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RESEARCH ARTICLE

Obstructive sleep apnea and cognitive functioning in the older general population: The moderating effect of age, sex, ApoE4, and obesity

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SUMMARY

Research on the relationship between obstructive sleep apnea and cognitive functioning has yielded conflicting results, particularly in the older population, and moderators of this association have rarely been studied. Here we investigated the cross-sectional association between obstructive sleep apnea and cognitive functioning as well as the moderating effect of age, sex, apolipoprotein E4, and obesity on this association among community-dwelling older people. We analysed data from 496 participants (71.4 ± 4.4 years; 45.6% men) of the HypnoLaus study who underwent polysomnography and a battery of neuropsychological tests. The sample was categorised as no-to-mild obstructive sleep apnea (apnea–hypopnea index 0–14.9/h; reference), moderate obstructive sleep apnea (apnea–hypopnea index 15.0–29.9/h), or severe obstructive sleep apnea (apnea–hypopnea index ≥30/h). Regression and moderation analyses were performed with adjustment for confounders. Apolipoprotein E4 and obesity moderated the association between severe obstructive sleep apnea and processing speed, whereas no moderating effects were found for age and sex. In apolipoprotein E4 carriers only, severe obstructive sleep apnea was associated with

lower performance in Stroop condition 1 ($B = 3.13$, $p = 0.024$). In obese participants only, severe obstructive sleep apnea was associated with lower performance in Stroop condition 1 ($B = 3.02$, $p = 0.025$) and Stroop condition 2 ($B = 3.30$, $p = 0.034$). Severe obstructive sleep apnea was also associated with lower executive function in the whole sample according to Stroop condition 3 ($B = 3.44$, $p = 0.020$) and Stroop interference score ($B = 0.24$, $p = 0.006$). Our findings support associations of severe obstructive sleep apnea (but not moderate obstructive sleep apnea) with lower performance in processing speed and executive function in the older general population. Apolipoprotein E4 and obesity appear to be vulnerability factors that strengthen the association between severe obstructive sleep apnea and lower performance in processing speed.

KEYWORDS
ageing, cognitive impairment, dementia, interaction, moderation analysis, sleep-disordered breathing

1 | INTRODUCTION

Obstructive sleep apnea (OSA) is characterised by repeated upper airway obstruction, leading to sleep fragmentation and intermittent hypoxaemia (White, 1995). Polysomnography (PSG) is considered the gold standard for the diagnosis of OSA. The prevalence of moderate to severe OSA (defined as an apnea–hypopnea index [AHI] ≥15/h) is estimated to be at least 30% in the elderly population (Heinzer et al., 2015; Senaratna et al., 2017). Evidence suggests that OSA promotes oxidative stress, neuroinflammation, brain oedema, cerebral small vessel disease, and neurodegenerative processes, resulting in brain structural alterations and cognitive dysfunction (Gosselin et al., 2019; Liguori et al., 2021). Cross-sectional studies have reported associations between OSA and cognitive impairment in young and middle-aged adults with effect sizes ranging from weak to strong (Bubu et al., 2020). However, cross-sectional and longitudinal studies conducted in older people have generally shown a weaker, or no association between OSA and cognitive dysfunction (Blackwell et al., 2011, 2015; Lutsey et al., 2016; Martin et al., 2015; Sforza et al., 2010). Similarly, a meta-analysis that investigated the relationship between OSA and cognitive functioning at a single time point in old age showed small associations between OSA and lower performance in combined measures of cognition, processing speed, and declarative memory (Cross et al., 2017). Positive findings were mainly documented in case–controls studies conducted in sleep clinics, whereas larger cohort studies generally did not reveal significant associations (Cross et al., 2017). The influence of age on the association between OSA and cognitive functioning still remains controversial. The cross-sectional analysis of stroke-free participants in the Reasons for Geographic and Racial Difference in Stroke (REGARDS) study revealed that individuals with high risk of OSA (as measured by the Berlin Sleep Questionnaires) had lower performance on semantic fluency task in middle age, but not in older age (Addison-Brown et al., 2014). In contrast, the longitudinal analysis conducted by Kaur et al. in the Hispanic Community Health Study/Study of Latinos (HCHS/SOL) showed that association between OSA (as measured by a limited channel device) and cognitive decline was more pronounced in older age than in middle age (Kaur et al., 2021).

The heterogeneous results observed particularly in older people might be related to differences in OSA measures (questionnaires, limited-channel devices, or PSG). However, these results might also be due partly to unequally distributed individual characteristics across studies, including sex, apolipoprotein E4 (ApoE4) allele, and obesity, which could modulate the association between OSA and cognitive functioning (Legault et al., 2021). Unfortunately, large cohort studies of OSA and cognitive functioning tended to statistically control for the effect or provided results stratified by these characteristics without assessing the interaction terms. Only a few studies have formally tested whether these features interact with OSA to predict cognitive functioning in the general population (Addison-Brown et al., 2014; Kaur et al., 2021; Nikodemova et al., 2013; Ramos et al., 2015; Spira et al., 2008). Kaur et al. who examined the modifying effect of sex did not find a significant interaction (Kaur et al., 2021), although a previous cross-sectional analysis of more than 8000 middle-aged and older participants in the same population-based cohort (HCHS/SOL) showed an association between OSA and lower cognitive performance in women compared with men (Ramos et al., 2015). With respect to ApoE4, cross-sectional analyses of the Study of Osteoporotic Fractures (SOF; including older women with a mean age of 82 years) (Spira et al., 2008) and Wisconsin Sleep Cohort (WSC; including middle-aged and older individuals with a mean age of 54 years) (Nikodemova et al., 2013) revealed some evidence for interactions indicating stronger associations between PSG measures of OSA severity and lower cognitive performance in ApoE4 carriers. Finally, only a community study has tested interactions with obesity (Kaur et al., 2021). Although this study (Kaur et al., 2021) did not support a modifying effect of obesity in the entire cohort, there was such

