Obstructive sleep apnoea and cognitive decline in mild-to-moderate Alzheimer's disease

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Untreated OSA did not decrease the cognitive evolution of a population with mild and moderate Alzheimer's disease https://bit.ly/3e55zYH

Cite this article as: Jorge C, Targa A, Benítez ID, *et al*. Obstructive sleep apnoea and cognitive decline in mild-to-moderate Alzheimer's disease. *Eur Respir J* 2020; 56: 2000523 [https://doi.org/10.1183/13993003.00523-2020].

ABSTRACT We evaluated the influence of untreated obstructive sleep apnoea (OSA) on the magnitude of cognitive decline and on several cognitive subdomains in patients with mild-to-moderate Alzheimer's disease.

In this single-centre study, 144 patients were recruited prospectively from a cognitive impairment unit and underwent overnight polysomnography.

The mean±SD change in the Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog) score at 12 months was 3.19±5.61 in the non-OSA group and 0.08±5.62 in the OSA group, with an intergroup difference of −3.36 (95% CI 0.19–0.16; p=0.002). We did not observe a significant difference in any cognitive subdomains at 12 months. Regarding Mini-Mental State Examination scores at 36 months, the mean change was 1.69 (95% CI −1.26–4.64; p=0.445). No significant differences were found among different OSA severity groups.

We observed that ADAS-cog scores were better in the OSA group than in the non-OSA group by a statistically but not clinically significant margin. We did not find differences in the different cognitive subdomains after 1 year or in global cognition after 3 years of follow-up.

This article has supplementary material available from erj.ersjournals.com

This study is registered as a clinical trial: NCT02814045. Additional data from NCT02814045 will be shared by request from any qualified investigator.

Received: 5 March 2020 | Accepted after revision: 9 June 2020

Introduction

Obstructive sleep apnoea (OSA) represents the most frequent cause of sleep-disordered breathing (SDB) and is characterised by episodes of upper airway occlusion that are often associated with a decrease in blood oxygen saturation and with arousals detectable on electroencephalography [1]. OSA is a risk factor for hypertension, diabetes, heart failure, stroke, depression, traffic accidents and dementia [2, 3].

Alzheimer's disease is the most common type of dementia, affecting 50 million people worldwide. This number is expected to increase to 140 million in 2050 if no new treatments or preventive measures are applied [4]. Therefore, this disease will represent an economic, social and health problem of great magnitude in the near future. Age, sex and the presence of the apolipoprotein E (*APOE*) ε4 allele are the main nonmodifiable risk factors for Alzheimer's disease. There are also modifiable risk factors such as hypertension, diabetes mellitus, hypercholesterolaemia, depression and OSA. It remains unclear how all these factors contribute to the appearance of amyloid plaques and neurofibrillary tangles, which are pathological hallmarks of Alzheimer's disease [5].

The prevalence of OSA in Alzheimer's disease patients ranges from 45 to 90% [6]. Studies on cognitively healthy elderly subjects with OSA have reported increased amyloid β-42 (Aβ-42) and phosphorylated tau (p-tau) levels measured in cerebrospinal fluid (CSF) or by positron emission tomography (PET) [7]. Moreover, the association of OSA and sleep disturbances with cognitive impairment is relatively well established. Olaithe *et al.* [8] observed that OSA was related to deficits in attention, memory, executive function, psychomotor function and language abilities. Both OSA and sleep deprivation are accompanied by deficits in attention and memory, suggesting that short-term sleep disturbance in OSA may contribute to deficits in these domains [8]. In addition, Blackwell *et al.* [9] showed that men who spent 1% or more of their sleep time with oxygen saturation (S_{aO_2}) <90% had an adjusted annualised cognitive decline of 0.43 points, compared with 0.25 for men in the reference group (p=0.003). Although modest, these findings supported the importance of overnight oxygenation for cognitive function.

There are several reports demonstrating that treatment with continuous positive airway pressure (CPAP) can improve some of these cognitive deficits [10]. In AD patients, there are several studies investigating the effect of CPAP and cognition [10–12]. In some of these studies, although changes in neuropsychological functioning between treatment groups (3 weeks of active CPAP *versus* 3 weeks of placebo CPAP) were not significantly different when considered individually, composite neuropsychological outcomes suggested modest but statistically significant improvements in cognitive functioning after 3 weeks of therapeutic CPAP [13]. A small pilot study with three years of follow-up showed that CPAP treatment of severe OSA in patients with mild-to-moderate Alzheimer's disease was associated with a significant decrease in the pace of cognitive decline [14].

Considering the relationship between OSA and cognition, the aims of this study were: 1) to evaluate the impact of nontreated OSA on the cognitive evolution of patients with mild-to-moderate Alzheimer's disease; 2) to investigate whether the severity of the cognitive decline was associated with the severity of OSA; and 3) to evaluate the influence of OSA on several cognitive subdomains in Alzheimer's disease patients.

