Sleep Medicine 123 (2024) 29–36

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Verbal memory is linked to average oxygen saturation during sleep, not the apnea-hypopnea index nor novel hypoxic load variables

K. Thorisdottir [a,b,*], H. Hrubos-Strøm [c,d], T. Karhu [e,f], S. Nikkonen [e,f], T. Dammen [d,g], I.H. Nordhus [h], T. Leppänen [e,f,i], M.K. Jónsdóttir [a,b,j,1], E.S. Arnardottir [a,j,1]

[a] Reykjavik University Sleep Institute, School of Technology, Reykjavik University, Reykjavik, Iceland
[b] Department of Psychology, Reykjavik University, Reykjavik, Iceland
[c] Akershus University Hospital, Akershus, Norway
[d] Institute of Clinical Medicine, University of Oslo, Oslo, Norway
[e] Department of Technical Physics, University of Eastern Finland, Kuopio, Finland
[f] Diagnostic Imaging Center, Kuopio University Hospital, Kuopio, Finland
[g] Department of Research and Innovation, Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway
[h] Department of Clinical Psychology, University of Bergen, Bergen, Norway
[i] School of Information Technology and Electrical Engineering, The University of Queensland, Brisbane, Australia
[j] Landspitali – The National University Hospital of Iceland, Iceland

ARTICLE INFO

Keywords:
Obstructive sleep apnea
Apnea-hypopnea Index
Hypoxic load
Rey Auditory Verbal Learning Test
Stroop Test
Verbal learning
Executive function

ABSTRACT

Introduction: The apnea-hypopnea index (AHI) is the current diagnostic parameter for diagnosing and estimating the severity of obstructive sleep apnea (OSA). It is, however, poorly associated with the main clinical symptom of OSA, excessive daytime sleepiness, and with the often-seen cognitive decline among OSA patients. To better evaluate OSA severity, novel hypoxic load parameters have been introduced that consider the duration and depth of oxygen saturation drops associated with apneas or hypopneas. The aim of this paper was to compare novel hypoxic load parameters and traditional OSA parameters to verbal memory and executive function in OSA patients.

Method: A total of 207 adults completed a one-night polysomnography at sleep laboratory and two neuropsychological assessments, the Rey Auditory Verbal Learning Test and Stroop test. ***Results*:** Simple linear regression analyses were used to evaluate independent associations between each OSA parameter and cognitive performance. Associations were found between immediate recall and arousal index, hypoxia <90 %, average SpO_2 during sleep, and DesSev100+RevSev100. Total recall was associated with all OSA parameters, and no associations were found with the Stroop test. Subsequently, sex, age, and education were included as covariates in multiple linear regression analyses for each OSA parameter and cognitive performance. The main findings of the study were that average SpO_2 during sleep was a significant predictor of total recall ($p < .007$, $\beta = -.188$) with the regression model explaining 21.2 % of performance variation. Average SpO_2 during sleep was also a significant predictor of immediate recall ($p < .022$, $\beta = -.171$) with the regression model explaining 11.4 % of performance variation. Neither traditional OSA parameters nor novel hypoxic load parameters predicted cognitive performance after adjustment for sex, age, and education.

Conclusion: The findings validate that the AHI is not an effective indicator of cognitive performance in OSA and suggest that average oxygen saturation during sleep may be the strongest PSG predictor of cognitive decline seen in OSA. The results also underline the importance of considering age when choosing neurocognitive tests, the importance of including more than one test for each cognitive domain as most tests are not pure measures of a single cognitive factor, and the importance of including tests that cover all cognitive domains as OSA is likely to have diffuse cognitive effects.

* Corresponding author. Reykjavik University Sleep Institute, School of Technology, Reykjavik University, Reykjavik, Iceland.
[1] Co-senior authors.

https://doi.org/10.1016/j.sleep.2024.08.028
Received 28 June 2023; Received in revised form 15 July 2024; Accepted 26 August 2024
Available online 27 August 2024

1. Introduction

Obstructive sleep apnea (OSA) is the most common sleep-related breathing disorder, with a prevalence of up to one billion adults worldwide based on current diagnostic criteria [1]. The disorder is characterized by increased respiratory effort and repeated complete or partial upper airway obstructions during sleep [2]. These events lead to cortical arousals, sleep fragmentation, and decreased oxygen saturation (SpO_2), affecting sleep quality and often daytime functioning, with excessive daytime sleepiness being the main clinical symptom [2,3].

The current diagnosis of OSA and its severity classification are based on the apnea-hypopnea index (AHI), which counts only the number of respiratory events per hour of sleep. However, several additional physiological parameters can be drawn from polysomnography (PSG), which may provide further information for diagnosing OSA and estimating its severity, e.g., the duration and depth of respiratory events and respiratory effort [4–6]. These features should be included when evaluating the severity of the disorder since increasing length of apnea and hypopnea events most likely leads to more severe oxygen desaturation events, causing more physiological stress [4]. They may also be potential mechanisms for the cognitive difficulties seen in OSA. The greatest cognitive impact is seen in attention and vigilance, verbal memory, executive function, and information processing speed [7–12]. These negative impacts are repeatedly seen but are poorly correlated with the AHI [10,13–15].

Kulkas et al. [4] introduced novel parameters to bring additional information for the evaluation of OSA severity, based on desaturation events severity and duration. Azarbarzin et al. [16] later introduced hypoxic burden, measuring the same area under the desaturation curve. Since then, the term hypoxic load has been familiarized and describes novel blood SpO_2-based parameters [17]. Associations of cognitive performance with SpO_2-based indices has been more evident than its association with the AHI. For example, sustained attention/vigilance and immediate recall have been independently linked to hypoxemia [10, 18]. Moreover, before the introduction of novel SpO_2-based indices, we had shown that average SpO_2 was independently associated with immediate recall in the same cohort [14]. Finally, the main clinical symptom of OSA, excessive daytime sleepiness, is also poorly associated with the AHI [19–21]. It has been found to be associated with longer respiratory events [22], lower mean SpO_2 levels [23], and longer and deeper desaturations [19].

The aim of this study was to compare the associations between novel hypoxic load parameters and cognitive function to that between traditional OSA indices and cognitive function. Specifically, the aim was to evaluate which parameter is most associated with verbal memory (i.e., immediate recall, total recall, and learning over trials), and executive function (i.e., inhibitory control). In line with previous findings, we hypothesized that hypoxic load would show a stronger association with verbal memory and executive function than the traditional OSA indices.

