Sleep Science and Practice

RESEARCH

Open Access

Sleep fragmentation and hypoxaemia as key indicators of cognitive impairment in patients with obstructive sleep apnoea

Thomas Georgeson[1,2], Lacey Atkins[3†], Alex Zahnleiter[2†], Philip I Terrill[4†], Eamonn Eeles[5], Elizabeth J Coulson[2,3†] and Irene Szollosi[1,2*†]

Abstract

Background This study aimed to identify characteristics associated with cognitive impairment in older individuals with obstructive sleep apnoea (OSA) using the Addenbrooke's Cognitive Examination-Revised (ACE-R) that could aid in stratifying those at higher risk for impairment.

Methods We analysed existing cross-sectional datasets that measured the performance of 89 adult patients (aged 50–85 years) with OSA on the ACE-R cognitive test. Receiver operating characteristic curves and logistic regression analysis were utilised to identify associations between impairment status and various factors, including demographic characteristics, self-reported sleepiness, cognitive complaints, and OSA severity.

Results According to established thresholds (ACE-R ≤ 88), 36% of participants were cognitively impaired. When adjusted for age and education, the strongest factors associated with impairment status were prior measures of arousal index (cut-off: ≥28events/hr, OR: 5.67, $p < 0.01$), sleep mean SpO_2 (cut-off: ≤92%, OR: 3.52, $p < 0.05$), 3% oxygen desaturation index (cut-off: ≥27events/hr, OR: 3.75, $p < 0.05$), and sleep time spent under 90% SpO_2 (cut-off: ≥9%, OR: 3.16, $p < 0.05$). Combining these factors achieved a high sensitivity (≥ 93%) of detecting impairment within this cohort. Conversely, the apnoea-hypopnoea index, daytime sleepiness, and cognitive complaints were not associated with impairment status.

Conclusions The ACE-R identified a significant proportion of patients with OSA as having cognitive impairment. Traditional indices of sleep fragmentation and hypoxaemia may allow clinicians to identify at-risk patients for cognitive evaluation, however further studies are needed to validate these findings and explore whether poor cognitive performance can be remediated via OSA treatment.

Keywords OSA, Cognitive impairment, Cognitive complaint, ACE-R, PSG, ESS

†Lacey Atkins and Alex Zahnleiter contributed equally to this work.

†Philip I Terrill, Elizabeth J Coulson and Irene Szollosi contributed equally to this work.

*Correspondence:
Irene Szollosi
irene.szollosi@health.qld.gov.au
Full list of author information is available at the end of the article

Background

Obstructive sleep apnoea (OSA) is associated with impairments in multiple neurocognitive domains, including attention/vigilance, executive function, memory, motor control, and processing speed (Bucks et al. 2017; Stranks and Crowe 2016). Additionally, OSA is a known risk factor for dementia, with systematic reviews indicating an increased risk of Alzheimer's Disease in older adults and a higher prevalence of OSA among those with dementia (Bubu et al. 2020; Guay-Gagnon et al. 2022). Proposed mechanisms of neurological harm in OSA include intermittent hypoxaemia and sleep fragmentation, metrics which are routinely recorded in overnight polysomnography (PSG).

Clinicians should consider the use of cognitive screening in sleep clinics prior to therapeutic intervention to identify impaired individuals and to establish a baseline for post-intervention comparison. However, generalised cognitive evaluations are resource intensive and may not be a feasible option within sleep clinics where more targeted patient selection may be required. Additionally, subjective cognitive complaints, such as poor concentration, are common yet weak predictors of objective cognitive deficits in this population (Vaessen et al. 2015). It is therefore necessary to use objective assessments of cognition, such as validated screening instruments, to provide quantitative estimates of cognitive performance, offering a valuable means to assess clinical outcomes before and after OSA treatment.

The Mini-Mental State Examination (MMSE) is the most widely used cognitive screening instrument, but in addition to an observed ceiling effect, it has been reported to lack sensitivity for single domain impairment in mild cognitive impairment (MCI) (Pendlebury et al. 2012). The Addenbrooke's Cognitive Examination – Revised (ACE-R) in which the MMSE is embedded, was developed to be more sensitive for MCI and includes items to evaluate executive function (Mioshi et al. 2006; Larner and Mitchell 2014). It has been shown as accurate in identifying persons with either MCI and dementia in a wide range of prevalence settings, with two published cut-offs for detecting dementia, a score of 88 (sensitivity = 0.94, specificity = 0.89) and a score of 82 (sensitivity = 0.84, specificity = 1.0). The ACE-R has also previously been utilised in the OSA population (Karapin et al. 2022; Rosenzweig et al. 2016). Although slightly longer than the MMSE, it requires little training and can be administered within a single session with additional benefits of assessing multiple cognitive domains of attention & orientation, memory, verbal fluency, language, and visuospatial abilities.

In this study, we employed the ACE-R in middle-aged and older adults with OSA who had no prior medical history of cognitive impairment, to evaluate the cognitive profile of this population. It is important to note that cognitive screening was used to evaluate the effects of untreated OSA on cognition and not to evaluate dementia risk per se, given OSA treatment may modify risk (Dunietz et al. 2021). Our aim was to explore associations that could help sleep clinics target individuals for cognitive screening. Specifically, we investigated whether factors such as participant demographics, cognitive complaints, daytime sleepiness, and OSA severity—measured by both the apnoea-hypopnoea index (AHI) and other PSG metrics—could serve as indicators for those likely to have cognitive impairment. We hypothesized that PSG measures that more accurately quantify sleep fragmentation and hypoxaemia would better identify cognitively impaired patients than subjective complaints.

Methods

Study design and population

This study combines the research datasets of two previous studies conducted at a tertiary hospital sleep laboratory. Both studies were cross-sectional in nature and aimed to identify associations between OSA and multiple neurocognitive endpoints. The two cohorts exhibited comparable population characteristics, and the ACE-R assessment served as a common outcome measure in both. Both studies were approved by the institutional Human Research Ethics Committees and all participants provided written informed consent. The present study combining these records was approved by the institutional Human Research Ethics Committee (ethics reference: LNR/2020/QPCH/66041).

All participants were referred for a continuous positive airway pressure (CPAP) treatment study for OSA based on a Type-I or Type-II diagnostic PSG and were not currently treated with CPAP. Recruitment occurred on the night of treatment study.

