Interaction between apolipoprotein E genotypes, excessive daytime sleepiness, and cognitive function in obstructive sleep apnea patients

Interação entre genótipos da apolipoproteína E, sonolência excessiva diurna e função cognitiva em pacientes com apneia obstrutiva do sono

Fernanda Maurer Balthazar[1] Walter André dos Santos Moraes[1] James Richard Hunter[2]
Gilmar Fernandes do Prado[1] Luciane Bizari Coin de Carvalho[1]

[1] Universidade Federal de São Paulo, Escola Paulista de Medicina, Departamento de Neurologia e Neurocirurgia, Setor Neuro-Sono, Disciplina de Neurologia, São Paulo SP, Brazil.
[2] Universidade Federal de São Paulo, Departamento de Medicina, Disciplina de Infectologia, São Paulo SP, Brazil.

Address for correspondence Walter André dos Santos Moraes
(e-mail: walterasmoraes@gmail.com).

Abstract

Background Some studies show an association between the apolipoprotein E ε4 allele (ApoEε4) and obstructive sleep apnea syndrome (OSAS), and other studies, an association between ApoEε4 and excessive daytime sleepiness (EDS), but there are no data in the literature on the interaction between EDS, cognitive function, and ApoEε4 in patients with OSA.

Objective To examine the cognitive function of adults with and without EDS and with and without ApoEε4.

Methods A total of 21 male and female patients aged between 33 and 79 years, underwent a clinical interview, ApoE genotyping, neuropsychological evaluation, polysomnography, and the application of the Epworth Sleepiness Scale.

Results Excessive daytime sleepiness was associated with lower intelligence quotient (IQ; total performance) and worse immediate visual memory, regardless of the ApoE genotype. Patients carrying the ApoEε3/ε4 genotype had a worse performance in divided attention, constructional praxis, perceptual organization, and cognitive flexibility. A combination of the ε4 allele and EDS potentiates the negative effect on cognition, except for immediate visual memory. In this case, patients had a worse

Keywords
► Apolipoproteins E
► Sleep Apnea, Obstructive
► Disorders of Excessive Somnolence
► Cognitive Dysfunction

performance in terms of processing speed, selective attention, and visuomotor coordination.

Conclusions   Excessive daytime sleepiness and the ApoEε3/ε4 genotype are associated with worse cognitive performance in OSA patients. The combination of EDS and ε4 allele potentiates cognitive impairment.

Resumo

Antecedentes   Alguns estudos mostram uma associação entre o alelo ε4 da apolipoproteina E (ApoEε4) e a síndrome da apneia obstrutiva do sono (SAOS), e outros, entre ApoEε4 e a sonolência excessiva diurna (SED), mas não há dados na literatura sobre a interação entre SED, função cognitiva e ApoEε4 em pacientes com SAOS.

Objetivo   Avaliar a função cognitiva em adultos com SAOS com e sem SED e com e sem ApoEε4.

Métodos   Ao todo, 21 pacientes, de 33 a 79 anos, homens e mulheres, foram avaliados clinicamente, e submetidos a genotipagem ApoE, avaliação neuropsicológica, polissonografia, e aplicação da Escala de Sonolência de Epworth.

Resultados   A SED esteve associada com menor quociente de inteligência (QI; desempenho geral) e pior memória visual imediata, independentemente do genótipo ApoE. Pacientes com genótipo ApoEε3/ε4 apresentaram pior desempenho na atenção dividida, praxe construcional, organização perceptiva e flexibilidade cognitiva. A combinação do alelo ε4 com a SED potencializa esse efeito deletério na cognição, exceto na memória visual imediata. Nesse caso, os pacientes tiveram uma menor velocidade de processamento cognitivo, e piores atenção seletiva e coordenação visiomotora.

Conclusões   A SED e o genótipo ApoEε3/ε4 estão associados a um pior desempenho cognitivo em pacientes com SAOS. A combinação de SED e do alelo ε4 potencializa esse efeito.

