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APOE Polymorphism, Obstructive Sleep Apnea, and Cognitive Function

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Abstract

Objective Obstructive sleep apnea (OSA) is associated with the apolipoprotein E *ε4* polymorphic allele (*APOE ε4*) and with worse cognitive function. However, the influence of *APOE ε4* on cognitive function in patients with moderate-to-severe OSA is controversial. The present study evaluated the influence of *APOE ε4* polymorphism and cognitive function in sedentary OSA patients with no other major comorbidities.

Materials and Methods In total, 55 middle-aged patients underwent conventional nocturnal polysomnography, *APOE ε4* polymorphism genotyping, cognitive evaluation (attention, inhibitory control, frontal functions, processing speed, and episodic memory), and they filled out the International Physical Activity Questionnaire.

Results Overall, 13 patients had no or mild OSA, and 42 had moderate-to-severe OSA (apnea-hypopnea index [AHI] $\geq$ 15 events/h of sleep) and *APOE ε4* was present in 7.7% and 21.4% of the patients in each group respectively. Among patients with moderate-to-severe OSA, the sleep parameters were similar in the groups of *APOE ε4* carriers and noncarriers. Compared with patients with no or mild OSA, the cognitive parameters were worse for processing speed (Digit Symbol Test) and attention (Stroop Color Word Test, SCWT-Part 2) among the patients with moderate-to-severe OSA. The difference was present even after the exclusion of *APOE ε4* carriers. Among patients with moderate-to-severe OSA, *APOE ε4* carriers presented worse episodic memory, evaluated through the Rey Auditory Verbal Learning Test, than *APOE ε4* noncarriers.

Conclusion Moderate-to-severe OSA is associated with poor cognitive function that is further impaired by the presence of *APOE ε4* polymorphism.

Keywords
- sleep
- cognition
- apolipoprotein

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Introduction

Obstructive sleep apnea (OSA) is characterized by recurrent episodes of partial (hypopnea) and complete (apnea) obstruction of the upper airway during sleep, resulting in intermittent hypoxemia and sleep fragmentation.[1,2] It is also a risk factor for other health problems, such as hypertension, sudden death, stroke,[3–5] and psychiatric conditions like depression, irritability,[6] and cognitive impairment.[7]

The repeated events of hypoxia and reoxygenation during OSA episodes induce an increase in oxidative stress, inflammatory process,[8] and neurodegeneration.[9,10] Evidence suggests that moderate-to-severe OSA (apnea-hypopnea index [AHI] $\geq$ 15 events/h of sleep) is associated with increased cognitive decline and brain morphological changes.[11,12] However, most studies have failed to reliably establish a relationship between OSA and neurocognitive changes[13] because of a heterogeneity of factors related to cognitive decline that include age, sex, obesity, menopause, hypertension, cardiovascular diseases, level of alcohol consumption, smoking,[14] physical activity,[15] and level of schooling. Also, the apolipoprotein E *ε4* polymorphic allele (*APOE ε4*) confers a high risk of developing cognitive deficits.[16]

The *APOE ε4* is produced primarily by astrocytes in the central nervous system as a carrier of cholesterol and other lipids to support membrane homeostasis, synaptic integrity, and injury repair. It increases the risk of dementia by initiating and accelerating amyloid-β accumulation, aggregation, and deposition in the brain. Conversely, *APOE ε4* is more frequently present in patients with OSA for reasons that are not fully understood, but *APOE* genes have also been proposed as a cause of OSA susceptibility.[17] Despite this evidence, few studies[24,27] have included the analysis of *APOE ε4* in the assessment of cognitive functioning among patients with OSA.

Therefore, in the present study, we investigated sleep parameters and cognitive function in patients with different degrees of OSA severity, with particular interest in the modulation of *APOE* in the cognitive function in middle-aged adults with moderate-to-severe OSA. We hypothesized that moderate-to-severe OSA is associated with worse performance in tests for the attention domain, and when the interaction between OSA and *APOE ε4* occurs, there is a further reduction in performance on the test for the memory domain. To this end, we studied sedentary patients without other major diseases.

