Obstructive sleep apnoea and 5-year cognitive decline in the elderly

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In a sample of elderly people from the general population, obstructive sleep apnoea parameters, particularly those of nocturnal hypoxaemia, predicted steeper cognitive decline over 5 years
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Abstract

Background The relationship between obstructive sleep apnoea (OSA) and cognitive decline remains controversial, especially in the elderly population. We used data from the HypnoLaus study to assess associations between OSA and longitudinal cognitive changes in a sample of community-dwelling elderly individuals.

Methods We studied associations between polysomnographic OSA parameters (of breathing/hypoxaemia and sleep fragmentation) and cognitive changes over a 5-year period, after adjustment for potential confounders. The primary outcome was the annual change in cognitive scores. The moderating effects of age, sex and apolipoprotein E4 (ApoE4) status were also examined.

Results 358 elderly individuals without dementia were included (mean±SD age 71.0±4.2 years; 42.5% males). A lower mean peripheral oxygen saturation (S_{pO_2}) during sleep was associated with a steeper decline in Mini-Mental State Examination (B= −0.12, p=0.004), Stroop test condition 1 (B=0.53, p=0.002) and Free and Cued Selective Reminding Test delayed free recall (B= −0.05, p=0.008). A longer time spent asleep with S_{pO_2} <90% was associated with a steeper decline in Stroop test condition 1 (B=0.47, p=0.006). Moderation analysis showed that apnoea–hypopnoea index and oxygen desaturation index were associated with a steeper decline in global cognitive function, processing speed and executive function only in older participants, men and ApoE4 carriers.

Conclusions Our results provide evidence of the contribution of OSA and nocturnal hypoxaemia to cognitive decline in the elderly population.

Introduction

Obstructive sleep apnoea (OSA) is a chronic condition characterised by recurrent upper airway obstructions during sleep. OSA is common, especially in the elderly, with an estimated prevalence of at least 30% [1]. Increasing evidence indicates that OSA has a detrimental effect on brain health [2], yet its role in cognitive decline remains controversial in the elderly population [3–5]. Seminal prospective studies conducted in elderly individuals have suggested that OSA is a risk factor for the development of mild cognitive

impairment and dementia [6–8]. However, the few studies that have examined the association between objectively measured OSA and longitudinal changes in cognitive performance (as measured by cognitive tests) have reported mixed results [9–12]. These studies have shown no association [9, 10] or only modest associations [11, 12] between OSA and cognitive decline in the elderly population.

As cognitive decline in old age can result from many different factors, assessing the specific contribution of OSA appears to be a difficult task [4, 5]. The question remains whether the impact of OSA on cognitive decline varies according to the presence of non-modifiable risk factors for dementia, such as older age, female sex or the presence of the apolipoprotein E4 (ApoE4) allele [13]. The ApoE4 allele is the strongest genetic risk factor for sporadic Alzheimer's disease [14] and is associated with poorer performance in various cognitive domains, even in elderly people without dementia [15].

A systematic review observed weaker associations between OSA and cognitive impairment in studies conducted in the elderly than in studies conducted in young and middle-aged adults [16]. Furthermore, two cohort studies reported associations between OSA and poorer cognitive function in middle-aged participants, but not in the elderly [17, 18]. This has led to the hypothesis that ageing is associated with a decrease in the strength of the association between OSA and cognitive impairment, potentially because the effect of OSA is blurred by other factors that impact cognition [13]. The two cohort studies also suggested a stronger relationship between OSA and cognitive impairment in women than in men [17, 18]. Furthermore, an epidemiological study found that women (but not men) with OSA were more likely to develop dementia over a 5-year period than age- and sex-matched controls without OSA [19]. Taken together, these studies suggest that women with OSA may have a higher risk of cognitive decline than men [17–19]. Finally, most previous evidence, although based on cross-sectional studies, suggests a stronger association between OSA and cognitive impairment in ApoE4 carriers [20–22]. However, only a part of these studies empirically examined the moderating effect of age, sex or ApoE4 using moderation analysis [17, 21, 22], whereas the remaining studies performed a stratified analysis without assessing the interaction terms [18–20].

The present study aimed to determine associations between OSA and cognitive decline over 5 years in a sample of community-dwelling elderly people. We also performed moderation analysis to examine the effect of age, sex and ApoE4 on the association between OSA and cognitive changes. We expected OSA to have weak associations with cognitive decline in the whole sample, but that these associations would be stronger in younger participants, women and ApoE4 carriers.

Methods

Study population

Data came from participants of the CoLaus|PsyCoLaus study, a prospective cohort of middle-aged and older adults randomly selected from the residents of Lausanne, Switzerland [23, 24]. Polysomnography (PSG) was performed during the first follow-up. Cognitive assessment was performed in participants aged ⩾65 years at the first and second follow-up. The present study included participants, aged ⩾65 years, who underwent PSG and a cognitive assessment at the first follow-up (baseline of the present study), followed by a second cognitive assessment 5 years later (follow-up of the present study). We excluded participants without ApoE genotyping, with dementia (defined as a Clinical Dementia Rating score ⩾1 [25]) and with central sleep apnoea (supplementary figure S1) [26]. The CoLaus|PsyCoLaus and HypnoLaus studies were approved by the ethics committee of the Vaud Canton and all participants provided written informed consent.

OSA parameters

Home-based PSG recordings were performed as part of the HypnoLaus study (see supplementary material for more details) [1]. PSG was performed a mean±SD 0.97±0.94 years after the first cognitive assessment. Respiratory events were scored according to the 2012 American Academy of Sleep Medicine criteria [27]: apnoea was defined as a ⩾90% decrease in airflow from baseline lasting ⩾10 s and hypopnoea was defined as a ⩾30% decrease in airflow lasting ⩾10 s with either an arousal or a ⩾3% oxygen desaturation. We selected six OSA parameters of breathing/hypoxaemia and sleep fragmentation. These parameters were analysed as continuous and categorical variables: apnoea–hypopnoea index (AHI; <15 *versus* ⩾15 events·h^{-1}), oxygen desaturation index ⩾3% (ODI; <15 *versus* ⩾15 events·h^{-1}), mean peripheral oxygen saturation during sleep (mean S_{pO_2}; ⩽92.5%=lower quartile *versus* >92.5%), sleep time with S_{pO_2} <90% (TST90; <4.5% *versus* ⩾4.5%=upper quartile), sleep efficiency (⩽72%=lower quartile *versus* >72%) and arousal index (<32 *versus* ⩾32 events·h^{-1}=upper quartile). In addition, we also studied hypoxic burden [28] as a continuous and categorical variable (<42 *versus* ⩾42%min·h^{-1}=upper quartile); 18 participants had missing data for this variable due to technical failure and/or insufficient quality of the pulse oximeter signal.

Cognitive assessment

Cognitive assessment included the Mini-Mental State Examination (MMSE; global cognitive function) [29], Stroop test Victoria version (Stroop test; processing speed and executive function) [30], verbal fluency tasks (executive control and verbal ability) [31], Free and Cued Selective Reminding Test (FCSRT; episodic verbal memory) [32, 33], 40-DO naming test (language) [34] and constructional praxis task from the Consortium to Establish a Registry for Alzheimer's Disease neuropsychological battery (visuospatial function) [35]. The primary outcome was the annual change in cognitive scores (=($score_{follow\text{-}up}$–$score_{baseline}$)/years of follow-up). Negative annual changes corresponded to a cognitive decline for all tests except the Stroop test, for which positive values corresponded to a decline. The secondary outcome was the incidence of significant cognitive decline, defined as a decrease in performance of >1.0SD above the mean annual change (table 1 and supplementary table S1).

