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Association between sleep quality and aging

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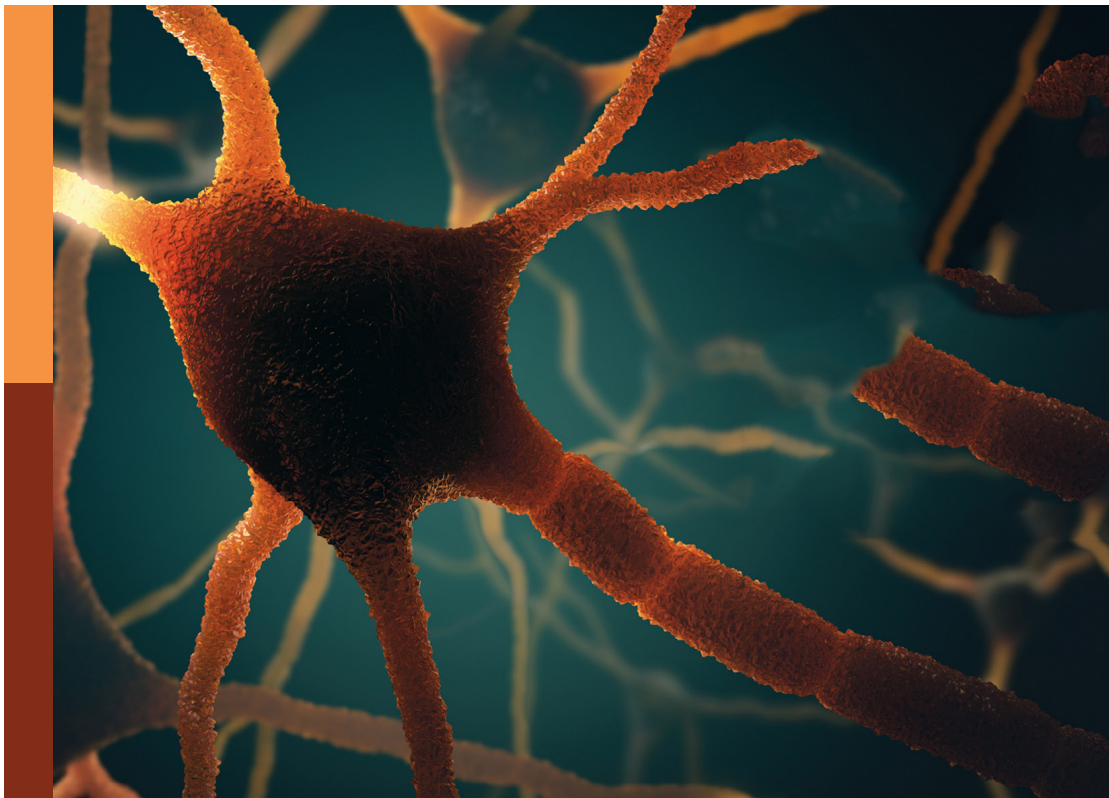

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Association between sleep quality and aging

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Associations between abdominal obesity and the risk of stroke in Chinese older patients with obstructive sleep apnea: Is there an obesity paradox?

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Background and purpose: Abdominal obesity (AO) is a well-known independent risk factor for stroke in the general population although it remains unclear in the case of the elderly, especially in Chinese older patients with obstructive sleep apnea (OSA), considering the obesity paradox. This study aimed to investigate the association between AO and stroke among Chinese older patients with OSA.

Methods: Data were collected from January 2015 to October 2017, and 1,290 older patients (age 60–96 years) with OSA (apnea–hypopnea index $\geq$ 5 events/h on polysomnography) were consecutively enrolled from sleep centers at six hospitals, evaluated for AO defined as waist circumference (WC) using the standardized criteria for the Chinese population, and followed up prospectively for a median period of 42 months. Logistic regression and Cox regression analyses were used to determine the cross-sectional and longitudinal associations between AO and stroke risk in these participants and different groups of the severity of OSA.