Materials and Methods

Patients

Male and female patients aged between 40 and 65 years underwent nocturnal conventional polysomnography. The level of physical activity, cognitive function, and *APOE ε4* genotyping were collected for every participant. We excluded patients with body mass index (BMI) $> 40\,kg/m^2$, diabetes mellitus, resting blood pressure (BP) $> 140/90$ mmHg, smoking or alcohol abuse (2 or more drinks/d), cardiopulmonary disease, chronic renal disease, a history of major psychiatric disorders, use of medicines that affect sleep and the neurovascular system, those with < 2 years of schooling, shift workers, and patients with any sleep apnea treatment. Because hormonal variability during the regular menstrual cycle can affect cognitive function, all nonmenopausal women were studied between the first and fifth days after the onset of menstruation. The present study was approved by the Institutional Committee on Human Research of the Heart Institute at the Teaching Hospital of the School of Medicine of Universidade de São Paulo (Instituto do Coração, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, InCor-HCFMUSP, in Portuguese; 0833/10), and all subjects provided written informed consent.

Sleep Study

All participants underwent overnight polysomnography (Embla N7000, Medcare Flaga, Reykjavik, Iceland) in the Sleep Laboratory of InCor-HCFMUSP. Polysomnography was performed using standardized techniques, with a standard staging system for the sleep stages used as described in previous studies.[18,19] The AHI was determined by the sum of apneas and hypopneas per hour of sleep. We used a conservative AHI cutoff of $\geq$ 15 events/hour of sleep, considering the consistent evidence from brain imaging analysis, highlighting the presence of tissue damage in the brains of several patients with moderate to severe OSA, as well as a decline in cognition in several domains.[11]

Cognitive Function

The procedures and descriptions of the cognitive tests used in the present study have been published elsewhere.[19] The cognitive tests were performed on the same day as the sleep studies. Attention and executive function were evaluated using the Trail Making Test-Parts A and B, Forward Digits test, Backward Digits test, Digit Symbol test, Stroop Color Word Test (SCWT), and Frontal Assessment Battery. Episodic verbal memory and learning abilities were assessed using the Rey Auditory Verbal Learning Test: RAVLT5–sum of 5 recall trials of 15 words; and RAVLT late – delayed recall after 30 minutes.

The Trail Making Test-Part A consists of a series of numbers that must be linked with a pencil by the patient in ascending order. In Part B, the participant alternates between numbers and letters, with numbers in ascending order and letters in alphabetical order. The Forward Digits test requires the verbal repetition of digits in the same order, whereas, in the Backward Digits test, the participant is asked to repeat the sequence of numbers in the inverse order. In the Digit Symbol test, a visual key consisting of paired geometric figures and numbers is provided. Participants are asked to apply a key to supply the proper number that is associated with the specific symbol. The outcome is the number of correct responses in 90 seconds. The SCWT comprises three cards containing six lines with four items: part 1 has colored cards (green, pink, blue, and brown); part 2 consists of neutral words written with the colors of the tags; and part 3 has the names of colors written in colors that contrast with the those of the printed words. The participant is asked to verbalize the names of the colors printed on each card presented as soon as possible. The time starts right after the instructions, and the time it takes the subject to read each

card is recorded. The Frontal Assessment Battery contains six subtests, which assess conceptualization, abstraction, lexical fluency, and mental flexibility: motor programming and sensitivity to interference, including tendency to distraction, inhibitory control, and autonomy. Each of the subtests is equivalent to a maximum of three points. Together, the 6 subtests total 18 points, which is the maximum possible score obtained in the Frontal Assessment Battery. The RAVLT consists of 15 nonrelated words that should be orally repeated by the patients in 5 consecutive trials testing immediate verbal memory and learning abilities and remembered after 30 minutes: delayed recall. The Mini-Mental State Examination, which is a screening neurocognitive tool that covers domains such as orientation, memory, registration, recall, constructional ability, language, and the ability to understand and follow commands, was also applied. The intelligence quotient (IQ) was estimated by using the Wechsler abbreviated scale for intelligence (WASI).