Potential confounders and moderators

Potential confounders and moderators were recorded at the baseline of the present study. Education level was dichotomised into <high school or ⩾high school. Participants were categorised into ApoE4 carriers (one or two E4 alleles) or non-carriers (see supplementary material for details on genotyping). Body mass index (BMI) was calculated as weight/height^2 (kg·m^{-2}). Presence of diabetes was defined as fasting blood glucose ⩾7 mmol·L^{-1} and/or antidiabetic drug use. Hypertension was defined as systolic blood pressure ⩾140 mmHg and/or diastolic blood pressure ⩾90 mmHg and/or antihypertensive drug use. Smoking status was dichotomised into current or ex-smoker *versus* never-smoker. Alcohol consumption was dichotomised into ⩾14 or <14 units per week. Daytime sleepiness was evaluated using the Epworth Sleepiness Scale (ESS) [36]. Medication was coded according to the World Health Organization Anatomic Therapeutic Chemical classification. We considered hypnotics, benzodiazepines or derivates, antidepressants, neuroleptics and antihistamines as psychotropic drug categories having a potential major effect on sleep and/or cognition. Depression was defined as a remitted and/or current major depressive disorder according to the Diagnostic and Statistical Manual of Mental Disorders IV criteria. Use of continuous positive airway pressure (CPAP) treatment was reported. In the case of CPAP treatment, participants were asked to stop

TABLE 1 Cognitive assessment

Cognitive domain	Test	Task	Score
Global cognitive function	MMSE [29]	Complete subtests of orientation, registration and recall of words, attention and calculation, language and constructional praxis	0–30 points (lower score=poorer performance)
Processing speed	Stroop test Victoria version [30]	Condition 1 (dot condition): name the colour (red, blue, green, yellow) of dots as quickly as possible	Time (s) to complete the task (higher score=poorer performance)
		Condition 2 (neutral-word condition): name the colour (red, blue, green, yellow) of neutral words as quickly as possible	Time (s) to complete the task (higher score=poorer performance)
Executive function	Stroop test Victoria version [30]	Condition 3 (colour-word condition): name the colour of the words *blue*, *green*, *yellow* and *red* written in one of the three other colours as quickly as possible	Time (s) to complete the task (higher score=poorer performance)
	Phonemic fluency [31]	Give as many words beginning with the letter "P" as possible in a 2-min period	Number of words (lower score=poorer performance)
	Semantic fluency [31]	Give as many examples of "animals" as possible in a 2-min period	Number of words (lower score=poorer performance)
Episodic verbal memory	FCSRT [32]	Delayed free recall: recall as many words as possible during the delayed recall (20 min after learning phase)	0–16 points (lower score=poorer performance)
		Delayed total recall: delayed free recall+correct delayed cued recall for words that were not recalled during the delayed free recall	0–16 points (lower score=poorer performance)
Language	DO-40 naming test [34]	Name 40 pictures	0–40 points (lower score=poorer performance)
Visuospatial function	Constructional praxis task from the CERAD neuropsychological battery [35]	Copy four figures of increasing complexity (circle, diamond, overlapping rectangles and Necker cube)	0–11 points (lower score=poorer performance)

MMSE: Mini-Mental State Examination; FCSRT: Free and Cued Selective Reminding Test; CERAD: Consortium to Establish a Registry for Alzheimer's Disease.

using the device 1 week before the PSG. Presence of COPD was based on the question: "Has a doctor ever said that you have COPD, emphysema or chronic bronchitis?".

Statistical analysis

For descriptive analysis, we categorised the sample into subgroups with an AHI <15 *versus* ⩾15 events·h^{-1}. Normal distribution of continuous variables was tested using Q–Q plots. Between-group differences in baseline characteristics were analysed using the unpaired t-test, Mann–Whitney U-test, Chi-squared test or Fisher's exact test, as appropriate. Associations between OSA parameters and annual change in cognitive scores were assessed using linear regression. Assumptions of the linear regression were tested (no violation was observed). Findings were expressed as unstandardised β-coefficient (*B*) and 95% confidence interval. Analyses with the incidence of significant cognitive decline as the outcome variable were conducted using logistic regression. Goodness-of-fit of the model was assessed through the Hosmer–Lemeshow test (no evidence of poor fit was observed). Findings were expressed as odds ratio and 95% confidence interval. Three models were constructed to further explore the impact of confounders. Model 1 was adjusted for age, sex, education and ApoE4. Model 2 was additionally adjusted for BMI, diabetes, hypertension, smoking, alcohol consumption and psychotropic drugs. Model 3 was additionally adjusted for depression, ESS, CPAP and COPD. We used Hayes' SPSS Process macro version 4.1 [37] to explore the moderating effects of age, sex and ApoE4 on the association between OSA parameters and cognitive changes, with adjustment for all of the aforementioned confounders. For the assessment of age as a potential moderator, we used the Johnson–Neyman technique to determine the age range for which the moderator effect was significant [37]. Findings were expressed as interaction term (OSA parameter×moderator) and conditional effects of the OSA parameter at the moderator values. The sensitivity analyses tested: 1) additional AHI thresholds (⩾20, ⩾25 and ⩾30 events·h^{-1}), 2) hypoxic burden as a predictor (after excluding the 18 participants missing these data) and 3) the impact of excluding participants treated with CPAP (n=8). A description of how missing data were handled is provided in the supplementary material. The level of significance was set at two-sided p<0.05 for descriptive analysis and lowered to p<0.01 for regression and moderation analyses.

Results

Baseline characteristics

The final sample consisted of 358 community-dwelling elderly individuals with a mean±SD age of 71.0±4.2 years, of whom 152 (42.5%) were male (table 2). The average follow-up time between the two cognitive assessments was 5.2±0.5 years. At baseline, participants with AHI ⩾15 events·h^{-1} were more likely to be men, had higher BMI, had higher prevalence of diabetes and hypertension, were more likely to be smokers, had higher alcohol consumption, and had higher ESS score. All PSG measures of interest were significantly different between groups. The AHI ⩾15 events·h^{-1} group was more likely to have lower performances on the MMSE, Stroop test conditions 2 and 3, and FCSRT delayed free recall. Baseline characteristics of included participants *versus* individuals who were excluded because they did not complete the second cognitive assessment are shown in supplementary table S2. The excluded individuals had higher prevalence of diabetes, higher use of psychotropic drugs, lower prevalence of depression, higher AHI and ODI, lower sleep efficiency, higher arousal index, and lower performance on some cognitive tests.