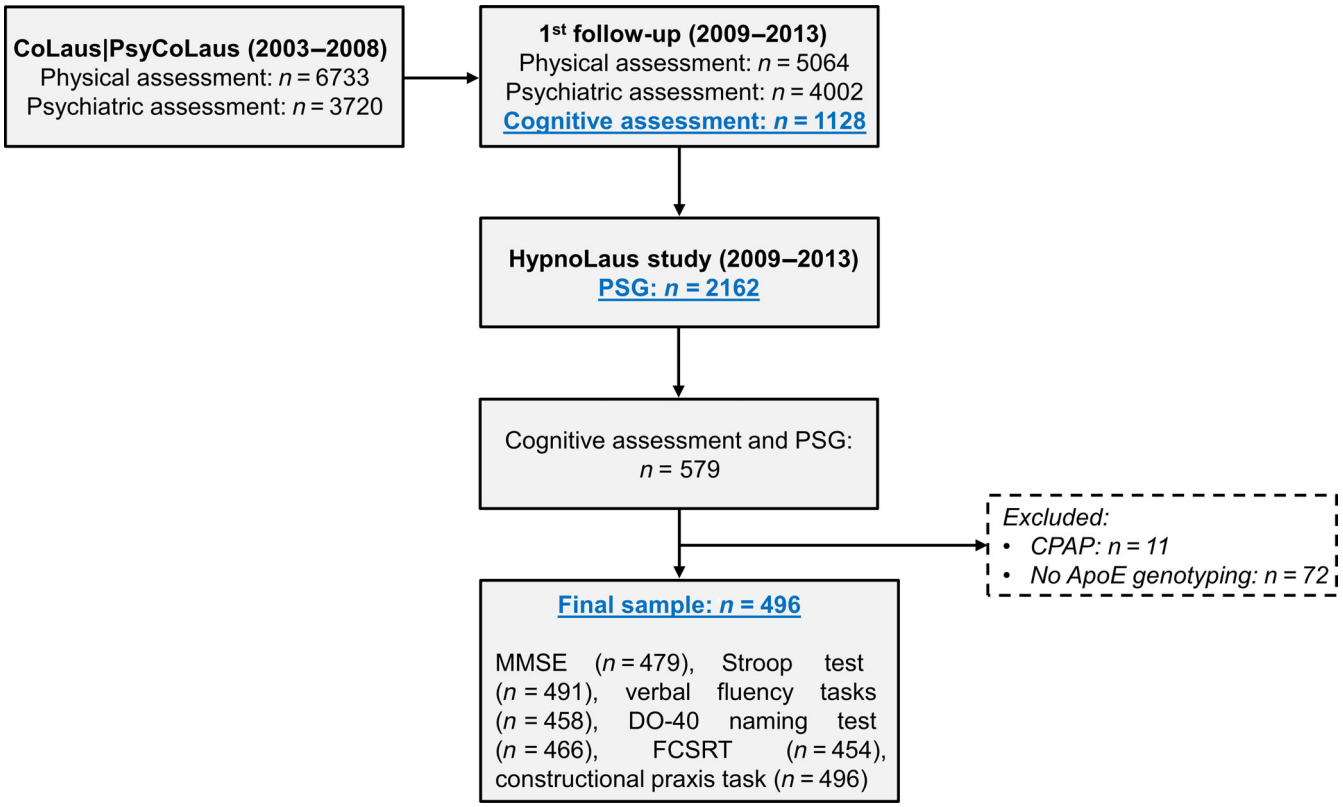

FIGURE 1 Flowchart of the study population. Abbreviations: ApoE, apolipoprotein E; CPAP, continuous positive airway pressure; FCSRT, Free and Cued Selective Reminding Test; MMSE, Mini-Mental State Examination; PSG, polysomnography.

an interaction among participants of 65 years and older, indicating a stronger association of OSA with decline in declarative memory and global cognition in non-obese participants compared with those with obesity.

The present study aimed to investigate the association between OSA (as measured by PSG) and cognitive functioning as well as the moderating effect of age, sex, ApoE4, and obesity on this association in a cohort of adults aged ≥65 years recruited from the community. We hypothesised associations between greater OSA severity and poorer cognitive performance in processing speed, executive function, and declarative memory. Moreover, we expected these associations to be stronger in youngest-old participants, women, ApoE4 carriers, and non-obese participants.

2 | METHODS

2.1 | Study population

Data stemmed from CoLaus|PsyCoLaus, a prospective cohort study on middle-aged and older adults randomly selected from the residents of Lausanne, Switzerland (Firmann et al., 2008; Preisig et al., 2009). In this study, cognitive assessment was performed in participants aged ≥65 years. The present paper included participants aged ≥65 years who underwent both PSG and cognitive assessment during the first follow-up evaluation of the study. We excluded participants treated with continuous positive airway pressure and without ApoE genotyping, resulting in a final sample of 496 participants (Figure 1). None of the participants had central sleep apnea (American Academy of Sleep Medicine, 2014) or dementia (defined as a Clinical Dementia Rating scale ≥1 [Morris, 1993]). The CoLaus|PsyCoLaus and HypnoLaus studies were approved by the ethics committee of the Vaud Canton and all participants provided written informed consent.

