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Sleep characteristics and cognitive impairment in the general population

The HypnoLaus study

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ABSTRACT

Objective: To assess the association between sleep structure and cognitive impairment in the general population.

Methods: Data stemmed from 580 participants aged >65 years of the population-based CoLaus/PsyCoLaus study (Lausanne, Switzerland) who underwent complete sleep evaluation (HypnoLaus). Evaluations included demographic characteristics, personal and treatment history, sleep complaints and habits (using validated questionnaires), and a complete polysomnography at home. Cognitive function was evaluated using a comprehensive neuropsychological test battery and a questionnaire on the participant's everyday activities. Participants with cognitive impairment (global Clinical Dementia Rating [CDR] scale score > 0) were compared with participants with no cognitive impairment (global CDR score = 0).

Results: The 291 participants with a CDR score > 0 (72.5 ± 4.6 years), compared to the 289 controls with CDR = 0 (72.1 ± 4.6 years), had significantly more light (stage N1) and less deep (stage N3) and REM sleep, as well as lower sleep efficiency, higher intrasleep wake, and higher sleepiness scores (all $p < 0.05$). Sleep-disordered breathing was more severe in participants with cognitive impairment with an apnea/hypopnea index (AHI) of 18.0 (7.8–35.5)/h (p50 [p25–p75]) (vs 12.9 [7.2–24.5]/h, $p < 0.001$), and higher oxygen desaturation index (ODI). In the multivariate analysis after adjustments for confounding variables, the AHI and the ODI ≥4% and ≥6% were independently associated with cognitive impairment.

Conclusions: Participants aged >65 years with cognitive impairment have higher sleepiness scores and a more disrupted sleep. This seems to be related to the occurrence of sleep-disordered breathing and the associated intermittent hypoxia. ***Neurology*® 2017;88:1–7**

GLOSSARY

AASM = American Academy of Sleep Medicine; **AD** = Alzheimer dementia; **AHI** = apnea-hypopnea index; **BMI** = body mass index; **CDR** = Clinical Dementia Rating; **CI** = cognitive impairment; **DSM-IV** = Diagnostic and Statistical Manual of Mental Disorders, 4th edition; **ESS** = Epworth Sleepiness Scale; **MCI** = mild cognitive impairment; **MDD** = major depressive disorder; **MEQ** = Horne and Östberg Morningness-Eveningness Questionnaire; **ODI** = oxygen desaturation index; **PLMS** = periodic leg movements during sleep; **PSG** = polysomnography; **PSQI** = Pittsburgh Sleep Quality Index; **SDB** = sleep-disordered breathing; **TST** = total sleep time; **WHR** = waist-hip ratio.

Sleep is a vital biological function, essential for brain restoration and memory consolidation.[1] Significant changes in sleep quantity and architecture occur through life,[2] with increased susceptibility to sleep disorders with aging.[3] Sleep disturbances are particularly frequent in individuals with cognitive deficits such as mild cognitive impairment (MCI) and dementias.[4] These often have been dismissed as consequences of the disease process underlying the cognitive decline, or of its related somatic and psychiatric comorbidities. Nevertheless, accumulating evidence suggests that sleep duration,[5–8] sleep fragmentation,[9–12] and sleep pathologies, such as sleep-disordered breathing (SDB),[13,14] can play a role in the pathogenic process leading to cognitive impairment (CI). These studies suggest that alterations in sleep might be an early marker or

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Supplemental data at Neurology.org

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precipitating factors of cognitive decline, but most relied on self-reported sleep duration or rest-activity cycles measured by actigraphy.

Polysomnography (PSG) is the gold standard to measure sleep, giving detailed information about sleep stages and disorders, and can provide a deeper insight into the relationship between CI and sleep, but only a limited number of studies have used PSG to assess sleep in this context.[13–15] In addition, some previous studies have been conducted in clinical or selected populations (i.e., only women[13] or only men[14,15]), did not provide data on both subjective and objective sleep characteristics, and many of them did not control for conditions known to impair sleep and cognition (e.g., cardiovascular disorders, medications, depression).