Annual change in cognitive scores

Table 3 shows significant associations between OSA parameters and annual change in cognitive scores (complete results are presented in supplementary table S3). Participants with mean S_{pO_2} ⩽92.5% had a steeper decline in MMSE (*B*= −0.12, p=0.004, according to Model 3) and Stroop test condition 1 (*B*=0.53, p=0.002, according to Model 3). Lower mean S_{pO_2} (as a continuous variable) was associated with decreased performance in FCSRT delayed free recall (*B* for 1% decrease= −0.05, p=0.008, according to Model 3). Participants with TST90 ⩾4.5% also had a greater annual decline in Stroop test condition 1 (*B*=0.47, p=0.006, according to Model 3).

Incidence of significant cognitive decline

Significant associations between OSA parameters and incidence of significant cognitive decline are presented in table 4 (complete results are reported in supplementary table S4). Mean S_{pO_2} ⩽92.5% was associated with increased odds of significant decline in MMSE (OR 3.27, p=0.001, according to Model 3; corresponding to a decline of ⩾2.0 points during the follow-up) and in Stroop test condition 1 (OR 4.64, p=0.007, according to Model 3; corresponding to an increase of ⩾7.3 s to complete the task during follow-up). In Model 1, lower mean S_{pO_2} (as a continuous variable) was associated with incidence of significant decline in FCSRT delayed free recall (OR for 1% decrease 1.21, p=0.007; corresponding to a

TABLE 2 Baseline characteristics of the sample

	All sample (n=358 (100%))	AHI <15 events·h^{-1} (n=184 (51.4%))	AHI ⩾15 events·h^{-1} (n=174 (48.6%))	Test	p-value
Sociodemographic characteristics					
Age, years	71.0±4.2	70.8±4.2	71.2±4.1	t=0.8	0.402
Men	152 (42.5)	51 (27.7)	101 (58.0)	χ^2=33.6	**<0.001**
Education (⩾high school)	150 (41.9)	79 (42.6)	71 (40.8)	χ^2=0.2	0.683
Clinical characteristics					
ApoE4 carrier	83 (23.2)	43 (23.9)	40 (23.0)	χ^2=0.0	0.932
BMI, kg·m^{-2}	26.8±4.6	25.4±3.9	28.3±4.6	t=6.6	**<0.001**
Diabetes	54 (15.1)	18 (9.8)	36 (20.7)	χ^2=8.3	**0.004**
Hypertension	236 (65.9)	110 (59.8)	126 (72.4)	χ^2=6.3	**0.012**
Smoking	199 (55.6)	92 (50.0)	107 (61.5)	χ^2=4.8	**0.029**
Alcohol (⩾14 units per week)	65 (18.2)	24 (13.0)	41 (23.6)	χ^2=6.7	**0.010**
Psychotropic drugs	67 (18.7)	31 (16.8)	36 (20.7)	χ^2=0.9	0.352
Epworth Sleepiness Scale score	5.2±3.4	4.8±3.2	5.6±3.5	t=2.3	**0.027**
Depression	138 (38.5)	75 (40.8)	63 (36.2)	χ^2=0.8	0.376
CPAP	8 (2.2)	2 (1.1)	6 (3.4)	Fisher	0.164
COPD	10 (2.8)	4 (2.2)	6 (3.4)	Fisher	0.533
Sleep characteristics					
AHI, events·h^{-1}	14.0 (0.0–135.1)	7.3 (0.0–14.4)	28.2 (15.0–135.1)	U=0.0	**<0.001**
ODI, events·h^{-1}	13.9 (0.1–121.3)	7.0 (0.1–23.7)	27.2 (11.1–121.3)	U=589	**<0.001**
Mean S_{pO_2}, %	93.6±1.6	94.0±1.5	92.8±1.5	t=6.9	**<0.001**
TST90, %	7.0 (0.0–91.9)	0.1 (0.0–91.5)	3.5 (0.0–91.9)	U=5392	**<0.001**
Hypoxic burden, %min·h^{-1}	19.3 (0.1–269.3)	7.3 (0.1–49.5)	42.0 (2.9–269.3)	U=1595	**<0.001**
Sleep efficiency, %	80.9 (29.6–96.6)	83.0 (51.2–96.2)	79.7 (29.6–96.6)	U=13 446	**0.009**
Arousal index, events·h^{-1}	23.1 (4.4–104.6)	18.8 (4.4–63.4)	28.0 (6.2–104.6)	U=7231	**<0.001**
Cognitive characteristics					
MMSE, points	30.0 (22.0–30.0)	30.0 (22.0–30.0)	30.0 (22.0–30.0)	U=12 574	**0.001**
Phonemic fluency, points	21.6±8.1	22.1±8.2	21.0±7.9	t=1.2	0.244
Semantic fluency, points	30.9±8.4	31.5±8.8	30.4±7.9	t=1.4	0.170
FCSRT delayed free recall, points	11.9±2.5	12.2±2.3	11.5±2.7	t=2.4	**0.018**
FCSRT delayed total recall, points	16.0 (10.0–16.0)	16.0 (13.0–16.0)	16.0 (10.0–16.0)	U=14 164	0.667
DO-40 naming test, points	40.0 (24.0–40.0)	40.0 (37.0–40.0)	40.0 (24.0–40.0)	U=14 411	0.746
Constructional praxis task, points	11.0 (5.0–11.0)	11.0 (6.0–11.0)	11.0 (5.0–11.0)	U=14 785	0.129
Stroop test condition 1, s	16.4±6.4	16.0±6.9	16.7±5.8	t=1.0	0.337
Stroop test condition 2, s	21.0±6.6	20.1±5.7	22.0±7.2	t=2.7	**0.007**
Stroop test condition 3, s	32.9±12.1	30.7±9.6	35.3±12.0	t=3.6	**<0.001**

Data are presented as mean±SD, n (%) or median (range), unless otherwise stated. Data were analysed using the unpaired t-test (t), Mann–Whitney U-test (U), Chi-squared test (χ^2) or Fisher's exact test. AHI: apnoea–hypopnoea index; ApoE4: apolipoprotein E4; BMI: body mass index; CPAP: continuous positive airway pressure; ODI: oxygen desaturation index; S_{pO_2}: peripheral oxygen saturation; TST90: sleep time with S_{pO_2} <90%; MMSE: Mini-Mental State Examination; FCSRT: Free and Cued Selective Reminding Test. Bold indicates significant result (p<0.05).

decline of ⩾3.2 points during follow-up); a trend towards significance was observed in the other models (OR 1.22, p=0.010, according to Model 2 and OR 1.22, p=0.011, according to Model 3).

Moderation analysis

Significant moderating effects are presented in table 5 and figure 1 (baseline characteristics of the sample according to age, sex and ApoE4 status are shown in supplementary tables S5–S7). AHI ⩾15 events·h^{-1} was associated with a steeper decline in Stroop test condition 1 and condition 2 only in older participants (p<0.05 for participants aged >75 years and p<0.01 for those aged >78 years). AHI ⩾15 events·h^{-1} and ODI ⩾15 events·h^{-1} were associated with a more pronounced decline in phonemic fluency only in men (B= −0.70, p=0.003 and B= −0.71, p=0.002, respectively). AHI ⩾15 events·h^{-1} and ODI ⩾15 events·h^{-1} were associated with a greater decline in MMSE only in ApoE4 carriers (B= −0.21, p=0.007 and B= −0.21, p=0.009, respectively). No significant moderating effect was observed for the associations between OSA parameters and significant cognitive decline.