Methodology

Patients

Patients were consecutively and prospectively recruited from the Cognitive Disorders Unit of the Hospital Universitari Santa Maria (Lleida, Spain) from November, 2014, to November, 2017, according to the protocol of NCT02814045, which was designed to evaluate the cognitive evolution of Alzheimer's disease patients with and without OSA after one year of follow-up. The eligibility criteria were as follows: 1) males and females over 60 years old, not specifically treated for dementia at the time of inclusion, and with a new diagnosis of mild or moderate Alzheimer's disease (Mini-Mental State Examination (MMSE) score ⩾20) according to the National Institute on Aging/Alzheimer's Association (NIA-AA) criteria [15]; 2) absence of visual or hearing problems that, in the investigator's judgement, would decrease the compliance with the neuropsychological examination; 3) an informed consent form signed by the patient and the responsible caregiver (and/or if applicable, the legal representative if different from the responsible caregiver); and 4) a knowledgeable and reliable caregiver who accompanied the patient to all clinic visits during the study.

The exclusion criteria were as follows: 1) previous diagnosis of OSA; 2) severe Alzheimer's disease, other types of dementia or mild-to-moderate Alzheimer's disease with current acetylcholinesterase inhibitor treatment or memantine; or 3) presence of any previously diagnosed sleep disorder: narcolepsy, severe insomnia or chronic sleep deprivation. All exclusion criteria are available in the protocol for NCT02814045.

A total of 144 consecutive patients with mild-to-moderate Alzheimer's disease who had given consent to participate in the study underwent a detailed interview about their personal history, a general clinical examination for associated conditions and comorbidities and anthropometric data collection. Parents or caregivers were asked about the patients' sleep characteristics. Participants were evaluated by a polysomnographic study at baseline, and a complete battery of neuropsychological assessments, as described below, was performed at baseline and after one year of follow-up. At baseline, blood and CSF samples were obtained to determine *APOE* genotypes and levels of Aβ42, total tau (t-tau) and p-tau), respectively.

After completing the baseline visit and all complementary exams, the patients received acetylcholinesterase inhibitor treatment at the discretion of the physician. Patients who agreed were followed for 3 years according to usual clinical practice, and the MMSE was used as a tool for cognitive monitoring. Patients received no intervention for OSA during the study.

Sociodemographic and anthropometric variables

The following variables were collected: age, date of birth, sex, marital status, years of schooling, toxic habits (alcohol drinking and smoking), vascular risk factors (hypertension, diabetes mellitus, dyslipidaemia), personal psychiatric history and family psychiatric and neurological history. Body mass index was calculated as body weight (in kg) divided by height (in m) squared. Excessive daytime sleepiness was evaluated by the Epworth Sleepiness Scale (ESS), and was defined as a total ESS score >10 [16].

Neuropsychological battery

Patients underwent a neuropsychological evaluation at the beginning of the study and after one, two and three years of follow-up. The evaluations at baseline and 12 months included several neuropsychological tests. The ADAS-cog was the primary endpoint. The ADAS-cog includes 11 tasks, comprising both subject-completed tests and observer-based assessments. Together, these tasks assess the cognitive domains of memory, language and praxis. All 11 tasks were administered and scored on a single scale from 0 to 70. The other tests used were the MMSE, the Hachinski ischaemic score, the Digit Span component of the Wechsler Adult Intelligence Scale (WAIS-III), the Stroop Colour-Word Interference Test, the verbal fluency test, Trail Making Tests (TMTs) A and B, the Spanish version of the California Verbal Learning Test (CVLT), the Rey-Osterrieth Complex Figure Test (RCFT), the Cornell Depression Scale and the Neuropsychiatric Inventory (NPI). The degree of caregiver overload was assessed using the Zarit scale. In the second and third years, the cognitive evaluation was based on the MMSE.

Polysomnographic recording

Polysomnographic studies were performed in the sleep laboratory of the Sleep Unit at the Hospital Universitari Santa Maria (Lleida, Spain). Overnight sleep studies for all subjects were carried out using digital polysomnography (PSG) equipment (Alice6; Philips, Amsterdam, the Netherlands) that included the following channels: an electroencephalogram (EEG) (C3/A2-C4/A1 O2/A1 and O1A2, according to the international electrode placement system), a bilateral electrooculogram (EOG), a chin electromyogram (EMG), a chest and abdominal respiratory belt, air-flow measurement (using oral and nasal thermocouple and nasal pressure records), pulse oximetry, an electrocardiogram (ECG), body-position recording, a snore microphone and bilateral piezoelectric sensors to detect leg movements.

The evaluated respiratory parameters were average oxygen saturation, nadir oxygen saturation, and whether T90% (the time during which oxygen saturation <90%) accounted for more than 30% of the sleep registration period. Apnoea was defined as the absence of airflow for >10 s. Hypopnoea was defined as any airflow reduction that lasted more than >10 s and resulted in arousal or oxygen desaturation. We considered a decrease in S_{aO_2} by more than 3% to be desaturation. The apnoea–hypopnoea index (AHI) was defined as the sum of the number of apnoeas plus hypopnoeas per hour of sleep.

Participants were categorised into three OSA severity groups defined by AHI ranges: 5.0–14.9 events·h^{-1}(mild sleep apnoea), 15–29.9 events·h^{-1} (moderate sleep apnoea), or more than 30.0 events·h^{-1} (severe sleep apnoea). The polysomnographic scoring and diagnosis of patients were based on the American Academy of Sleep Medicine guidelines [17, 18].