Palavras-chave
► Apolipoproteínas E
► Apneia Obstrutiva do Sono
► Distúrbios do Sono por Sonolência Excessiva
► Disfunção Cognitiva

INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is associated with many etiological factors, including obesity, genetic inheritance, aging, craniofacial patterns, and sedative substances.[1,2] A sleep respiratory event is a partial or complete obstruction of the upper airway during sleep that is associated with negative intrathoracic pressure, oxygen desaturation, and increased respiratory effort, leading to arousal and sleep fragmentation.[3] Patients with OSAS present important functional impairment, including cognitive deficit and excessive daytime sleepiness (EDS).[4–6]

The apolipoprotein E (ApoE) gene is located in the long arm of chromosome 19 and presents 3 different alleles (ε2, ε3, and ε4) paired independently.[7] The ApoEε4 allele is associated with a cognitive deficit in otherwise normal individuals, age-related cognitive decline, Alzheimer disease, and cardiovascular disorders,[7–11] as well as OSAS in adults and children.[9–11] The ApoEε2 allele is considered neuroprotective and is associated with a lower age-related cognitive decline and a lesser predisposition to Alzheimer's disease.[12] The ApoEε3 allele is the most frequent in the general population, and it is considered neutral to cognitive performance.[13]

The association between OSAS and EDS is well established in the literature, and EDS is considered a predisposing factor for cognitive impairment.[14,15] Patients with OSAS and EDS present impairment in attention, alertness, memory, learning, and executive function.[16] Some OSAS patients do not present EDS and cognitive impairment, suggesting that other factors may be involved in the etiology of these disturbances.[17]

Some hypotheses have been proposed to explain how OSAS can affect cognitive performance independently from EDS. Several studies[18–20] have shown the direct association between cognitive dysfunction and OSAS. Intermittent hypoxemia can affect cognition due to neuronal damage in the cortex by increased oxidative stress.[21] Sleep fragmentation may also influence neuropsychological deficits.[14] The literature is not unanimous about the areas of cognition affected by OSAS. A meta-analysis by Wallace and Bucks[22] showed that OSAS is related to impaired episodic, verbal, and visuospatial memories. Other studies found that motor coordination, alertness, executive functions, and attention were the most affected functions.[23,24] In general, OSAS patients present long-term verbal memory and auditory working memory deficits, while OSAS patients with the ε4 allele have spatial working memory deficit.[25] A cohort study[26] found that OSAS

patients with the ε4 allele have impaired memory and executive functions. Another study[10] found that children with OSAS and the ε4 allele present more intense cognitive impairment.

A study by Caselli et al.[27] showed that EDS is associated with a decline in verbal memory in ApoEε4 homozygotes compared with heterozygotes. There are no data in the literature on the interaction between EDS, cognitive function, and ApoE4 in patients with OSAS. Considering that EDS could be related to the cognitive deficit in OSAS patients with different ApoE genotypes, we have proposed this study to evaluate this hypothesis.

METHODS

Patients and ethics

In total, 36 patients were consecutively recruited in the Sleep Medicine Clinic at Neuro-Sleep Center, Department of Neurology, Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo, Brazil. All patients were submitted to baseline polysomnography (PSG). Patients with apnea-hypopnea index (AHI) > 15 were included. We did not select patients with other sleep disturbances and neurological, psychiatric, and clinical conditions that could affect cognitive performance and alertness at the discretion of the assisting physician. We did not select patients using substances that could affect cognitive function and alertness. Twelve patients were excluded because they did not meet the eligibility criteria or due to genotyping failure. The final sample was composed of 21 patients, 10 male and 11 female individuals, aged between 33 and 79 years. All patients signed a consent form. The present study was approved by the Research Ethics Committee of the Universidade Federal de São Paulo (#0494/16).

Procedure

The patients underwent a clinical interview, a physical examination, and the aplication of the Epworth Sleepiness Scale (ESS). Scores ≥ 10 on the ESS were indicative of EDS.[28–31] As aforementioned, all selected patients underwent baseline PSG. Blood samples were collected in ethylenediaminetetraacetic (EDTA) acid tubes and underwent polymerase chain reaction (PCR)-based genotyping for ApoE alleles. Genotypes ε3/ε3, ε2/ε4, and ε3/ε4 were identified in our sample. We compared patients (14) carrying the ε3/ε4 genotype with patients (7) carrying genotypes ε3/ε3 and ε2/ε4. Based on previous research,[13] in the latter group, ε2 was considered neuroprotective, ε3, neutral, and ε4, a predisposing allele.