Using a large and well-characterized sample drawn from the general population, the aim of this epidemiologic observational study was to compare subjective sleep characteristics, assessed by questionnaires, and objective sleep features, measured by PSG, of elderly participants with CI to those of participants with normal cognition.

METHODS

Population sampling. Data stemmed from participants of the population-based CoLaus/PsyCoLaus study.[16,17] Briefly, the baseline CoLaus/PsyCoLaus study (between 2003 and 2006) included a representative sample of 6,733 participants (aged 35–75 years) selected from the residents of the city of Lausanne, Switzerland. The age, sex distribution, and zip codes of the participants were comparable to the source population.[16] Five years after the baseline investigation, participants underwent a new physical (n = 5,064) and psychiatric (n = 4,002) evaluation.

Cognitive evaluation. During the psychiatric follow-up investigation, 1,128 participants older than 65 years accepted a cognitive evaluation (72.7% participation rate). The neuropsychological test battery, performed by trained neuropsychologists, included the Mini-Mental State Examination,[18] the Grober and Buschke Double Memory Test,[19] the DO 80 naming task,[20] the Stroop Test,[21] the letter fluency task,[22] and the figures from the Consortium to Establish a Registry for Alzheimer's Disease neuropsychological test battery.[23] Overall cognitive and functional status was determined using the Clinical Dementia Rating (CDR) scale, a validated scale used for the clinical staging of CI that incorporates information concerning cognitive performance and related activities of daily life in 6 areas: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care.[24] The participants with a global CDR score = 0 were considered to have normal cognitive abilities while the participants with CDR > 0 were considered to have CI.[24]

Sleep evaluation. As a nested project of CoLaus/PsyCoLaus, the HypnoLaus study evaluated sleep characteristics of this population (figure e-1 at Neurology.org). We evaluated subjective sleep habits and complaints with the Pittsburgh Sleep Quality Index (PSQI),[25] the Epworth Sleepiness Scale (ESS),[26] the Horne and Östberg Morningness-Eveningness Questionnaire (MEQ),[27] and the Berlin Questionnaire for sleep apnea risk.[28]

In addition, we invited 3,043 consecutive participants to undergo a full-night PSG recording at home, and 2,162 accepted (71% participation rate; 723 older than 65 years). Participants were equipped with the PSG recorder (Titanium, Embla Flaga, Reykjavik, Iceland) by qualified technicians between 5 and 8 PM at the Center for Investigation and Research in Sleep (Lausanne University Hospital, Switzerland), and sleep recordings took place in the participants' home environment. The participants were not selected on the basis of the responses to questionnaires and the investigators were unaware of the questionnaires' results. Participants under continuous positive airway pressure for SDB (n = 38, 1.75% of the entire sample) were asked to stop their treatment 1 week prior to the PSG.

We used the same methodology for the PSG recordings as the one described in previous studies.[3,29] PSG recordings included the following channels: 4 EEG (F3/M2, F4/M1, C3/M2, C4/M1, O1/M2, and O2/M1), electro-oculography (right and left), surface EMG channels (submental and right and left anterior tibialis), ECG, nasal pressure, thoracic and abdominal respiratory inductance belts, body position, oxygen saturation, and pulse rate in accordance with the American Academy of Sleep Medicine (AASM) 2007 recommended setup.[30]

PSG recordings were visually scored by 2 trained sleep technicians using Somnologica software (version 5.1.1, Embla Flaga) and reviewed by an expert sleep physician. A second sleep expert performed random quality checks. Sleep stages, arousals, and respiratory events were scored according to the 2007 AASM recommended criteria.[30] Periodic leg movements during sleep (PLMS) were scored according to the official World Association of Sleep Medicine standards.[31] Apnea was defined as a drop of at least 90% of airflow from baseline lasting 10 seconds or longer. Hypopnea was defined as a ≥30% drop of airflow for ≥10 seconds associated with a ≥4% O_2 drop. The average number of apneas/hypopneas per hour of sleep (apnea-hypopnea index [AHI]) was calculated. The oxygen desaturation index (ODI) represents the number of oxygen saturation drops per hour of sleep (≥3%, ≥4%, or ≥6%). The periodic leg movement in sleep index was calculated by dividing the total number of PLMS by total sleep time (TST) in hours.