Sensitivity analyses

Participants with AHI ⩾20 events·h^{-1} were more likely to show significant decline in phonemic fluency (OR 2.99, p=0.003, according to Model 3; corresponding to a decline of ⩾7.6 points during follow-up)

TABLE 3 Associations between obstructive sleep apnoea (OSA) parameters and annual change in cognitive scores

	Annual change in cognitive scores					
	Model 1		Model 2		Model 3	
	B (95% CI)	p-value	*B* (95% CI)	p-value	*B* (95% CI)	p-value
MMSE						
Mean S_{pO_2} (%)						
⩽92.5 (n=88)	−0.12 (−0.20– −0.04)	**0.003**	−0.12 (−0.21– −0.04)	**0.004**	−0.12 (−0.21– −0.04)	**0.004**
>92.5 (n=270)	1 (reference)		1 (reference)		1 (reference)	
Continuous (1-unit decrease)	−0.02 (−0.05–0.00)	0.024	−0.03 (−0.05–0.00)	0.024	−0.03 (−0.05–0.00)	0.023
FCSRT delayed free recall						
Mean S_{pO_2} (%)						
⩽92.5 (n=88)	−0.12 (−0.26–0.01)	0.079	−0.15 (−0.30– −0.01)	0.034	−0.16 (−0.30– −0.02)	0.026
>92.5 (n=270)	1 (reference)		1 (reference)		1 (reference)	
Continuous (1-unit decrease)	−0.04 (−0.08–0.00)	0.035	−0.05 (−0.09– −0.01)	**0.006**	−0.05 (−0.09– −0.01)	**0.008**
Stroop test condition 1						
Mean S_{pO_2} (%)						
⩽92.5 (n=88)	0.45 (0.13–0.77)	**0.006**	0.51 (0.18–0.84)	**0.002**	0.53 (0.20–0.86)	**0.002**
>92.5 (n=270)	1 (reference)		1 (reference)		1 (reference)	
Continuous (1-unit decrease)	0.05 (−0.03–0.13)	0.249	0.07 (−0.02–0.15)	0.133	0.08 (−0.01–0.17)	0.080
TST90 (%)						
⩾4.5 (n=92)	0.37 (0.05–0.70)	0.028	0.43 (0.09–0.76)	0.013	0.47 (0.14–0.80)	**0.006**
<4.5 (n=266)	1 (reference)		1 (reference)		1 (reference)	
Continuous (1-unit increase)	0.00 (−0.01–0.01)	0.992	0.00 (−0.01–0.01)	0.956	0.00 (−0.01–0.01)	0.888

Data are presented as unstandardised β-coefficient (*B*) (95% CI), unless otherwise stated. MMSE: Mini-Mental State Examination; S_{pO_2}: peripheral oxygen saturation; FCSRT: Free and Cued Selective Reminding Test; TST90: sleep time with S_{pO_2} <90%. Data were analysed by multivariable linear regression models using annual change in cognitive scores as dependent variable and OSA parameter as independent variable. Model 1: adjusted for age (continuous), sex (male, female), education (⩾high school, <high school) and apolipoprotein E4 (carriers, non-carriers). Model 2: Model 1 additionally adjusted for body mass index (continuous), diabetes (yes, no), hypertension (yes, no), smoking (current or ex-smoker, never-smoker), alcohol (⩾14, <14 units per week) and psychotropic drugs (yes, no). Model 3: Model 2 additionally adjusted for depression (yes, no), Epworth Sleepiness Scale score (continuous), continuous positive airway pressure (yes, no) and COPD (yes, no). Bold indicates significant result (p<0.01).

(table 4, and supplementary tables S8 and S9). Participants with hypoxic burden ⩾42%min·h^{-1} showed a trend towards higher likelihood of significant decline in phonemic fluency (OR 2.26, p=0.033, according to Model 3) (supplementary tables S10 and S11). The exclusion of participants treated with CPAP had no impact on the results (data not shown). Figure 2 provides an overview of the main results of the study.

Discussion

In this cohort of community-dwelling elderly individuals, AHI and indices of nocturnal hypoxaemia (but not those of sleep fragmentation) were associated with steeper cognitive decline over 5 years. This decline was observed in global cognitive function, processing speed, executive function and episodic verbal memory, but not in language or visuospatial function. Mean S_{pO_2} and TST90 were the parameters most consistently related to changes in cognitive functioning. AHI and ODI were specifically associated with steeper cognitive decline in older participants, men and ApoE4 carriers. This study provides evidence of the contribution of OSA to cognitive decline in the elderly population. It also highlights the detrimental role of hypoxaemia and the presence of demographic and genetic moderating factors.

Two previous cohort studies have examined the relationship between PSG measures of OSA and cognitive changes in the elderly [9, 12]. The Osteoporotic Fractures in Men Study found an association between TST90 and 3-year decline in Modified MMSE in 2636 men aged 76 years [12]. However, in the Atherosclerotic Risk in Communities study, which included 966 participants aged 61 years, there was no association between OSA parameters and 15-year changes in the three cognitive tests examined [9]. Two other studies have used non-PSG respiratory devices to assess the association between OSA and cognitive decline [10, 11]. In an analysis of the Proof-Synapse Cohort, in which 559 participants (aged 67 years) were followed over 8 years, AHI ⩾30 events·h^{-1} was associated with greater decline in the attentional domain [11]. Furthermore, AHI (as a continuous variable) and parameters of hypoxaemia were associated with changes in attention and executive function [11]. These results contrast with those of the Hispanic Community Health Study/Study of Latinos (HCHS/SOL), which showed no association between the presence of sleep disordered breathing (defined as a respiratory event index ⩾15 events·h^{-1}) and 7-year

TABLE 4 Associations between obstructive sleep apnoea (OSA) parameters and incidence of significant cognitive decline

	Incidence of significant cognitive decline					
	Model 1		Model 2		Model 3	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
MMSE						
Mean S_{pO_2} (%)						
⩽92.5 (n=88)	2.88 (1.48–5.59)	**0.002**	3.23 (1.58–6.61)	**0.001**	3.27 (1.60–6.72)	**0.001**
>92.5 (n=270)	1 (reference)		1 (reference)		1 (reference)	
Continuous (1-unit decrease)	1.17 (1.01–1.31)	0.043	1.20 (1.02–1.35)	0.028	1.20 (1.01–1.35)	0.034
FCSRT delayed free recall						
Mean S_{pO_2} (%)						
⩽92.5 (n=88)	2.30 (1.22–4.34)	0.015	2.09 (1.11–4.33)	0.031	2.33 (1.17–4.66)	0.021
>92.5 (n=270)	1 (reference)		1 (reference)		1 (reference)	
Continuous (1-unit decrease)	1.21 (1.07–1.34)	**0.007**	1.22 (1.05–1.35)	0.010	1.22 (1.05–1.35)	0.011
Stroop test condition 1						
Mean S_{pO_2} (%)						
⩽92.5 (n=88)	3.95 (1.54–9.96)	**0.004**	4.33 (1.57–11.90)	**0.004**	4.64 (1.52–14.15)	**0.007**
>92.5 (n=270)	1 (reference)		1 (reference)		1 (reference)	
Continuous (1-unit decrease)	1.24 (1.00–1.42)	0.088	1.23 (0.96–1.43)	0.092	1.26 (0.96–1.47)	0.103
Phonemic fluency						
AHI (events·h^{-1})						
⩾20 (n=135)	2.36 (1.22–4.55)	0.011	2.99 (1.46–6.11)	**0.003**	2.99 (1.46–6.15)	**0.003**
<20 (n=223)	1 (reference)		1 (reference)		1 (reference)	
Continuous (10-unit increase)	1.03 (0.89–1.19)	0.154	1.05 (0.89–1.24)	0.066	1.21 (0.99–1.47)	0.070