The first study (Study 1) was approved for commencement in 2015 with a total of 50 participants enrolled between April-September 2016. Cognitive testing with the ACE-R took place on the night of the CPAP study (prior to CPAP commencement). The second study (Study 2) was approved for commencement in 2017 with a total of 42 participants enrolled between April 2018 and February 2020. Cognitive testing with the ACE-R took place 1–2 weeks post CPAP sleep study and prior to commencement of treatment at home, after the patient's clinical consultation.

Common inclusion criteria for both studies were diagnosis of OSA through PSG, and fluent in written and spoken English. Shared exclusion criteria were intracranial injury, previous diagnosis of cognitive impairment, and Cheyne-Stokes respiration. The two studies differed in

the AHI threshold for inclusion, with Study 1 including those with AHI ≥ 5 events per hour, and Study 2 including those with AHI ≥ 15 events per hour. Additionally, Study 1 included individuals ≥ 50 years old, whist Study 2 imposed an age restriction of 55–75 years old. Finally Study 2 imposed a maximum bodyweight exclusion of ≥ 130 kg, due to the requirements of an MRI scan that was an additional outcome. Population characteristics of both original datasets and PSG study types are supplied in supplementary Table S2 and S3 respectively.

For this analysis, we excluded three participants due to undisclosed CPAP use at the time of testing ($n=2$) and incomplete ACE-R testing ($n=1$). The remaining 89 participants were included in the combined dataset.

Polysomnography and OSA severity

All participants had previously completed either a Type-1 attended ($n=59$, 66%) or Type-2 unattended ($n=30$, 34%) diagnostic PSG prior to recruitment. Overnight recording of physiological signals included electroencephalography, electrooculography, electromyography, electrocardiography, thoracoabdominal movement, nasal pressure, oronasal airflow, snoring volume, body position and finger pulse oximetry (SpO_2). Sleep stages, arousals, and respiratory events were scored according to AASM guidelines.

Due to changes in respiratory scoring guidelines by the AASM and Australasian Sleep bodies, different hypopnoea scoring rules were used in the analysis of patient PSG data. Over 65% of the PSGs in this study used the current 2012 AASM recommended criteria. The remainder used the previous 2007 criteria. To ensure consistency, all studies scored using the 2007 criteria were converted to the 2012 AASM method (i.e., 30% reduction in nasal airflow with 3% oxygen desaturation and/or EEG arousal) using published regression equations (Duce et al. 2015). All studies were reported by an accredited sleep physician.

Frequency of respiratory events and sleep fragmentation were defined by the PSG metrics of the AHI and arousal index, respectively. For hypoxaemic severity, the frequency of 3% oxygen desaturations (oxygen desaturation index, ODI), mean peripheral oxyhaemoglobin saturation during sleep (mean SpO_2), and total sleep time spent under 90% saturation (T90) were used.

Addenbrooke's Cognitive Examination – Revised

The ACE-R evaluates cognition across five broad cognitive domains including attention & orientation, memory, verbal fluency, language, and visuospatial abilities, combined to generate a total score out of 100 (individual items are presented in the supplementary Table S1) (Mioshi et al. 2006; Larner and Mitchell 2014). Two cut-offs for detecting dementia were defined in the original validation study: a score of 88 (sensitivity = 0.94, specificity = 0.89) and a score of 82 (sensitivity = 0.84, specificity = 1.0). For this study, we opted for the more liberal cut-off of 88, as our focus was on identifying cognitive impairment rather than specifically quantifying dementia risk. Additionally, a portion of these items also generate a MMSE score. This instrument can be derived from 30 points across 11 items in the ACE-R (no verbal fluency items), with a cut-off of 24 indicative of impairment (Pangman et al. 2000; Folstein et al. 1975).

Clinical data and cognitive complaints

All participants had their height and weight recorded at the time of enrolment. Additionally, as part of their routine clinical visit, they completed a comprehensive medical questionnaire. This questionnaire not only gathered detailed information on their medical history and current medications but also focused on aspects related to sleep. Importantly, it included specific questions aimed at identifying issues with short-term memory or concentration, with participants responding in a binary yes/no format.

Epworth Sleepiness Scale

Participants completed an Epworth Sleepiness Scale (ESS) questionnaire as part of their routine clinical care; an ordinal-scale, self-reported measure of daytime sleepiness commonly employed in sleep clinics (Johns 1991). Participants were asked to give a number ranging from 0-3 of 'dozing' likelihood during certain daytime activities, with 0 being 'unlikely to doze' and 3 being 'high chance of dozing'. A total score ≥ 11 is indicative of excessive daytime sleepiness (EDS).

Educational background

Participants were asked to indicate the age they left compulsory schooling and to select their highest educational level from six responses: Primary School, Secondary School, Certificate/Trade, University Enrolment, Undergraduate Degree, and Postgraduate Degree.

Statistical analysis

Statistical analysis was performed using SPSS V27.0 (IBM Corp. Released 2020. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp). Statistical analysis and data visualization was also performed using the Python programming language (V3.9.7) and the following libraries: Matplotlib (V3.4.3), Seaborn (V0.11.2), Pandas (V1.3.4), SciPy (V1.7.1), and NumPy (V1.20.3).

Categorical variables were described as count (%), and continuous variables were described as mean (± SD). Receiver operating characteristic (ROC) analysis was employed to identify the optimal cut-off values

(utilising Youden's Index) (Fluss et al. 2005) for age and the following continuous predictors; AHI, arousal index, mean SpO_2, ODI, T90, and ESS. The continuous measures were dichotomised based on ROC derived cut-offs (dummy coded, with 1 = greater severity, 0 = lesser severity). To assess the association between patient characteristics and cognitive impairment status (defined as an ACE-R score ≤ 88), logistic regression was performed with ACE-R as the dependent variable, calculating the odds ratio (OR) for both the untransformed (continuous) and transformed (dichotomised) predictors. Binary predictors included were the presence of memory and concentration complaints. Covariates of cognitive performance considered in the logistic regression were age (dichotomised only), sex (male), and educational attainment, with both lower education (< 14 years compulsory schooling) and higher education (minimum of undergraduate degree) being categorised as ordinal data. Only covariates found to be significant were included in adjusting the logistic regression model.

Different combinations of significant predictors for cognitive impairment were integrated into models using a 'rule-in' approach. This method dictates that if any single predictor within a combination indicates potential impairment, the overall model result is classified as positive. This approach is employed to ensure that no potential cases of impairment are overlooked, maximizing sensitivity in detecting conditions. To address missing PSG data, pairwise deletion was used, with the sample size specified where possible. All statistical tests were two-tailed with $p < 0.05$ being considered statistically significant.