We analyzed the neuropsychological parameters supposedly affected by OSAS.[32] The evaluation occurred in a controlled environment with adequate lighting and temperature. All neuropsychological tests were applied in a single session lasting approximately 2 hours and 30 minutes, with a 20-minute interval 90 minutes after the beginning of the evaluation. The evaluator was blinded to patient data on ESS, PSG, and ApoE. The cognitive tests applied were total intelligence quotient (IQ), verbal IQ,
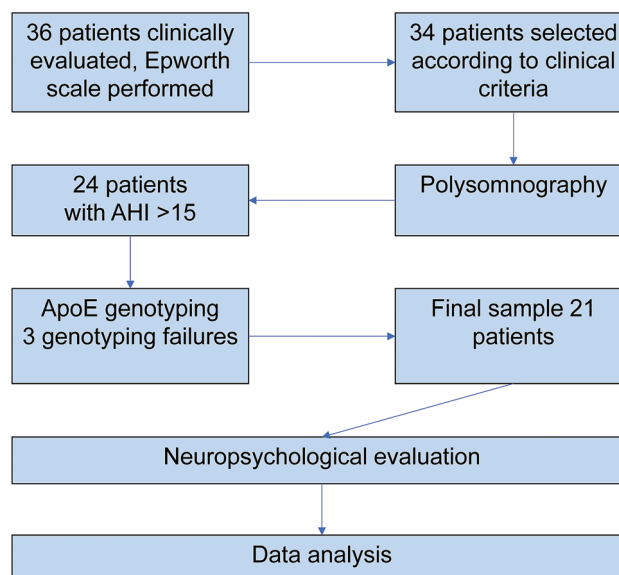

Figure 1 Experimental procedures.

performance IQ, processing-speed index, symbol searching, Stroop color-word tests A, B, and C, the trail making test and the trail making test B, block design, matrix reasoning, Rey figure, forward digit span, forward and backward digit span, Rey auditory verbal learning test (RAVLT), and backward digit span.[33–37] The experimental procedures are summarized in ►Figure 1.

Statistics

We calculated the means of the neuropsychological tests using gross scores for each cognitive function. The sample size was not calculated prior to the study. We normalized the results of different tests in terms of mean and standard deviation on a scale ranging from 0 to 100 and shown in a radar graph. The tests in which shorter times (in seconds) represented a better performance, the algebraic signal was inverted to be compared to the other neuropsychological parameters. We selected the Kruskal-Wallis test to compare the ε3/ε4 and non-ε3/ε4 groups for each cognitive function. The Chi-squared test was used to analyze the sociodemographic variables of gender, age, income, body mass index (BMI), and level of schooling. The Pearson correlation coefficient and Kruskal Wallis test were used to determine the influence of these variables in cognitive tests. We used the R (R Foundation for Statistical Computing, Vienna, Austria) statistical software for the statistical analysis and data management.[38–40]

RESULTS

A total of 4 (19%) patients had genotype ε2/ε4, 3 (14.3%) had genotype ε3/ε3, and 14 (66.7%), genotype ε3/ε4. We found no significant differences between groups concerning the sociodemographic parameters (►Table 1), and 61.9% of the patients had ESS scores ≥ 10, and 38.1%, < 10.

The distribution of patients in groups was as follows: EDS-ε3/ε4 (n = 8; 38.1%); EDS-non-ε3/ε4 (n = 5; 23.8%); non-EDS-

Table 1 Sociodemographic parameters of the study sample (n = 21)

	All genotypes		ApoE ε3/ε4		non-ApoE ε3/ε4	
	Mean	SD	Mean	SD	Mean	SD
Age	59.0	10.7	58.8	12.2	59.3	8.0
BMI	31.7	5.6	29.5	1.8	33.6	7.9
Gender	Frequency	Distribution	Frequency	Distribution	Frequency	Distribution
Male	10	47.6%	5	35.7%	5	71.4%
Female	11	52.4%	9	64.3%	2	28.6%
Schooling (years)	Frequency	Distribution	Frequency	Distribution	Frequency	Distribution
0-8	14	66,7%	10	71.4%	4	57.1%
9-12	4	19.0%	1	7.2%	3	42.9%
13-16	3	14.3%	3	21.4%	0	0%
Income group*	Frequency	Distribution	Frequency	Distribution	Frequency	Distribution
Low	12	57.1%	8	57.1%	4	57.1%
Medium	8	38.1%	5	35.7%	2	28.6%
High	1	4.8%	1	7.2%	1	14.3%

Abbreviations: ApoE, apolipoprotein E; BMI, Body Mass Index; SD, standard deviation.
Notes: *low: ≤ 3 monthly minimum wages; medium: 3 to 9 monthly minimum wages; high: > 9 monthly minimum wages.