The Short Cognitive Performance Test (Syndrom-Kurztest, SKT),[20] which assesses memory, attention, and related cognitive functions, and the speed of information processing, was also applied. All cognitive evaluations and data analyses were conducted by a single investigator, blinded by the study protocol.

DNA Extraction and *APOE* Genotyping

Genomic DNA was extracted from leukocytes in samples of whole blood. Genomic DNA was isolated from peripheral leukocytes. Genotypes for *APOE ε2/ε3/ε4* were determined by polymerase chain reaction (PCR) followed by restriction fragment length polymorphism analysis.[21] Briefly, PCR with fluorescent DNA-intercalating SYTO9 (Thermo Fisher Scientific Inc., Waltham, MA, United States) was performed using the primer sequences 5'-GCCGATGACCTGCAGAAG-3' and 5'-CACGCGGCCCTGTTCCAC-3' (fragment size 117 pairs base). The individuals were classified into *ε2/ε2*, *ε2/ε3*, *ε3/ε3*, *ε4/ε4*, *ε3/ε4*, and *ε2/ε4* genotypes. Individuals with at least one copy of the *APOE ε4* allele were considered *APOE ε4* carriers.

Level of Physical Activity

The level of physical activity was evaluated using the International Physical Activity Questionnaire (IPAQ), which estimates the weekly time spent in moderate and intense physical activity, as well as walking, in the following domains of everyday life: domestic, work, transportation, leisure, and the time that a person remains seated.[22]

Statistical Analysis

In the present study, the OpenEpi (open source) interface developed for epidemiological statistics was used for the sample size calculation. A power of 80% and 95% confidence intervals (95%CIs) were adopted. The sample size calculation was considered based on our previous study[23] investigating the *APOE ε4* allele and cognition. As a result, a value of 36 patients was obtained. However, considering a possible loss in data collection, we included 55 participants. Data were expressed as mean ± standard deviation (SD) values. The Chi-squared test (χ^2) was used to assess the difference in sex and polymorphism proportions between the groups. To assess the homogeneity of the sample, we used the Levene test. The normality of each sample was tested using the Kolmogorov-Smirnov test. The student *t*-test for non-repeated measures was used in case of homogeneous and Gaussian variables. For non-homogeneous and/or non-Gaussian variables, the Mann-Whitney test, unpaired data was used to assess the differences in each group. Differences with $p \leq 0.05$ were considered statistically significant. Correlations between the AHI and the cognitive variables were performed using multiple linear regressions through the input method. All analyzes were performed using the SPSS Statistics for Windows (IBM Corp., Armonk, NY, United States) software, version 20.0.

Results

The study included 42 patients with moderate-to-severe OSA (AHI $\geq$ 15 events/h of sleep) and 13 patients with no or mild OSA (AHI $<$ 15 events/h of sleep). The baseline characteristics of the subjects with no or mild OSA and moderate-to-severe OSA were similar regarding age (49 ± 7 versus 52 ± 7 years respectively; $p = 0.30$), body mass index (28 ± 1 versus 29 ± 1 kg/m^2 respectively; $p = 0.17$), leisure physical activity (105 versus 450 min/week respectively; $p = 0.63$). The presence of at least 1 *APOE ε4* allele was found in 1 subject with no or mild OSA and in 9 subjects with moderate-to-severe OSA.

Regarding sleep apnea patterns, the AHI and arousal index were higher and lower in the minimum O_2 saturation in the moderate-to-severe OSA group than in the no or mild OSA group (►**Table 1**). These results remained when excluding carriers of *APOE ε4*. (See ►**Table S1** in the supplemental file for sleep parameters excluding *APOE ε4* carriers in the

Table 1 Sleep parameters of the study participants.