Results

Between 2016-2020, 89 OSA-confirmed individuals aged 66.0 ± 7yrs were cognitively screened using the ACE-R. Characteristics of these individuals are summarised in Table 1. A total of 32 individuals were classified as being cognitively impaired on the ACE-R (Fig. 1), receiving a score equal to or less than 88/100 (36%), whereas only 2 individuals received an MMSE score equal to or less than 24/30 (2%). Additionally, over 38% of participants received a perfect score on the MMSE, with very little spread observed amongst the assessed items (28.7 ± 1.6) compared to the total ACE-R items (89.2 ± 6.1).

Performance varied considerably across the ACE-R cognitive domains (Fig. 2). Scores were high for the attention/orientation domain, with over 73% of participants receiving a perfect score for all items. This was observed to a lesser degree in the visuospatial (36%) and language domains (26%) and least of all in the memory (12%) and verbal fluency (4%) domains. On further exploration of this, the combined results of 3 items (delayed verbal recall and both phonemic/categorical fluency) explained 68% of the variance in total ACE-R score. Scores on the items corresponding to the MMSE within the ACE-R were also high, with 73% of participants scoring perfectly on attention/orientation, 57% on memory items, 77% on language items, and 92% on the single visuospatial item.

Table 1 Characteristics of cohort and cognitive profile

Characteristics	Sample size	Mean ± SD or n (%)
Age (years)	89	66.0 ± 7.0
BMI (kg/m^2)	89	35.7 ± 7.4
Obesity (BMI ≥ 30)		70 (79%)
Sex (male)	89	42 (47%)
ESS	89	9.7 ± 4.9
EDS		38 (43%)
< 14 years Compulsory Education	89	10 (11%)
Higher Education		9 (10%)
Memory Complaints	85	49 (58%)
Concentration Complaints	78	33 (42%)
Both	77	29 (38%)
Hypertension	89	60 (67%)
COPD		15 (17%)
Type-2 Diabetes		31 (35%)
Depression		44 (49%)
AHI (events/hr)	88	32.4 ± 18.0
Arousal Index (events/hr)	86	31.3 ± 17.4
Mean SpO_2(%)	81	92.9 ± 2.2
ODI (events/hr)	76	25.6 ± 19.6
T90 (%)	76	11.7 ± 16.7
ACE-R Total (/100)	89	89.2 ± 6.1
Attention (/18)		17.6 ± 0.9
Memory (/26)		22.4 ± 3.2
Verbal Fluency (/14)		10.3 ± 1.9
Language (/26)		24.2 ± 1.8
Visuospatial (/16)		14.7 ± 1.4

Our ROC analysis revealed the following Area Under the Curve (AUC) results for each continuous predictor with impairment status; age (AUC = 0.644, p-value = .025), arousal index (AUC = 0.657, p-value = .016), mean SpO_2 (AUC = 0.633, p-value = .050), T90 (AUC = 0.619, p-value = .088), ODI (AUC = 0.599, p-value = .154), AHI (AUC = 0.535, p-value = .584), ESS (AUC = 0.496, p-value = .956). A summary of the individual ROC curves, including optimal cut-offs for these predictors and their associated sensitivity & specificity values are presented in Fig. 3.

The logistic regression results are presented in Table 2. All predictors were adjusted for age and educational level, with age ≥ 64yrs being associated with an increase in odds of cognitive impairment (OR = 3.634, 95%CI = 1.298–10.174, p-value = .014), and each successive level

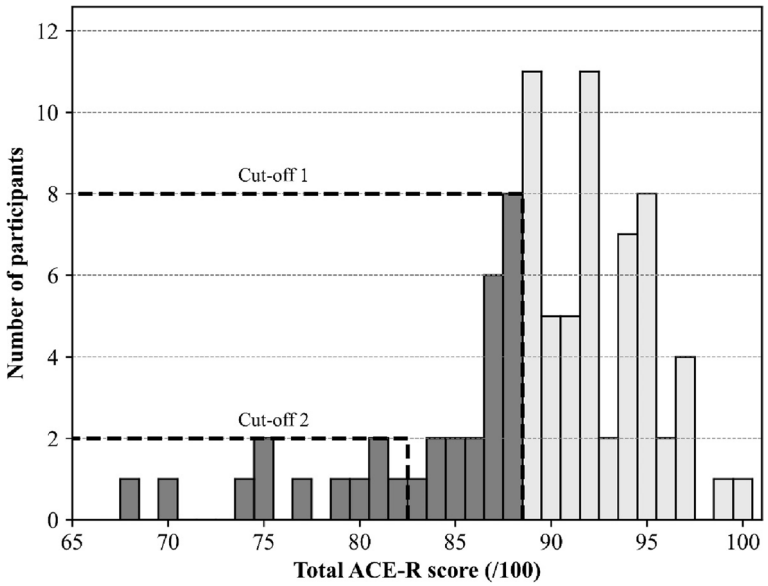

Fig. 1 Distribution of ACE-R scores. The indicated cut-offs represent thresholds that maximized detection of dementia in the original validation study. Cut-off 1 was used in this analysis to define cognitive impairment