ε3/ε4 (n = 6; 28.6%); and non-EDS-non-ε3/ε4 (n = 2; 9.5%). We assessed the differences among the groups by normalized data on a scale ranging from 0 to 100, as aforementioned (►Table 2). The EDS-ε3/ε4 group presented the worst cognitive performance, scoring below average in 9 categories (►Figure 1): total IQ (18.2 points below), performance IQ (24.6 points), processing-speed index (29.1 points), selective attention (21.8 points), constructional praxis (21.7 points), perceptual organization (37.1 points), visuomotor coordination (23.3 points), and cognitive flexibility (28.8 points) (►Figure 2). Polisomnography data are shown in ►Table 3.

Patients with genotype ε3/ε4, with and without EDS, presented a worse performance in divided attention (31.9 points), constructional praxis (21.7), perceptual organization (37.1), and cognitive flexibility (28.8). Those with EDS from both genotype groups presented a worse performance in total IQ (18.2), performance IQ (24.6), and immediate visual memory (19.4). Patients without EDS and genotypes other than ε3/ε4 presented a higher performance in total IQ (18.2), performance IQ (24.6), divided attention (31.1), perceptual organization (37.1), attention span (40.5), and cognitive flexibility (28.8 points) (►Figure 2).

DISCUSSION

Our results suggest that the ApoEε3/ε4 genotype in patients with moderate to severe sleep apnea and EDS is associated with impaired cognitive performance. The mechanisms through which the ε4 allele may affect cognition are not yet understood. According to some studies,[25] individuals with the ε4 allele have a higher incidence of cerebrovascular disease. Other studies[41] report that the presence of the ε4 allele is associated with lower metabolic rates in the poste-

rior cingulate, inferior parietal cortex, and lateral temporal cortex. The ε4 allele is also related to a neurotoxic process that affects the mitochondria, cytoskeleton, and synaptogenesis, impairing cognitive function.[42]

In the sample of the present study, similarly to other studies, we found that EDS alone was associated with global cognitive impairment, which was evidenced by lower IQ scores, regardless of the association with the ε4 allele.[16]

A proposed mechanism for the etiology of EDS in OSAS is the fragmentation of sleep due to frequent arousals caused by respiratory effort, modifying sleep architecture.[6] Poor sleep quality is associated with memory disturbances. Sleep deprivation affects the hippocampus, compromising memory codification and retention and impairing its interaction with the visual cortex.[43] It can be related to low immediate visual memory performance in patients with EDS.

In the sample of the present study, when EDS and the ApoEε3/ε4 genotype occurred in the same patient, the cognitive disturbance was more intense than when they occurred isolatedly. A possible explanation is that genetic predisposition increases the vulnerability to the prejudicial effects of EDS on cognition.[44]

The main weakness of the present study is the small sample size, which limited the power of statistical analysis. We consider it a preliminary study that opens the path for future research in larger samples. Another limitation is the use of the ESS to assess EDS. Although the ESS is a validated and recognized instrument, it uses the patient's subjective perception, with the risk of false positives and false negatives.[31] Future studies with objective methods to assess sleepiness like the multiple sleep latency test and the maintenance of wakefulness test can lead to more accurate results.

In conclusion, the present study found that patients with OSAS, the ApoEε3/ε4 genotype, and EDS had impaired