2.2 | OSA assessment

PSG data were recorded within the nested HypnoLaus study, as described previously (Heinzer et al., 2015) (see the Supporting information for more details). On average, included participants underwent the PSG less than 1 year after the cognitive assessment (0.8 ± 0.9 years). Sleep stages and arousals were scored according to the 2007 American Academy of Sleep Medicine (AASM) manual (Iber et al., 2007), while respiratory events were scored according to the 2012 AASM criteria (Berry et al., 2012). The sample was categorised as no-to-mild OSA (AHI 0–14.9/h; reference), moderate OSA (AHI

TABLE 1 Cognitive assessment

Cognitive domain	Test	Task	Outcome
Global cognitive function	Mini-mental state examination (MMSE) (Folstein et al., 1975)	Complete subtests of orientation, registration and recall of words, attention and calculation, language and constructional praxis	≤27 points (= poorer performance) versus 28–30 points
Processing speed	Stroop test Victoria version (Bayard et al., 2011)	Condition 1 (dot condition): name the colour (red, blue, green, yellow) of dots as quickly as possible	Time in seconds (higher time = poorer performance)
		Condition 2 (neutral-word condition): name the colour (red, blue, green, yellow) of neutral words as quickly as possible	Time in seconds (higher time = poorer performance)
Executive function	Stroop test Victoria version (Bayard et al., 2011)	Condition 3 (colour-word condition): name the colour of words *blue*, *green*, *yellow*, and *red* written in one of the three other colours as quickly as possible	Time in seconds (higher time = poorer performance)
		Interference score: time for Condition 3/time for Condition 1	Absolute score (higher score = poorer performance)
Executive control and verbal ability	Verbal fluency tasks (Cardebat et al., 1990)	Phonemic fluency: give as many words beginning with the letter "P" as possible in a 2 min period	Number of words (lower number = poorer performance)
		Semantic fluency: give as many examples of "animals" as possible in a 2 min period	Number of words (lower number = poorer performance)
Episodic verbal memory	Free and Cued Selective Reminding Test (FCSRT) (Van der Linden et al., 2004)	Free recall: Recall as many words as possible during the three recall trials	Range: 0–48 words (lower number = poorer performance)
		Total recall: Free recall + correct cued recall for words that were not recalled during the free recall	≤42 words (= poorer performance) versus 43–46 words
Language	DO-40 naming test (Thuillard Colombo & Assal, 1992)	Name 40 pictures	≤39 words (= poorer performance) versus 40 words
Visuospatial function	Constructional praxis task from the CERAD test battery (Morris et al., 1988)	Copy of four figures of increasing complexity (circle, diamond, overlapping rectangles, and Necker cube)	≤9 points (= poorer performance) versus 10–11 points

Abbreviations: CERAD, Consortium to Establish a Registry for Alzheimer's Disease.

15.0–29.9/h), or severe OSA (AHI ≥ 30/h). The following parameters were reported to describe sleep characteristics of OSA groups: total sleep time, proportion of sleep stages N1, N2, N3, and REM sleep, microarousal index (defined as the number of microarousals per hour of sleep), 3% oxygen desaturation index, and sleep time spent with oxygen saturation <90%.

2.3 | Cognitive assessment

The neuropsychological test battery was administered during the first follow-up of the CoLaus|PsyCoLaus study and included the Mini-Mental State Examination (MMSE; global cognitive function) (Folstein et al., 1975), Stroop test Victoria version (processing speed and executive function) (Bayard et al., 2011), Free and Cued Selective Reminding Test (FCSRT; episodic verbal memory) (Van der Linden et al., 2004), DO-40 naming test (language) (Thuillard Colombo & Assal, 1992), verbal fluency tasks (executive control and verbal ability) (Cardebat et al., 1990), and constructional praxis task from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) test battery (visuospatial function) (Morris et al., 1988). Cognitive measures were analysed as continuous variables, except for four measures (MMSE, FCSRT total recall, DO-40 naming test, and CERAD constructional praxis task) that were dichotomised by the 10th percentile because of their skewed distribution (Table 1 and Supporting information).

2.4 | Confounders and moderating factors

Sociodemographic and clinical characteristics were recorded during the first follow-up of the CoLaus|PsyCoLaus study. Participants were categorised into ApoE4 carriers (one or two E4 alleles) or non-carriers (details