2. Methods

2.1. Participants and demographic characteristics

A total of 207 participants were drawn from a screening sample of 16,302 subjects from the Akershus Sleep Apnea Project (ASAP) study in Ahus, Norway [14,24]. Out of the 16,302 respondents, a random sample of 654 was approached for study participation, all at high risk for OSA according to the Berlin Questionnaire [25]. This resulted in 290 respondents and a total of 207 who completed a one-night PSG and two neurocognitive assessments during recruitment in 2006–2007. The sample consisted of 92 females and 115 males, aged 30–67 years. For data analysis, age was grouped into 30–39, 40–49, 50–59, and 60+ years. Demographic data and information on comorbidities were collected via a screening questionnaire and medical records before the PSG and neurocognitive administration. Education was grouped into three categories; completed preschool, completed/in high school, or completed/in any college or university degree. The presence of asthma, diabetes, and cardiovascular disease was self-reported (yes/no) in the screening questionnaire and confirmed in medical records. Current smoking was solely based on self-reported daily smoking (yes/no). Body mass index (BMI) was calculated from self-reported weight and height, with BMI 18.5–24.9 kg/m^2 defined as healthy, 25.0–29.9 kg/m^2 as overweight, and $\geq$30 kg/m^2 as obese. One participant had a BMI of 18.3 kg/m^2 and was included in the healthy group.

2.2. Cognitive measures

All cognitive assessments were conducted the day before the PSG [24]. The Rey Auditory Verbal Learning Test (RAVLT) [26] measuring verbal memory was administered. RAVLT consisted of 15 nouns (List A) that were read aloud five times in the same order, and participants were asked to recall as many words as possible after each trial (A1 – A5). Next, a second 15-word list, list B, was presented, and participants were asked to recall as many words as possible (Trial B) [26]. The delayed recall of List A was performed with a variable 10–20-min delay, instead of the traditional 20-min delay and was therefore not used in the analysis. Immediate recall (A1), total recall (A1+A2+A3+A4+A5) and learning over trials (LOT) ((total recall) – (Trial A1) x 5) were included in the analysis.

A shortened version of the Comalli and Kaplan version of the Stroop test, measuring the ability to inhibit an overlearned response in favor of an unusual one, was administered [27,28] ,. This version consisted of three trials, each including 48 items. The first trial was a color-naming trial (C) where participants were instructed to name the color of patches in red, blue, and green as quickly as possible. The second trial was a word-naming trial (W) where the color names were printed in black ink, and participants were asked to read the words as quickly as possible. The third trial was an interference trial/color-word naming (CW) containing color names printed in inconsistent ink color, and participants were asked to name the color of the words and not the typed word as quickly as possible. A ratio score for the interference was calculated by dividing the color-naming trial by the interference trial/color-word naming multiplied by 10 (C/CW x 10) where a higher score indicates worse performance [29]. The administrator (HHS) timed each trial, and scores for analysis were the number of seconds it took to finish each trial.

2.3. Sleep apnea assessment

All participants slept with a Embla PSG device (Flaga, Reykjavík, Iceland) for one night at the Akershus University Hospital, Norway. The PSG included the following sensors: two-channel electrooculography, two-channel electroencephalography (C4/A1 and C3/A2), one-channel submental electromyography, finger plethysmography measuring pulse and SpO_2 (Nonin, Plymouth, MN, USA), left and right leg electromyography (anterior tibialis), nasal and oral airflow assessment (Protech, Woodinville, WA, USA), respiratory inductance plethysmography (Respitrace; Ambulatory Monitoring, Ardsley, NY, USA), body position, and activity monitoring. Scoring was performed in the Somnologica 3.2 software package (Flaga-Medcare, Buffalo, NY, USA) by two US board-certified sleep technologists by the Kales and Rechtchaffen scoring manual within weeks after the sleep study [30]. The AHI and arousal index were calculated as the sum of apneas plus hypopneas and the sum of arousals per hour of sleep, respectively. Hypopneas were scored if the nasal airflow dropped below 70 % of the reference amplitude for $\geq$10 s and was followed by an oxygen desaturation of $\geq$4 %. Apneas were scored if the nasal airflow dropped below 10 % of the reference amplitude for $\geq$10 s [31]. Oxygen desaturation index (ODI) was defined as the number of oxygen desaturation events of $\geq$4 % per hour of sleep [32]. Average SpO_2 during sleep was registered, and arousals were documented and classified according to the Sleep

Disorders Atlas Task Force of the American Sleep Disorders Association report [33]. The Automatic Blood Oxygen Saturation (ABOSA) signal analysis software was used to automatically calculate novel SpO_2-indices capturing hypoxic load [17,34]. Hypoxia was calculated as the percentual time during total sleep time in which SpO_2 values are <90 %. ABOSA was used to additionally calculate ODI with≥4 % and ≥3 % desaturations. Novel desaturation and recovery event indices included were desaturation severity (DesSev) defined as the fall area (i.e., the sum of the areas of oxygen desaturation events starting from the onset of desaturation and ending to the nadir, divided by total sleep time), desaturation severity from 100 % baseline (DesSev100) (i.e., the sum of the areas of oxygen desaturation events starting from 100 % SpO_2 baseline and ending to the nadir, divided by total sleep time), and desaturation duration (DesDur) defined as the fall duration (i.e., the percentage of total sleep time in desaturation). The same kind of indices were calculated for recovery events which are areas from the nadir to the end of the desaturation event i.e., where saturation levels reach baseline (RecSev, RecSev100, and RecDur) [17]. Desaturation and recovery events were also combined (DesSev + RecSev, DesSev100 + RecSev100, and DesDur + RecDur (i.e., hypoxic duration)) to capture whole desaturation events from onset back to baseline. Participants were divided into OSA severity groups according to current clinical standards based on the AHI; no OSA is indicated by 0–4.9 events/hour, mild OSA by 5–14.9 events/hour, moderate by 15–29.9, and severe OSA by ≥ 30 events/hour [35].

2.4. Statistical analysis

Differences between comparison groups were assessed using the Chi-square test for categorical variables, where a ≥10 % difference was interpreted as significant. For continuous variables, one-way analysis of variance was used for comparison groups, followed by a Bonferroni post hoc test if there were more than two variables. For the continuous polysomnography variables which were all non-normally distributed, a non-parametric test called Kruskal-Wallis Test was used for comparison groups followed by a post hoc test if more than two variables. An independent sample *t*-test was used for two categorical variables. Independent simple linear regression models were generated for each sleep parameter and cognitive skill, i.e., immediate recall, total recall, LOT, and inhibitory control. The models were then modified to multiple linear regression analysis and included sex, age, and education. All OSA severity indices were logarithmically transformed for regression analysis as their distributions were positively skewed. A reflection adjustment was made to average SpO_2 as it was negatively skewed (Log_{10}(1 + highest value – average SpO_2)). The Statistical Package for Social Sciences (SPSS, version 27.0) was used for all analyses, and two-sided *p*values < .05 were considered statistically significant.