Results: Participants with AO had a higher prevalence of stroke at baseline. A higher incidence of stroke during a median follow-up period of 42 months in participants with AO than in participants without AO (12.4% *vs.* 6.8% and 8.3% *vs.* 2.4%, respectively; both $P < 0.05$) was predicted. Cross-sectional analysis revealed an association between AO and stroke (odds ratio [OR]1.96, 95%

confidence interval [CI] 1.31–2.91), which was stronger among participants with moderate OSA only (OR 2.16, 95%CI 1.05–4.43). Cox regression analysis showed that, compared to participants without AO, participants with AO had a higher cumulative incidence of stroke (hazard ratio [HR] 2.16, 95% CI 1.12–4.04) during a median follow-up of 42 months, and this association was observed in patients with severe OSA only (HR 3.67, 95% CI 1.41–9.87) but not for individuals with mild OSA (HR = 1.84, 95% CI 0.43–6.23) and moderate OSA (HR = 1.98, 95% CI 0.73–6.45).

Conclusion: The risk of stroke is associated with AO among Chinese older patients who have OSA, both at baseline and during follow-up, and the strength of the association varied by OSA severity. Active surveillance for early detection of AO could facilitate the implementation of stroke-preventive interventions in the Chinese older OSA population.

KEYWORDS

abdominal obesity, obstructive sleep apnea, elder, stroke, prospective study

Introduction

Obstructive sleep apnea (OSA) is the most common sleep disorder and is a leading health concern due to its strong association with the increasing burden of major adverse cardiovascular and cerebrovascular diseases and all-cause mortality (Chan et al., 2019; Gottlieb and Punjabi, 2020). Furthermore, OSA confers a higher risk of stroke-predisposing conditions, including vascular aging, transient ischemic attack, acute ischemic stroke, and wake-up stroke, for which the current OSA treatment strategies remain inadequate (Koo et al., 2016; Bravata et al., 2018; Catalan-Serra et al., 2019; Lisan et al., 2021). The public health burden of these complications remains largely because of their higher prevalence and incidence in patients with OSA, especially in the older population. Thus, a better understanding of the risk factors of OSA is essential for developing effective preventive strategies against stroke in older patients with OSA.

Abdominal obesity (AO) is common in patients with OSA, and AO increases the risk of OSA. The results from two observational longitudinal studies confirmed a strong association between AO and OSA, whereas another study reported a stronger, more significant association in younger than in older individuals (Nakagawa et al., 2011; Unal et al., 2019; Zhao et al., 2019; Balat et al., 2020; Liu et al., 2021; Qin et al., 2021). Moreover, the health risks of patients with AO differ from that of patients with non-AO. First, individuals with AO have a higher risk for metabolic syndrome, which is associated with cerebrovascular diseases, such as stroke (Gaudio et al., 2017; Park et al., 2018). Second, AO is potentially related to both brain structure and function (Després et al., 2008). The relationship between AO and stroke risk has been investigated in several studies, all of which were conducted in the general population or non-OSA populations (Suk et al., 2003; Abete et al., 2015; Rodríguez-Campello et al., 2017; Liu S. et al., 2020; Zhai et al., 2020). Suk et al. (2003) showed that, compared with the body mass index (BMI), AO was a stronger risk factor for stroke and increased the overall odds ratio (OR) of stroke by threefold. Zhai et al. (2020) reported that waist circumference (WC), an AO index measure, was an important predictor of all-cause mortality, including stroke-related mortality, independent of the BMI. Rodríguez-Campello et al. (2017) found that AO was associated with stroke risk in only women, which indicated a sex-specific stroke risk of AO in the general population, and this finding is aligned with the results of the Spanish EPIC cohort study (Abete et al., 2015). Notably, Liu S. et al. (2020) demonstrated significant associations between obesity, regardless of general adiposity or AO and the risk of incident stroke in Chinese participants during a median follow-up of 12 years. Although the abovementioned studies examined a direct association between AO and stroke, studies that simultaneously evaluated the association between AO and the prevalence risk and/or incidence of stroke in patients with OSA, especially in the older population, are limited. AO is associated with a higher risk of stroke, whereas this is presenting a controversy in older populations. Numerous

