε4 allele) group and APOE ε4 positive (APOE ε4+, with at least one APOE ε4 allele) group.

2.4. Statistics

Differences between OSA-/+ in socio-demographics and clinical outcomes were measured in the non-demented group and APOE ε4 status (carriers and non-carriers) using student's *t*-test for continuous variables and chi-squared for categorical variables. The multivariable linear regression was performed to examine the independent and interactive relationship of OSA -/+ and age on globe cognition and verbal memory performance (RAVLT immediate recall scores) in non-demented subjects and APOE ε4 carriers and non-carriers. In model 1, we evaluated the independent effects of OSA -/+ and age. Then, the OSA * age interaction was added to model 2, but it was eliminated if not significant ($p > 0.05$). All analyses were adjusted for gender and education. R-3.6.1 was used to perform all statistical analyses. A p-value < 0.05 was considered to be statistically significant.

Table 1
Non-dementia sample characteristics by sleep apnea (n = 1422, mean and Std. Err.).

characteristic	OSA-, n = 1299	OSA+, n = 123	P-value
MCI, n (%)	823(63.4)	106(86.2)	<0.001[b]
Age, y	73.4(7.1)	72.3(6.8)	0.08[a]
Sex, female, n (%)	595(45.8)	34(27.6)	<0.001[b]
Education, y	16.1(2.8)	16.1(2.8)	0.8[a]
APOE ε4, positive, n (%)	549(42.3)	46(37.4)	0.3[b]
MMSE, score	28.1(1.8)	27.8(1.8)	0.06[a]
ADAS-cog11, score	8.9(4.4)	10.0(4.6)	0.01[a]
CDR-SOB, score	0.9(1.0)	1.5(1.0)	<0.001[a]
FAQ, score	2.0(3.5)	3.7(4.4)	<0.001[a]
RAVLT immediate recall	38.4(11.8)	35.6(10.6)	0.01[a]

Values are mean ± SD or %.
Abbreviations: MCImild cognitive impairment; OSAobstructive sleep apnea; APOE ε4apolipoprotein 4; MMSEMini-Mental State Examination; ADAS-Cog11Alzheimer's Disease.
Assessment Scale-Cognitive Subscale 11; CDR, clinical dementia rating; FAQ, Functional Activities Questionnaire; RAVLT, Rey Auditory Verbal Learning Test; SD, standard deviation.
[a] Two-sample *t*-test.
[b] The χ2 test.

3. Result

3.1. Demographic data in non-dementia groups

Tables 1 and 2 showed the demographic and clinical characteristics of the non-demented elders. This study comprised 1422 non-demented elderly people including 493 normal control subjects and 929 individuals with aMCI (Table 1 and 2). The mean age of the non-demented subjects was 73.3 years (SD 7.1, range 54–91) and 44 % were women. On average, the value of the MMSE, ADS-cog11, CDR-SOB, FAQ and RAVLT immediate recall in non-demented elders were 28.1 (SD 1.8, range 19–30), 9 (SD 4.5, rang 0–27.7), 1.0 (SD 1.0, range 0–5.5), 2.1 (SD 3.6, range 0–22) and 38.1 (SD 11.7, range 11–71).

In non-demented individuals, several variables differed significantly across two groups with or without OSA (Table 1). The number of individuals with OSA was 123 (37.4 % in subjects with at least one APOE ε4 allele and MCI 86.2 %), and the number of individuals without OSA was 1299 (42.3 % in subjects with at least one APOE ε4 allele and MCI 63.7 %). Overall, the OSA + group had a higher percentage of subjects with aMCI than the OSA- group ($p < 0.001$). Compared to the OSA- group, the OSA+ group showed a higher score on various of cognitive assessments such as ADS-cog11, CDR-SOB, FAQ and RAVLT immediate recall ($p < 0.01$).

A comparison of OSA-/+ samples within APOE ε4 carriers and non-carriers separately demonstrated that the OSA + samples showed lower scores of MMSE and RAVLT immediate recall ($p < 0.05$) and a higher score of ADAS-cog11 ($p = 0.02$) than the OSA+ group within APOE ε4- group (Table 2).