Data are presented as odds ratio (OR) (95% CI), unless otherwise stated. MMSE: Mini-Mental State Examination; S_{pO_2}: peripheral oxygen saturation; FCSRT: Free and Cued Selective Reminding Test. Data were analysed by multivariable logistic regression models using incidence of significant cognitive decline as dependent variable and OSA parameter as independent variable. Model 1: adjusted for age (continuous), sex (male, female), education (⩾high school, <high school) and apolipoprotein E4 (carriers, non-carriers). Model 2: Model 1 additionally adjusted for body mass index (continuous), diabetes (yes, no), hypertension (yes, no), smoking (current or ex-smoker, never-smoker), alcohol (⩾14, <14 units per week) and psychotropic drugs (yes, no). Model 3: Model 2 additionally adjusted for depression (yes, no), Epworth Sleepiness Scale score (continuous), continuous positive airway pressure (yes, no) and COPD (yes, no). Bold indicates significant result (p<0.01).

cognitive decline in a sample of 5247 participants with a mean age of 63 years [10]. Similarities with our study include the relatively weak association between AHI and cognitive changes [11], the role of measures of hypoxaemia [11, 12], and the decline observed in global cognitive function and executive function [11, 12]. Discrepancies may be due to differences in demographics (age and sex of the samples), measures of OSA (PSG *versus* non-PSG devices), follow-up time and cognitive tests.

The moderation analysis was a novel aspect of this study. AHI and ODI were associated with a steeper decline in some cognitive tests only in older participants, men and ApoE4 carriers. Results concerning the effect of ApoE4 agreed with our hypothesis, while those concerning the effect of age and sex did not. Our results of an increased risk of OSA-related cognitive decline in ApoE4 carriers are in line with most previous cross-sectional studies [20–22]. However, further longitudinal investigations are needed to corroborate this hypothesis.

We expected a stronger association between OSA and cognitive decline in younger than older participants. This speculation was based on a systematic review [16] and two cross-sectional cohort studies using data from the HCHS/SOL [17] and the Canadian Longitudinal Study of Aging (CLSA) [18]. Age-stratified analysis of these cohort studies showed that associations between AHI (measured by respiratory polygraphy) [17] or OSA risk (defined by the combination of STOP score and whole-body fat percentage) [18] and poorer cognitive performance were more evident in middle-aged than in older women. Our results, combined with previous findings, may indicate a non-linear relationship between OSA and cognitive impairment in ageing, with more pronounced associations visible before 60 and after 75 years of age; however, this hypothesis requires further investigation.

As already mentioned, findings from the HCHS/SOL and the CSLA suggest a stronger relationship between OSA and cognitive impairment in women than in men [17, 18]. Furthermore, in an

TABLE 5 Characteristics moderating the association between obstructive sleep apnoea (OSA) parameters and cognitive changes

	B (95% CI)	p-value
Moderating effect of age		
Stroop condition 1 (annual change)		
Interaction		
AHI (⩾15; <15)×age	0.10 (0.03–0.16)	**0.004**
Conditional effect		
66.7 years (1SD below mean)	−0.36 (−0.79–0.07)	0.100
71.0 years (mean)	0.05 (−0.26–0.37)	0.748
75.1 years (1SD above mean)	0.46 (0.05–0.87)	0.026
78.4 years	0.79 (0.21–1.38)	**0.008**
Stroop condition 2 (annual change)		
Interaction		
AHI (⩾15; <15)×age	0.12 (0.04–0.21)	**0.003**
Conditional effect		
66.7 years (1SD below mean)	−0.48 (−1.02–0.05)	0.073
71.0 years (mean)	0.03 (−0.35–0.41)	0.876
75.1 years (1SD above mean)	0.55 (0.04–1.05)	0.034
78.4 years	0.95 (0.24–1.67)	**0.009**
Moderating effect of sex		
Phonemic fluency (annual change)		
Interaction		
AHI (⩾15; <15)×sex	−0.84 (−1.44– −0.24)	**0.006**
Conditional effect		
Women	0.14 (−0.26–0.54)	0.499
Men	−0.70 (−1.16– −0.25)	**0.003**
Phonemic fluency (annual change)		
Interaction		
ODI (⩾15; <15)×sex	−0.79 (−1.39– −0.19)	**0.008**
Conditional effect		
Women	0.08 (−0.32–0.50)	0.686
Men	−0.71 (−1.16– −0.25)	**0.002**
Moderating effect of ApoE4		
MMSE (annual change)		
Interaction		
AHI (⩾15; <15)×ApoE4	−0.25 (−0.42– −0.08)	**0.004**
Conditional effect		
ApoE4 non-carriers	0.03 (−0.05–0.12)	0.455
ApoE4 carriers	−0.21 (−0.37– −0.06)	**0.007**
MMSE (annual change)		
Interaction		
ODI (⩾15; <15)×ApoE4	−0.23 (−0.40– −0.06)	**0.008**
Conditional effect		
ApoE4 non-carriers	0.02 (−0.07–0.11)	0.627
ApoE4 carriers	−0.21 (−0.36– −0.05)	**0.009**

Data are presented as unstandardised β-coefficient (*B*) (95% CI), unless otherwise stated. AHI: apnoea–hypopnoea index (events·h^{-1}); ODI: oxygen desaturation index (events·h^{-1}); MMSE: Mini-Mental State Examination; ApoE4: apolipoprotein E4. Data were analysed by Hayes' SPSS Process macro version 4.1 [37] for moderation analysis using annual change in cognitive score as dependent variable, OSA parameter as independent variable and age, sex or ApoE4 status as moderator. Models were corrected for age (continuous), sex (male, female), education (⩾high school, <high school), ApoE4 (carriers, non-carriers), body mass index (continuous), diabetes (presence, absence), hypertension (presence, absence), smoking (current or ex-smoker, never-smoker), alcohol consumption (⩾14, <14 units per week), psychotropic drugs (presence, absence), depression (presence, absence), Epworth Sleepiness Scale score (continuous), continuous positive airway pressure (yes, no) and COPD (yes, no). Bold indicates significant result (p<0.01).

epidemiological study based on data from Taiwan's National Health Insurance Research Database, only women with *versus* without OSA were more likely to develop dementia over a 5-year period [19]. However, these studies included women in the perimenopausal period (45–54 years) [17–19] and associations between OSA and cognitive impairment were mostly evident during this age span [17, 18].