Table 2 Neuropsychological data of the study sample

Cognitive function	Tests	EDS-ε3/ε4 (n = 8; 38.1%)		EDS-non-ε3/ε4 (n = 5; 23.8%)		Non-EDS-ε3/ε4 (n = 6; 28.6%)		Non-EDS-non-ε3/ε4 (n = 2; 9.5%)	
		Score: mean ± SD	n/%*	Score: mean ± SD)	n/%*	Score: mean ± SD)	n/%*	Score: mean ± SD)	n/%*
Selective attention	SyS	17.25 ± 7.36	1/12.5%	23.80 ± 5.80	0/0%	22.33 ± 5.80	0/0%	18.50 ± 0.70	0/0%
Divided attention	TMT	127.8 ± 68.30	3/37.5%	77.20 ± 48.44	2/40%	114.33 ± 58.89	3/50%	64.50 ± 33.94	0/0%
Constructional praxis	Cb	12.75 ± 16.15	7/87.5%	23.40 ± 13.14	3/60%	17.83 ± 15.31	4/66.7%	19.00 ± 4.24	1/50%
Perceptual organization	RF	7.00 ± 1.19	5/62.5%	6.60 ± 1.14	1/20%	6.16 ± 2.85	3/50%	9.00 ± 1.41	0/0%
Attention span	Dg	7.00 ± 1.19	0/0%	6.60 ± 1.14	0/0%	6.16 ± 2.85	2/33.3%	9.00 ± 1.41	0/0%
Immediate visual memory	RFR	13.43 ± 4.29	2/25%	13.40 ± 4.37	1/20%	17.66 ± 6.92	0/0%	16.75 ± 1.76	0/0%
Visuomotor coordination	Cd, Cb	24.12 ± 14.42	7/87.5%	34.60 ± 10.36	2/40%	30.66 ± 14.61	3/50%	30.50 ± 7.07	1/50%
Cognitive flexibility	TMT-B	201.37 ± 125.36	3/37.5%	109.60 ± 68.75	1/20%	183.83 ± 101.72	3/50%	95.00 ± 56.56	0/0%
Total IQ	Vc, Cb, Sm, MR	76.37 ± 17.57	7/87.5%	82.40 ± 13.90	3/60%	86.50 ± 20.40	3/50%	87.50 ± 7.77	1/50%
Verbal IQ	Sm, Vc	0.95 ± 0.55	6/75%	1.34 ± 0.75	4/80%	0.80 ± 0.31	3/50%	1.40 ± 0.56	1/50%
Execution IQ	Cb, MR,	81.62 ± 18.03	7/87.5%	81.60 ± 10.83	3/60%	89.16 ± 15.35	3/50%	89.00 ± 9.89	1/50%
Processing speed index	SyS, Cd	99.87 ± 8.27	1/12.5%	112.20 ± 8.25	0/0%	115.33 ± 16.02	0/0%	108.00 ± 11.31	0/0%

Abbreviations: EDS, excessive daytime sleepiness; Cb, cubes; Cd, Codes; Dg, Digits; IQ, intelligence quotient; MR, Matrix Reasoning; RF, Rey figure; RFR, Rey figure recall; SD, standard deviation; Sm, Similarities; SyS, Symbol Search; TMT, Trail Making test; TMT-B, Trail Making test B; Vc, Vocabulary.
Note: *n/% = % altered.

Table 3 Polysomnography data of the study sample

	All genotypes		ApoEε3/ ε4		non-ApoEε3/ε4	
	Mean	SD	Mean	SD	Mean	SD
TST (minutes)	346.8	53.0	357.0	58.3	326.3	35.4
WASO (minutes)	75.6	38.2	72.5	35.0	81.7	46.4
Sleep latency (minutes)	16.3	11.8	14.3	11.8	20.4	11.7
REM latency (minutes)	146.6	48.8	127.3	33.4	185.4	53.9
REM (%)	15.2	4.8	16.7	3.8	12.2	5.5
N1 (%)	16.1	8.8	15.5	9.0	17.4	9.0
N2 (%)	54.3	13.3	50.7	12.3	61.5	13.2
N3 (%)	17.2	15.7	17.9	9.7	15.8	24.8
AHI (events per hour)	34.1	15.9	32.6	16.1	37.2	16.3
Sat < 90% (%TST)	0.9	1.6	0.7	1.5	1.5	1.9
PLMI (events per hour)	3.9	13.9	5.6	16.9	0.6	1.6
Arousal index (events per hour)	32.8	16.2	32.5	15.9	33.5	18.0
ESS	9.0	5.2	8.0	5.8	10.9	3.5