3.2. Linear regression results

The hypothesis that the OSA has disadvantage on verbal memory would vary by age. This was supported by the finding of a significant OSA * age interaction for RAVLT immediate recall ($p = 0.046$, Table 3 and Fig. 2) and ADAS-cog11 ($p = 0.004$, Table 3 and Fig. 3) within APOE ε4- group, but not in in MMSE ($p = 0.19$). However, among APOE ε4 carriers, there was no significant OSA * age interaction for all three cognition tests, including MMSE ($p = 0.52$, Table 3 and Fig. 1), ADAS-cog11 ($p = 0.78$, Table 3 and Fig. 3) and immediate recall of RAVLT ($p = 0.29$, Table 3 and Fig. 2).

Table 2
Sample characteristics by sleep apnea and APOE4 -/+ (mean and Std. Err.).

Characteristic	APOE ε4-, n = 827			APOE ε4+, n = 595		
	OSA-, n = 750	OSA+, n = 77	p	OSA-, n = 549	OSA+, n = 46	p
MCI, n (%)	406(54.1)	63(81.8)	<0.001[b]	417(76)	43(93.5)	0.006[b]
Age, y	74.0(7.3)	73.2(6.7)	0.4[a]	72.7(6.9)	70.6(6.9)	0.06[a]
Sex, female, n (%)	349(46.5)	19(24.7)	<0.001[b]	246(44.8)	15(32.6)	0.1[b]
Education, y	16.3(2.7)	16.1(2.8)	0.5[a]	15.9(2.8)	16.3(2.7)	0.3[a]
MMSE, score	28.4(1.6)	28.0(1.7)	0.04[a]	27.8(1.9)	27.5(1.8)	0.4[a]
ADAS-cog11, score	8.1(4.0)	9.5(4.9)	0.02[a]	10.1(4.7)	10.9(4.1)	0.2[a]
CDR-SOB, score	0.7(0.9)	1.3(1.1)	<0.001	1.2(1.0)	1.7(0.9)	0.003[a]
FAQ, score	1.4(2.9)	3.5(4.6)	<0.001[a]	2.7(4.1)	4.0(4.0)	0.04[a]
RAVLT immediate recall	40.3(11.4)	36.6(11.5)	0.008[a]	35.7(11.7)	34.7(8.9)	0.4[a]

Values are mean ± SD or %.
Abbreviations: MCI, mild cognitive impairment; OSA, obstructive sleep apnea; APOE ε4, apolipoprotein 4; MMSE, Mini-Mental State Examination; ADAS-Cog11, Alzheimer's Disease Assessment Scale-Cognitive Subscale 11; CDR, clinical dementia rating; FAQ, Functional Activities Questionnaire; RAVLT, Rey Auditory Verbal Learning Test; SD, standard deviation.
[a] Two-sample *t*-test.
[b] The $\chi 2$ test.

Table 3
Results of multivariable linear regression analyses modeling the independent and interactive effects of OSA and Age on verbal memory performance.

Sample/outcome	Multivariable linear regression models					
	Model 1: No interactions in model				Model2: Interaction in model, OSA * AGE	
	OSA (- vs. +)		AGE			
	B(SE)	p value	B(SE)	p value	B(SE)	p value
APOE4-						
MMSE	−0.33(0.19)	0.07	−0.03(0.007)	<0.001	−0.04(0.027)	0.19
Immediate recall	−2.25(1.23)	0.07	−0.37(0.05)	<0.001	−0.36(0.18)	**0.046**
ADAS-cog11	1.04(0.29)	0.03	0.04(0.019)	0.03	0.21(0.07)	**0.004**
APOE4+						
MMSE	−0.33(0.28)	0.24	−0.04(0.01)	<0.001	−0.03(0.04)	0.52
Immediate recall	−1.44(1.66)	0.38	−0.38(0.07)	<0.001	0.26(0.24)	0.29
ADAS-cog11	1.02(0.71)	0.14	0.11(0.03)	<0.001	−0.03(0.1)	0.78

Abbreviations: OSA, obstructive sleep apnea; APOE ε4, apolipoprotein 4; MMSE, Mini-Mental State Examination; SE, standard error; B, unstandardized regression coefficient.