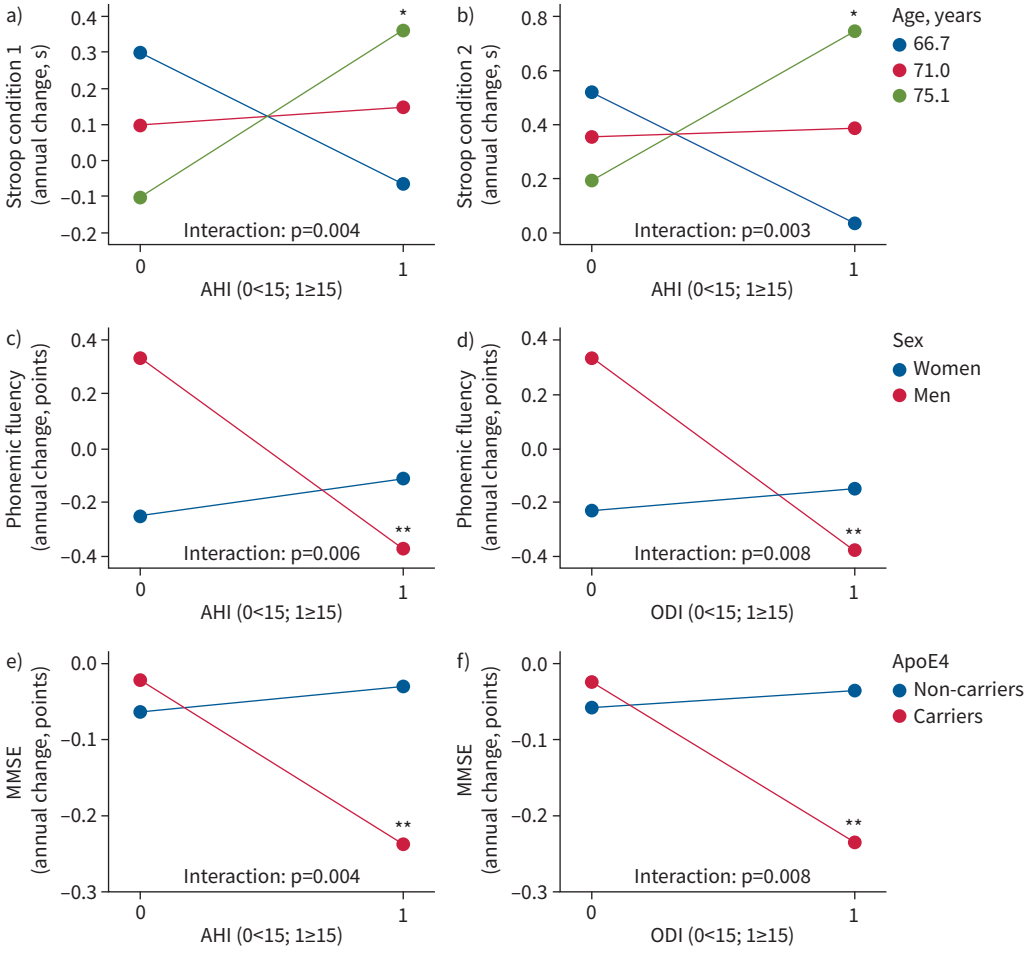

FIGURE 1 Conditional effects of obstructive sleep apnoea (OSA) parameters at moderator values. Data were analysed by Hayes' SPSS Process macro version 4.1 [37] for moderation analysis using annual change in cognitive score as dependent variable, OSA parameter as independent variable and a, b) age, c, d) sex or e, f) apolipoprotein E4 (ApoE4) status as moderator. Asterisks indicate significant difference between apnoea–hypopnoea index (AHI; events·h^{-1}) or oxygen desaturation index (ODI; events·h^{-1}) groups: *: p<0.05; **; p<0.01. Models were corrected for age (continuous), sex (male, female), education (≥high school, <high school), ApoE4 (carriers, non-carriers), body mass index (continuous), diabetes (presence, absence), hypertension (presence, absence), smoking (current or ex-smoker, never-smoker), alcohol consumption (≥14, <14 units per week), psychotropic drugs (presence, absence), depression (presence, absence), Epworth Sleepiness Scale score (continuous), continuous positive airway pressure (yes, no) and COPD (yes, no). MMSE: Mini-Mental State Examination.

This suggests that perimenopause may increase women's vulnerability to the detrimental effects of OSA on brain health [13]. The fact that our sample did not include women in the perimenopausal period may partly explain our results. Moreover, the prevalence of OSA in women increases mainly during the perimenopause, whereas in men OSA often appears at a younger age. Therefore, the negative effects of OSA on cognition in men may accumulate over a greater number of years than in women.

OSA parameters were related to a greater decline in global cognitive function (MMSE), processing speed (Stroop test condition 1 and condition 2), executive function (phonemic fluency) and episodic verbal memory (FCSRT delayed free recall), whereas no association was observed for language or visuospatial function. This pattern of cognitive changes is consistent with previous literature [3, 16] and appears to be similar to that seen in frontal-subcortical syndrome, which is mainly characterised by dysexecutive symptoms and decreased psychomotor speed [38]. One of the main causes of frontal-subcortical syndrome are microvascular lesions in the white matter and the deep grey nuclei, which can lead vascular dementia [39]. This suggests that OSA may promote microvascular pathology that ultimately results in cognitive

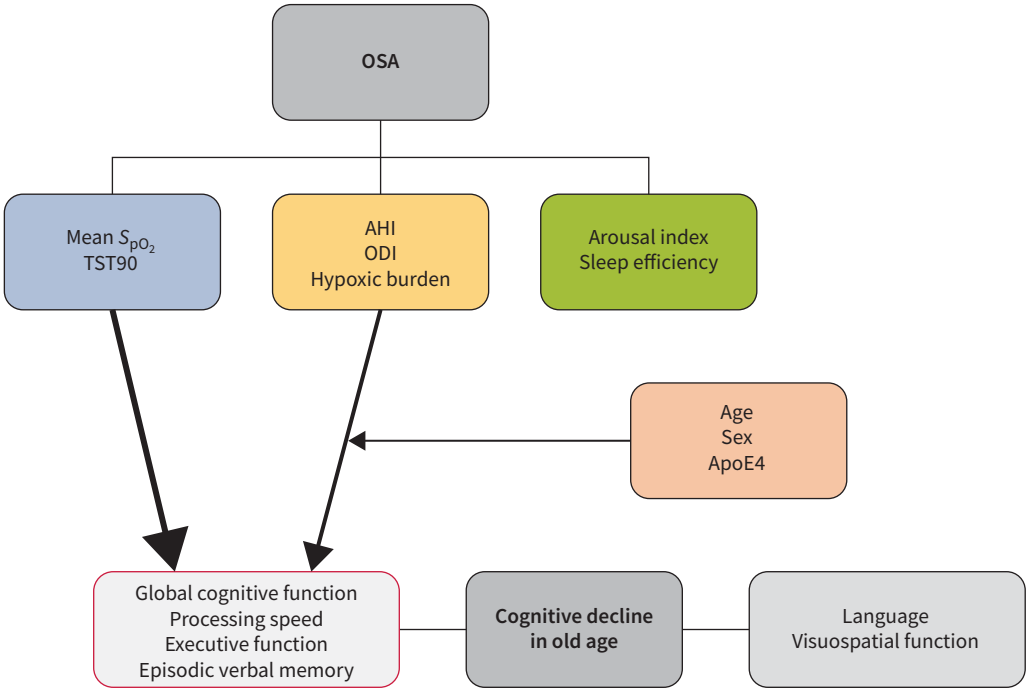

FIGURE 2 Overview of the results. The thickness of the arrows indicates the strength of the associations. Mean peripheral oxygen saturation during sleep (mean S_{pO_2}) and sleep time with S_{pO_2} <90% (TST90) were the parameters most consistently associated with cognitive decline. Apnoea–hypopnoea index (AHI), oxygen desaturation index (ODI) and hypoxic burden were less consistently associated with cognitive decline, and their associations were partly moderated by age, sex and apolipoprotein E4 (ApoE4) status. OSA: obstructive sleep apnoea.