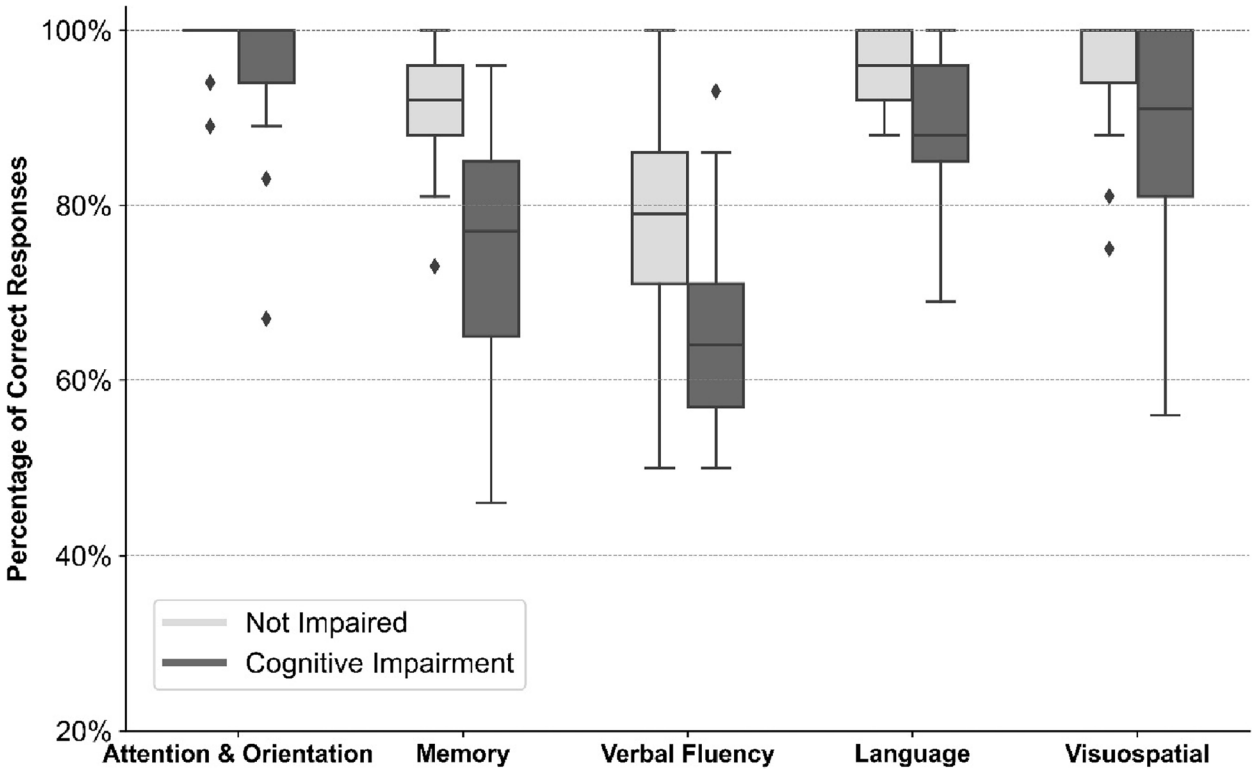

Fig. 2 Performance in ACE-R cognitive domains comparing participants classified as cognitively impaired (total ACE-R score ≤ 88) and those not impaired

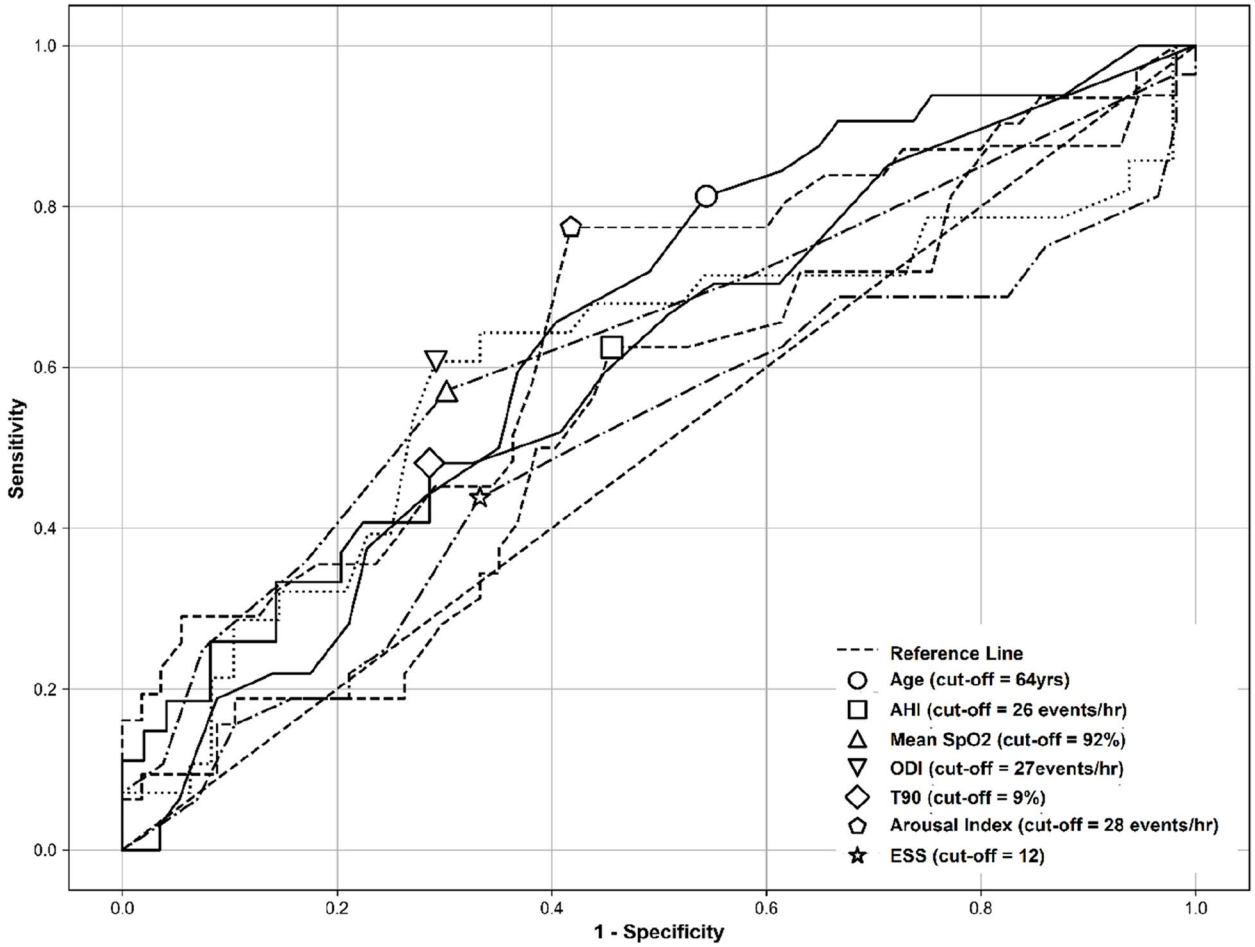

Fig. 3 Receiver operating characteristic (ROC) curves for continuous predictors against cognitive impairment status, with optimal cut-off values identified using Youden's Index indicated on graph

of educational attainment being associated with a decrease in odds (OR = 0.229, 95%CI = 0.072–0.724, *p*-value = .012). However, gender was not considered as a covariate due to lack of association with impairment status (OR = 1.768, 95%CI = 0.738–4.238, *p*-value = .201). The arousal index and T90 were significantly associated with cognitive impairment odds in both the continuous and dichotomised models. Mean SpO_2 and ODI also showed significance when dichotomised, whilst AHI, ESS, and subjective cognitive complaints showed no association. The unadjusted models are presented in supplementary Table S4.