Ethical approval

The study protocol was approved in 2005 by the Regional Committee for Medical Research Ethics in eastern Norway, ID 138543, the National Data Inspectorate, and the Norwegian Social Science Data Services. All participants signed an informed consent for their data to be stored for further research.

3. Results

The demographic and sleep results, separately for males and females, are presented in Table 1. Males and females differed in BMI, where more females were grouped healthy, and more males were overweight or obese. Cardiovascular disease was significantly more common among males than in females. Smoking status differed between sexes, where more females were current smokers than males. Males scored higher on all OSA severity indices besides hypoxia time <90 %, where no difference was found. Males and females did not significantly differ in age, education, diabetes, or asthma prevalence.

Table 1
Demographic data and polysomnography indices of the study population according to sex. Data are shown as mean (standard deviation, SD), percentage, or median (interquartile range) and significant findings are in bold.

Demographics	All subjects (N = 207)	Male (N = 115)	Female (N = 92)	*p*-value
Age in years, mean (SD)	49.3 (11.3)	50.3 (11.3)	48.1 (11.3)	.17
Education, %				
Primary/Middle school	21.6	24.8	17.6	.12
High school	49.0	51.3	46.2	
College/University	29.4	23.9	36.3	
Body mass index, %				
Healthy	23.9	13.2	37.4	**<.001**
Overweight	38.0	44.7	29.7	
Obese	38.0	42.1	33.0	
Diabetes, %	12.6	13.9	10.9	.33
Asthma, %	11.6	11.3	12.0	.52
Cardiovascular disease, %	19.3	28.7	7.6	**<.001**
Smoking status, %				
Current smoker	25.9	19.8	33.3	**.002**
Previous smoker	37.3	47.7	24.4	
Never smoked	36.8	32.4	42.2	
Polysomnography indices, median (interquartile range)				
Apnea-hypopnea index (events/hour)	6.8 (19.9)	11.4 (27.6)	4.8 (9.65)	**<.001**
Oxygen desaturation index ≥4 % manual (events/hour)	6.3 (19.0)	9.8 (23.7)	4.1 (9.5)	**<.001**
Oxygen desaturation index ≥4 % auto (events/hour)	8.4 (19.8)	12.2 (20.2)	6.0 (15.7)	**<.001**
Oxygen desaturation index ≥3 % auto (events/hour)	17.3 (25.7)	20.8 (31.2)	13.5 (21.7)	**<.001**
Arousal index (events/hour)	15.6 (14.3)	18.2 (15.2)	12.4 (12.0)	**<.001**
Average SpO_2 (%)	94.1 (2.3)	93.6 (2.4)	94.4 (2.0)	**<.001**
Desaturation Severity	.57 (.51)	.66 (.73)	.43 (.51)	**.010**
Desaturation Severity from 100 % baseline	1.31 (1.3)	1.54 (1.4)	1.02 (1.2)	**.003**
Desaturation Duration	17.51 (13.7)	20.19 (14.2)	14.17 (12.3)	**.001**
Recovery Severity	.17 (.17)	.21 (.18)	.14 (.16)	**.004**
Recovery Severity from 100 % baseline	.47 (.42)	.55 (.42)	.37 (.41)	**.002**
Recovery Duration	6.6 (4.9)	7.7 (.5.0)	5.8 (4.6)	**<.001**
DesSev + RecSev (%)	.4 (.8)	.6 (.9)	.3 (.6)	**<.001**
DesSev100 + RecSev100 (%)	1.2 (2.1)	1.5 (2.3)	.8 (1.6)	**<.001**
Hypoxic duration (%)	18.3 (26.4)	23.1 (30.1)	14.2 (22.6)	**<.001**
Hypoxia <90 % (%)	1.3 (5.2)	2.0 (6.9)	1.2 (3.3)	.05

SpO^2 = oxygen saturation, DesSev = desaturation severity, RecSev = recovery severity, DesSev100 = desaturation severity from 100 % baseline, RecSev100 = recovery severity from 100 % baseline.

The traditional OSA severity groups based on the AHI are shown in Table 2 with demographics and other PSG indices assessed. The patients in the severe OSA group were the oldest, predominantly males, and had the highest BMI and prevalence of cardiovascular disease. OSA severity groups did not differ in education, diabetes, or asthma. Other OSA severity indices assessed as well as the arousal index was also highest in the severe OSA group.

Scores on the neurocognitive tests, Stroop and RAVLT, are shown in Table 3 by demographic and OSA severity groups based on the AHI. Even though no significant sex differences were found in education or average age, females scored higher on immediate recall, total recall, and LOT. Patients in age groups 50–59 and 60+ years scored worse on inhibitory control than patients in the younger groups. Scores on immediate recall, total recall on RAVLT, and inhibitory control differed significantly between education groups. Those with diabetes scored lower on total recall, LOT, and inhibitory control, and previous smokers scored lower on total recall than those who never smoked. OSA severity

Table 2
Demographics and polysomnography indices of the study population according to traditional obstructive sleep apnea severity (OSA) severity groups. Data are shown as mean (standard deviation, SD) or percentage and significant findings are in bold.