impairment in the elderly, as previously postulated [40]. In support of this hypothesis, it has been shown that OSA and nocturnal hypoxaemia are associated with frontal white matter lesions [41, 42] and morphometric changes in the deep grey nuclei [43, 44]. In addition, it has recently been reported that neurofilament light chain (a marker of white matter integrity) increases in plasma of patients with severe OSA as a function of TST90 after CPAP withdrawal [45]. Decline in episodic verbal memory only concerned the delayed free recall task, but not the delayed total recall task. This also appears consistent with frontal-subcortical syndrome, as a poor free recall performance associated with a normal total recall suggests reduced memory retrieval (which is dependent on the frontal lobe) rather than reduced memory encoding/storage (which is dependent on the medial temporal lobe) [46].

From a clinical perspective, our results suggest that individuals with OSA who have more severe hypoxaemia are at increased risk of developing cognitive impairment. Intriguingly, mean S_{pO_2} and TST90 were more consistently related to cognitive decline than intermittent hypoxaemia parameters. This may suggest that the brain is more vulnerable to lower basal oxygen levels during sleep than to episodes of intermittent hypoxaemia; however, this hypothesis requires further investigation. Older age, male sex and ApoE4 also appear to be vulnerability factors for cognitive decline in OSA. These insights may be useful in identifying “at-risk” OSA patients who can be selected for interventional studies. The implications are important because cognitive impairment and dementia are often irreversible conditions for which management of modifiable risk factors is of paramount importance.

To date, it remains unclear whether CPAP treatment prevents or delays cognitive decline in the elderly. Small single-centre trials have shown improvements in cognitive functioning during CPAP treatment [47, 48]. In contrast, larger multicentre trials have shown no effect [49, 50] or only slight improvement in cognition [51, 52]. Nevertheless, it should be mentioned that the benefit of CPAP is expected to increase with good adherence and that low adherence has been reported in some of these trials [50, 52]. Moreover, these trials mostly included highly educated participants with high baseline cognitive scores, which could have led to a ceiling effect [49–52].

The strengths of our study were the longitudinal design, PSG measures of OSA, cognitive assessment using an extensive battery of tests, availability of information about many potential confounders and moderating analysis. Limitations were the assessment of sleep on a single night only because studies have reported night-to-night variations in the assessment of OSA [53]. However, multi-night PSG recordings are rare in both clinical and research settings, and were not available in our cohort. We had to exclude participants who did not complete the second cognitive assessment. This could have led to selection bias because, as mentioned earlier, the included compared with excluded sample had some more favourable characteristics at baseline. Finally, the results should be interpreted with caution because we examined a 5-year time window only, and some relevant associations between OSA and cognitive decline might lie outside this window.

In conclusion, OSA parameters (particularly those measuring nocturnal hypoxaemia) were independent predictors of 5-year cognitive decline in our sample of community-dwelling elderly individuals. Older age, male sex and ApoE4 emerged as vulnerability factors exacerbating this association. This study provides new insights that may be useful for identifying OSA patients at increased risk of cognitive decline and for designing new interventional studies.

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References

1 Heinzer R, Vat S, Marques-Vidal P, *et al.* Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. *Lancet Respir Med* 2015; 3: 310–318.
2 Bubu OM, Andrade AG, Umasabor-Bubu OQ, *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.
3 Cross N, Lampit A, Pye J, *et al.* is obstructive sleep apnoea related to neuropsychological function in healthy older adults? A systematic review and meta-analysis. *Neuropsychol Rev* 2017; 27: 389–402.
4 Gosselin N, Baril AA, Osorio RS, *et al.* Obstructive sleep apnea and the risk of cognitive decline in older adults. *Am J Respir Crit Care Med* 2019; 199: 142–148.
5 Osorio RS, Martínez-García MÁ, Rapoport DM. Sleep apnoea in the elderly: a great challenge for the future. *Eur Respir J* 2022; 59: 2101649.
6 Yaffe K, Laffan AM, Harrison SL, *et al.* Sleep-disordered breathing, hypoxia, and risk of mild cognitive impairment and dementia in older women. *JAMA* 2011; 306: 613–619.
7 Osorio RS, Gumb T, Pirraglia E, *et al.* Sleep-disordered breathing advances cognitive decline in the elderly. *Neurology* 2015; 84: 1964–1971.
8 Lutsey PL, Misialek JR, Mosley TH, *et al.* Sleep characteristics and risk of dementia and Alzheimer's disease: the Atherosclerosis Risk in Communities study. *Alzheimers Dement* 2018; 14: 157–166.
9 Lutsey PL, Bengtson LGS, Punjabi NM, *et al.* Obstructive sleep apnea and 15-year cognitive decline: the Atherosclerosis Risk in Communities (ARIC) study. *Sleep* 2016; 39: 309–316.
10 Ramos AR, Tarraf W, Wu B, *et al.* Sleep and neurocognitive decline in the Hispanic Community Health Study/Study of Latinos. *Alzheimers Dement* 2020; 16: 305–315.
11 Martin MS, Sforza E, Roche F, *et al.* Sleep breathing disorders and cognitive function in the elderly: an 8-year follow-up study. The Proof-Synapse Cohort. *Sleep* 2015; 38: 179–187.
12 Blackwell T, Yaffe K, Laffan A, *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: 453–461.