TABLE 2 Sample characteristics

	All sample $n = 496$ (100%)	No-to-mild OSA $n = 244$ (49.2%)	Moderate OSA $n = 135$ (27.2%)	Severe OSA $n = 117$ (23.6%)	Test	p
Sociodemographic characteristics						
Age, years	71.4 ± 4.4	71.1 ± 4.2[c]	70.8 ± 4.0[c]	72.8 ± 4.8[a,b]	$F = 8.2$	**<0.001**
Men, *n* (%)	226 (45.6)	77 (31.6)[b,c]	72 (53.3)[a]	77 (65.8)[a]	$\chi^2 = 41.9$	**<0.001**
Education (≥high school), *n* (%)	208 (41.9)	103 (42.2)	60 (44.4)	45 (38.5)	$\chi^2 = 0.9$	0.626
Clinical characteristics						
ApoE4, *n* (%)	115 (23.2)	54 (22.1)	35 (25.9)	26 (22.2)	$\chi^2 = 0.8$	0.676
Obesity, *n* (%)	106 (21.4)	34 (13.9)[b,c]	34 (25.2)[a]	38 (32.5)[a]	$\chi^2 = 17.8$	**<0.001**
Diabetes, *n* (%)	87 (17.5)	29 (11.8)[b,c]	29 (21.5)[a]	29 (24.8)[a]	$\chi^2 = 11.1$	**0.004**
Hypertension, *n* (%)	333 (67.1)	148 (60.7)[c]	93 (68.9)	92 (78.6)[a]	$\chi^2 = 11.8$	**0.003**
Smoking, *n* (%)	279 (56.3)	125 (51.2)	81 (60.0)	73 (62.4)	$\chi^2 = 5.1$	0.079
Alcohol (≥14 units/week), *n* (%)	88 (17.7)	32 (13.1)[c]	29 (21.5)	27 (23.1)[a]	$\chi^2 = 7.1$	**0.028**
ESS, points	5.0 ± 3.3	4.7 ± 3.2	5.4 ± 3.7	5.4 ± 3.2	$F = 2.9$	0.055
Depression, *n* (%)	21 (4.2)	13 (5.3)	4 (3.0)	4 (3.4)	Fisher	0.569
Psychotropic medication, *n* (%)	113 (22.8)	50 (20.5)	29 (21.5)	34 (29.1)	$\chi^2 = 3.5$	0.176
Sleep characteristics						
Total sleep time, min	387.0 ± 75.0	390.3 ± 70.8	388.3 ± 71.6	376.3 ± 87.6	$F = 1.3$	0.275
Stage N1, %	13.9 ± 9.3	11.1 ± 5.8[b,c]	13.7 ± 8.5[a,c]	19.8 ± 12.0[a,b]	$F = 41.7$	**<0.001**
Stage N2, %	49.7 ± 12.0	48.7 ± 11.5	50.7 ± 12.8	50.4 ± 12.2	$F = 1.6$	0.194
Stage N3, %	16.8 ± 8.6	19.4 ± 8.9[b,c]	15.8 ± 7.7[a,c]	12.6 ± 7.7[a,b]	$F = 30.9$	**<0.001**
REM sleep, %	19.6 ± 6.8	20.8 ± 6.6[c]	19.7 ± 6.6[c]	17.1 ± 7.1[a,b]	$F = 12.3$	**<0.001**
Microarousal index, events/h	23.1 [16.5, 31.9]	17.8 [13.6, 23.4][b,c]	23.5 [19.1, 28.7][a,c]	35.4 [26.8, 47.5][a,b]	$H = 176.3$	**<0.001**
AHI, events/h	15.1 [7.2, 28.8]	7.2 [4.1, 10.2][b,c]	21.3 [17.6, 24.3][a,c]	46.2 [36.3, 57.4][a,b]	$H = 419.6$	**<0.001**
ODI, events/h	14.7 [7.0, 27.3]	7.0 [3.9, 10.9][b,c]	19.8 [16.2, 23.9][a,c]	40.2 [32.5, 52.5][a,b]	$H = 391.0$	**<0.001**
TST90, %	1.0 [0.1, 5.6]	0.2 [0.0, 1.2][b,c]	2.0 [0.5, 6.6][a,c]	6.6 [2.5, 15.0][a,b]	$H = 156.0$	**<0.001**

Note: Data are presented as mean ± standard deviation, median [interquartile range], or number of participants (%). Data were analysed using one-way analysis of variance (*F*), Kruskal-Wallis test (*H*), chi-squared test (χ^2), or Fisher's exact test. Bold text indicates $p < 0.05$.

Abbreviations: AHI, apnea–hypopnea index; ApoE4, apolipoprotein E4; ESS, Epworth Sleepiness Scale; ODI, oxygen desaturation index; OSA, obstructive sleep apnea; REM, rapid eye movement; TST90, sleep time with oxygen saturation <90%.

[a]Significant difference compared with the no-to-mild OSA group.

[b]Significant difference compared with the moderate OSA group.

[c]Significant difference compared with the severe OSA group.

on genotyping are presented in the Supporting information). Education was dichotomised into ≥high school (high school or university) or <high school (mandatory or apprenticeship). Obesity was defined as a body mass index ≥30 kg/m^2. Presence of diabetes was defined as a fasting blood glucose ≥7 mmol/L and/or antidiabetics use. Hypertension was defined as a systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg and/or antihypertensive drug use. Smoking status was dichotomised into current or former smoker versus never smoked. Excessive alcohol consumption was defined as ≥14 units/week. Daytime sleepiness was evaluated with the Epworth Sleepiness Scale (ESS) (Johns, 1991). Depression was defined as a current major depressive disorder according to the Diagnostic and Statistical Manual of Mental Disorders IV criteria. Medication was coded according to the WHO ATC classification (https://www.whocc.no/atc_ddd_index/). We considered hypnotics (ATC code: N05CF), benzodiazepines or derivates (N05BA, N05CD, N03AE), antidepressants (N06A), and neuroleptics (N06A) as psychotropic medications categories having a potential effect on cognition.