Sleep parameters	AHI $<$ 15 (n = 13): mean ± SD	AHI $\geq$ 15 (n = 42): mean ± SD	*p*-value
TST (in minutes)	356 ± 63	377 ± 54	0.25
N1 (% TST)	6 ± 4	8 ± 6	0.49
N2 (% TST)	57 ± 8	58 ± 9	0.75
N3 (% TST)	18 ± 7	15 ± 10	0.31
REM (%TST)	18 ± 6	19 ± 7	0.71
Arousal index (events/hour)	20 ± 5	32 ± 16	0.01*
AHI (events/hour)	7 ± 3	44 ± 28	$<$ 0.001*
Minimum O_2 saturation (%)	89 ± 2	80 ± 9	$<$ 0.001*
APOE ε4 carriers (n, %)	1 (7.7)	9 (21.4)	

Abbreviations: AHI: apnea-hypopnea index; APOE, apolipoprotein E; N1, N2, N3, sleep stages (non-rapid eye movement); REM: rapid eye movement sleep; SD, standard deviation; TST, total sleep time.
Note: *$p \leq 0.05$.

Table 2 Assessment of sleep parameters among carriers and noncarriers of apolipoprotein E (*APOE*) ε4 polymorphic allele with moderate-to-severe sleep apnea (AHI ≥ 15 events/hour).

Sleep parameters	*APOE ε4* (+) (n = 9): mean ± SD	*APOE ε4* (-) (n = 33): mean ± SD	*p*-value
TST (in minutes)	404 ± 30	369 ± 57	0.08
N1 (% TST)	9 ± 8	8 ± 6	0.83
N2 (% TST)	60 ± 8	57 ± 10	0.36
N3 (% TST)	13 ± 8	16 ± 10	0.44
REM Sleep (%)	18 ± 8	19 ± 6	0.71
Arousal index (events/hour)	34 ± 23	31 ± 14	0.72
AHI (events/hour)	35 ± 30	46 ± 27	0.29
Minimum O_2 Saturation (%)	83 ± 10	79 ± 9	0.21

Abbreviations: AHI: apnea-hypopnea index; N1, N2, N3, sleep stages (non-rapid eye movement); REM: rapid eye movement sleep; SD, standard deviation; TST, total sleep time.

groups.) No significant differences were found in total sleep efficiency, N1, N2, N3, and rapid eye movement (REM) sleep stages between both groups. In patients with moderate-to-severe OSA, the comparison between *APOE ε4* carriers and noncarriers presented no significant differences ($p > 0.05$) in sleep parameters (►**Table 2**).

Cognitive function was worse in terms of processing speed, attention, and inhibitory control evaluated through the Digit Symbol test and the SCWT-Part 2 in the moderate-to-severe OSA ($p < 0.05$; ►**Table 3**). When excluding *APOE ε4* carriers, these results remained worse in the moderate-to-severe OSA compared to the no or mild OSA group. (See ►**Table S2** in the supplemental file for the cognitive evaluation excluding *APOE ε4* carriers in the groups.) Furthermore, a multiple linear regression analysis among *APOE ε4* noncarriers found that the AHI explained 61% of the results in the SCWT-Part 2 ($p < 0.05$). The correlation between AHI and the SCWT-Part 2 was significant ($\beta = 0.610$; 95%CI = 0.035–0.214; $p = 0.008$).

In the moderate-to-severe OSA group, the comparison between *APOE ε4* carriers and noncarriers presented significant differences ($p = 0.038$) in the memory domain evaluated by the RAVLT A1-A5 test (►**Table 4**).

Discussion

In the present study, we evaluated sleep and cognitive parameters in patients with and without moderate-to-severe OSA considering the presence of *APOE ε4* polymorphism. Important findings emerged from the study. First, in line with previous studies,[7] patients with moderate-to-severe OSA had lower cognitive performance in terms of processing speed, divided attention, and inhibitory control (Symbol Digit Test, SCWT-Part 2), then patients with no or mild OSA. In both groups, when

Table 3 Results of the cognitive evaluation in all patients.