Abbreviations: AHI, apnea-hypopnea index; ApoE, apolipoprotein E; ESS, Epworth Sleepiness Scale; N1, non-REM sleep stage 1; N2, non-REM sleep stage 2; N3, non-REM sleep stage 3; PLMI, periodic limb movement index; REM, rapid eye movement sleep; Sat, oxygen saturation; SD, standard deviation; TST, total sleep time; WASO, wake after sleep onset.
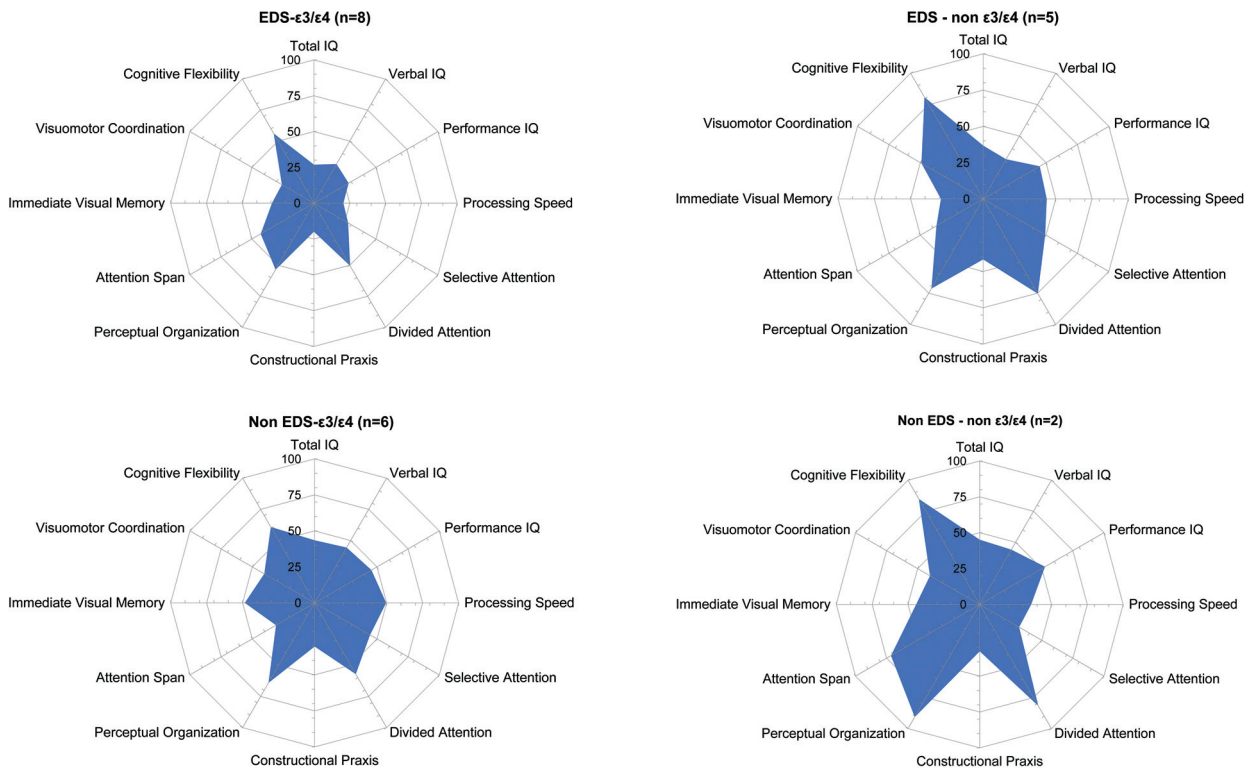

Figure 2 Differences in cognitive results among the groups (normalized data).

cognitive performance, and that a genetic factor may potentiate the harmful effect of EDS on cognition. Future investigations in this field can contribute to a better understanding and management of the clinical consequences of OSAS.

Authors' Contributions
FMB: hypothesis conception, data collection, analysis; WASM: hypothesis conception, data collection, article writing, analysis; JRH: hypothesis conception, statistics, analysis; GFP, LBCC: hypothesis conception, analysis, review.

References

1 Kryger MH, Roth T, Dement WC. Principles and Practice of Sleep Medicine. Philadelphia, PA: Saunders/Elsevier; 2011

2 Juliano ML, Machado MA, de Carvalho LB, et al. Polysomnographic findings are associated with cephalometric measurements in mouth-breathing children. J Clin Sleep Med 2009;5(06):554–561

3 American Academy of Sleep Medicine. International Classification of Sleep Disorders. 3rd ed.Darien, IL2014

4 Carvalho LB, Prado LF, Silva L, et al. Cognitive dysfunction in children with sleep-disordered breathing. J Child Neurol 2005;20 (05):400–404

5 de Carvalho LB, do Prado LB, Ferrreira VR, et al. Symptoms of sleep disorders and objective academic performance. Sleep Med 2013; 14(09):872–876. Doi: 10.1016/j.sleep.2013.05.011

6 Campostrini DDA, Prado LBF, Prado GF. Obstructive Sleep Apneaand Cardiovascular Diseases (Apneia Obstrutiva do Sono e Doenças Cardiovasculares). Revista Neurociências. 2014;22 (01):102–112. Doi: 10.4181/RNC.2014.22.930.11p