2.5 | Statistical analysis

Univariate analyses comparing OSA groups on clinical and sleep characteristics relied on one-way analysis of variance, Kruskal-Wallis test,

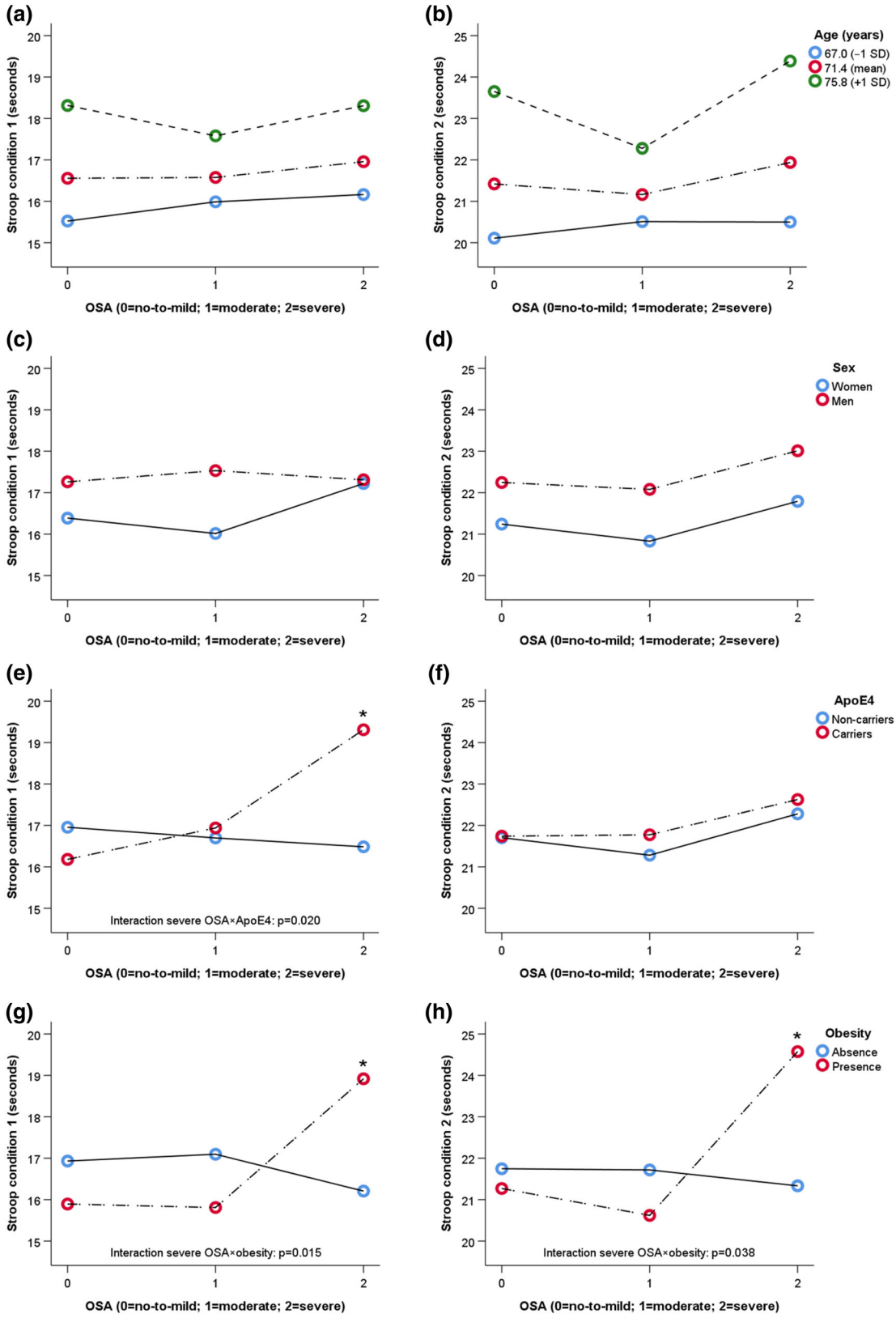

FIGURE 2 Cognitive performance scores in function of potential moderators and OSA severity levels. Data were analysed by Hayes's SPSS Process macro version 4.1 for moderation analysis using cognitive performance as dependent variable, OSA severity as independent variable and (a, b) age, (c, d) sex, (e, f) apolipoprotein E4 status, or (g, h) obesity as moderator. Asterisks indicate significant difference compared with the no-to-mild OSA group. Analyses adjusted for education (≥high school vs. <high school), diabetes (presence vs. absence), hypertension (presence vs. absence), smoking (current or former vs. never), alcohol (≥14 vs. <14 units/week), depression (presence vs. absence), Epworth Sleepiness Scale (continuous), and psychotropic medication (presence vs. absence). Abbreviations: ApoE4, apolipoprotein E4; OSA, obstructive sleep apnea; SD = standard deviation.

chi-squared test, or Fisher's exact test, as appropriate. We used Hayes's SPSS Process macro version 4.1 to conduct moderation analysis (Hayes, 2013). We tested the interactions between the four potential moderators (age [continuous], sex [men vs. women], ApoE4 [carriers vs. non-carriers], and obesity [presence vs. absence]) and the two OSA severity levels (moderate OSA vs. no-to-mild OSA and severe OSA vs. no-to-mild OSA) regarding cognitive functions using multiple linear regressions (for continuous cognitive scores) and logistic regressions (for dichotomised cognitive scores). In the case of significant interaction between a potential moderator and an OSA severity level with respect to a cognitive outcome, results for the strata according to the moderator variable are presented. If there was no interaction, the results in the whole sample are presented. Analyses were adjusted for education, diabetes, hypertension, smoking, excessive alcohol consumption, depression, ESS, and psychotropic medication. A description of how missing data were handled is provided in the Supporting information. We considered bivariate tests with p <0.05 as significant. Statistical analysis was performed with SPSS version 26 (IBM Corp., Armonk, USA).