When combining all dichotomised predictors (including age) using a 'rule-in' approach, we identified the following optimal configurations that maximised sensitivity whilst minimising specificity loss. The first combination, 'mean SpO_2 or ODI or arousal index', resulted in 54 participants meeting the rule-in criteria, with 26 being impaired and 28 being false positives (sensitivity: 96%, specificity: 42%, $n = 75$). The second combination, 'ODI or T90 or arousal index', identified 51 participants as meeting the rule-in criteria, including 26 true positives and 25 false positives (sensitivity: 96%, specificity: 47%, $n = 74$). Lastly, the combination of 'T90 or Arousal Index' had 51 participants satisfying the rule-in criteria, with 25 being impaired and 26 being false positives (sensitivity: 93%, specificity: 47%, $n = 76$). Full results are presented in supplementary Table S5.

Discussion

This study reports several key findings related to cognitive impairment in patients with OSA. First, we found that measures of sleep fragmentation and hypoxaemia were significantly associated with increased odds of cognitive impairment. Second, we observed a high prevalence of cognitive impairment (36%) that does not correlate with subjective symptoms such as daytime sleepiness or cognitive complaints. Third, a combination

Table 2 Results of the logistic regression analysis evaluating the association between cognitive impairment status and participant characteristics. For the dichotomised variables, the continuous predictors were transformed based on the optimal cut-offs previously identified via ROC analysis, with greater severity coded as positive. Age adjusted for education, all other predictors adjusted for age and education level. Sample size is displayed for each variable due to the absence of data for some cases

		n	B	Odds Ratio (95% CI)	*p*-value
Age	Continuous	89	0.069	1.07 (1.00 – 1.15)	.050
	Dichotomised (64yrs)		1.426	4.16 (1.41 – 12.30)	**.010**
AHI	Continuous	88	0.017	1.02 (0.99 – 1.04)	.209
	Dichotomised (26events/hr)		0.686	1.99 (0.75 – 5.27)	.168
Arousal Index	Continuous	86	0.045	1.05 (1.01 – 1.08)	**.008**
	Dichotomised (28 events/hr)		1.735	5.67 (1.84 – 17.53)	**.003**
Mean SpO_2	Continuous	81	-0.212	0.81 (0.64 – 1.03)	.079
	Dichotomised (92%)		1.258	3.52 (1.17 – 10.55)	**.025**
ODI	Continuous	76	0.026	1.03 (1.00 – 1.055)	.068
	Dichotomised (27 events/hr)		1.323	3.75 (1.24 – 11.37)	**.019**
T90	Continuous	76	0.035	1.04 (1.00 – 1.07)	**.044**
	Dichotomised (9%)		1.152	3.16 (1.01 – 9.89)	**.048**
ESS	Continuous	89	0.035	1.04 (0.94 – 1.14)	.497
	Dichotomised (12)		0.828	2.29 (0.81 – 6.44)	.117
Memory Complaint		85	-0.663	0.52 (0.19 – 1.41)	.197
Concentration Complaint		78	-0.728	0.48 (0.15 – 1.52)	.212

of factors using a 'rule-in' approach led to a substantial improvement in impairment identification at the cost of specificity. The high sensitivity of these routinely collected PSG metrics in identifying cognitive impairment suggests that risk stratification may be possible for targeted cognitive screening in clinical settings.

The lack of association between daytime sleepiness or presence of cognitive complaints with cognitive impairment, is in line with previous studies that have reported that subjective measures of sleepiness and memory complaints correlate poorly with their objective counterparts in this population (Vaessen et al. 2015; Scharf 2022). Similarly, the AHI is known to be an unreliable marker of comorbid prediction (Borsini et al. 2018). Patients with identical AHI values can experience varying levels of hypoxaemia and sleep fragmentation, leading to inconsistent results when correlating AHI severity with multiple cognitive endpoints (Kainulainen et al. 2019; Hayward et al. 1992; Ayalon et al. 2009; Boland et al. 2002).

We did, however, find significant associations between mean SpO_2 (OR 3.52), T90 (OR 3.16), ODI (OR 3.75), and arousal index (OR 5.67) with cognitive impairment. Although methodological limitations prevent causal inference, there is strong biological plausibility for these mechanisms contributing to cognitive harm. Intermittent hypoxia is considered one of the primary mechanisms of neurocognitive injury in OSA, causing short-term, localized neural tissue damage during sleep (e.g., ischemia-reperfusion injury) and systemic metabolic maladaptation's in response to chronic exposure (Navarrete-Opazo and Mitchell 2014; Alex et al. 2017; Durgan and Bryan 2012). Similarly, sleep fragmentation can induce cognitive harm through chronic sympathetic overactivity and disruption of homeostatic mechanisms essential for healthy cognitive function, such as memory consolidation (Rasch and Born 2013; Venkataraman et al. 2020). Studies in rodent models have shown that both intermittent hypoxia and sleep fragmentation can lead to hippocampal damage, impairing neurogenesis, neuroplasticity, and cell excitability (Navarrete-Opazo and Mitchell 2014; Tartar et al. 2006, 2010; Roman et al. 2005; Vecsey et al. 2009). As such, mean SpO_2, T90, ODI, and arousal index have all been previously shown to be correlated with multiple cognitive endpoints (Beaudin et al. 2021; Blackwell et al. 2015; Li et al. 2019; Tsai et al. 2022), however, this is the first study that reports this relationship with the ACE-R instrument and proposes thresholds that may be utlised to stratify risk of cognitive impairment.

Despite the well-established link between OSA and cognitive impairment, the prevalence of impairment in this population has not been thoroughly established. This is most likely due to the lack of standardisation in the tools and thresholds used to discern impairment, as well as the infrequent routine cognitive testing conducted in sleep clinic populations (Bucks et al. 2013). Beaudin et al. using the Montreal Cognitive Assessment screening instrument to identify a prevalence of MCI in patients

with moderate-to-severe OSA reported a prevalence of 42–55% depending on the threshold that was applied (Beaudin et al. 2021). Other studies using a comprehensive neuropsychological battery to clinically diagnose MCI in patients with OSA report prevalence of 36–40% (Gagnon et al. 2019; Gagnon et al. 2018) in contrast to a recent meta-analysis that found global prevalence of MCI to be 21% in those aged 50 years and older (Song et al. 2023). Whilst the present study evaluated cognitive impairment in OSA and not clinical MCI, the prevalence found is broadly in line with previous studies.