Demographics	No OSA (N = 87)	Mild OSA (N = 49)	Moderate OSA (N = 33)	Severe OSA (N = 38)	ANOVA *p*-value
Age in years, mean (SD)	45.3 (11.7)	49.5 (9.8) <	53.5 (10.5) *	54.8 (9.1)*	**<.001**
Sex, %					
Female	55.2	53.1	30.3	21.1	**<.001**
Male	44.8	46.9	68.7	78.9	
Education, %					.82
Primary/Middle school	17.2	27.1	21.9	24.3	
High school	49.4	50.0	46.9	48.9	
College/ University	33.3	22.9	31.3	27.0	
Body mass index, kg/m^2	27.5 (4.7) <	27.8 (5.0)	30.0 (4.0)*	31.5 (4.6)#	**<.001**
Diabetes, %	8.0	8.2	24.2	18.4	.05
Asthma, %	8.0	16.3	18.2	7.9	.25
Cardiovascular disease, %	11.5	18.4	24.2	34.2	**.02**
Smoking status, %					**.02**
Current smoker	26.4	28.9	33.3	13.9	
Previous smoker	26.4	37.8	42.4	58.3	
Never smoked	47.1	33.3	24.2	27.8	
Polysomnography indices, median (interquartile range)					
Oxygen desaturation index ≥4 % manual (events/ hour)	2.0 (3.1)	7.9 (1.9) *$<	20.9 (9.0) *#	43.8 (24.7)*#	**<.001**
Oxygen desaturation index ≥4 % auto (events/hour)	3.6 (4.1)	8.7 (6.4) *$<	21.3 (7.6) *#	39.6 (23.3)*#	**<.001**
Oxygen desaturation index ≥3 % auto (events/hour)	8.9 (7.1)	17.4 (8.5) *$<	33.5 (13.2) *#	52.3 (21.3) *#	**<.001**
Arousal Index (events/hour)	11.8 (10.6)	15.6 (13.5)	17.0 (11.6) *	29.9 (31.4)*$	**<.001**
Average SpO_2 (%)	94.7 (1.8)	94.1 (2.1)	93.1 (2.2)*	92.8 (2.5)*#	**<.001**
Desaturation Severity	.22 (.33)	.38 (.25) $<	.75 (.34) *#	1.4 (.92) *#	**<.001**
Desaturation Severity from 100 % baseline	.54 (.67)	1.0 (.69) *$<	1.8 (.81) *#	2.9 (1.5) *#	**<.001**
Desaturation Duration	8.32 (7.8)	14.4 (6.9) *$<	24.3 (7.7) *#	36.7 (12.3) *#	**<.001**
Recovery Severity	.70 (1.0)	.13 (.7) *$<	.25 (1.2) *#	.42 (.18) *#	**<.001**
Recovery Severity from 100 % baseline	.20 (.21)	.37 (.23) *$<	.67 (.29) *#	1.0 (.44) *#	**<.001**
Recovery Duration	3.16 (2.7)	5.32 (2.5) *$<	9.2 (3.2) *#	13.8 (3.8) *#	**<.001**
DesSev + RecSev (%)	.2 (.2)	.4 (.3) *$<	.9 (.4)*#	1.5 (.9) *#	**<.001**
DesSev100 + RecSev100 (%)	.5 (.6)	1.2 (.8) *$<	2.3 (1.0)*#	3.6 (2.5)*#	**<.001**
Hypoxic Duration (%)	9.2 (7.5)	18.6 (8.9) *$<	35.1 (8.2) *#	48.7 (21.9)*#	**<.001**
Hypoxia <90 % (%)	.5 (1.1)	1.1 (4.4) $<	3.6 (8.4)*#	7.4 (13.6)*#	**<.001**

From post hoc tests, *compared to No OSA, # compared to mild OSA, $ compared to moderate OSA, < compared to severe OSA.

SpO^2 = oxygen saturation, DesSev = desaturation severity, RecSev = recovery severity, DesSev100 = desaturation severity from 100 % baseline, RecSev100 = recovery severity from 100 % baseline.

Table 3
Average scores on RAVLT and Stroop for demographics and obstructive sleep apnea severity groups.

Demographics	Immediate recall (RAVLT)	Total recall (RAVLT)	Learning Over Trials (RAVLT)	Inhibitory control (Stroop test)
Sex				
Male	4.7 (1.4)	31.4 (6.8) 36.2 (6.8)	8.1 (4.9)	19.1 (3.5)
Female	5.3 (1.4)	**<.001**	9.9 (4.9)	19.1 (4.1)
p-value	**.003**		**.009**	.99
Age (years)				
30-39	5.4 (1.3)	36.1 (6.6)	9.3 (5.6)	17.7 (2.2) <
40-49	4.7 (1.4)	32.9 (6.8)	9.4 (5.6)	17.5 (3.5) <
50-59	4.9 (1.4)	33.5 (7.1)	8.9 (4.2)	19.9 (4.0) *,#
60+	4.9 (1.5)	32.4 (7.6)	8.1 (4.5)	20.7 (4.1)
p-value	.14	.06	.47	**<.001**
Education				
Primary/ Middle	4.4 (1.4)	30.3 (6.9)	8.2 (4.9)	20.4 (3.9)
High school	4.9 (1.3)	33.5 (6.7)*	9.1 (4.8)	18.6 (3.7)*
College/ University	5.4 (1.5) *	36.0 (7.2)*	8.9 (5.3)	18.8 (3.8)
p-value	**.002**	**<.001**	.61	**.02**
Diabetes				
No	4.9 (1.4)	34.2 (6.9)	9.2 (4.9)	18.7 (3.3)
Yes	4.5 (1.5)	28.9 (7.8)	6.4 (4.3)	21.3 (5.9)
p-value	.10	**<.001**	**.006**	**<.001**
Smoking status				
Current smoker	4.8 (1.5)	33.9 (7.2)	9.8 (5.6)	18.4 (3.1)
Previous smoker	4.7 (1.5)	31.8 (7.4)	8.1 (4.9)	19.5 (4.1)
Never smoked	5.3 (1.3)	35.2 (6.5)#	8.9 (4.5)	19.1 (4.0)
p-value	.06	**.01**	.17	.27
OSA severity groups				
No OSA	5.1 (1.5)	34.7 (6.9)	9.4 (4.8)	18.4 (3.4)
Mild OSA	4.9 (1.4)	32.9 (6.9)	8.2 (5.4)	19.3 (3.9)
Moderate OSA	4.8 (1.3)	33.6 (8.0)	9.5 (4.4)	19.2 (4.2)
Severe OSA	4.7 (1.4)	31.3 (7.1)	8.0 (5.2)	20.3 (4.1)
p-value	.49	.08	.30	.07

AHI = Apnea-hypopnea Index, OSA = Obstructive Sleep Apnea, RAVLT = Rey Auditory Verbal Learning Test.
From Bonferroni post hoc test, *compared to the first group within cell, # compared to the second group within cell, $ compared to the third group within cell, < compared to the fourth group within cell.

groups did not differ in any cognitive domain. Other OSA severity parameters were split into quartiles for comparison, but no difference was found in performance on the neurocognitive tests between four severity groups for any index (data not shown).

To examine the association between different PSG parameters and cognitive function, simple linear regression analysis was used for each parameter and cognitive outcome variable. Sex, age, and education were then included as confounders in multiple linear regression analyses. No assumptions were violated, including the assumption of normality, autocorrelation, and multicollinearity. In Table 4, simple linear regression models show that the arousal index, average SpO_2, DesSev100+RecSev100, and hypoxia <90 % were independently significantly associated with immediate recall. Multiple linear regression models, adjusted for sex, age, and education, showed that average SpO_2 was significantly and strongly associated with immediate recall ($\beta = -.171$). In that multiple regression model, education was a strong predictor ($p = .005$, $\beta = .195$) whereas sex and age were not. No other PSG parameter was significantly associated with immediate recall after

Table 4
Results from linear regression analyses for immediate recall independently fitted by different obstructive sleep apnea severity indices (simple linear regression) and including covariates, sex, age and education (multiple linear regression). Statistically significant findings are shown in bold.