3 | RESULTS

3.1 | Sample characteristics

Table 2 summarises sociodemographic, clinical, and sleep characteristics for the total sample and by OSA groups. The sample consisted of 496 participants aged 71.4 ± 4.4 years (range: 65–83 years), of whom 226 (45.6%) were men. Compared with participants with no-to-mild OSA, those with moderate or severe OSA were older, were more likely to be men, had a higher prevalence of obesity, diabetes, and hypertension and were more likely to present an excessive alcohol consumption. The moderate and severe OSA groups had higher indices of sleep fragmentation and nocturnal hypoxaemia than the no-to-mild OSA group.

3.2 | Moderation analysis

Three significant interactions were found, which all involved the severe OSA level (Figure 2). ApoE4 and obesity interacted with severe

TABLE 3 Associations between OSA severity and cognitive functioning

	Moderate OSA		Severe OSA	
Continuous scores	***B* (95% CI)**	***p***	***B* (95% CI)**	***p***
Stroop condition 1	−0.13 (−1.34, 1.08)	0.833	-	-
ApoE4 non-carriers	-	-	−0.42 (−1.92, 1.08)	0.583
ApoE4 carriers	-	-	3.13 (0.41, 5.84)	**0.024**
No obesity	-	-	−0.71 (−2.24, 0.82)	0.362
Obesity	-	-	3.02 (0.39, 5.66)	**0.025**
Stroop condition 2	−0.35 (−1.75, 1.04)	0.619	-	-
No obesity	-	-	−0.43 (−2.21, 1.35)	0.636
Obesity	-	-	3.30 (0.25, 6.35)	**0.034**
Stroop condition 3	1.46 (−1.12, 4.06)	0.268	3.44 (0.53, 6.44)	**0.020**
Stroop interference score	0.06 (−0.09, 0.22)	0.435	0.24 (0.07, 0.42)	**0.006**
FCSRT free recall	−0.55 (−1.84, 0.75)	0.410	−0.71 (−2.18, 0.75)	0.342
Phonemic fluency task	−0.03 (−1.76, 1.70)	0.971	−0.29 (−2.26, 1.67)	0.771
Semantic fluency task	−1.67 (−3.44, 0.08)	0.062	−0.65 (−2.66, 1.31)	0.506
	Moderate OSA		**Severe OSA**	
Dichotomised scores	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
MMSE ≤27 points	1.46 (0.70, 3.04)	0.314	0.59 (0.24, 1.47)	0.258
FCSRT total recall ≤42 points	1.77 (0.77, 3.91)	0.176	1.61 (0.66, 3.91)	0.294
DO-40 naming test ≤39 points	1.06 (0.55, 2.03)	0.856	1.05 (0.51, 2.18)	0.885
Constructional praxis task ≤9 points	1.06 (0.52, 2.12)	0.878	1.25 (0.60, 2.58)	0.546

Note: Data are presented as unstandardised beta coefficient (*B*) or odds ratio (OR) with respective 95% confidence interval (CI) against the reference group. Data were analysed by multiple linear or logistic regressions using cognitive scores as dependent variable and OSA groups as independent variable. Bold text indicates p <0.05. Analyses adjusted for age (continuous), sex (men vs. women), apolipoprotein E4 (carriers vs. non-carriers), education (≥high school vs. <high school), obesity (presence vs. absence), diabetes (presence vs. absence), hypertension (presence vs. absence), alcohol (≥14 vs. <14 units/week), smoking (current or former vs. never), depression (presence vs. absence), Epworth Sleepiness Scale (continuous), and psychotropic medication (presence vs. absence).
Abbreviations: ApoE4, apolipoprotein E4; FCSRT, Free and Cued Selective Reminding Test; MMSE, Mini-Mental State Examination; OSA, obstructive sleep apnea.

OSA regarding Stroop condition 1, indicating that ApoE4 carriers ($p = 0.020$; Figure 2e) or obese individuals ($p = 0.015$; Figure 2g) had poorer performance on this Stroop test. Obesity also interacted with severe OSA regarding Stroop condition 2 ($p = 0.038$; Figure 2h), again indicating lower performance of obese individuals on this Stroop test. No significant moderating effects were found for age and sex.

3.3 | Associations between OSA and cognitive functioning

Associations between OSA and cognitive functioning are presented in Table 3. The severe OSA group showed lower performance in Stroop test condition 1 only among ApoE4 carriers or among those with obesity. Similarly, the severe OSA group revealed decreased performance in Stroop test condition 2 only among those with obesity. In addition, the severe OSA group demonstrated poorer performance according to the Stroop test condition 3 and the Stroop interference score in the whole sample.

4 | DISCUSSION

In the present study, we used data from a sample of 496 community-dwelling older adults, the diagnosis of OSA was based on PSG and analyses were adjusted for multiple potential confounders. The most salient findings were that (i) severe OSA (but not moderate OSA) was associated with a lower processing speed and executive function according to the Stroop test and (ii) ApoE4 and obesity moderated the association between severe OSA and processing speed in the sense that the significant association between severe OSA and lower processing speed was restricted to ApoE4 carriers or obese participants.