Other variables. Information on sociodemographic characteristics, medical and treatment history, smoking habits (current smoker/ex-smoker or never smoker), and alcohol consumption (currently drinking or no alcohol consumption) was elicited by trained interviewers using questionnaires. Educational level was characterized as primary school, high (secondary) school, professional school, and university or non-university higher education. Medication at the time of the sleep evaluation was coded according to the WHO ATC classification (whocc.no/atcddd). We considered hypnotics (ATC code: N05CF), benzodiazepines or derivates (N05BA, N05CD, N03AE), antidepressants (N06A), neuroleptics (N05A), and antihistaminics (R06A) as the drug categories having a potential major effect on sleep.

During the physical examination, we collected fasting blood samples for various clinical analyses (including glucose, cholesterol, and triglycerides). We measured the height and weight and we calculated the body mass index (BMI) and the

Table 1 General characteristics of the CoLaus/PsyCoLaus population >65 years and studied population (participants with Clinical Dementia Rating [CDR] evaluation and polysomnography)

	CoLaus/PsyCoLaus		
	No CDR evaluation or no polysomnography	CDR evaluation and polysomnography	p Value
Total	972 (62.6)	580 (37.4)	
Age, y	71.0 ± 4.9	70.4 ± 4.4	0.017
Female sex	556 (57.2)	316 (54.5)	0.296
BMI, kg/m^2	26.8 ± 4.6	27.0 ± 4.6	0.535
Waist-hip ratio	0.93 ± 0.07	0.92 ± 0.07	0.300
Smokers/ex-smokers	570 (59.2)	315 (58.0)	0.654
Regular alcohol consumption	763 (79.2)	438 (76.0)	0.022
Diabetes	185 (19.1)	105 (18.1)	0.609
Metabolic syndrome	427 (44.8)	251 (43.3)	0.566
Current depression	27 (4.7)	28 (5.0)	0.817
Depression in life	191 (33.0)	207 (36.7)	0.195

Abbreviation: BMI = body mass index.
Values are mean ± SD or n (%).

waist-hip ratio (WHR). We measured blood pressure in triplicate and averaged values between the last 2 readings. We defined arterial hypertension as a systolic blood pressure ≥140 mm Hg or a diastolic blood pressure ≥90 mm Hg or if the participant was taking antihypertensive drugs. We defined diabetes as a fasting blood glucose level ≥7 mmol/L (126 mg/dL) or if the participant was taking antidiabetic drugs (oral hypoglycemic or insulin). We defined the metabolic syndrome according to the Adult Treatment Panel III report.

We collected diagnostic information on mental disorders according to the DSM-IV, including major depressive disorder (MDD), during the psychiatric evaluation using the French version of the semi-structured Diagnostic Interview for Genetic Studies.[32]

Statistical analysis. We performed all statistical analysis with Stata 11 (StataCorp, College Station, TX). For descriptive statistics, we summarized continuous variables as mean ± SD and categorical variables as number of participants or percentages. We also used descriptive statistics to show sleep characteristics of the participants based on presence or absence of cognitive deficits. We used Student t tests, χ^2 tests, or one-way analysis of variance to assess univariate differences between sleep variables, one at a time.

At a second step, to determine the independent association of PSG-derived variables with a CDR > 0, we constructed a multivariate logistic regression model for each PSG variable after adjustment for age, sex, hypertension, diabetes, metabolic syndrome, current MDD, lifetime MDD, BMI, alcohol and tobacco consumption, drugs influencing sleep, and level of education. We expressed results as multivariate-adjusted odds ratios and 95% confidence intervals for 10-unit increase of each sleep-related variable. We considered statistical significance for a 2-sided test $p < 0.05$.