Genetic analysis

DNA was extracted from the buffy coat cells using a Maxwell RCS Blood DNA Kit (Promega, Madison, WI, USA), and 20 µL of DNA was used for apolipoprotein genotyping by polymerase chain reaction (PCR).

CSF biomarker analysis

All patients underwent lumbar puncture between 8:00 and 10:00 h to avoid variations related to the circadian rhythm. Samples were collected in polypropylene tubes, centrifuged at 2000×g for 10 min at 4°C

and stored at −80°C until use. The levels of CSF Aβ42 (Innotest β-Amyloid(1–42)), t-tau (Innotest hTAU Ag) and p-tau (Innotest Phospho-Tau (181P) were determined by the enzyme immunoassay method according to the manufacturer's (Fujirebio, Barcelona, Spain) instructions. All samples were measured in duplicate, and the values were expressed in pg·mL^{-1}. Samples were obtained with support from IRBLleida Biobank (B.0000682) and PLATAFORMA BIOBANCOS PT17/0015/0027.

Sample size

This was an observational cohort study that included 144 consecutive patients with mild-to-moderate Alzheimer's disease. The sample size was calculated according to the objectives of the NCT02814045 study, which was designed to evaluate the change in ADAS-cog scores from baseline to 12 months in Alzheimer's disease patients with and without OSA. The calculations assumed a two-sided test with an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test was accepted to detect a difference equal to or greater than 3.5 units on the ADAS-cog scale during the follow-up, a common standard deviation of seven, and 12% loss to follow up.

This sample size was calculated with the intention of recruiting two groups of equal size (OSA *versus* control). Due to the high prevalence of OSA in our cohort, this was not possible.

This study was conducted in accordance with the Declaration of Helsinki, and it was approved by the care ethics committee of Hospital Arnau de Vilanova de Lleida (CE-1218). All patients signed informed consent.

Statistical methods

Descriptive statistics consisting of the mean±SD or median (interquartile range) were estimated for quantitative variables with a normal or non-normal distribution, respectively. The absolute and relative frequencies were used for qualitative variables. The normality of the distribution was assessed using the Shapiro–Wilk test.

A bivariate analysis was performed for the demographic and clinical data of the patients with OSA (AHI ⩾15) compared with the patients without OSA (AHI <15) using Student's t-test or a nonparametric Mann–Whitney U-test for quantitative variables (depending on the distribution of the data) and Fisher's exact test for qualitative variables. The short-term change in cognition measurements (after 12 months of follow-up) was compared between groups (no OSA or OSA) using linear models that included a group term and an adjustment for the baseline measurement. The change in MMSE over the long term (after

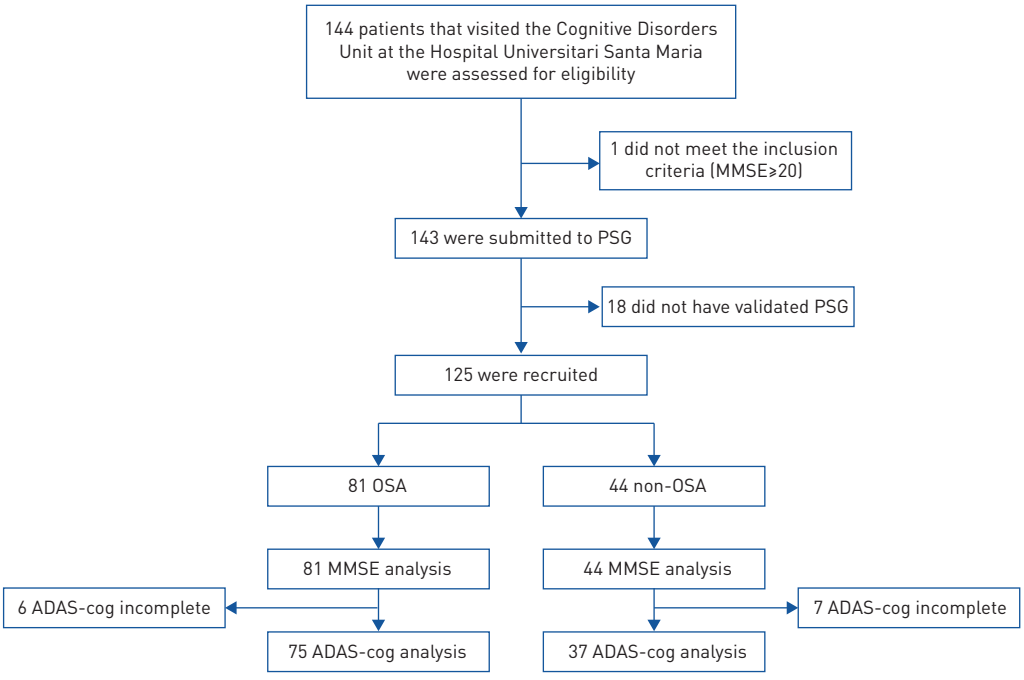


FIGURE 1 Flow diagram showing screening and enrolment of subjects. MMSE: Mini-Mental State Examination; PSG: polysomnography; OSA: obstructive sleep apnoea; ADAS-cog: Alzheimer's disease Assessment Scale cognitive subdomain.