	Simple linear regression			Multiple linear regression		
	R^2	β	Coefficient *p*-value	R^2	β	Coefficient *p*-value
Apnea-hypopnea index (events/hour)	.012	−.111	.115	.095	.018	.812
Oxygen desaturation index ≥4 % manual (events/hour)	.007	−.083	.239	.093	.035	.641
Oxygen desaturation index ≥4 % auto (events/hour)	.008	−.089	.203	.090	.006	.934
Oxygen desaturation index ≥3 % auto (events/hour)	.013	−.112	.108	.090	−.022	.761
Arousal Index (events/hour)	.021	−.144	**.039**	.095	−.066	.351
Average SpO_2 (%)	.057	−.238	**<.001**	.114	−.171	**.022**
Desaturation Severity	.012	−.110	.114	.090	−.009	.900
Desaturation Severity from 100 % baseline	.017	−.130	.062	.091	−.030	.689
Desaturation Duration	.013	−.115	.101	.090	−.018	.810
Recovery Severity	.010	−.102	.145	.090	−.012	.873
Recovery Severity from 100 % baseline	.016	−.126	.071	.091	−.033	.649
Recovery Duration	.011	−.106	.128	.090	−.018	.807
DesSev + RecSev (%)	.012	−.109	.119	.090	−.010	.895
DesSev100 + RecSev100 (%)	.022	−.150	**.031**	.096	−.069	.335
Hypoxic duration (%)	.013	−.114	.104	.090	−.018	.810
Hypoxia <90 % (%)	.036	−.190	**.006**	.105	−.124	.092
Sex	–	–	–	–	(-.095–.165)	(.023 −.180)
Age (years)	–	–	–	–	(-.053–.106)	(.147 −.567)
Education	–	–	–	–	(.195 - .211)	**(.003 -.005)**

SpO^2 = oxygen saturation, DesSev = desaturation severity, RecSev = recovery severity, DesSev100 = desaturation severity from 100 % baseline, RecSev100 = recovery severity from 100 % baseline.

adjustment for sex, age, and education.

Simple linear regression models showed that all OSA severity indices were independently significantly associated with total recall (Table 5). Multiple linear regression models, adjusted for sex, age, and education, showed that average SpO_2 remained significantly and strongly associated with total recall (β = −.188). In that multiple regression model, sex ($p < .001$, β = .237) and education ($p < .001$, β = .213) were also strong predictors, whereas age was not. Regression models for LOT and inhibitory control are not shown because there was no association with any of the assessed indices.

4. Discussion

The primary aim of this study was to compare how traditional OSA severity parameters and novel hypoxic load parameters [17] associate with cognitive function. We hypothesized that novel hypoxic load parameters associate better with cognitive outcomes compared to the traditional OSA parameters, including the currently used diagnostic parameter the AHI. The main findings were that OSA severity based on the AHI was not associated with cognitive function and that average SpO_2 was the only parameter associated with cognitive function, more specifically immediate recall and total recall. The novel hypoxic load parameters were also not associated with cognitive performance, which does not support our primary hypothesis. However, the results are supported by previous studies where the AHI was not associated with cognitive performance [10,13–15].

The participants were Norwegian and Norwegian norms for RAVLT [36] are similar to the group's average scores on immediate recall. Average total recall was, however, lower (33.5 (SD = 7.1) versus 45.6 (SD = 9.6)), and younger participants had low scores. These findings are not consistent with Alchanatis et al. [37] who argue that younger patients with OSA are more likely to compensate for the cognitive

Table 5
Results from linear regression analyses for total recall from RAVLT independently fitted by obstructive sleep apnea severity indices (simple linear regression) and covariates, sex, age, and education (multiple linear regression). Statistically significant findings are shown in bold.

Polysomnography Indices	Simple linear regression			Multiple linear regression		
	R^2	β	Coefficient *p*-value	R^2	β	Coefficient *p*-value
Apnea-hypopnea index (events/hour)	.026	−.161	**.021**	.188	.027	.713
Oxygen desaturation index ≥4 % manual (events/hour)	.021	−.144	**.041**	.188	.029	.682
Oxygen desaturation index ≥3 % auto (events/hour)	.027	−.165	**.018**	.184	−.026	.700
Oxygen desaturation index ≥4 % auto (events/hour)	.019	−.138	**.049**	.183	.006	.927
Arousal Index (events/hour)	.029	−.171	**.014**	.188	−.062	.355
Average SpO_2 (%)	.096	−.310	**<.001**	.212	−.188	**.007**
Desaturation Severity	.025	−.159	**.023**	.183	−.005	.946
Desaturation Severity from 100 % baseline	.037	−.193	**.005**	.184	−.039	.582
Desaturation Duration	.029	−.170	**.015**	.183	−.021	.767
Recovery Severity	.022	−.149	**.033**	.183	−.011	.874
Recovery Severity from 100 % baseline	.036	−.190	**.006**	.185	−.046	.505
Recovery Duration	.025	−.159	**.022**	.184	−.330	.742
DesSev + RecSev (%)	.024	−.156	**.025**	.183	−.005	.948
DesSev100 + RecSev100 (%)	.039	−.196	**.005**	.189	−.071	.294
Hypoxic Duration (%)	.028	−.168	**.016**	.183	−.020	.774
Hypoxia <90 % (%)	.053	−.230	**<.001**	.195	−.133	.056
Sex	–	–	–	–	(-.237 to −.289)	**<.001**
Age (years)	–	–	–	–	(-.104–.270)	**(.016 -.040)**
Education	–	–	–	–	(.213 - .230)	**<.001**

SpO^2 = oxygen saturation, DesSev = desaturation severity, RecSev = recovery severity, DesSev100 = desaturation severity from 100 % baseline, RecSev100 = recovery severity from 100 % baseline.

symptoms caused by OSA compared to older adults where symptoms are more noticeable. Education was strongly associated with cognitive performance as expected, as educational levels have been repeatedly associated with cognitive performance and increased risk of dementia [38]. Females performed better on RAVLT which was also expected because females were more highly educated compared to males. There were no significant sex differences on the Stroop test which does support prior research. However, the literature on sex differences in the test has been equivocal [39]. Scores on the Stroop test were similar to Finish normative data found from Sisco et al. [29] across age groups.