Cognitive Tests	AHI < 15 (n = 13): mean ± SD	AHI ≥ 15 (n = 42): mean ± SD	*p*-value
Years of schooling	13 ± 4	12 ± 5	0.57
IQ	80 ± 16	80 ± 13	0.93
MMSE score	27 ± 2	27 ± 3	0.51
Trail A (in seconds)	39 ± 21	49 ± 27	0.26
Trail B (in seconds)	128 ± 76	173 ± 147	0.30
Direct Digits (number of correct answers)	6 ± 2	5 ± 3	0.41
Indirect Digits (number of correct answers)	5 ± 2	4 ± 2	0.20
Digit Symbol test (number of correct answers)	46 ± 17	35 ± 12	0.01*
SCWT- Part 1 (in seconds)	17 ± 3	22 ± 17	0.32
SCWT- Part 2 (in seconds)	20 ± 5	26 ± 9	0.002*
SCWT- Part 3 (in seconds)	31 ± 8	43 ± 23	0.07
Total Frontal Assessment Battery	16 ± 2	16 ± 2	0.85
SKT Attention	2 ± 1	3 ± 2	0.20
SKT Memory	1 ± 1	2 ± 1	0.10
Memory and Learning			
RAVLT A1-A5	47 ± 9	42 ± 9	0.09
RAVLT late	10 ± 2	8 ± 3	0.17

Abbreviations: AHI, apnea-hypopnea index; IQ: intelligence quotient; MMSE: Mini-Mental State Examination; SCWT, Stroop Color Word Test; SD, standard deviation; SKT, Syndrom-Kurztest; RAVLT, Rey Auditory Verbal Learning Test (RAVLT A1-A5–sum of 5 recall trials; RAVLT late – delayed recall after 30 minutes).
Note: *$p \leq 0.05$.

Table 4 Results of the cognitive evaluation between apolipoprotein E (*APOE*) ε4 polymorphic allele carriers (+) and noncarriers (-) among patients with moderate-to-severe sleep apnea (AHI $\geq$ 15 events/hour).

Cognitive Tests	APOE ε4 (-) (n = 33): mean ± SD	APOE ε4 (+) (n = 9): mean ± SD	*p*-value
Years of schooling	12 ± 4	12 ± 8	0.37
MMSE score	27 ± 2	27 ± 3	0.93
Trail A (in seconds)	49 ± 26	47 ± 32	0.67
Trail B (in seconds)	189 ± 162	116 ± 41	0.28
Direct Digits (number of correct answers)	5 ± 3	5 ± 2	0.83
Indirect Digits (number of correct answers)	4 ± 2	4 ± 1	0.47
Digit Symbol Test (number of correct answers)	35 ± 12	32 ± 14	0.42
SCWT – Part 1 (in seconds)	20 ± 5	30 ± 36	0.61
SCWT – Part 2 (in seconds)	26 ± 9	27 ± 8	0.87
SCWT – Part 3 (in seconds)	40 ± 18	53 ± 38	0.85
Total Frontal Assessment Battery	16 ± 2	17 ± 2	0.12
SKT Attention	3 ± 1	4 ± 3	0.11
SKT Memory	2 ± 1	1 ± 1	0.24
Memory and Learning			
RAVLT A1-A5	43 ± 9	37 ± 8	0.038*
RAVLT late	9 ± 3	7 ± 3	0.29

Abbreviations: AHI, apnea-hypopnea index; MMSE: Mini-Mental State Examination; SCWT, Stroop Color Word Test; SD, standard deviation; SKT, Syndrom-Kurztest; RAVLT, Rey Auditory Verbal Learning Test (RAVLT A1-A5–sum of 5 recall trials; RAVLT late – delayed recall after 30 minutes).
Note: *$p \leq 0.05$.

excluding *APOE ε4* carriers, who tend to be associated with moderate-to-severe OSA, lower cognitive performance remained for processing speed and attention domains in patients with moderate-to-severe OSA. Second, among patients with moderate-to-severe OSA, the sleep parameters were similar in *APOE ε4* carriers and noncarriers, but the carriers presented significantly worse memory (RAVLT A1-A5).