4.1 | Comparison with previous community studies conducted in older adults

Previous population-based studies on the association between OSA and cognitive functioning revealed inconsistent findings, particularly in older people (Bubu et al., 2020; Cross et al., 2017). Our study may provide some explanations for the partially conflicting findings of previous studies. First, we only found severe OSA, but not moderate OSA, to be associated with cognitive functioning, indicating the importance of the diagnostic approach to obtain a precise OSA severity assessment (i.e., PSG, limited-channel devices, or questionnaires). This also suggests that only analysis using a relatively high AHI threshold for the diagnosis of OSA was likely to yield positive results. Indeed, our results corroborates those of the Proof-Synapse Cohort, which revealed reduced cognitive performance among individuals with severe OSA (Sforza et al., 2010). Consequently, it is not surprising that some studies have yielded non-significant results when they used lower AHI thresholds for defining OSA, such as the Sleep Heart Health Study (AHI >10/h) (Quan et al., 2006) or the Brazilian Longitudinal Study of Adult Health study (AHI ≥15/h) (Suemoto et al., 2022), or when they analysed AHI only as a continuous variable (Blackwell et al., 2011; Parker et al., 2021). Second, all observed associations in our study were restricted to processing speed and executive function according to the Stroop test, whereas no significant associations were found with respect to episodic verbal memory, language, or visuospatial function. This underlines the importance of performing a comprehensive cognitive assessment, as associations with OSA may be limited to certain cognitive domains or specific tests.

4.2 | Moderating effect of age, sex, ApoE4, and obesity

In contrast to our initial hypothesis, our study did not provide evidence for a moderating effect of age or sex. The absence of an age-specific effect contrasts with the results of two previous population-based studies which showed age modified the association between OSA and cognitive functioning, but in opposite ways. In the REGARDS study (Addison-Brown et al., 2014) a weaker association between OSA and cognitive dysfunction was found with increasing age, whereas in the HCHS/SOL study (Kaur et al., 2021) a stronger association between OSA and cognitive decline was documented with increasing age particularly in participants of 65 years and older. The results of the present study are also in contrast to those of a recently published longitudinal study by our group in which only oldest-old participants (aged ≥75 years) with OSA demonstrated a greater longitudinal decline in processing speed over a 5 year period (Marchi et al., 2023). However, the different sample characteristics and methodological approaches make it difficult to compare the present study with those published earlier (Addison-Brown et al., 2014; Kaur et al., 2021; Marchi et al., 2023). In particular, the REGARDS and HCHS/SOL studies included middle-aged and older participants, whereas our study included a sample of older adults with a relatively narrow age distribution. Other significant differences with previous studies were the study design (cross-sectional vs. longitudinal design) (Kaur et al., 2021; Marchi et al., 2023), cognitive outcome (Addison-Brown et al., 2014; Kaur et al., 2021), and OSA diagnostic method (PSG vs. limited-channel system or questionnaires) (Addison-Brown et al., 2014; Kaur et al., 2021). Differential results may also be attributable to cultural aspects, as our study focussed on the Caucasian population of Lausanne, whereas the REGARDS study included 34% of black individuals (Addison-Brown et al., 2014) and the HCHS/SOL study was restricted to Hispanic/Latino individuals from the United States (Kaur et al., 2021).

The observed absence of a modifying effect of sex is consistent with the findings of HCHS/SOL study (Kaur et al., 2021), but contrasts with those of an earlier analysis of the same cohort (Ramos et al., 2015) and those of a recent longitudinal analysis by our group (Marchi et al., 2023). Because of significant differences in sample characteristics and methodological approaches, it is again complicated to compare the results of these studies; however, we can make a few considerations. In the study of Ramos et al. (Ramos et al., 2015), AHI

was associated with a poorer cognitive functioning among women (but not among men). However, this sex-specific effect was most pronounced in middle-aged participants (45–54 years), an age group that was not analysed in the present study. In line with the results of the study by Ramos et al. (2015), a sex-stratified analysis of the Canadian Longitudinal Study of Aging (Thompson et al., 2022) also observed that associations between a higher risk of OSA and poorer cognitive performance were mostly present in women within a similar age range (45–59 years). These results may suggest that during the perimenopausal period the association between OSA and cognitive functioning may be more pronounced (Legault et al., 2021). Our recent longitudinal study focussing on older adults (mean age 71 years at baseline) found that men (but not women) with OSA showed a more marked decline in phonemic fluency (Marchi et al., 2023). Similarly, a cross-sectional analysis of selected older individuals (mean age 74 years) who participated in the Study of Neurocognitive Outcomes, Radiological and retinal Effects of Aspirin in Sleep Apnoea (SNORE-ASA) showed that men with OSA (but not women) had poorer performance in declarative memory (Ward et al., 2022). Therefore, the relationship between OSA and cognitive dysfunction with regard to some specific cognitive domains might be more pronounced among middle-aged/perimenopausal women and older men; however, further research is needed to confirm this hypothesis. Hence, it seems crucial that the moderating effect of sex can be compared across different age groups in future research.

We found that ApoE4 moderates the association between severe OSA and processing speed, which is consistent with the previous population-based studies (Marchi et al., 2023; Nikodemova et al., 2013; Spira et al., 2008). Despite some differences in study design and sample characteristics, all these studies concurred in observing stronger associations between OSA and cognitive dysfunction in some cognitive domains among ApoE4 carriers as compared with non-carriers (Marchi et al., 2023; Nikodemova et al., 2013; Spira et al., 2008). Results of some other studies that investigated clinical samples of patients with OSA were also consistent with these observations, although the presence of an interaction between OSA and ApoE4 status was not formally verified in these studies (Cosentino et al., 2008; O'Hara et al., 2005). Several studies showed that ApoE4 allele is associated with increased brain vulnerability to many insults that may include OSA (Bliwise, 2002). In particular, the ApoE4 allele may increase neuronal vulnerability to hypoxia-induced oxidative stress experienced during respiratory events (Nunomura et al., 2006). However, more studies are needed to elicit exact mechanisms by which OSA facilitates cognitive impairment in ApoE4 carriers.