Dichotomizing the ACE-R allowed for a clear and clinically relevant categorization of individuals into impaired and non-impaired groups based on established validated thresholds. This approach simplifies the interpretation and application of the results in clinical settings, where clear decision points are needed to guide patient management. Additionally, our cut-off threshold for cognitive impairment (ACE-R≤88) was set liberally to maximize sensitivity for detecting all-cause impairment, rather than exclusively identifying cases that are more likely to represent a population with dementia, for which a more conservative threshold (e.g., ≤ 82) would have been appropriate. However, the original paper by Mioshi et al., did publish a range of dementia likelihood ratios to overcome the 'grey-zone' between the proposed cut-off values of 88 and 82 (Mioshi et al. 2006). Whilst a score of 88 is 8.4 times more likely to come from someone with dementia than without, a score of 82 was 100 times more likely. Eleven individuals in our sample (12%) scored at or below an ACE-R score of 82. However, we cannot extrapolate these patients to have elevated dementia risk, as there may be full or partial reversal of cognitive impairment with OSA treatment (Wang et al. 2020).

When investigating the individual items comprising the ACE-R (see supplementary Table S1), we found that most items presented with a possible ceiling effect, notably in the attention & orientation domain, and some items of the memory, language, and visuospatial domains. Without further testing, it is unclear whether these items were not sufficiently sensitive to detect mild cognitive deficits, or if participants were indeed unimpaired and performing at maximal test levels. If the former were true, this limitation may mask subtle relationships between OSA and cognitive function. This is especially pertinent with attentional function, as this domain is known to be significantly affected by sleep disruption/fragmentation (Angelelli et al. 2020). Conversely, we observed that three specific tasks—the delayed verbal recall test, and both phonemic and semantic verbal fluency tasks— accounted for a substantial portion of variation in total ACE-R score. These cognitive tasks may be particularly sensitive to the effects of OSA, as intermittent hypoxaemia can impair the hippocampus, affecting memory, while sleep fragmentation disrupts the frontal lobe, impacting executive function (Navarrete-Opazo and Mitchell 2014; Sen and Tai 2023). Delayed recall and verbal fluency tasks have previously been found to be impaired in the population with OSA and are sensitive measures of both MCI and Alzheimer's Disease (Mueller et al. 2015; Zhao et al. 2012; Wallace and Bucks 2013; Makanikas et al. 2021).

Limitations and future research

Methodological limitations within this cross-sectional investigation include the small sample size and potential bias introduced by the modest difference in inclusion criteria between the two datasets (see Table S2 and S3 for statistical comparison). Additionally, given the exploratory nature of our second aim, we chose not to apply a correction for multiple comparisons. This decision was made to minimize the risk of Type II errors (i.e., false negatives) which could potentially mask important correlates of cognitive performance. However, we acknowledge both the increase in risk of Type 1 errors, and the overfitting of our variables to this cohort, therefore further larger studies are needed to confirm the associations here and validate their clinical use as predictors of impairment. Additionally, novel methods that provide greater precision in measuring hypoxaemia and sleep micro/macro-architecture, such as the hypoxic burden (Terrill 2020), and advanced quantitative-EEG measures (e.g., arousal intensity, odds ratio product) (Malhotra et al. 2021) are emerging as potential biomarkers of cognitive status (D'Rozario et al. 2017). However, these advanced metrics are not typically available in routine clinical settings and should therefore be prioritized in future clinical research, particularly during methodological planning, to enhance the understanding and detection of cognitive impairment in OSA.

It is also important to note that the ACE-R has been superseded by the ACE-III. However, given the almost perfect degree of correlation between the two (99.3% R^2) with most items remaining unchanged (no changes to memory/fluency items), the results of this study would remain generalisable for both instruments (So et al. 2018).

Clinical impact

Our findings highlight that routinely collected PSG and demographic metrics may be used either alone or in combination to identify patients with OSA at risk of cognitive impairment who may benefit from formal risk assessment and/or post-treatment evaluation. Specifically, patients that are older (≥64yrs), have significant hypoxaemia (mean SpO_2 ≤92%, ODI≥27events/hr, T90≥9%), or sleep disruption (arousal index≥28 events/hr) are at a greater risk for cognitive impairment.

Specific combinations of these measures using a rule-in criterion may enhance sensitivity, potentially allowing over a third of patients to avoid unnecessary screening. However, it is important to acknowledge that more than half of the patients identified by this approach may still have an ACE-R score within the normal range. Despite this limitation to our targeted approach, we believe this trade-off is necessary to ensure that individuals with true impairment are identified and can benefit from early detection. Even a one-third reduction in those needing to be screened will result in substantially reduced labour costs, while those identified as cognitively impaired can benefit from post-OSA treatment testing to monitor treatment response. Nevertheless, the cut-offs identified in this study should be validated in larger cohorts before firm clinical recommendations can be established.

Moreover, our research, alongside existing literature, underscores the inadequacy of current patient-reported measures of sleepiness and cognitive complaints in capturing the full spectrum of neurocognitive health in patients with OSA. Although our results are preliminary, they provide foundational insights that could guide further research in this field.

Conclusion

Our findings are the first to show that routinely collected indices available in polysomnography can be utilised to identify patient at risk of cognitive impairment. Specifically, dichotomised measures of hypoxaemia and sleep disruption show promise for targeted patient selection. The ACE-R offers a valuable tool for identifying cognitive deficits in sleep clinics, particularly through tasks like delayed verbal recall and verbal fluency, which significantly contribute to the variance in overall cognitive scores among patients with OSA. However, it is important to acknowledge that while these associations are notable, these measures alone are not sufficient to reliably predict cognitive impairment, especially given the potential for cognitive recovery following treatment of the underlying OSA. Instead, these metrics should be used to guide clinicians towards targeted cognitive evaluations with screening tools such as the ACE-R.

Abbreviations

ACE-R	Addenbrooke's Cognitive Examination – Revised
AHI	Apnoea-Hypopnoea Index
CPAP	Continuous Positive Airway Pressure
EDS	Excessive Daytime Sleepiness
ESS	Epworth Sleepiness Scale
MCI	Mild Cognitive Impairment
MMSE	Mini-Mental State Examination
ODI	Oxygen Desaturation Index (3%)
OR	Odds Ratio
OSA	Obstructive Sleep Apnoea
PSG	Polysomnography
SpO_2	Peripheral Capillary Oxygen Saturation
T90	Sleep Time Spent < 90% SpO_2

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s41606-024-00120-9.