When comparing average SpO_2 to the other sleep parameters included in the analysis, all parameters measure time limited events of arousals, apneas, hypopneas or drops in SpO_2, whereas average SpO_2 is calculated from the whole time period of sleep measurement or total sleep time. That includes timepoints of all the above-mentioned events along with frequent snoring and respiratory effort. These are characteristics of sleep disordered breathing (SDB) which is a general term for breathing difficulties during sleep that ranges from frequent loud snoring to severe OSA [40]. A review by Leng et al. [41], concluded that SDB is an important modifiable risk factor for cognitive impairment and Gouveris et al. [42] found that snoring was associated with low average SpO_2 levels among females with SDB. Thus, it may be that average SpO_2 captures SDB rather than OSA severity which would explain the association between SpO_2 and verbal memory in this study. Cognitive decline over time is also something to consider in OSA where the disorder onset could be long before symptoms of cognitive decline appear. A recent study showed that SpO_2 was associated with decline in cognition over a 5-year period [43]. In addition, Marchi et al. [44] investigated the association between traditional PSG parameters (i.e., mean SpO_2, lowest SpO_2, hypoxia <90 %, ODI, and the AHI), and brain anatomy in a cohort of 775 individuals from the general population (ages 45–86 years). They found that mean SpO_2 (lower mean SpO_2 during sleep) was the only parameter associated with gray matter volume and volume of brain regions that are associated with cognitive function and are highly sensitive to oxygen supply.

The prevalence of OSA has been rising and 425 million adults aged 30–69 have moderate to severe OSA using the AHI threshold for $\geq$15 events per hour [1]. However, the majority of those with AHI $\geq$15 do not have symptoms of sleepiness or impaired vigilance [13,45]. This is important to consider and thus the lack of significant findings in this study may be explained by the fact that the study cohort is from the general population, not from a typical clinical cohort seeking medical care due to a sleep problem. Therefore some participants may have symptomless or even incidental OSA findings due to the inflated OSA prevalence measured using current clinical standards, and the results could be very different in a clinical cohort of OSA patients [46]. Another limitation of this study is not including subjective cognitive measures to compare with the objective measures. That would allow us to see if there are differences across age groups in subjective measures and if they coincide with the objective cognitive measures. Even though the neurocognitive tests used in this study, the Stroop test and RAVLT, are considered good options for detecting inhibitory control and verbal learning in sleep research [47], they may lack sensitivity in young and healthy populations. With the average age being relatively low and the sample healthy, more sensitive and demanding neurocognitive tests should have been considered. Jóhannsdóttir et al. [47] proposed that sleep disorder studies should include tests covering all cognitive systems because sleep disorders are likely to have diffuse cognitive effects. Therefore, tests that cover all cognitive domains should be included more often in sleep research. Finally, not having a comparison group of low OSA risk from the general population according to the Berlin Questionnaire is a limitation, considering both OSA severity and cognitive performance.

A considerable strength of the study is the use of PSG for all participants instead of home sleep apnea testing, allowing for the assessment of the arousal index and more accurate index time for OSA severity assessments [48]. Another strength is the Stroop interference score. Traditionally, the Stroop interference is calculated by the difference between the time on the color-word and color-naming trial [49], primarily capturing processing speed, which is problematic for populations with a potential decline in processing speed, such as OSA patients [50]. The alternative algorithm used in this study controls for processing speed, calculating the ratio between color-word and color-naming word trials [51]. This also controls for age-related decline in processing speed which applies here with the age range being 30–67 years.

In conclusion, verbal memory (immediate and total recall) and inhibitory control did not associate with the novel hypoxic load parameters or the traditional AHI. However, immediate recall and total recall were strongly associated with average SpO_2 during sleep. Given these results and prior research where SpO_2 was a strong predictor of OSA and cognitive decline over time, SpO_2 may be the strongest predictor for cognitive decline seen in OSA. A longitudinal study would be of value analyzing cognitive decline over time including OSA characteristics, such as frequent loud snoring, when looking at the relationship between OSA severity and cognitive function.

Funding

This work was supported by the Icelandic Research Fund (228899–051) and NordForsk (NordSleep project 90458) through the Icelandic Research Fund, Business Finland (5133/31/2018) and via the Norwegian Research Council (Norsk Forskningsråd 298845) as well as from the European Union's Horizon 2020 Research and Innovation Programme (Grant 965417). TL reports additional research funding from the Research Committee of the Kuopio University Hospital Catchment Area for the State Research Funding (Project 5041794).

CRediT authorship contribution statement

K. Thorisdottir: Writing – original draft, Writing – review & editing, Conceptualization, Methodology. **H. Hrubos-Strøm:** Conceptualization, Funding acquisition, Methodology, Writing – review & editing. **T. Karhu:** Conceptualization, Funding acquisition, Methodology, Writing – review & editing. **S. Nikkonen:** Conceptualization, Methodology, Writing – review & editing. **T. Dammen:** Conceptualization, Methodology, Writing – review & editing. **I.H. Nordhus:** Conceptualization, Methodology, Writing – review & editing. **T. Leppänen:** Conceptualization, Funding acquisition, Methodology, Writing – review & editing. **M.K. Jónsdóttir:** Supervision, Conceptualization, Validation, Writing – review & editing. **E.S. Arnardottir:** Supervision, Funding acquisition, Conceptualization, Validation, Writing – review & editing.

Declaration of competing interest

KTH: no conflict of interest.
HH: no conflict of interest.
TK: no conflict of interest.
SN: no conflict of interest.
TD: no conflict of interest.
IHN: no conflict of interest.
TL: no conflict of interest.
ESA: honoraria from Nox Medical, Philips, ResMed, Jazz Pharmaceuticals, Linde Healthcare, Alcoa – Fjardaral, WinkSleep, ApniMed and Vistor. She is also a member of the Philips Sleep Medicine & Innovation Medical Advisory Board.
MKJ: no conflict of interest.

Acknowledgements

Xin Feng, postdoctoral, University of Oslo – contributed to the RAVLT data acquisition in this study. Supervised running sleep measures through the ABOSA software.

References

[1] Benjafield AV, Ayas NT, Eastwood PR, Heinzer R, Ip MSM, Morrell MJ, Nunez CM, Patel SR, Penzel T, Pépin J-L, Peppard PE, Sinha S, Tufik S, Valentine K, Malhotra A. Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. Lancet Respir Med 2019;7(8):687–98. https://doi.org/10.1016/S2213-2600(19)30198-5.

[2] Bassetti C, McNicholas W, Paunio T, Peigneux P. Sleep medicine textbook. second ed. Regensburg, Germany: European Sleep Research Society (ESRS); 2021 2nd ed. https://esrs.eu/sleep-medicine-textbook/.

[3] Sánchez AI, Martínez P, Miró E, Bardwell WA, Buela-Casal G. CPAP and behavioral therapies in patients with obstructive sleep apnea: effects on daytime sleepiness, mood, and cognitive function. Sleep Med Rev 2009;13(3):223–33. https://doi.org/10.1016/j.smrv.2008.07.002.