4. Discussion

Among non-demented group, we investigated whether OSA status modifies the association between age and cognition in two different groups (APOE ε4 carriers and non-carriers). In present study, compared to the control group, we found that OSA + group showed a significantly steeper cognitive decline (as measured by ADS-cog11, CDR-SOB, FAQ and RAVLT immediate recall) relative to the OSA- group. In major study, to identify how OSA adjusts the association between cognition and age, we demonstrated that the cognitive deficit was modified by OSA status and age together. Results were driven by the OSA and age interaction in the APOE ε4- group but the effect was absent among the APOE ε4+ subjects.

Firstly, there is a significant difference in the proportion of subjects with MCI between OSA- and OSA + groups (Table 1). Consistent with the previous studies, this finding supports that there is an increased risk of developing MCI or even AD in OSA + subjects [7,25]. The reduced and fragmented slow wave sleep (SWS) and OSA-related REM disruption may be responsible for this association [26,27]. Further, compared to OSA- group, our finding demonstrated that OSA + group had worse performances on cognition. Similarly, a recent mini-review concluded that intermittent hypoxia and sleep fragmentation have been found to alter β-amyloid and T-tau protein levels, and to cause neurodegenerative changes in brain [28].

Age is an independent factor increasing cognitive decline, and it is assessed that over 20 % of the population will be over 65 years by 2050 in modern western societies [18,19]. For old adults with OSA, a decline of cognition needs to be pay more attention to old adults with OSA than those who without. A recent study showed that the diverse roles of APOE ε4 allele in cognitive abilities according to different ages [29,30]. The relationship between hippocampus size and delayed recall memory might be affected by APOE ε4 status among early AD [30]. Our study demonstrated that OSA * age interaction has an important effect on the cognitive impairment (ADAS-cog 11, p = 0.004, Fig. 3) of old subjects without APOE ε4 allele (Table 3). More specifically, the detrimental effect of OSA on cognitive performance by ageing such that this effect was most evident on globe cognition (ADAS-cog 11, p = 0.03) among APOE 4 non-carriers, but this disadvantage was weaker or even absent on memory (immediate recall, p = 0.07). No significant interaction was observed in the APOE ε4 carriers.

In the present study, there are several potential limitations. First of all, in this cross-sectional analysis, we could not measure the degrees of memory decline in OSA-/OSA + individuals. Longitudinal studies are needed to more accurately validate. Additionally, the diagnosis of OSA was based on self-report, which may cause several misclassifications. Hence, objective assessments, such as AHI4%, should be a better choice in future studies. Moreover, we extracted the subjects from a dataset online (ADNI study), which may undermine the ability to extend our study to other populations. In the future, a further study based on another population is needed to test our findings.

In APOE ε4 non-carriers, our findings demonstrated that OSA status may affect the association of age with cognitive performance among non-demented older people.

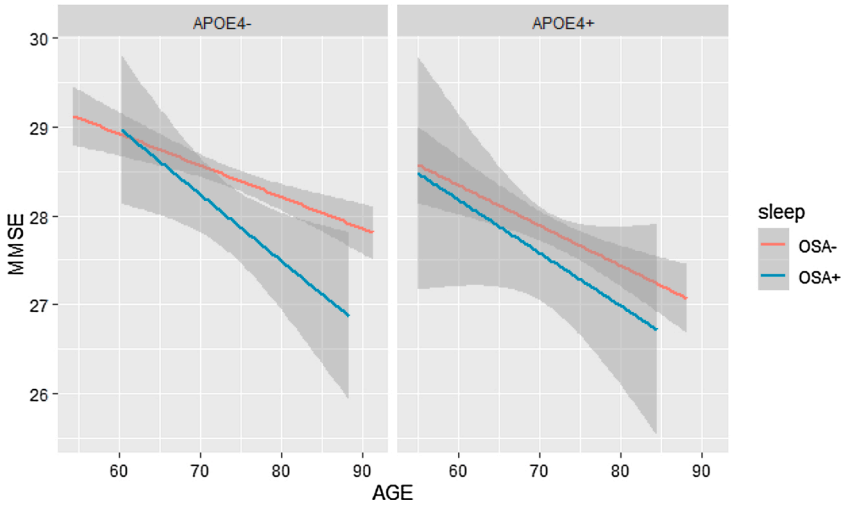

Fig. 1. Relationship between Age and Global cognition (MMSE) in OSA- and OSA + groups. MMSE as a function of Age and OSA -/+ status in APOE ε4- (left) and APOE ε4+ (right) groups.