We also found that obesity was a significant moderator of the association between severe OSA and processing speed. Obesity may potentially promote cognitive dysfunction in OSA through pro-inflammatory cytokines secreted by adipocytes that may contribute to neuroinflammatory processes (Miller & Spencer, 2014) and/or an increased severity of oxygen desaturations following respiratory events which is positively associated with body weight (Peppard et al., 2009). The presence of diurnal hypercapnia in some of the obese individuals with OSA may also contribute to impaired cognitive performance, as previously indicated in a case–control study (Kung et al., 2018). However, our observation of an association between severe OSA and poorer performance in processing speed in obese people contrasts with the findings of HCHS/SOL study, which, to our knowledge, is the only previous community-based study to have tested this interaction (Kaur et al., 2021). In the HCHS/SOL study, which included more than 5000 middle-aged and older adults, there was no interaction with obesity in the entire sample but evidence for a moderating effect of obesity in participants of 65 years and older (Kaur et al., 2021). Specifically, they found that older individuals who were not obese and had a combined OSA (defined as respiratory event index ≥15/h) and short sleep duration (defined as a self-reported sleep time <6 h) phenotype showed a more pronounced decline in declarative memory and global cognition compared with both other obese as well as non-obese counterparts (Kaur et al., 2021). The longitudinal design, the use of a lower threshold for the diagnosis of OSA, and the investigation of combined OSA/sleep duration phenotypes may explain the discrepant findings between the study by Kaur et al. (Kaur et al., 2021) and the present study. Hence, the potentially modifying effect of obesity of the association between OSA and cognitive functioning, which may also vary across age, remains uncertain and needs to be elucidated by future studies comparing results in different age groups and using different thresholds for the diagnosis of OSA.

4.3 | Strengths and limitations

The present study has some strengths, including analyses performed on a large sample of older adults recruited from the community, the diagnosis of OSA based on the gold standard PSG, the analysis of an extensive battery of cognitive tests, the moderation analysis, and the adjustment of analyses for multiple confounders (which in most cases were measured objectively). However, our study also presents limitations. First, the average time elapsed between cognitive assessment and PSG was less than 1 year, but in some participants, this period was greater than 1 year, which may have diminished the established association between OSA and cognitive functioning. However, OSA is a relatively stable condition that tends to increase slightly with age, but rarely shows major changes in severity unless there are substantial changes in BMI. As we did not record BMI at the time of PSG, the analyses were not adjusted for changes in BMI; yet, it does not seem likely that major changes in BMI can be observed over a period of less than 1 year and, given the large sample size, an increase in BMI in some participants is likely compensated for by a decrease in BMI in others. Furthermore, the lack of significant modifying effect of age is another argument in favour of the reliability of the results, despite the time lag between the cognitive assessment and PSG. Second, the cross-sectional design did not allow us to draw conclusions regarding the direction of established associations. However, from a pathophysiological point of view and according to a growing body of evidence (Bubu et al., 2020; Gosselin et al., 2019; Liguori et al., 2021), it

appears plausible that OSA may promote cognitive impairment. In contrast, the possibility that cognitive impairment may promote OSA is unlikely, as OSA is mainly due to anatomical features of the upper airway. Third, although our neuropsychological test battery covered most cognitive domains, attention-vigilance and working memory, which may also be impaired in OSA, were not assessed (Cross et al., 2017).

5 | CONCLUSIONS

This study supports the association between severe OSA and poorer executive function in community-dwelling older adults. Furthermore, it highlights the moderating effects of ApoE4 and obesity on the association between severe OSA and lower processing speed. Although limited to the severe OSA group and the Stroop test, the results may have clinical and public health implications. Indeed, they were observed in an unselected sample of older adults without dementia, suggesting that OSA may exert a detrimental role on cognitive functioning at the population level, visible even in cognitively normal individuals.

AUTHOR CONTRIBUTIONS

Study concept and design: Nicola Andrea Marchi, Marie-Pierre Françoise Strippoli, Martin Preisig, and Raphael Heinzer. Data curation: Marie-Pierre Françoise Strippoli, Martin Preisig, José Haba-Rubio, Pedro Marques-Vidal, Peter Vollenweider, Armin von Gunten, and Raphael Heinzer. Statistical analysis: Nicola Andrea Marchi, Marie-Pierre Françoise Strippoli, and Martin Preisig. Writing review and editing: Nicola Andrea Marchi, Mathieu Berger, Geoffroy Solelhac, Virginie Bayon, José Haba-Rubio, Julie Legault, Cynthia Thompson, Nadia Gosselin, Peter Vollenweider, Pedro Marques-Vidal, Armin von Gunten, Marie-Pierre Françoise Strippoli, Martin Preisig, Bogdan Draganski, and Raphael Heinzer.

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CONFLICT OF INTEREST STATEMENT

Raphael Heinzer is member of the medical advisory board of Dreem and Nightbalance (Philips) and received speaker's fees or honorarium from ResMed, Philips, Jazz, and Inspire. Nadia Gosselin received speaker's honorarium from Eisai and sponsorships from Paladin and Jazz Pharmaceuticals. All remaining authors report no conflicts of interest.

DATA AVAILABILITY STATEMENT

Due to the sensitivity of the data and the lack of consent for online posting, individual data cannot be made accessible. Only metadata will be made available in digital repositories. Metadata requests can also be performed via the study website www.colaus-psycolaus.ch.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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