Supplementary Material 1.

Acknowledgements

We extend our sincere gratitude to Dr Deanne Curtin and the staff of The Prince Charles Hospital Sleep Disorders Centre. Their continuous support was instrumental in the execution of this research study.

Authors' contributions

AZ and LA contributed to the conception/design of the original studies and acquisition of the data analysed here. EC, PT, EE, and IS all contributed to the conception/design of this study, interpretation of the data, and revision of the written work. TG contributed to the conception, data management, statistical analysis, and drafting of the paper, as well as all other aspects of the work here. All authors have seen and approved of the current manuscript.

Funding

The medical imaging component that was not analysed in this study was funded by grants from the Mason Foundation National Medical Program and supported by the Helpful Foundation. The work undertaken by Thomas Georgeson and Lacey Atkins was supported by an Australian Post Graduate Award from the federal government.

Data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The present study was approved by the institutional Human Research Ethics Committee (ethics reference: LNR/2020/QPCH/66041).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]Sleep Disorders Centre, The Prince Charles Hospital, Brisbane, Australia. [2]School of Biomedical Sciences, The University of Queensland, Brisbane, Australia. [3]Clem Jones Centre for Ageing Dementia Research, Queensland Brain Institute, Brisbane, Australia. [4]School of Information Technology and Electrical Engineering, The University of Queensland, Brisbane, Australia. [5]Internal Medicine, The Prince Charles Hospital, Brisbane, Australia.

Received: 2 July 2024 Accepted: 29 October 2024
Published online: 10 January 2025

References

Alex RM, Mousavi ND, Zhang R, Gatchel RJ, Behbehani K. Obstructive sleep apnea: brain hemodynamics, structure, and function. J Appl Biobehavioral Res. 2017;22(4):e12101.

Angelelli P, Macchitella L, Toraldo DM, Abbate E, Marinelli CV, Arigliani M, et al. The Neuropsychological Profile of attention deficits of patients with obstructive sleep apnea: an update on the Daytime Attentional Impairment. Brain Sci. 2020;10(6):325.

Ayalon L, Ancoli-Israel S, Aka AA, McKenna BS, Drummond SP. Relationship between obstructive sleep apnea severity and brain activation during a sustained attention task. Sleep. 2009;32(3):373–81.