13 Legault J, Thompson C, Martineau-Dussault MÈ, *et al.* Obstructive sleep apnea and cognitive decline: a review of potential vulnerability and protective factors. *Brain Sci* 2021; 11: 706.
14 Poirier J, Davignon J, Bouthillier D, *et al.* Apolipoprotein E polymorphism and Alzheimer's disease. *Lancet* 1993; 342: 697–699.
15 Bondi MW, Salmon DP, Monsch AU, *et al.* Episodic memory changes are associated with the APOE-epsilon 4 allele in nondemented older adults. *Neurology* 1995; 45: 2203–2206.
16 Bubu OM, Andrade AG, Umasabor-Bubu OQ, *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.
17 Ramos AR, Tarraf W, Rundek T, *et al.* Obstructive sleep apnea and neurocognitive function in a Hispanic/Latino population. *Neurology* 2015; 84: 391–398.
18 Thompson C, Legault J, Moullec G, *et al.* Association between risk of obstructive sleep apnea, inflammation and cognition after 45 years old in the Canadian Longitudinal Study on Aging. *Sleep Med* 2022; 91: 21–30.
19 Chang WP, Liu ME, Chang WC, *et al.* Sleep apnea and the risk of dementia: a population-based 5-year follow-up study in Taiwan. *PLoS One* 2013; 8: e78655.
20 Cosentino FII, Bosco P, Drago V, *et al.* The APOE epsilon4 allele increases the risk of impaired spatial working memory in obstructive sleep apnea. *Sleep Med* 2008; 9: 831–839.
21 Spira AP, Blackwell T, Stone KL, *et al.* Sleep-disordered breathing and cognition in older women. *J Am Geriatr Soc* 2008; 56: 45–50.
22 Nikodemova M, Finn L, Mignot E, *et al.* Association of sleep disordered breathing and cognitive deficit in *APOE* ε4 carriers. *Sleep* 2013; 36: 873–880.
23 Firmann M, Mayor V, Vidal PM, *et al.* The CoLaus study: a population-based study to investigate the epidemiology and genetic determinants of cardiovascular risk factors and metabolic syndrome. *BMC Cardiovasc Disord* 2008; 8: 6.
24 Preisig M, Waeber G, Vollenweider P, *et al.* The PsyCoLaus study: methodology and characteristics of the sample of a population-based survey on psychiatric disorders and their association with genetic and cardiovascular risk factors. *BMC Psychiatry* 2009; 9: 9.
25 Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology* 1993; 43: 2412–2414.
26 American Academy of Sleep Medicine. International Classification of Sleep Disorders. 3rd Edn. Darien, AASM, 2014.
27 Berry RB, Budhiraja R, Gottlieb DJ, *et al.* Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. *J Clin Sleep Med* 2012; 8: 597–619.
28 Azarbarzin A, Sands SA, Taranto-Montemurro L, *et al.* Hypoxic burden captures sleep apnoea-specific nocturnal hypoxaemia. *Eur Heart J* 2019; 40: 2989–2990.
29 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: 189–198.
30 Bayard S, Erkes J, Moroni C. Victoria Stroop Test: normative data in a sample group of older people and the study of their clinical applications in the assessment of inhibition in Alzheimer's disease. *Arch Clin Neuropsychol* 2011; 26: 653–661.
31 Cardebat D, Doyon B, Puel M, *et al.* Evocation lexicale formelle et sémantique chez des sujets normaux. Performances et dynamiques de production en fonction du sexe, de l'âge et du niveau d'étude. [Formal and semantic lexical evocation in normal subjects. Performance and dynamics of production as a function of sex, age and educational level.] *Acta Neurol Belg* 1990; 90: 207–217.
32 Van der Linden M, Coyette F, Poitrenaud J, *et al.* L'épreuve de rappel libre/rappel indicé à 16 items (RL/RI-16). [The 16-item free recall/cued recall test (RL/RI-16).] *In:* Van der Linden M, Adam S, Agniel A, *et al.* eds. L'évaluation des troubles de la mémoire. Présentation de quatre tests de mémoire épisodique (avec leur étalonnage). [Evaluation of memory disorders. Presentation of four episodic memory tests (with their calibration).] Marseille, Solal, 2004; pp. 25–47.
33 Grober E, Buschke H. Genuine memory deficits in dementia. *Dev Neuropsychol* 1987; 3: 13–36.
34 Thuillard Colombo F, Assal G. Adaptation française du test de dénomination de Boston. Versions abrégées. [French adaptation of the Boston naming test. Abbreviated versions.] *Rev Eur Psychol Appl* 1992; 42; 67–71.
35 Morris JC, Mohs RC, Rogers H, *et al.* Consortium to Establish a Registry for Alzheimer's Disease (CERAD) clinical and neuropsychological assessment of Alzheimer's disease. *Psychopharmacol Bull* 1988; 24: 641–652.
36 Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991; 14: 540–545.
37 Hayes A. Introduction to Mediation, Moderation, and Conditional Process Analysis: A Regression-Based Approach. New York, Guilford, 2013.
38 Pugh KG, Lipsitz LA. The microvascular frontal-subcortical syndrome of aging. *Neurobiol Aging* 2002; 23: 421–431.

39 Wardlaw JM, Smith C, Dichgans M. Small vessel disease: mechanisms and clinical implications. *Lancet Neurol* 2019; 18: 684–696.

40 Zimmerman ME, Aloia MS. Sleep-disordered breathing and cognition in older adults. *Curr Neurol Neurosci Rep* 2012; 12: 537–546.

41 Chokesuwattanaskul A, Lertjitbanjong P, Thongprayoon C, *et al.* Impact of obstructive sleep apnea on silent cerebral small vessel disease: a systematic review and meta-analysis. *Sleep Med* 2020; 68: 80–88.

42 Zacharias HU, Weihs A, Habes M, *et al.* Association between obstructive sleep apnea and brain white matter hyperintensities in a population-based cohort in Germany. *JAMA Netw Open* 2021; 4: e2128225.

43 Marchi NA, Ramponi C, Hirotsu C, *et al.* Mean oxygen saturation during sleep is related to specific brain atrophy pattern. *Ann Neurol* 2020; 87: 921–930.

44 Kumar R, Farahvar S, Ogren JA, *et al.* Brain putamen volume changes in newly-diagnosed patients with obstructive sleep apnea. *Neuroimage Clin* 2014; 4: 383–391.

45 Kam K, Jun J, Parekh A, *et al.* Acute OSA impacts diurnal Alzheimer's biomarkers through nocturnal hypoxemia and state transitions. *Am J Respir Crit Care Med* 2022; 206: 1039–1042.

46 Sarazin M, Berr C, De Rotrou J, *et al.* Amnestic syndrome of the medial temporal type identifies prodromal AD: a longitudinal study. *Neurology* 2007; 69: 1859–1867.

47 Aloia MS, Ilniczky N, Di Dio P, *et al.* Neuropsychological changes and treatment compliance in older adults with sleep apnea. *J Psychosom Res* 2003; 54: 71–76.

48 Dalmases M, Solé-Padullés C, Torres M, *et al.* Effect of CPAP on cognition, brain function, and structure among elderly patients with OSA: a randomized pilot study. *Chest* 2015; 148: 1214–1223.

49 Ponce S, Pastor E, Orosa B, *et al.* The role of CPAP treatment in elderly patients with moderate obstructive sleep apnoea: a multicentre randomised controlled trial. *Eur Respir J* 2019; 54: 1900518.

50 McMillan A, Bratton DJ, Faria R, *et al.* Continuous positive airway pressure in older people with obstructive sleep apnoea syndrome (PREDICT): a 12-month, multicentre, randomised trial. *Lancet Respir Med* 2014; 2: 804–812.

51 Martínez-García MÁ, Chiner E, Hernández L, *et al.* Obstructive sleep apnoea in the elderly: role of continuous positive airway pressure treatment. *Eur Respir J* 2015; 46: 142–151.

52 Kushida CA, Nichols DA, Holmes TH, *et al.* Effects of continuous positive airway pressure on neurocognitive function in obstructive sleep apnea patients: the Apnea Positive Pressure Long-term Efficacy Study (APPLES). *Sleep* 2012; 35: 1593–1602.

53 Stöberl AS, Schwarz EI, Haile SR, *et al.* Night-to-night variability of obstructive sleep apnea. *J Sleep Res* 2017; 26: 782–788.