7 Tudorache IF, Trusca VG, Gafencu AV, Apolipoprotein E. Apolipoprotein E - A Multifunctional Protein with Implications in Various Pathologies as a Result of Its Structural Features. Comput Struct Biotechnol J 2017;15:359–365. Doi: 10.1016/j.csbj.2017.05.003

8 Piskunowicz MT, Linkowska K, Gołota S, Grzybowski T, Kędziora-Kornatowska K, Borkowska A. The Association of Apolipoprotein E Gene Polymorphism With Cognitive Performance in Nondemented Polish Adults Aged 55 to 75. Int J Aging Hum Dev 2018; 87(02):124–140. Doi: 10.1177/0091415017724548

9 Gottlieb DJ, DeStefano AL, Foley DJ, et al. APOE epsilon4 is associated with obstructive sleep apnea/hypopnea: the Sleep Heart Health Study. Neurology 2004;63(04):664–668

10 Gozal D, Capdevila OS, Kheirandish-Gozal L, Crabtree VM. APOE epsilon 4 allele, cognitive dysfunction, and obstructive sleep apnea in children. Neurology 2007;69(03):243–249

11 Kadotani H, Kadotani T, Young T, et al. Association between apolipoprotein E epsilon4 and sleep-disordered breathing in adults. JAMA 2001;285(22):2888–2890

12 Suri S, Heise V, Trachtenberg AJ, Mackay CE. The forgotten APOE allele: a review of the evidence and suggested mechanisms for the protective effect of APOE ε2. Neurosci Biobehav Rev 2013;37(10 Pt 2):2878–2886. Doi: 10.1016/j.neubiorev.2013.10.010

13 Wu L, Zhao L. ApoE2 and Alzheimer's disease: time to take a closer look. Neural Regen Res 2016;11(03):412–413. Doi: 10.4103/1673-5374.179044

14 He K, Kapur VK. Sleep-Disordered Breathing and Excessive Daytime Sleepiness. Sleep Med Clin 2017;12(03):369–382. Doi: 10.1016/j.jsmc.2017.03.010

15 Lo JC, Ong JL, Leong RL, Gooley JJ, Chee MW. Cognitive Performance, Sleepiness, and Mood in Partially Sleep Deprived Adolescents: The Need for Sleep Study. Sleep 2016;39(03):687–698. Doi: 10.5665/sleep.5552

16 Zhou J, Camacho M, Tang X, Kushida CA. A review of neurocognitive function and obstructive sleep apnea with or without daytime sleepiness. Sleep Med 2016;23:99–108. Doi: 10.1016/j.sleep.2016.02.008

17 Koehler U, Apelt S, Augsten M, et al. [Daytime sleepiness in patients with Obstructive Sleep Apnoea (OSA) - pathogenetic factors]. Pneumologie 2011;65(03):137–142. Doi: 10.1055/s-0030-1255838

18 Uyrum E, Balbay O, Annakkaya AN, Gulec Balbay E, Silan F, Arbak P. The relationship between obstructive sleep apnea syndrome and apolipoprotein E genetic variants. Respiration 2015;89(03): 195–200. Doi: 10.1159/000369560

19 O'Hara R, Schröder CM, Kraemer HC, et al. Nocturnal sleep apnea/hypopnea is associated with lower memory performance in APOE epsilon4 carriers. Neurology 2005;65(04):642–644

20 Larkin EK, Patel SR, Redline S, Mignot E, Elston RC, Hallmayer J. Apolipoprotein E and obstructive sleep apnea: evaluating whether a candidate gene explains a linkage peak. Genet Epidemiol 2006;30(02):101–110

21 Daurat A, Sarhane M, Tiberge M. [Obstructive sleep apnea syndrome and cognition: A review]. Neurophysiol Clin 2016;46(03): 201–215. Doi: 10.1016/j.neucli.2016.04.002

22 Wallace A, Bucks RS. Memory and obstructive sleep apnea: a meta-analysis. Sleep 2013;36(02):203–220. Doi: 10.5665/sleep.2374

23 Beebe DW, Groesz L, Wells C, Nichols A, McGee K. The neuropsychological effects of obstructive sleep apnea: a meta-analysis of norm-referenced and case-controlled data. Sleep 2003;26(03): 298–307