Standard protocol approvals, registrations, and patient consents. The Ethics Committee of the University of Lausanne approved CoLaus/PsyCoLaus and HypnoLaus studies, and all participants signed a written informed consent.

RESULTS

Characteristics of the sample. Of 1,552 participants aged >65 years at the first follow-up of CoLaus/PsyCoLaus, 580 (37.4%) completed both the neuropsychological evaluation and a PSG, and constitute the sample for the present analyses. These participants were slightly younger (70.4 ± 4.4 vs 71.0 ± 4.9, $p = 0.017$), but did not differ regarding other characteristics from the other participants older than 65 years (table 1).

Comparison of participants with and without CI. CI (CDR > 0) was present in 291 participants, representing 50.2% of the sample. All included participants with CI had a CDR = 0.5, which is generally considered to correspond to mild CI. The results of the comparison between participants with and without CI are summarized in table 2. Participants with CI included a higher proportion of men, regular alcohol consumption, a higher WHR but a similar BMI, and a higher incidence of hypertension and diabetes. No significant differences were found for age, prevalence of metabolic syndrome, or current or lifetime MDD. Results of the neuropsychological tests according to CDR status are presented in table e-1.

Subjective sleep characteristics. Table 3 summarizes the subjective sleep characteristics of the sample according to CDR status. Compared to participants with no CI, participants with a CDR > 0 had higher ESS scores, yet still in the normal ranges (5.4 ± 3.2 vs 4.7 ± 3.4, $p = 0.024$), and the percentage of participants presenting excessive daytime sleepiness (ESS > 10) was similar in both groups.

More participants with CI exhibited sleep apnea risk, according to the Berlin questionnaire (34.0% vs 25.1%, $p = 0.019$). There were no significant differences in global sleep quality, with similar mean PSQI score and similar percentages of PSQI >5, or concerning subjective sleep latency or subjective sleep duration. Finally, no significant differences emerged concerning their chronotype, with similar mean scores at the MEQ.

Objective sleep characteristics. The results of objective sleep characteristics according to presence or absence of CI are summarized in figure 1 and in table e-2. Participants with CI spent more sleep time in light (stage N1) sleep and less time in deep (stage N3) sleep and in REM sleep than participants without CI. Sleep efficiency of participants with CI was also significantly lower, with higher intrasleep wake. Participants with CI had more severe SDB, with a higher mean AHI. Even though the mean SaO_2 during sleep was similar in both groups, the SaO_2 nadir was lower in participants with CI, as well as the oxygen desaturation indexes, using different oxygen desaturation thresholds. No differences were found concerning other sleep-related parameters.

Table 2 General characteristics of the studied population (participants with Clinical Dementia Rating [CDR] evaluation and polysomnography) according to CDR status

	CDR = 0	CDR > 0	*p* Value
Total	289 (49.8)	291 (50.2)	
Age, y	72.1 ± 4.6	72.5 ± 4.6	0.352
Female sex	190 (65.7)	126 (43.3)	<0.001
BMI, kg/m^2	26.7 ± 4.5	27.2 ± 4.7	0.135
Waist-hip ratio	0.91 ± 0.06	0.93 ± 0.07	<0.001
Smokers/ex-smokers	143 (52.0)	172 (63.0)	0.418
Regular alcohol consumption	216 (78.6)	222 (81.3)	0.009
Hypertension	179 (61.9)	213 (73.4)	0.003
Diabetes	40 (13.8)	65 (22.3)	0.008
Metabolic syndrome	116 (40.1)	136 (46.7)	0.109
Current depression	15 (5.3)	13 (4.6)	0.698
Depression in life	106 (37.6)	282 (35.8)	0.662

Abbreviation: BMI = body mass index.
Values are mean ± SD or n (%).