In the present study, the presence of at least 1 *APOE ε4* allele was found in 7.7% of the patients with no or mild OSA and in 21.4% of those with moderate-to-severe OSA. The apparent higher prevalence of the *APOE ε4* allele in patients with moderate-to-severe OSA is in line with previous studies[17,24] that have indicated that *APOE* genes are associated with OSA susceptibility. Furthermore, in a previous study[25] in the general population, the *APOE ε4* allele was associated with characteristics typical of OSA, including obesity, elevated total cholesterol levels, low-density lipoprotein cholesterol, and elevated uric acid levels. However, others studies[26,27] found no relationship between *APOE ε4* and OSA susceptibility. Importantly, hypertension was identified as a plausible source of heterogeneity and a confounding factor among studies.[26] Therefore, in the present study, we evaluated the influence of *APOE ε4* polymorphism and cognitive functioning in sedentary OSA patients with no other major comorbidities.

Consistent with the literature, we also found that patients with moderate-to-severe OSA had lower cognitive performance in the domains of processing speed and attention than patients with no or mild OSA.[7]

These differences remained even when all *APOE ε4* carriers were excluded. Furthermore, by excluding the *APOE ε4* carriers from the moderate-to-severe OSA group, the AHI explained 61% of the results in the attention test of the SCWT-Part 2 ($\beta = 0.610$; 95%CI = 0.035-0.214; $p = 0.008$). The lower cognitive performance may be related to detrimental effects on the neurocognitive system caused by intermittent hypoxia in brain tissue.[28,29]

Studies have shown that structural brain changes have been associated with deficits in cognitive function in patients with moderate-to-severe OSA,[11,30] including the domains of attention, memory, executive function, and information processing speed.[31]

In line with the studies, we also found lower cognitive performance for processing speed and attention domains in patients with moderate-to-severe OSA. Except for the Digit Symbol test and the SCWT-Part 2, none of the other attention tests showed significant differences between both OSA groups. We speculate that OSA affects attentional performance differently. The SCWT-Part 2 involves inhibitory control and processing speed, whereas the Digit Symbol test involves divided attention and visual scanning. These cognitive functions are specifically associated with the prefrontal region, which is known to be an area strongly affected by intermittent hypoxia.[32] Areas of structural brain damage are consistent with deficits in attention, processing speed, and inhibitory functions in OSA. A review study[33] examining neuroimaging in OSA suggested that the causes may be impairment in white-matter tracts in the frontal region

(important for speedy and efficient neural transmission) and a lack of activation in the dorsolateral prefrontal cortices (crucial brain region for inhibitory control, an executive function essential for behavioral self-regulation). Impaired attentional skills, which can occur in patients with more severe OSA, can also lead to reduced quality of life[34] and increased traffic and work accidents.[35,36] Furthermore, impaired inhibitory control may be associated with serious difficulties and traits of impulsivity when trying to inhibit inappropriate behaviors to control problems which, in turn, may interfere with sleep quality.

The *APOE* is a plasma protein that influences lipid metabolism,[25] nervous system growth and repair, synaptic and dendritic remodeling, and amyloid clearance.[37] Carriers of *APOE ε4* have decreased expression of the *APOE* protein, making them more susceptible to cerebrovascular disease and Alzheimer disease.[38] The prevalence of *APOE ε4* carriers varies among populations worldwide, with rates of about 20% among Americans and Europeans.[38,39] Among the patients with moderate-to-severe OSA in the present study, the genotype frequency of the *APOE ε4* was of 21.4%, close to a previous study that reported a rate of 23.8%.[23] Considering only patients with moderate-to-severe OSA, our results revealed that the *APOE ε4* carriers had significantly worse memory on the RAVLT test compared with noncarriers. Our results differ from those of the study by Cosentino et al.,[23] who showed a difference in the memory domain in patients with OSA compared with controls. However, the authors[23] found no impact of *APOE ε4* carriers. We speculate that the difference from our investigation may be explained by the fact that, in this previous study,[23] factors associated with cognitive decline, including higher BMI, diabetes mellitus, and smoking,[40,41] were significantly higher in the OSA group. A previous study[42] reported dose-response relationship between BMI and the risk of cognitive impairment and dementia, indicating that the risk is significantly increased when BMI surpasses 29 kg/m^2 in middle age. Also, diabetes can influence cognitive function directly (by increasing fluctuations in blood glucose levels or insulin resistance) or indirectly (leading to microangiopathy of the brain) increasing the risk of stroke. Furthermore, chronic nicotine use has been linked to impaired cognitive functioning in middle age.[43,44] A meta-analysis[45] identified a cross-sectional association between chronic tobacco smoking and impairments in several neuropsychological domains, including attention, short- and long-term memory, cognitive flexibility, cognitive impulsivity, and intelligence. On the other hand, in the present study, we controlled the groups for a similar level of physical activity, because physical activity is known to improve cognition and brain function,[46] and it could affect the results of the analysis.