Beaudin AE, Raneri JK, Ayas NT, Skomro RP, Fox N, Hirsch Allen AJM, et al. Cognitive function in a sleep clinic cohort of patients with obstructive sleep apnea. Ann Am Thorac Soc. 2021;18(5):865–75.
Blackwell T, Yaffe K, Laffan A, Redline S, Ancoli-Israel S, Ensrud KE, et al. Associations between sleep-disordered breathing, nocturnal hypoxemia, and subsequent cognitive decline in older community-dwelling men: the osteoporotic fractures in men Sleep Study. J Am Geriatr Soc. 2015;63(3):453–61.
Boland LL, Shahar E, Iber C, Knopman DS, Kuo TF, Nieto FJ, et al. Measures of cognitive function in persons with varying degrees of sleep-disordered breathing: the Sleep Heart Health Study. J Sleep Res. 2002;11(3):265–72.
Borsini E, Nogueira F, Nigro C. Apnea-hypopnea index in sleep studies and the risk of over-simplification. Sleep Sci. 2018;11(1):45–8.
Bubu OM, Andrade AG, Umasabor-Bubu OQ, Hogan MM, Turner AD, de Leon MJ, et al. Obstructive sleep apnea, cognition and Alzheimer's disease: a systematic review integrating three decades of multidisciplinary research. Sleep Med Rev. 2020;50:101250.
Bucks RS, Olaithe M, Eastwood P. Neurocognitive function in obstructive sleep apnoea: a meta-review. Respirology. 2013;18(1):61–70.
Bucks RS, Olaithe M, Rosenzweig I, Morrell MJ. Reviewing the relationship between OSA and cognition: where do we go from here? Respirology. 2017;22(7):1253–61.
D'Rozario AL, Cross NE, Vakulin A, Bartlett DJ, Wong KKH, Wang D, et al. Quantitative electroencephalogram measures in adult obstructive sleep apnea - potential biomarkers of neurobehavioural functioning. Sleep Med Rev. 2017;36:29–42.
Duce B, Milosavljevic J, Hukins C. The 2012 AASM respiratory event criteria increase the incidence of Hypopneas in an adult Sleep Center Population. J Clin Sleep Med. 2015;11(12):1425–31.
Dunietz GL, Chervin RD, Burke JF, Conceicao AS, Braley TJ. Obstructive sleep apnea treatment and dementia risk in older adults. Sleep. 2021;44(9):zsab076.
Durgan DJ, Bryan RM Jr. Cerebrovascular consequences of obstructive sleep apnea. J Am Heart Assoc. 2012;1(4):e000091.
Fluss R, Faraggi D, Reiser B. Estimation of the Youden Index and its associated cutoff point. Biom J. 2005;47(4):458–72.
Folstein MF, Folstein SE, McHugh PR. Mini-mental state. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12(3):189–98.
Gagnon K, Baril AA, Montplaisir J, Carrier J, Chami S, Gauthier S, et al. Detection of mild cognitive impairment in middle-aged and older adults with obstructive sleep apnoea. Eur Respir J. 2018;52(5):1801137.
Gagnon K, Baril AA, Montplaisir J, Carrier J, De Beaumont L, D'Aragon C, et al. Disconnection between self-reported and objective cognitive impairment in obstructive sleep apnea. J Clin Sleep Med. 2019;15(3):409–15.
Guay-Gagnon M, Vat S, Forget MF, Tremblay-Gravel M, Ducharme S, Nguyen QD, et al. Sleep apnea and the risk of dementia: a systematic review and meta-analysis. J Sleep Res. 2022;31(5):e13589.
Hayward L, Mant A, Eyland A, Hewitt H, Purcell C, Turner J, et al. Sleep disordered breathing and cognitive function in a retirement village population. Age Ageing. 1992;21(2):121–8.
Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 1991;14(6):540–5.
Kainulainen S, Toyras J, Oksenberg A, Korkalainen H, Sefa S, Kulkas A, et al. Severity of desaturations reflects OSA-related daytime sleepiness better than AHI. J Clin Sleep Med. 2019;15(8):1135–42.
Karapin P, Siarnik P, Sucha B, Jurik M, Tedla M, Poddany M, et al. Cognition in patients with sleep-disordered breathing: can Obstructive and Central Apneic pauses play a different role in cognitive impairment? Life (Basel). 2022;12(8):1180.
Larner AJ, Mitchell AJ. A meta-analysis of the accuracy of the Addenbrooke's cognitive examination (ACE) and the Addenbrooke's cognitive examination-revised (ACE-R) in the detection of dementia. Int Psychogeriatr. 2014;26(4):555–63.
Li N, Wang J, Wang D, Wang Q, Han F, Jyothi K, et al. Correlation of sleep microstructure with daytime sleepiness and cognitive function in young and middle-aged adults with obstructive sleep apnea syndrome. Eur Arch Otorhinolaryngol. 2019;276(12):3525–32.
Makanikas K, Andreou G, Simos P, Chartomatsidou E. Effects of obstructive sleep apnea syndrome and medical comorbidities on language abilities. Front Neurol. 2021;12:721334.
Malhotra A, Ayappa I, Ayas N, Collop N, Kirsch D, McArdle N, et al. Metrics of sleep apnea severity: beyond the apnea-hypopnea index. Sleep. 2021;44(7):zsab030.
Mioshi E, Dawson K, Mitchell J, Arnold R, Hodges JR. The Addenbrooke's cognitive examination revised (ACE-R): a brief cognitive test battery for dementia screening. Int J Geriatr Psychiatry. 2006;21(11):1078–85.
Mueller KD, Koscik RL, LaRue A, Clark LR, Hermann B, Johnson SC, et al. Verbal fluency and early memory decline: results from the Wisconsin Registry for Alzheimer's Prevention. Arch Clin Neuropsychol. 2015;30(5):448–57.
Navarrete-Opazo A, Mitchell GS. Therapeutic potential of intermittent hypoxia: a matter of dose. Am J Physiol Regul Integr Comp Physiol. 2014;307(10):R1181–97.
Pangman VC, Sloan J, Guse L. An examination of psychometric properties of the mini-mental state examination and the standardized mini-mental state examination: implications for clinical practice. Appl Nurs Res. 2000;13(4):209–13.
Pendlebury ST, Mariz J, Bull L, Mehta Z, Rothwell PM. MoCA, ACE-R, and MMSE versus the National Institute of Neurological Disorders and Stroke-Canadian Stroke Network vascular cognitive impairment harmonization standards neuropsychological battery after TIA and stroke. Stroke. 2012;43(2):464–9.
Rasch B, Born J. About sleep's role in memory. Physiol Rev. 2013;93(2):681–766.
Roman V, Van der Borght K, Leemburg SA, Van der Zee EA, Meerlo P. Sleep restriction by forced activity reduces hippocampal cell proliferation. Brain Res. 2005;1065(1–2):53–9.
Rosenzweig I, Glasser M, Crum WR, Kempton MJ, Milosevic M, McMillan A, et al. Changes in neurocognitive architecture in patients with obstructive sleep apnea treated with continuous positive airway pressure. EBioMedicine. 2016;7:221–9.
Scharf MT. Reliability and efficacy of the Epworth Sleepiness Scale: is there still a place for it? Nat Sci Sleep. 2022;14:2151–6.
Sen A, Tai XY. Sleep duration and executive function in adults. Curr Neurol Neurosci Rep. 2023;23(11):801–13.
So M, Foxe D, Kumfor F, Murray C, Hsieh S, Savage G, et al. Addenbrooke's cognitive examination III: psychometric characteristics and relations to functional ability in Dementia. J Int Neuropsychol Soc. 2018;24(8):854–63.
Song WX, Wu WW, Zhao YY, Xu HL, Chen GC, Jin SY, et al. Evidence from a meta-analysis and systematic review reveals the global prevalence of mild cognitive impairment. Front Aging Neurosci. 2023;15:1227112.
Stranks EK, Crowe SF. The cognitive effects of obstructive sleep apnea: an updated meta-analysis. Arch Clin Neuropsychol. 2016;31(2):186–93.
Tartar JL, Ward CP, McKenna JT, Thakkar M, Arrigoni E, McCarley RW, et al. Hippocampal synaptic plasticity and spatial learning are impaired in a rat model of sleep fragmentation. Eur J Neurosci. 2006;23(10):2739–48.
Tartar JL, McKenna JT, Ward CP, McCarley RW, Strecker RE, Brown RE. Sleep fragmentation reduces hippocampal CA1 pyramidal cell excitability and response to adenosine. Neurosci Lett. 2010;469(1):1–5.
Terrill PI. A review of approaches for analysing obstructive sleep apnoea-related patterns in pulse oximetry data. Respirology. 2020;25(5):475–85.
Tsai CY, Hsu WH, Lin YT, Liu YS, Lo K, Lin SY, et al. Associations among sleep-disordered breathing, arousal response, and risk of mild cognitive impairment in a northern Taiwan population. J Clin Sleep Med. 2022;18(4):1003–12.
Vaessen TJ, Overeem S, Sitskoorn MM. Cognitive complaints in obstructive sleep apnea. Sleep Med Rev. 2015;19:51–8.
Vecsey CG, Baillie GS, Jaganath D, Havekes R, Daniels A, Wimmer M, et al. Sleep deprivation impairs cAMP signalling in the hippocampus. Nature. 2009;461(7267):1122–5.
Venkataraman S, Vungarala S, Covassin N, Somers VK. Sleep apnea, hypertension and the sympathetic nervous system in the adult population. J Clin Med. 2020;9(2):591.
Wallace A, Bucks RS. Memory and obstructive sleep apnea: a meta-analysis. Sleep. 2013;36(2):203–20.

Wang ML, Wang C, Tuo M, Yu Y, Wang L, Yu JT, et al. Cognitive effects of treating obstructive sleep apnea: a meta-analysis of Randomized controlled trials. J Alzheimers Dis. 2020;75(3):705–15.
Zhao Q, Lv Y, Zhou Y, Hong Z, Guo Q. Short-term delayed recall of auditory verbal learning test is equivalent to long-term delayed recall for identifying amnestic mild cognitive impairment. PLoS ONE. 2012;7(12):e51157.

Publisher's Note