3 years of follow-up) was compared between groups using a linear mixed-effects model. The model included subject as a random effect and visit, group and visit–group interaction as fixed effects. The same long-term analysis was carried out for the subgroups defined by tertiles of other polysomnographic parameters (apnoea index and cumulative sleep time with S_{aO_2} below 90% (CT90%)). Data management and statistical analyses were performed using R (version 3.4.2) [19].

Data availability

The data reported in this manuscript are available within the article and/or its supplementary material. Additional data from NCT02814045 will be shared by request from any qualified investigator.

Results

Characteristics of the sample

Between November 11, 2014, and November 8, 2017, 144 consecutive patients with mild-to-moderate Alzheimer's disease were included in the study. 125 patients (86.8%) had valid PSG data recorded for the diagnosis of OSA. 45 patients were considered not to have OSA (AHI <15), and 81 patients were considered to have OSA (AHI⩾15). 19 patients were withdrawn from the study. Z flowchart of the study is shown in figure 1.

The mean±SD age of the patients was 75.19±5.30 years; 72 (57.6%) participants were women, and the mean MMSE score was 23.5±2.24 points. Arterial hypertension was the most frequent vascular risk factor, present in 74 (59.2%) patients, followed by dyslipidaemia in 52 (41.6%) participants and diabetes in 27 (21.6%) participants. Regarding the sleep parameters, the mean ESS score was 5.86±4.42, and the mean AHI was 27.33±22.8. The characteristics of the patients at baseline were similar between the OSA and non-OSA groups. The baseline characteristics by OSA status are summarised in table 1.

Short-term cognitive evolution

The mean change in the ADAS-cog score at the 12-month follow-up was 3.19±5.61 in the non-OSA group and 0.08±5.62 in the OSA group. The difference in the change between the OSA and non-OSA groups

TABLE 1 Characteristics of Alzheimer's disease patients according their obstructive sleep apnoea (OSA) status

	No OSA (n=44)	OSA (n=81)	p-value
Demographic characteristics			
Age at baseline visit years	74.0 (72.0–79.2)	76.0 (72.0–80.0)	0.822
Female sex	33 (75.0)	39 (48.1)	0.007
Education years	7.06±2.37	7.56±3.11	0.317
BMI kg·m^{-2}	27.9±3.76	27.8±4.15	0.930
Medical disorders			
Hypertension	26 (59.1)	48 (59.3)	0.999
Diabetes	9 (20.5)	18 (22.2)	0.999
Hypercholesterolaemia	15 (34.1)	37 (45.7)	0.287
Depression	16 (37.2)	24 (29.6)	0.511
Smoker	3 (6.82)	1 (1.23)	0.125
History of stroke	2 (4.55)	4 (4.94)	0.999
History of myocardial infarction	4 (9.09)	17 (21.0)	0.147
Family history of Alzheimer's disease	21 (47.7)	31 (38.3)	0.404
Use of acetylcholinesterase inhibitors or memantine	42 (95.5)	73 (90.1)	0.492
Sleep parameters			
Epworth Sleepiness Scale (0–24)	5.00 (2.75–8.00)	5.00 (3.00–8.00)	0.724
AHI events·h^{-1}	6.46 (2.60–9.52)	32.1 (21.1–52.5)	<0.001
Alzheimer's disease biomarkers			
Aβ42 CSF pg·mL^{-1}	532 (419–654)	527 (419–638)	0.854
Total tau CSF pg·mL^{-1}	425 (314–620)	464 (308–621)	0.755
Phospho-tau CSF pg·mL^{-1}	68.0 (53.1–89.6)	78.1 (51.8–98.7)	0.190
APOE ε4 carrier	17 (40.5)	39 (48.8)	0.496

Data are presented as median (interquartile range), n (%) or mean±SD, unless otherwise stated. BMI: body mass index; AHI: apnoea-hypopnoea index per hour; CSF: cerebrospinal fluid; APOE ε4: apolipoprotein epsilon 4.

TABLE 2 Comparison of total score and subitems scores on the ADAS-cog evaluation at baseline and after 12 months of follow-up according the presence of OSA