Our results corroborate some findings of the study by Nikodemova et al.,[47] which found that *APOE ε4* carriers with OSA had a high risk of developing cognitive deficits in memory and executive function compared with *APOE ε4* noncarriers. In the present study, we added the important information that sleep parameters were similar in subjects with and without the *APOE ε4* polymorphism in the moderate-to-severe OSA group. The presence of moderate-to-severe OSA itself results in worse cognitive performance in the domains of processing speed, attention, and inhibitory control. The association between OSA and the presence of the *APOE ε4* polymorphism revealed a decline in episodic memory. Thus, studies on cognition and OSA may consider the genetic *APOE ε4* polymorphism as a factor that may interfere with the results. Future studies including many patients should also consider the presence of the *APOE ε2* allele, which, in OSA patients, can also cause harmful effects on sleep parameters, impacting quality of life. Carriers of the *APOE ε2* allele had longer sleep latency, lower sleep efficiency, and a higher number of arousals per hour compared with homozygous carriers of the *ε4* and ε3 alleles.[48]

The present study has several potential limitations. First, participants were classified as having no or mild OSA if the AHI was < 15 events/hour of sleep, and as having moderate-to-severe OSA if the AHI was ≥ 15 events/hour of sleep. This close cutoff between groups may have had the effect of decreasing the sensitivity for discovering differences between the groups. Recent studies indicate that elimination of wastes such as Aβ is improved when the individual has normal sleep,[49] whereas the concentration or accumulation of Aβ deposition is greater if sleep is fragmented.[50] However, available evidence suggests that a normal sleep pattern, including fewer nocturnal awakenings, decreases the negative effects of the *ε4* allele,[51] and cognitive impairment may be lower using a cutoff of AHI < 5 events/hour of sleep. Despite the use of this closed cutoff, we found significant differences between the groups. Second, the low rate of *APOE ε4* allele carriers in the no or mild OSA group does not enable a comparison of cognitive function regarding the the *APOE ε4* polymorphism carriers in the moderate-to-severe group. Third, our analyses were based on a single measurement of cognitive function without considering intraindividual variation, so the accuracy of the results may have been affected. Finally, the overall sample size was relatively small; therefore, the present study may have been insufficient to detect other cognitive changes. Despite these limitations, but using specific inclusion criteria, the present study[41–44] was able to provide a robust conclusion about the influence of *APOE ε4* polymorphism and cognitive function in sedentary patients with OSA without other major comorbidities.

The strengths of the present study are the application of cognitive tests sensitive to specific domains, the use of nocturnal polysomnography, which is a gold standard for sleep studies, the fact that the level of schooling and age corresponded in the two groups, the exclusion of cardiovascular disease, diabetes, and cigarette smoking, presence of hypertension, medication use (antidepressants, benzodiazepines, or non-benzodiazepine anxiolytics), and the inclusion only of sedentary patients, because studies[41–44] have proven that these variables can greatly interfere with cognitive function.

Conclusion

In conclusion, sedentary patients with OSA without other important comorbidities experience impairments in processing

speed, divided attention, and inhibitory control in attentional tasks. Episodic memory is further impaired by the presence of the *APOE ε4* allele.

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Conflict of Interests
The authors have no conflict of interests to declare.

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