Abbreviations: AO, abdominal obesity; OSA, obstructive sleep apnea; PSG, polysomnography; AHI, apnea–hypopnea index; TST, total sleep time; TSA90, duration of time with SaO_2 < 90%; ODI, oxygen desaturation index; $MSpO_2$, mean pulse oxygen saturation; $LSpO_2$, lowest pulse oxygen saturation; BMI, body mass index; NC, neck circumference; WC, waist circumference; WHR, waist/hip ratio; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; CAS, carotid atherosclerosis; AF, atrial fibrillation.

studies in free-living older populations and older individuals with chronic disease, including type 2 diabetes, coronary heart disease (CHD), heart failure, and cancer, reported that obese individuals have a better prognosis than non-obese individuals, a phenomenon termed the "obesity paradox" (Gregg et al., 2004; Lavie et al., 2009). The suggested explanations for this survival advantage are increased metabolic reserve, which can meet the metabolic needs of the disease, and lipoproteins, such as cholesterol, that can bind and remove endotoxins and neutralize inflammation (Bailly et al., 2020).

Given that the majority of the patients with OSA have AO, this obesity paradox may contribute to stroke outcomes and should be considered an important confounding factor. Thus, the present study was conducted with an aim to assess the association between AO and the prevalence of stroke among Chinese older patients with OSA at baseline and to determine the long-term effect of AO on incident stroke in a cohort of older OSA patients without stroke at baseline.

Materials and methods

Study design and participants

The project is a Chinese population-based, multicenter, prospective, observational study to assess the association of AO with stroke in older patients with OSA aged $\geq$ 60 years. The study began consecutively recruiting subjects on 1 January 2015 from sleep centers of six hospitals in China using a clinic's electronic classification system, and the data were cutoff on 30 October 2017. This study collected baseline information including basic demographics, clinical medical characteristics, and sleep parameters. OSA was defined as an apnea-hypopnea index (AHI) $\geq$ 5 events/h.

For the current study, a total of 1,290 patients with OSA were enrolled in six hospitals in six areas of China, including the General Hospital of the Chinese People's Liberation Army (PLA, Haidian District, Beijing, n = 313), the Peking University International Hospital (n = 238), and the Peking University People's Hospital (Changping District, Beijing, n = 242), the Beijing Chaoyang Hospital affiliated to Capital Medical University (Chaoyang District, Beijing, China, n = 337), the 960th Hospital of PLA (JiNan, Shandong Province, n = 48), and the affiliated Hospital of Gansu University of Chinese Medicine (Lanzhou, Gansu Province, n = 112), who had completed polysomnography (PSG) study within 7 days after admission, at baseline, during which we performed a cross-sectional analysis. After following up prospectively for approximately 4 years, we excluded 88 patients based on the following criteria for the longitudinal analysis: (1) previous history of myocardial infarction and hospitalization for unstable angina or heart failure (n = 34); (2) patients with malignant tumors (n = 3); (3) patients with aphasia mental disorders (n = 4); and those whose blood pressure was not controlled with antihypertensive agents (n = 47). Furthermore, we excluded 95 patients who were lost during the follow-up (n = 17) and patients with stroke at baseline (n = 78). Eventually, the final sample included in the prospective analysis contained 1,107 participants, and the study participant-selection flowchart is presented in **Figure 1**. The cohort was followed up from the OSA diagnosis of PSG assessment to December 2020.