[4] Kulkas A, Tiihonen P, Eskola K, Julkunen P, Mervaala E, Töyräs J. Novel parameters for evaluating severity of sleep disordered breathing and for supporting diagnosis of sleep apnea-hypopnea syndrome. J Med Eng Technol 2013;37(2):135–43. https://doi.org/10.3109/03091902.2012.754509.

[5] Mazzotti DR, Lim DC, Sutherland K, Bittencourt L, Mindel JW, Magalang U, Pack AI, Chazal P de, and TP. Opportunities for utilizing polysomnography signals to characterize obstructive sleep apnea subtypes and severity. Physiol Meas 2018;39(9):09TR01. https://doi.org/10.1088/1361-6579/aad5fe.

[6] Rundo JV, Downey R. Polysomnography. Handb Clin Neurol 2019;160:381–92. https://doi.org/10.1016/B978-0-444-64032-1.00025-4.

[7] Andreou G, Vlachos F, Makanikas K. Effects of chronic obstructive pulmonary disease and obstructive sleep apnea on cognitive functions: evidence for a common nature. Sleep Disorders 2014;2014:e768210. https://doi.org/10.1155/2014/768210.

[8] 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. https://doi.org/10.1111/resp.13140.

[9] Engleman H, Joffe D. Neuropsychological function in obstructive sleep apnoea. Sleep Med Rev 1999;3(1):59–78. https://doi.org/10.1016/S1087-0792(99)90014-X.

[10] Kainulainen S, Duce B, Korkalainen H, Oksenberg A, Leino A, Arnardottir E, Kulkas A, Myllymaa S, Töyräs J, Leppänen T. Severe desaturations increase PVT-based median reaction time and number of lapses in OSA patients. Eur Respir J 2020. https://doi.org/10.1183/13993003.01849-2019.

[11] Seda G, Matwiyoff G, Parrish JS. Effects of obstructive sleep apnea and CPAP on cognitive function. Curr Neurol Neurosci Rep 2021;21(7):32. https://doi.org/10.1007/s11910-021-01123-0.

[12] Vanek J, Prasko J, Genzor S, Ociskova M, Kantor K, Holubova M, Slepecky M, Nesnidal V, Kolek A, Sova M. Obstructive sleep apnea, depression and cognitive impairment. Sleep Med 2020;72:50–8. https://doi.org/10.1016/j.sleep.2020.03.017.

[13] Batool-Anwar S, Kales SN, Patel SR, Varvarigou V, DeYoung PN, Malhotra A. Obstructive sleep apnea and psychomotor vigilance task performance. Nat Sci Sleep 2014;6:65–71. https://doi.org/10.2147/NSS.S53721.

[14] Hrubos-Strøm H, Nordhus IH, Einvik G, Randby A, Omland T, Sundet K, Moum T, Dammen T. Obstructive sleep apnea, verbal memory, and executive function in a community-based high-risk population identified by the Berlin Questionnaire Akershus Sleep Apnea Project. Sleep & Breathing = Schlaf & Atmung 2012;16(1):223–31. https://doi.org/10.1007/s11325-011-0493-1.

[15] Quan SF, Chan CS, Dement WC, Gevins A, Goodwin JL, Gottlieb DJ, Green S, Guilleminault C, Hirshkowitz M, Hyde PR, Kay GG, Leary EB, Nichols DA, Schweitzer PK, Simon RD, Walsh JK, Kushida CA. The association between obstructive sleep apnea and neurocognitive performance—the apnea positive pressure long-term efficacy study (APPLES). Sleep 2011;34(3):303–14. https://doi.org/10.1093/sleep/34.3.303.

[16] Azarbarzin A, Sands SA, Stone KL, Taranto-Montemurro L, Messineo L, Terrill PI, Ancoli-Israel S, Ensrud K, Purcell S, White DP, Redline S, Wellman A. The hypoxic burden of sleep apnoea predicts cardiovascular disease-related mortality: the Osteoporotic Fractures in Men Study and the Sleep Heart Health Study. Eur Heart J 2019;40(14):1149–57. https://doi.org/10.1093/eurheartj/ehy624.

[17] Karhu T, Leppänen T, Korkalainen H, Myllymaa S, Duce B, Töyräs J, Nikkonen S. Desaturation event scoring criteria affect the perceived severity of nocturnal hypoxic load. Sleep Med 2022;100:479–86. https://doi.org/10.1016/j.sleep.2022.09.024.

[18] Alomri RM, Kennedy GA, Wali SO, Ahejaili F, Robinson SR. Differential associations of hypoxia, sleep fragmentation, and depressive symptoms with cognitive dysfunction in obstructive sleep apnea. Sleep 2021;44(4):Scopus. https://doi.org/10.1093/sleep/zsaa213.

[19] Kainulainen S, Töyräs J, Oksenberg A, Korkalainen H, Sefa S, Kulkas A, Leppänen T. Severity of desaturations reflects OSA-related daytime sleepiness better than AHI. J Clin Sleep Med: JCSM: Official Publication of the American Academy of Sleep Medicine 2019;15(8):1135–42. https://doi.org/10.5664/jcsm.7806.

[20] Svensson M, Franklin KA, Theorell-Haglöw J, Lindberg E. Daytime sleepiness relates to snoring independent of the apnea-hypopnea index in women from the general population. Chest 2008;134(5):919–24. https://doi.org/10.1378/chest.08-0847.

[21] Tam S, Woodson BT, Rotenberg B. Outcome measurements in obstructive sleep apnea: beyond the apnea-hypopnea index. Laryngoscope 2014;124(1):337–43. https://doi.org/10.1002/lary.24275.

[22] Bédard MA, Montplaisir J, Richer F, Malo J. Nocturnal hypoxemia as a determinant of vigilance impairment in sleep apnea syndrome. Chest 1991;100(2):367–70. https://doi.org/10.1378/chest.100.2.367.

[23] Mediano O, Barceló A, de la Peña M, Gozal D, Agustí A, Barbé F. Daytime sleepiness and polysomnographic variables in sleep apnoea patients. Eur Respir J 2007;30(1):110–3. https://doi.org/10.1183/09031936.00009506.

[24] Hrubos-Strøm H, Randby A, Namtvedt SK, Kristiansen HA, Einvik G, Benth J, Somers VK, Nordhus IH, Russell MB, Dammen T, Omland T, Kværner KJ. A Norwegian population-based study on the risk and prevalence of obstructive sleep apnea. The Akershus Sleep Apnea Project (ASAP). J Sleep Res 2011;20(1 Pt 2):162–70. https://doi.org/10.1111/j.1365-2869.2010.00861.x.

[25] Senaratna CV, Perret JL, Matheson MC, Lodge CJ, Lowe AJ, Cassim R, Russell MA, Burgess JA, Hamilton GS, Dharmage SC. Validity of the Berlin questionnaire in detecting obstructive sleep apnea: a systematic review and meta-analysis. Sleep Med Rev 2017;36:116–24. https://doi.org/10.1016/j.smrv.2017.04.001.