24 Olaithe M, Bucks RS, Hillman DR, Eastwood PR. Cognitive deficits in obstructive sleep apnea: Insights from a meta-review and comparison with deficits observed in COPD, insomnia, and sleep deprivation. Sleep Med Rev 2018;38:39–49. Doi: 10.1016/j.smrv.2017.03.005

25 Cosentino FI, Bosco P, Drago V, et al. The APOE epsilon4 allele increases the risk of impaired spatial working memory in obstructive sleep apnea. Sleep Med 2008;9(08):831–839

26 Nikodemova M, Finn L, Mignot E, Salzieder N, Peppard PE. Association of sleep disordered breathing and cognitive deficit in APOE ε4 carriers. Sleep 2013;36(06):873–880. Doi: 10.5665/sleep.2714

27 Caselli RJ, Reiman EM, Hentz JG, Osborne D, Alexander GE, Boeve BF. A distinctive interaction between memory and chronic daytime somnolence in asymptomatic APOE e4 homozygotes. Sleep 2002;25(04):447–453

28 Bertolazi AN, Fagondes SC, Hoff LS, Pedro VD, Menna Barreto SS, Johns MW. Portuguese-language version of the Epworth sleepiness scale: validation for use in Brazil. J Bras Pneumol 2009;35 (09):877–883

29 Fu Y, Xu H, Xia Y, et al. Excessive daytime sleepiness and metabolic syndrome in men with obstructive sleep apnea: a large cross-sectional study. Oncotarget 2017;8(45):79693–79702. Doi: 10.18632/oncotarget.19113

30 Murray BJ. Subjective and Objective Assessment of Hypersomnolence. Sleep Med Clin 2017;12(03):313–322. Doi: 10.1016/j.jsmc.2017.03.007

31 Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991;14(06):540–545

32 Gagnon K, Baril AA, Gagnon JF, et al. Cognitive impairment in obstructive sleep apnea. Pathol Biol (Paris) 2014;62(05): 233–240. Doi: 10.1016/j.patbio.2014.05.015

33 Malloy-Diniz LF, Fuentes D, Abrantes SSC, Lasmar VAP, Salgado JV. Teste de aprendizagem auditivo-verbal de Rey RAVLT. In: Malloy-Diniz LF, Fuentes D, Mattos P, Abreu N, eds. et col. Avaliação Neuropsicológica.São Paulo: Artmed; 2010

34 Nascimento E. Escala de inteligência Wechsler para adultos - manual para administração e avaliação. São Paulo: Casa do Psicólogo; 2004

35 Oliveira MS, Rigoni MS. Figuras complexas de Rey: teste de cópia e de reprodução de memória de figuras geométricas complexas. São Paulo: Casa do Psicólogo; 2010

36 Spreen O, Strauss E. A Compendium of Neuropsychological Test. New York: Oxford University Press; 1998

37 Trentini CM, Yates DB, Heck VS. Escala Wechsler Abreviada de Inteligência-WASI: manual. São Paulo: Casa do Psicólogo; 2014

38 Signorell A. DescTools: Tools for descriptive statistics. R package version 0.99.21. 2017 Nov 11. 2017; Fromhttps://cran.r-project.org/package=DescTools.

39 Wickham H. Tidy data. J Stat Softw 2014;59(10):1–23. Doi: 10.18637/jss.v059.i10

40 Wickham H. Tidyverse: easily install and load 'tidyverse' packages. R package version 1.1.1. 2017 Nov 11. 2017; From https://cran.rproject.org/web/packages/tidyverse/index.html

41 Small GW, Ercoli LM, Silverman DH, et al. Cerebral metabolic and cognitive decline in persons at genetic risk for Alzheimer's disease. Proc Natl Acad Sci U S A 2000;97(11):6037–6042. Doi: 10.1073/pnas.090106797

42 Zlokovic BV. Cerebrovascular effects of apolipoprotein E: implications for Alzheimer disease. JAMA Neurol 2013;70(04): 440–444

43 Yoo SS, Hu PT, Gujar N, Jolesz FA, Walker MP. A deficit in the ability to form new human memories without sleep. Nat Neurosci 2007; 10(03):385–392. Doi: 10.1038/nn1851

44 Johnson DA, Lane J, Wang R, et al; The Multi-Ethnic Study of Atherosclerosis. Greater cognitive deficits with sleep-disordered breathing among individuals with genetic susceptibility to Alzheimer Disease. Ann Am Thorac Soc 2017;14(11):1697–1705. Doi: 10.1513/AnnalsATS.201701-052OC