Multivariate analysis of the association between objective sleep characteristics and CI. For PSG-derived variables, we constructed a multivariable model, to determine independent associations. For each variable the model was adjusted for age, sex, BMI, alcohol and tobacco consumption, psychotropic drugs influencing sleep, level of education, and the presence of hypertension, diabetes, metabolic syndrome, and MDD (figure 2 and table e-3).

In this model only AHI, oxygen desaturation index ≥4%, and oxygen desaturation index ≥6% remained significantly and independently associated with the presence of CI. In more detailed analysis with increasing sleep apnea severity, measured by the AHI, we observed a worsening of specific cognitive scores, in particular the Grober and Buschke total free recall ($\rho = -0.126$, $p = 0.004$) and delayed free recall ($\rho = -0.092$, $p = 0.038$) scores, semantic verbal fluency ($\rho = -0.105$, $p = 0.017$), and Stroop dots condition ($\rho = -0.121$, $p = 0.004$).

Table 3 Subjective sleep characteristics according to Clinical Dementia Rating (CDR) status

	CDR = 0 (n = 289)	CDR > 0 (n = 291)	*p* Value
PSQI score	5.1 ± 3.3	5.4 ± 3.5	0.365
PSQI > 5 (out of 21)	120 (49.0)	117 (50.4)	0.751
Subjective sleep latency, min	18.4 ± 16.7	19.4 ± 17.3	0.474
Estimated sleep duration, h	7.1 ± 1.1	7.3 ± 1.3	0.150
Epworth Sleepiness Scale score	4.7 ± 3.4	5.4 ± 3.2	0.024
Epworth Sleepiness Scale score >10 (range 0–24)	16 (6.0)	14 (5.3)	0.723
MEQ score	53.3 ± 4.1	53.2 ± 4.6	0.821
Berlin questionnaire score >2 (out of 4)	72 (25.1)	99 (34.0)	0.019

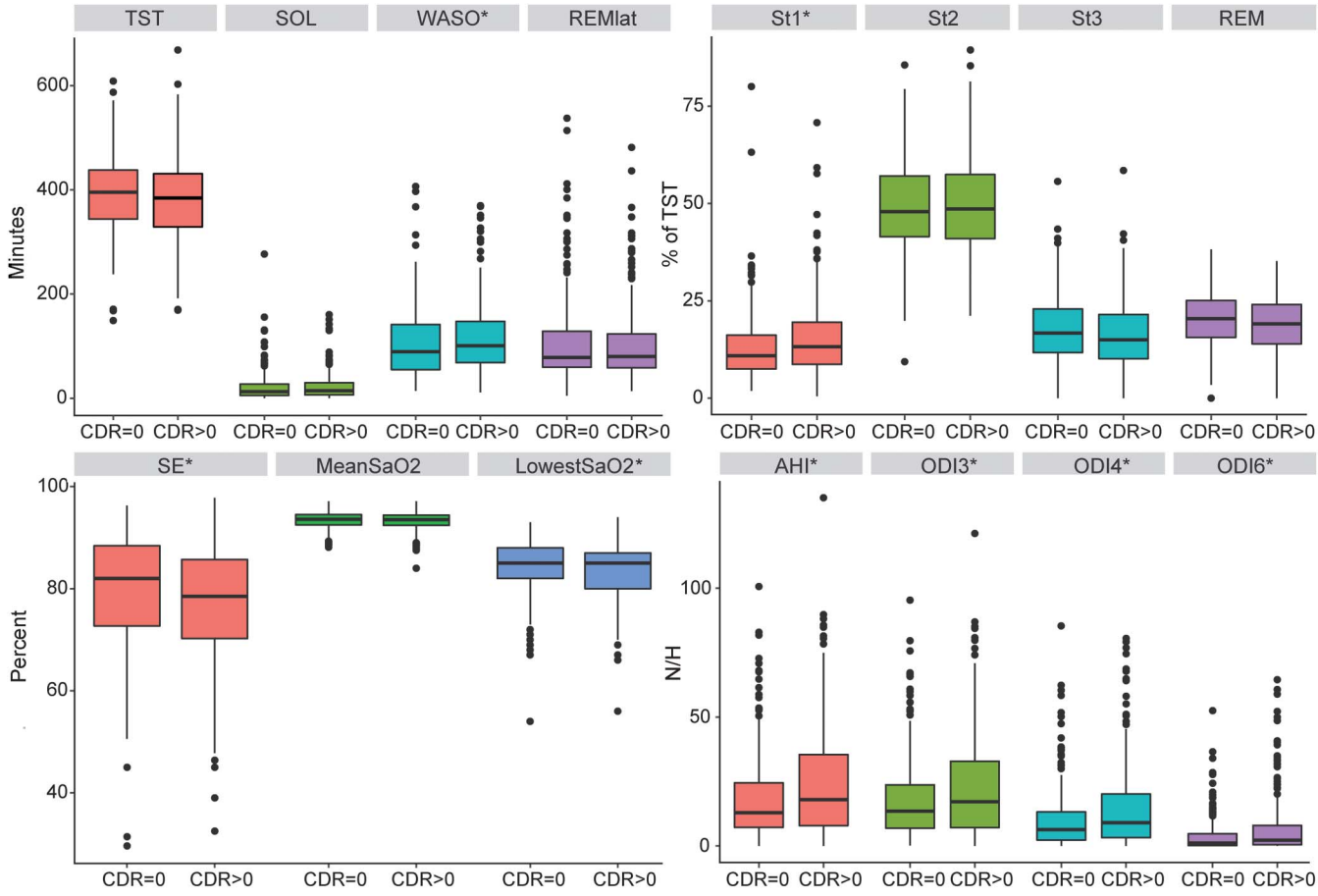
Abbreviations: MEQ = Horne and Östberg Morningness-Eveningness Questionnaire; PSQI = Pittsburgh Sleep Quality Index.
Values are mean ± SD or n (%).