	No OSA (n=37)	OSA (n=75)	Difference		
			Mean (95% CI)	p-value	p-value adjusted[#]
ADAS-cog					
Baseline	28.7±6.36	27.9±6.38			
12 months	31.9±6.36	27.9±7.09			
Change	3.19±5.61	0.08±5.62	−3.36 (0.19 to 0.16)	0.002	0.003
ADAS-cog subdomains					
Word recall					
Baseline	6.65±0.86	6.61±0.97			
12 months	6.49±1.48	6.49±1.16			
Change	−0.16±1.42	−0.12±0.99	0.03 (−0.41 to 0.47)	0.891	0.817
Commands					
Baseline	0.59±0.80	0.60±0.93			
12 months	1.24±1.55	0.63±0.91			
Change	0.65±1.75	0.03±1.15	−0.62 (−1.07 to −0.16)	0.009	0.002
Constructional praxis					
Baseline	0.78±0.63	0.80±0.66			
12 months	1.14±0.89	0.89±0.83			
Change	0.35±0.95	0.09±0.79	−0.25 (−0.56 to 0.06)	0.117	0.130
Long-term word recall					
Baseline	8.78±1.72	8.73±1.69			
12 months	9.08±1.77	8.73±1.74			
Change	0.30±2.39	0.00±1.70	−0.33 (−0.98 to 0.32)	0.321	0.474
Naming objects and fingers					
Baseline	1.16±0.80	1.27±0.81			
12 months	1.41±0.83	1.33±0.92			
Change	0.24±0.72	0.07±0.79	−0.14 (−0.43 to 0.14)	0.336	0.215
Ideational praxis					
Baseline	0.54±0.80	0.63±0.94			
12 months	1.00±0.97	0.69±0.88			
Change	0.46±1.04	0.07±0.96	−0.34 (−0.67 to −0.01)	0.045	0.049
Orientation					
Baseline	2.27±1.88	1.96±1.77			
12 months	3.14±2.26	2.40±1.97			
Change	0.86±2.21	0.44±1.84	−0.56 (−1.28 to 0.16)	0.128	0.253
Word recognition					
Baseline	6.43±2.24	6.03±2.55			
12 months	6.95±3.11	6.09±2.72			
Change	0.51±3.25	0.07±2.72	−0.66 (−1.69 to 0.37)	0.214	0.294
Remembering test instructions					
Baseline	0.59±0.96	0.55±0.96			
12 months	0.84±1.24	0.37±0.85			
Change	0.24±1.69	−0.17±1.26	−0.47 (−0.86 to −0.07)	0.022	0.038
Comprehension of spoken language					
Baseline	0.53±0.96	0.36±0.81			
12 months	0.32±0.94	0.13±0.49			
Change	−0.21±1.25	−0.23±0.88	−0.18 (−0.44 to 0.09)	0.195	0.184
Word finding difficulty					
Baseline	0.16±0.60	0.15±0.54			
12 months	0.16±0.55	0.11±0.39			
Change	0.00±0.85	−0.04±0.60	−0.95 (−1.1 to −0.8)	0.547	0.260
Language					
Baseline	0.22±0.82	0.17±0.62			
12 months	0.14±0.48	0.07±0.34			
Change	−0.08±0.80	−0.11±0.71	0.11 (−0.01 to 0.24)	0.412	0.280

Data are presented as mean±SD, unless otherwise stated. ADAS-cog: Alzheimer's disease Assessment Scale cognitive subdomain; OSA: obstructive sleep apnoea. [#]: adjusted by baseline measure, age, sex, body mass index, hypertension, pharmacological treatment and Alzheimer disease status.

TABLE 3 Comparison between cognitive performance on the cognitive domains evaluated at baseline and after 12 months of follow-up according the presence of OSA

	No OSA	OSA	Difference		
			Mean (95% CI)	p-value	p-value adjusted[#]
Verbal memory, recognition					
Recognition (CVLT)	n=35	n=74			
Baseline	−0.69±1.78	−0.64±1.58			
12 months	−0.31±2.32	−0.57±1.53			
Change	0.37±3.04	0.07±1.60	−0.27 (−0.98 to 0.45)	0.468	0.528
Long-term memory					
Long-term verbal memory, with clues	n=36	n=76			
Baseline	−2.11±1.09	−1.84±1.07			
12 months	−2.00±0.96	−1.74±0.96			
Change	0.11±1.19	0.11±1.36	0.22 (−0.16 to 0.6)	0.254	0.117
Long-term visual memory RCFT	n=37	n=71			
Baseline	3.62±2.34	4.14±2.67			
12 months	3.43±2.13	4.65±2.93			
Change	−0.19±2.63	0.51±2.38	0.91 (0.02 to 1.81)	0.048	0.080
Short-term memory					
Short-term verbal memory	n=36	n=76			
Baseline	−1.81±0.86	−1.66±1.10			
12 months	−1.75±0.69	−1.54±0.84			
Change	0.06±1.01	0.12±1.26	0.19 (−0.12 to 0.5)	0.234	0.127
Short-term visual memory RCFT	n=37	n=72			
Baseline	4.16±2.53	5.18±2.55			
12 months	4.24±2.54	5.39±2.81			
Change	0.08±3.15	0.21±2.38	0.61 (−0.35 to 1.57)	0.217	0.539
Constructional praxis					
Copy of the RCFT	n=37	n=74			
Baseline	6.24±3.79	6.92±3.92			
12 months	6.00±4.08	6.66±3.55			
Change	−0.24±4.62	−0.26±3.57	0.36 (−0.96 to 1.68)	0.592	0.812
Executive functions					
Stroop word-colour	n=36	n=73			
Baseline	7.61±3.74	8.21±3.24			
12 months	7.17±3.44	8.19±3.86			
Change	−0.44±3.97	−0.01±4.05	0.79 (−0.61 to 2.18)	0.272	0.105
Stroop interference	n=35	n=73			
Baseline	40.4±12.0	42.0±10.0			
12 months	40.0±12.3	44.3±12.0			
Change	−0.43±15.1	2.30±14.3	3.95 (−0.87 to 8.78)	0.112	0.111
Digit span (backwards)	n=37	n=76			
Baseline	8.05±3.15	8.84±2.78			
12 months	8.73±2.50	8.70±2.79			
Change	0.68±3.29	−0.14±3.21	−0.28 (−1.29 to 0.73)	0.591	0.308
TMT-B	n=2	n=17			
Baseline	6.50±4.95	6.88±1.90			
12 months	7.00±0.00	8.76±3.58			
Change	0.50±4.95	1.88±3.64	1.65 (−3.51 to 6.8)	0.540	0.935
Speed processing					
Stroop words	n=36	n=73			
Baseline	8.69±3.45	8.38±3.32			
12 months	7.47±3.01	7.70±3.27			
Change	−1.22±3.45	−0.68±3.18	0.37 (−0.73 to 1.48)	0.509	0.213
Stroop colour	n=36	n=73			
Baseline	9.44±4.33	8.74±4.36			
12 months	7.58±3.86	7.68±3.97			
Change	−1.86±4.07	−1.05±4.05	0.44 (−0.91 to 1.78)	0.528	0.157
TMT-A	n=35	n=69			
Baseline	5.74±3.30	6.71±3.01			
12 months	5.49±3.20	6.67±3.19			
Change	−0.26±2.75	−0.04±3.23	0.66 (−0.46 to 1.78)	0.252	0.189