This study is reported following the Strengthening the Reporting of Observational Studies in Epidemiology guideline, was conducted in compliance with the tenets underlying the Declaration of Helsinki, and was approved by the Ethics Committee of Chinese PLA General Hospital (S2019-352-01); all participants provided written informed consent for study participation.

Overnight sleep study

Polysomnography is a gold standard for diagnosis of OSA and all participants completed standardized full nocturnal PSG testing (from 21:00 to 07:00 the next day) in a sleep laboratory within 7 days after admission (Liu et al., 2022). Participants were asked to strictly abstain from consuming caffeine, sedatives, and hypnotic drugs in the 24 h preceding the full-night sleep study. The sleep analysis was performed on-site using laboratory-based PSG equipment (Compumedics, Melbourne, VIC, Australia) and standard methods that have been described previously (Liu et al., 2022). All essential parameters of the sleep tests with specific respiration events were recorded and included electroencephalography, electrooculography, electrocardiography, nasal and oral airflow, thoracic/abdominal movements, pulse oxygen saturation, tracheal microphone for snoring, body position, and sleep parameters, such as the AHI, oxygen desaturation indices (ODI), mean oxygen saturation ($MSpO_2$), lowest oxygen saturation ($LSpO_2$), and total sleep time (TST). Apnea was defined as a complete cessation of respiratory airflow for more than 10 s, whereas hypopnea was defined as at least a 30% reduction of air flow accompanied by a 4% or greater decrease in SaO_2 or arousal. The AHI was defined as the number of episodes of apnea and hypopnea per hour of sleep. Oxygen desaturation index (ODI) was defined as the average number of arterial oxygen saturation dips $\geq$ 4%/h. TST was defined as the time spent in all sleep stages. $LSpO_2$ was defined as the lowest value of whole oxygen saturation observed during sleep. $MSpO_2$ was defined as the mean value of whole oxygen saturation observed during sleep. TSA90 was defined as the total sleep time spent at oxygen saturation levels below 90% (Shaikh et al., 2013). Sleep scores were calculated in accordance with the Guideline of the American Academy of Sleep Medicine (Berry et al., 2012). The categories of OSA severity were defined using conventional clinical cutoffs of the AHI, which is the gold standard for OSA diagnosis: AHI $<$ 5, 5–15, 15–30, and $>$30