DISCUSSION We analyzed the sleep characteristics of participants with mild CI in a large sample of participants >65 years from the general population. Compared to participants with no CI, they presented significant differences in sleep patterns with more time spent in stage N1 and less in stage N3 and in REM sleep, lower sleep efficiency, and more wake after sleep onset according to univariate analyses. They also exhibited more severe SDB, with higher AHI and ODI, and higher ESS scores. However, multivariate analysis after adjustment for possible confounding factors revealed that only SDB indices (AHI, ODI ≥4%, and ODI ≥6%) were independently associated with impaired performance on cognitive tests.

Previous epidemiologic studies from general populations have suggested that sleep quantity is associated with cognition: self-reported short sleep or long sleep are associated with poorer cognitive function[5,7] and with a higher MCI/dementia risk.[6] It has also been reported that subjective sleep quality or having a complaint of excessive sleepiness during the day are associated with decreased cognitive performance and a higher risk of cognitive decline and dementia.[5,33] In some studies, this association seems mediated by other variables, such as comorbidities.[34] Prospective studies have shown that increased sleep fragmentation,[12] longer sleep latency, and lower sleep efficiency and TST,[8] measured using actigraphy, are associated with cognitive decline and incident Alzheimer dementia (AD), and that better sleep consolidation attenuates the effect of the ε4 allele of *APOE* on cognitive decline, the risk of AD, and cerebral neurofibrillary tangle density.[9] It has also been shown that decreased sleep efficiency measured by actigraphy, as well as reported frequent naps, were associated with higher levels of cerebral amyloid deposition as assessed by CSF Aβ42 levels,[10] and that among community-dwelling older adults, reports of shorter sleep duration and poorer sleep quality were associated with greater Aβ burden, assessed by Pittsburgh compound B PET imaging.[11]

In our study, we also found some of the previously described sleep alterations, as participants with CI had a more fragmented sleep, with more light sleep and less deep sleep and REM sleep, similar to that found in the prospective Osteoporotic Fractures in Men Study,[15] and higher sleepiness scores. However, in the multivariate analysis and after accounting for