Continued

TABLE 3 Continued

	No OSA	OSA	Difference		
			Mean (95% CI)	p-value	p-value adjusted[#]
Behaviour					
NPI	n=37	n=73			
Baseline	11.3±13.3	9.25±10.7			
12 months	12.6±13.6	10.0±10.9			
Change	1.35±16.3	0.77±10.1	−1.72 (−5.96 to 2.53)	0.430	0.412
Cornell	n=36	n=74			
Baseline	10.1±6.80	8.70±6.87			
12 months	8.53±7.61	5.68±6.03			
Change	−1.58±7.94	−3.03±6.45	−2.23 (−4.57 to 0.12)	0.066	0.078
Zarit	n=37	n=71			
Baseline	29.8±17.1	29.8±13.6			
12 months	36.1±14.2	36.4±12.6			
Change	6.32±18.5	6.62±15.1	0.29 (−4.69 to 5.27)	0.909	0.889

Data are presented as mean±SD, unless otherwise stated. OSA: obstructive sleep apnoea; CVLT: California Verbal Learning Test; RCFT: Rey-Osterrieth Complex Figure Test; TMT-A: Trail Making Test A; TMT-B: Trail Making Test B; NPI: neuropsychiatric inventory. [#]: adjusted by baseline measure, age, sex, body mass index, HTA, pharmacological treatment and Alzheimer status.

was −3.36 (95% CI 0.12 to 0.16; p=0.033). Regarding the changes of the ADAS-cog subitems, the groups showed differences in their changes in performance on commands, ideational praxis and remembering test instructions (p<0.05) (table 2). Regarding OSA severity, patients with moderate OSA (27.01±6.21 *versus* 26.29±6.33) had the lesser cognitive impairment, comparing baseline and 1 year follow-up, than those with severe OSA (28.58±6.50 *versus* 29.31±7.46) or those without OSA (28.67±6.36 *versus* 31.86±6.37) (figure E1).

An extensive battery of neuropsychological tests was carried out to evaluate the different cognitive domains at the 12-month follow-up. We did not observe significant differences in cognitive subdomains, such as memory or executive functioning, or in caregiver overload. We found a greater reduction in Cornell Depression Scale scores in OSA patients than in non-OSA patients, but the difference was not statistically significant (p=0.06) (table 3).

Long-term cognitive evolution

According to MMSE scores at the 3-year follow-up, a significant cognitive impairment was observed in both groups (p<0.001). The change at 3 years of follow-up was similar between the OSA and non-OSA groups (p=0.815) (fig. 2). No significant differences were found among the OSA severity groups (mild, moderate and severe OSA) (figure E2).

Ancillary analysis

CSF biomarkers (Aβ, t-tau and p-tau) were evaluated in 123 subjects, and 76 patients showed pathological values of Aβ (⩽600 pg·mL^{-1}). A study of short- and long-term cognitive evolution in the Aβ-positive population showed similar results to those found in the overall study population. (figures E3 and E4).