[26] Schmidt M. RAVLT- Rey auditory verbal learning test: a handbook. Western Psychological Services; 1996.

[27] Comalli PE, Wapner S, Werner H. Interference effects of Stroop color-word test in childhood, adulthood, and aging. J Genet Psychol 1962;100(1):47–53. https://doi.org/10.1080/00221325.1962.10533572.

[28] Mitrushina M, Boone KB, Razani J, D'Elia LF. Handbook of normative data for neuropsychological assessment. Oxford University Press; 2005.

[29] Sisco S, Slonena E, Okun MS, Bowers D, Price CC. Parkinson's disease and the Stroop color word test: processing speed and interference algorithms. Clin Neuropsychol 2016;30(7):1104–17. https://doi.org/10.1080/13854046.2016.1188989.

[30] Kales A, Rechtchaffen A. A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. United States Government Printing Office; 1968.

[31] American Academy of Sleep Medicine. The AASM manual for the scoring of sleep and associated events. 2007.

[32] Telakivi T, Kajaste S, Partinen M, Koskenvuo M, Salmi T, Kaprio J. Cognitive function in middle-aged snorers and controls: role of excessive daytime somnolence and sleep-related hypoxic events. Sleep 1988;11(5):454–62.

[33] American Sleep Disorders Association. EEG arousals: scoring rules and examples. 1992. p. 174–84.

[34] Karhu T, Leppänen T, Töyräs J, Oksenberg A, Myllymaa S, Nikkonen S. Abosa – freely available automatic blood oxygen saturation signal analysis software: structure and validation. Comput Methods Progr Biomed 2022;226:107120. https://doi.org/10.1016/j.cmpb.2022.107120.

[35] AASM. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. Sleep 1999;22(5):667–89.

[36] Espenes J, Eliassen IV, Öhman F, Hessen E, Waterloo K, Eckerström M, Lorentzen IM, Bergland C, Halvari Niska M, Timón-Reina S, Wallin A, Fladby T, Kirsebom B-E. Regression-based normative data for the Rey Auditory Verbal Learning Test in Norwegian and Swedish adults aged 49–79 and comparison with published norms. Clin Neuropsychol 2022;1–25. https://doi.org/10.1080/13854046.2022.2106890.

[37] Alchanatis M, Zias N, Deligiorgis N, Liappas I, Chroneou A, Soldatos C, Roussos C. Comparison of cognitive performance among different age groups in patients with obstructive sleep apnea. Sleep & Breathing = Schlaf & Atmung 2008;12(1):17–24. https://doi.org/10.1007/s11325-007-0133-y.

[38] Beydoun MA, Beydoun HA, Gamaldo AA, Teel A, Zonderman AB, Wang Y. Epidemiologic studies of modifiable factors associated with cognition and dementia: systematic review and meta-analysis. BMC Publ Health 2014;14(1):643. https://doi.org/10.1186/1471-2458-14-643.

[39] Mitrushina M, Boone KB, Razani J, D'Elia LF. Handbook of normative data for neuropsychological assessment. Oxford University Press; 2005.

[40] Foldvary-Schaefer NR, Waters TE. Sleep-disordered breathing. Continuum: Lifelong Learning in Neurology 2017;23(4):1093–116. https://doi.org/10.1212/01.CON.0000522245.13784.f6.

[41] Leng Y, McEvoy CT, Allen IE, Yaffe K. Association of sleep-disordered breathing with cognitive function and risk of cognitive impairment: a systematic review and meta-analysis. JAMA Neurol 2017;74(10):1237–45. https://doi.org/10.1001/jamaneurol.2017.2180.

[42] Gouveris H, Bahr K, Jahn C, Matthias C, Simon P. The apnea–hypopnea index underestimates systemic inflammation in women with sleep-disordered breathing. J Wom Health 2018;27(7):920–6. https://doi.org/10.1089/jwh.2017.6819.

[43] Marchi NA, Solelhac G, Berger M, Haba-Rubio J, Gosselin N, Vollenweider P, Marques-Vidal P, Popp J, Gunten A von, Preisig M, Draganski B, Heinzer R. Obstructive sleep apnoea and 5-year cognitive decline in the elderly. Eur Respir J 2023;61(4). https://doi.org/10.1183/13993003.01621-2022.

[44] Marchi NA, Ramponi C, Hirotsu C, Haba-Rubio J, Lutti A, Preisig M, Marques-Vidal P, Vollenweider P, Kherif F, Heinzer R, Draganski B. Mean oxygen saturation during sleep is related to specific brain atrophy pattern. Ann Neurol 2020;87(6):921–30. https://doi.org/10.1002/ana.25728.

[45] Arnardottir ES, Bjornsdottir E, Olafsdottir KA, Benediktsdottir B, Gislason T. Obstructive sleep apnoea in the general population: highly prevalent but minimal symptoms. Eur Respir J 2016;47(1):194–202. https://doi.org/10.1183/13993003.01148-2015.

[46] Pevernagie DA, Gnidovec-Strazisar B, Grote L, Heinzer R, McNicholas WT, Penzel T, Randerath W, Schiza S, Verbraecken J, Arnardottir ES. On the rise and fall of the apnea-hypopnea index: a historical review and critical appraisal. J Sleep Res 2020;29(4):e13066. https://doi.org/10.1111/jsr.13066.

[47] Jóhannsdóttir KR, Ferretti D, Árnadóttir BS, Jónsdóttir MK. Objective measures of cognitive performance in sleep disorder research. Sleep Medicine Clinics 2021;16(4):575–93. https://doi.org/10.1016/j.jsmc.2021.08.002.
[48] Arnardottir ES, Islind AS, Óskarsdóttir M. The future of sleep measurements: a review and perspective. Sleep Medicine Clinics 2021;16(3):447–64. https://doi.org/10.1016/j.jsmc.2021.05.004.
[49] Johns MW. Reliability and factor analysis of the epworth sleepiness scale. Sleep 1992;15(4):376–81. https://doi.org/10.1093/sleep/15.4.376.
[50] Kilpinen R, Saunamäki T, Jehkonen M. Information processing speed in obstructive sleep apnea syndrome: a review. Acta Neurol Scand 2014;129(4):209–18. https://doi.org/10.1111/ane.12211.
[51] Sisco S, Slonena E, Okun MS, Bowers D, Price CC. Parkinson's disease and the Stroop color word test: processing speed and interference algorithms. Clin Neuropsychol 2016;30(7):1104–17. https://doi.org/10.1080/13854046.2016.1188989.