Figure 1 Objective sleep characteristics according to Clinical Dementia Rating scale (CDR) status



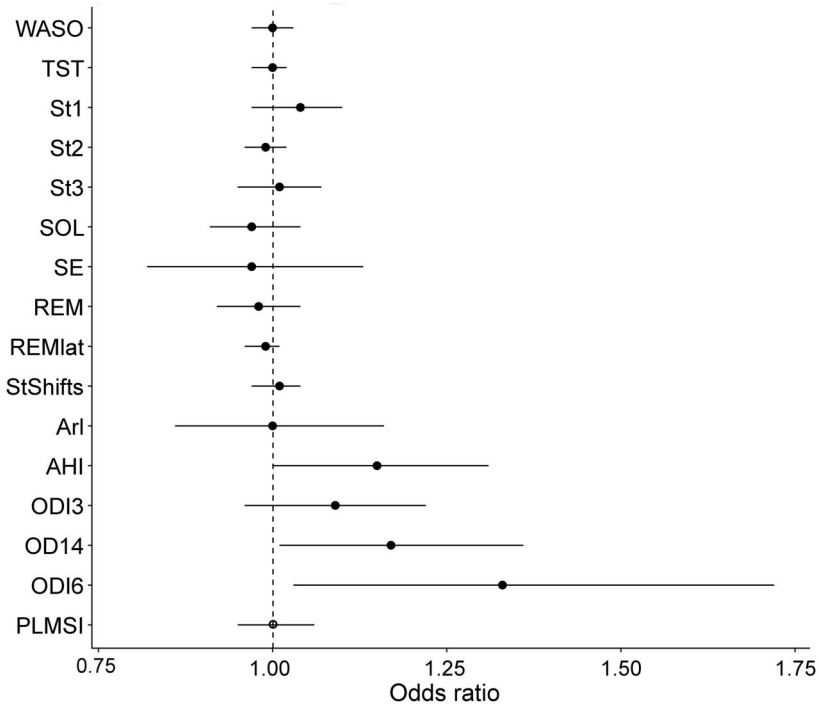
*$p < 0.05$. AHI = apnea/hypopnea index (n/h); LowestSaO2 = lowest oxygen saturation (in %) during sleep; MeanSaO2 = mean oxygen saturation (in %) during sleep; ODI3 = oxygen desaturation index ≥3% during sleep (n/h); ODI4 = oxygen desaturation index ≥4% during sleep (n/h); ODI6 = oxygen desaturation index ≥6% during sleep (n/h); REM = REM sleep (in % of total sleep time); REMlat = latency to REM sleep from sleep onset (min); St1 = stage N1 sleep (in % of total sleep time); SE = sleep efficiency; SOL = sleep onset latency (min); St2 = stage N2 sleep (in % of total sleep time); St3 = stage N3 sleep (in % of total sleep time); TST = total sleep time (min); WASO = wake after sleep onset (min).

potential confounders, only SDB measures remained significantly associated with cognitive deficits. SDB can be the cause of changes in sleep structure found here, as it provokes sleep fragmentation, profound changes in sleep architecture, and sleepiness.

Cross-sectional studies of SDB and cognitive function in elderly populations have reported conflicting results,[35–38] which may be due to population selection, differences in the measurement and definition of SDB, or the type of cognitive evaluation used. In a prospective substudy of the Study of Osteoporotic Fractures, the analysis of data from 298 women (mean age 82.3 years) showed that a higher proportion of those with prevalent SDB (AHI >15/h) at the initial evaluation developed mild CI or dementia in the 5 years of follow-up.[13] This study implies that SDB precedes dementia.