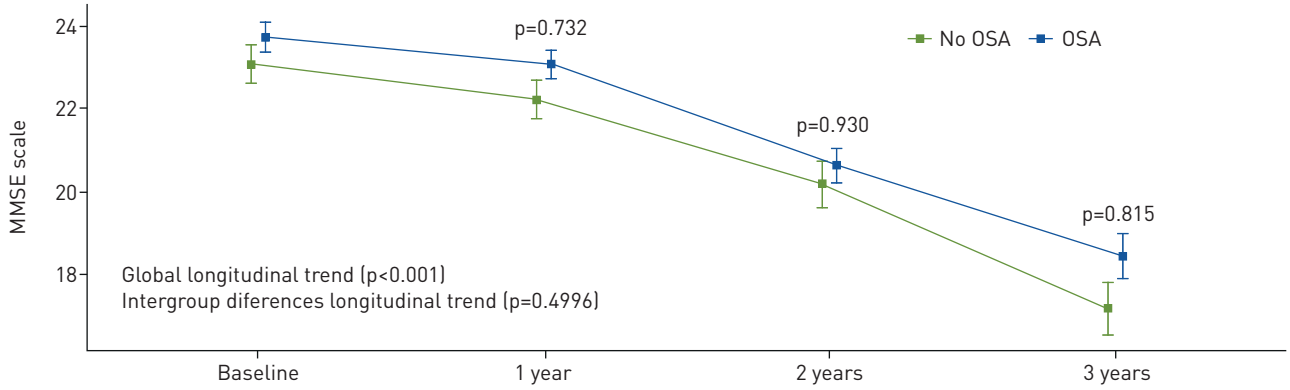
No differences were observed according to ApoE4 (data not shown), T90% or the arousal index (figures E5 and E6).

During patient follow-up, few comorbid pathologies were reported: 13 (12.7%) in the global population; four (12.1%) in the non-OSA group *versus* nine (13.0%) in the OSA group (p=0.99).

Discussion

This study evaluated the cognitive evolution of a large cohort of patients with mild-to-moderate Alzheimer's disease according to their OSA status. The study demonstrated that performance in global cognition and each specific cognitive domains was not worse in OSA patients than in non-OSA patients after 12 months of follow-up. After 3 years of follow-up, patients with OSA had not undergone clinically worse cognitive evolution than non-OSA patients.

In recent years, OSA has been shown to be a potential risk factor for Alzheimer's disease [20–22]. Some data in the asymptomatic population, and even among patients in the prodromal phases suggest the importance of OSA in the pathophysiology of Alzheimer's disease. Therefore, sleep fragmentation induced by OSA can alter the process of amyloid and tau clearance by reducing slow-wave sleep [23, 24]. In



OSA patients	n=81	n=80	n=60	n=26
LS means (95% CI)	23.7 (23 to 24.4)	23.1 (22.4 to 23.8)	20.6 (19.8 to 21.4)	18.5 (17.4 to 19.5)
Change (95% CI)		−0.6 (−1.3 to 0)	−3.1 (−3.9 to −2.3)	−5.3 (−6.3 to −4.2)
No OSA patients	n=44	n=42	n=31	n=19
LS means (95% CI)	23.1 (22.2 to 24)	22.2 (21.3 to 23.2)	20.2 (19.1 to 21.3)	17.2 (15.9 to 18.4)
Change (95% CI)		−0.9 (−1.8 to 0.1)	−2.9 (−4 to −1.8)	−5.9 (−7.2 to −4.7)

FIGURE 2 Mini-Mental State Examination (MMSE) evolution after 36 months of follow-up according to obstructive sleep apnoea (OSA) severity.

addition, OSA induces vascular changes that can alter the walls of the vessels, affect amyloid elimination and increase both brain vascular damage and the risk of hypertension, which is also a risk factor for Alzheimer's disease. In addition, OSA increases oxidative stress through intermittent hypoxia, leading to neuronal damage [25]. All these factors can converge and explain the increased risk of Alzheimer's disease in the OSA population [26].

To our knowledge, no previous studies have evaluated the cognitive evolution of Alzheimer's disease patients according to OSA status in patients diagnosed by PSG. Ancoli-Israel *et al.* [27] published data on the cognitive performance of nursing home patients with dementia according to OSA status. This cross-sectional study showed that particularly in patients with severe apnoea, OSA had severe effects on attention, perseveration, conceptualisation and memory tasks according to the Dementia Rating Scale. However, in this study, the patients were classified broadly as having dementia; no specific types of dementia, such as Alzheimer's disease, vascular dementia or other types of dementia, were considered. This cross-sectional study showed an association between sleep apnoea and the severity of dementia in institutionalised nursing home patients but not cognitive evolution according to OSA status**.** Several studies, including a study performed by Troussiere *et al.* with three years of follow-up, showed that CPAP treatment of severe OSA in patients with mild-to-moderate Alzheimer's disease was significantly associated with slower cognitive decline [10–12, 14]. Similarly, Ancoli-Israel *et al.* [13] observed that although changes in neuropsychological functioning between treatment groups were not significantly different when considered individually, composite neuropsychological outcomes suggested modest but statistically significant improvements in cognitive functioning after 3 weeks of therapeutic CPAP.

In the present article, we observed that the primary outcome, mean change in the ADAS-cog score at the 12-month follow-up, was 3.19±5.61 in the non-OSA group and 0.08±5.62 in the OSA group (the difference between groups was −3.36 (95% CI 0.12 to 0.16; p=0.033)). Although statistically significant, this difference did not seem to be clinically significant. Furthermore, this improvement was not confirmed in any of the other tests used; therefore, it must to be considered with caution. After 3 years of follow-up, we also did not find any statistically significant differences between the OSA and non-OSA groups. These data at 12 months should be considered with caution because we observed that all the groups had a less severe decline (according to MMSE and ADAS-cog scores) than would be expected according to historical cohorts. These results can be explained by the fact that acetylcholinesterase-inhibitor drugs were started after baseline neurocognitive and PSG evaluations, as these drugs could affect the real prevalence of OSA [28], although recent studies have not confirmed this hypothesis [29, 30].