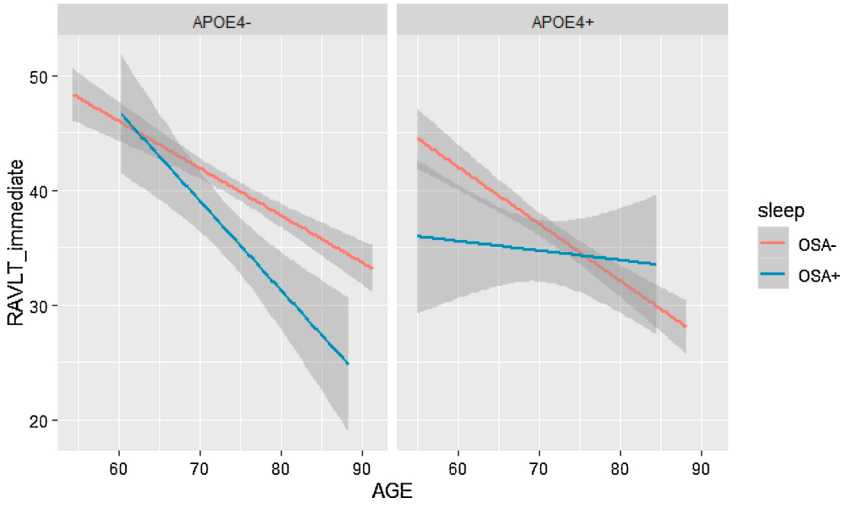

Fig. 2. Relationship between Age and RAVLT immediate recall scores in OSA- and OSA + groups. RAVLT immediate recall as a function of Age and OSA -/+ status in APOE ε4- (left) and APOE ε4+ (right) groups.

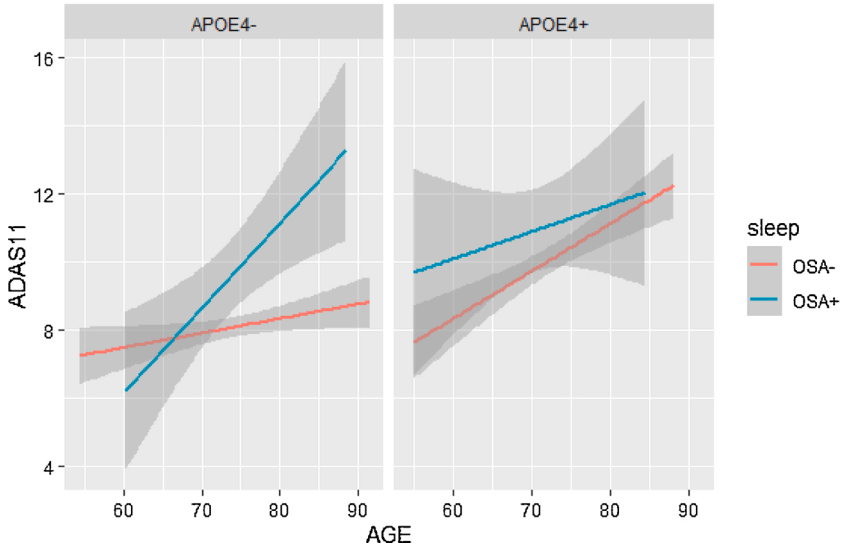

Fig. 3. Relationship between Age and ADAS-cog11 in OSA- and OSA + groups. ADAS-cog11 as a function of Age and OSA -/+ status in APOE ε4- (left) and APOE ε4+ (right) groups.

CRediT authorship contribution statement

Tengwei Pan: Conceptualization, Methodology, Software, Writing-Original draft preparation. **Suzhi Liu:** Data analysis, Writing- Original draft preparation. **Shaofa Ke:** Visualization, Investigation. **Shanshan Wang:** Writing- Reviewing and Editing, Supervision. **En Wang** and **Yiqing Jiang:** Validation, Supervision.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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