Each of the 2 main characteristics of SDB—sleep fragmentation and hypoxia—could have negative effects on cognitive function. In the Study of Osteoporotic Fractures, 2 measures of hypoxia (an ODI ≥3% of ≥15/h and a high percentage of TST in apnea or hypopnea) were associated with higher incidence of CI. Nocturnal hypoxemia and ODI were also predictors of global cognitive decline in the 2,636 community-dwelling older men (age 76.0 ± 5.3 years) without CI followed for 3.4 ± 0.5 years in the Osteoporotic Fractures in Men Sleep Study.[14] Similarly, in our study, ODI (≥4% and ≥6%) was independently associated with the presence of CI. Conversely, no independent significant association was found for sleep duration or measures of sleep fragmentation, such as the arousal index or the intrasleep wake. This suggests that hypoxia is likely to be the mechanism through which SDB is associated with CI. Furthermore, the fact that the mean SaO_2 during sleep time was not significantly associated with CI suggests that intermittent hypoxia, rather than continuous hypoxia, is the mechanism behind this relationship. It has been shown that intermittent hypoxia is associated with increased risk of oxidative stress and adverse outcomes.[39]

Figure 2 Association of polysomnographic variables with a Clinical Dementia Rating scale score >0, multivariate analysis



Odds ratio for an increase of 10 units. Multivariate logistic regression model adjusted for each variable for age, sex, hypertension, diabetes, metabolic syndrome, current depression, lifetime depression, body mass index, alcohol and tobacco consumption, drugs influencing sleep, and level of education. AHI = apnea/hypopnea index (n/h); ArI = arousal index (n/h); ODI3 = oxygen desaturation index ≥3% during sleep (n/h); ODI4 = oxygen desaturation index ≥4% during sleep (n/h); ODI6 = oxygen desaturation index ≥6% during sleep (n/h); PLMSI = periodic leg movement in sleep index (n/h); REM = REM sleep (in % of total sleep time); REMlat = latency to REM sleep from sleep onset (min); St1 = stage N1 sleep (in % of total sleep time); SE = sleep efficiency; SOL = sleep onset latency (min); St2 = stage N2 sleep (in % of total sleep time); St3 = stage N3 sleep (in % of total sleep time); StShifts = number of stage shifts; TST = total sleep time (min); WASO = wake after sleep onset (min).

These findings have major clinical implications given that SDB is a common[3] and treatable condition. Indeed, studies suggest that SDB treatment may partially restore CI and slow cognitive deterioration.[40]

The major strengths of our study are its population-based design, the large sample size for this type of studies, the access of comprehensive data on a large number of sociodemographic and clinical variables, the consideration and statistical control of significant potential confounders, the use of PSG to objectively assess sleep duration, sleep architecture, and sleep-related comorbidities, and the inclusion of subjective sleep evaluations, as both objective and subjective measures are important and complementary to characterize sleep.

Our study has several potential limitations. The cross-sectional design of the study does not allow drawing conclusions on the directionality of the association between sleep disturbances and CI. Moreover, the proportion of participants who underwent both cognitive testing and PSG was low, as only 37.4% of the potential candidates had both cognitive and sleep tests. The absence of statistical significance for certain associations could be due to the sample size. Furthermore, the underlying cerebral pathologies in the participants with CI remain unknown. Participants in this study were almost exclusively of European origin. Therefore, our findings will not necessarily generalize to ethnically different populations.

We found that participants in this study from the general population aged >65 years with CI, compared to participants with no cognitive deficits, have a more disrupted sleep. This was associated with the occurrence of SDB, SDB indices being the only ones to be independently associated with an increased risk of CI. Our results suggest that this relationship is related to the severity of the SDB-induced intermittent hypoxia. Additional longitudinal and interventional studies are needed to confirm these results.

AUTHOR CONTRIBUTIONS

J.H.-R., R.H., and J.P. were responsible for the study concept, design, data interpretation, and writing of the manuscript. N.T. and D.A. acquired and analyzed the polysomnographic data. H.M.-S. performed the statistical analysis. P.M.-V., G.W., P.V., A.v.G., M.P., E.C., and M.T. were responsible for the CoLaus/PsyCoLaus and HypnoLaus studies concept and design, supervised the study. and revised the manuscript for intellectual content.

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DISCLOSURE

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