Classically, OSA has been reported to affect cognition in cognitively healthy elderly subjects; specifically, OSA has been shown to affect attention and executive function with smaller effects on memory [31, 32]. However, there are conflicting results depending on the neuropsychological tests used and the degree of AHI considered in the different studies. Another aspect to consider is the age of onset of OSA. We also evaluated the potential effects on cognition according to the different degrees of OSA severity; we did not

find a dose–response relationship between OSA severity and cognitive evolution, making the biological plausibility of such a difference difficult to accept.

All data in our study suggest that in this phase of the disease, the cognitive deterioration that characterises Alzheimer's disease is predominant and is no longer influenced by the presence of any other comorbidity, such as OSA. Consistent evidence of a relationship between the severity of OSA (AHI, respiratory disturbance index (RDI), or indices of hypoxia severity, sleep fragmentation or sleepiness) and the severity of the cognitive deficits observed is also lacking in non-Alzheimer's disease subjects [33, 34].

Since patients were included in this study according to the clinical criteria of Alzheimer's disease [35], we evaluated the influence of CSF Alzheimer's disease biomarkers in this cohort. In contrast to what has been observed in cognitively healthy subjects, we did not observe changes in the levels of the different CSF Alzheimer's disease biomarkers (Aβ42, t-tau and p-tau) depending on OSA status. As described in the population with Alzheimer's disease [36], at the time when symptoms of dementia are presented, the levels of Aβ42 and other biomarkers have already plateaued, and possibly for this reason, the potential effect of OSA on biomarkers in this phase of the disease is not detectable. We also studied the effect of OSA on cognition based on the levels of Alzheimer's disease biomarkers. Patients with pathological deposits of Aβ showed no changes in cognitive evolution based on OSA status after 1 or 3 years of follow-up.

With all these results, it is questionable whether patients with OSA and mild Alzheimer's disease, particularly elderly patients and those with low daytime sleepiness, should be treated with CPAP. More studies are needed, involving more subjects with biological confirmation of Alzheimer's disease, a sufficient degree of compliance with the treatment and a longer treatment period, to confirm the effect of CPAP treatment [10–14].

The main strength of this study was the use of PSG, which is the gold standard test, as the diagnostic method for OSA. Extensive cognitive evaluations were performed, and the raters were blinded to the OSA status of the patients. The patients were evaluated according to clinical criteria and specific CSF biomarkers of Alzheimer's disease; thus, we were able to ensure that the patients had both clinically and biologically evident Alzheimer's disease, and we present the results according to these two aspects. This study also has some limitations. The study was designed assuming an OSA prevalence between 40 and 50% based on the previous literature [6]. However, in our study, the high prevalence of OSA in the Alzheimer's disease population led to unbalanced groups. This could have generated a group of insufficient size to obtain a representative sample of the target population. The low cognitive impairment observed during the first year of follow-up may have also limited the finding of significant differences. We used an inclusion threshold of MMSE >20; therefore, the results should be extrapolated cautiously to more advanced stages of the disease. Since the study was designed for one year of follow-up, we have data for global cognition supported by the MMSE, but we do not have data on the different cognitive subdomains after 3 years of follow-up.

In conclusion, in this large cohort of patients with Alzheimer's disease, we demonstrated that OSA did not worsen cognitive evolution after 1 year of follow-up, either in global cognition or in the different cognitive subdomains, and that OSA also did not worsen global cognition after 3 years of follow-up. Based on these findings and prior knowledge, OSA seems to be a risk factor for AD but does not modify the cognitive evolution of patients in the early or middle stages of the disease. However, due to the limitations of this study described above, further well-balanced, long-term double-blind longitudinal studies will be required to evaluate whether CPAP modifies the cognitive evolution of Alzheimer's disease patients and through which pathways.

Acknowledgements: Thanks to all the patients who have collaborated in the study and to all the members of the Sleep and Dementia Unit of the Santa Maria de Lleida University Hospital.

Author contributions: I.D. Benítez, G. Torres, G. Piñol-Ripoll, F. Barbé and M. Sánchez-de-la-Torre designed the study. C. Jorge, A. Targa and M. Pujol searched the literature. C. Jorge, R. Huerto, O. Minguez, A. Gibert and M. Pujol collected the data. I.D. Benítez and A. Targa analysed the data. R. Farré, F. Barbé, G. Piñol-Ripoll, A. Targa and C. Jorge interpreted the data. C. Jorge, A. Targa and G. Piñol-Ripoll wrote the manuscript draft. All authors revised the manuscript and approved it for submission.

Conflict of interest: None declared.

Support statement: This work was supported by "Fundació La Marató TV3" (to G. Piñol-Ripoll), the Spanish Respiratory Society (SEPAR), PERIS SLT008/18/00050, the Health Department of Generalitat de Catalunya, ALLER, IRBLleida Biobank (B.0000682) and PLATAFORMA BIOBANCOS PT17/0015/0027. Funding information for this article has been deposited with the Crossref Funder Registry.

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