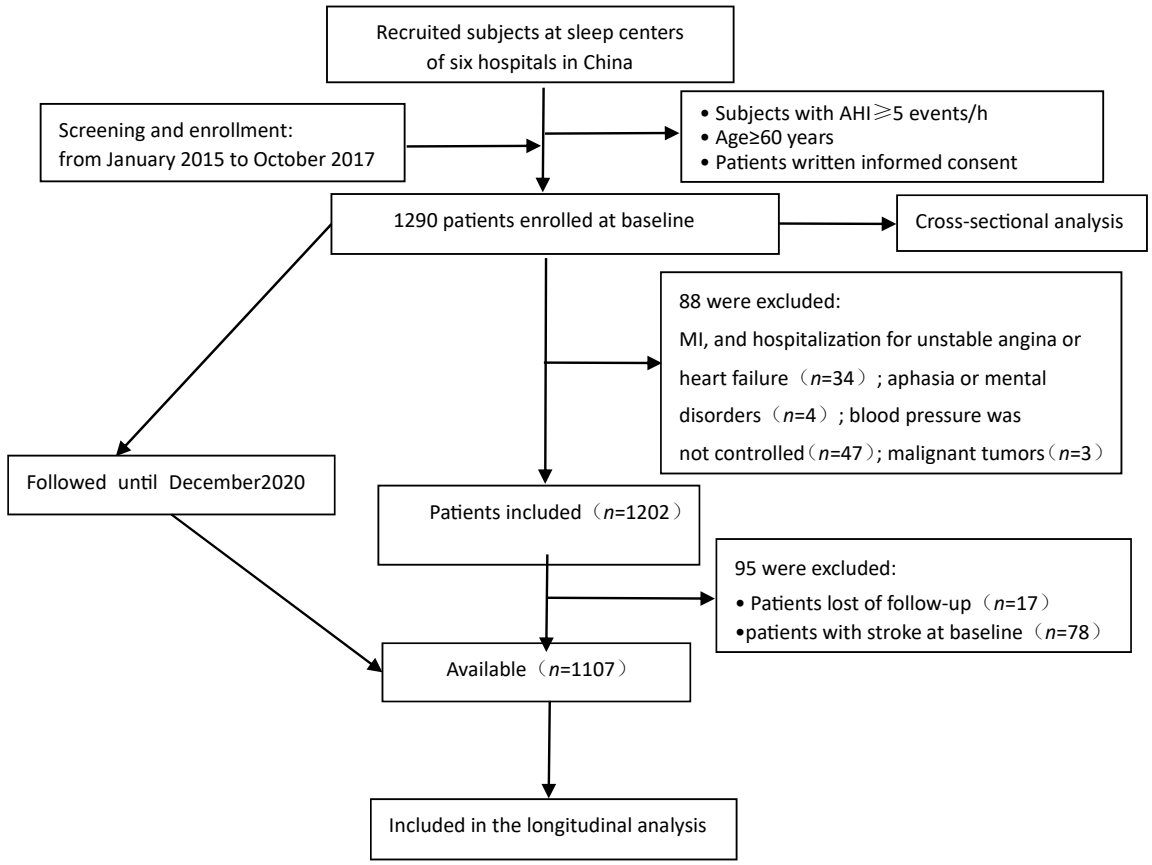

FIGURE 1
Study flowchart. AHI, the apnea-hypopnea index; MI, myocardial infarction.

events/h as no, mild, moderate, and severe OSA, respectively (Berry et al., 2012; Patil et al., 2019).

Covariates

Demographics included age, sex, BMI, waist–hip ratio, neck circumference, and WC. The waist circumference was measured according to the WHO recommended method (Who, 1995). The subject stood with feet apart, using a non-elastic soft ruler, along the midpoint of the line connecting the lower edge of the twelfth rib and the upper edge of the iliac crest in the mid-axillary line, wrapped horizontally for 1 week, and was measured at the end of calm expiration, with an accurate reading of 0.1 cm. The height reading was accurate to 0.1 cm and the weight reading was accurate to 0.1 kg. When measuring the hip circumference, both legs were held together and upright, both arms were naturally lowered, and the tape measure was placed horizontally in front of the pubic symphysis and behind the most convex part of the gluteus maximus. It was measured by a tape measure around the widest part of the hip for 1 week, and the result was accurate at 0.1 cm. Waist-to-hip ratio (WHR) was calculated as WC divided by hip circumference. All physical examination measurers received uniform training.

Lifestyle variables included self-reported current smoking (consecutively or cumulatively smoking for $>$ 6 months in the past year) and alcohol consumption (drinking $\geq$ 50 g/week of alcohol for $\geq$ 6 months).

Comorbidities included CHD, diabetes, hypertension, hyperlipidemia, atrial fibrillation (AF), carotid atherosclerosis (CAS), chronic obstructive pulmonary disease (COPD), and hyperlipidemia. Hypertension was defined as a previous diagnosis of hypertension or the use of antihypertensive medication (Ma et al., 2021). Hyperlipidemia was defined as total cholesterol $\geq$ 220 mg/dl, TG $\geq$ 150 mg/dl, or undergoing treatment for hyperlipidemia using the Chinese Guidelines for the management (Joint committee issued Chinese guideline for the management of dyslipidemia in adults, 2016). Atrial fibrillation was determined by self-reporting or atrial fibrillation on ECG at the inpatient center based on the ESC guidelines (Kirchhof et al., 2016). CHD and COPD were determined by a record of a relevant diagnostic clinical (Read) code indicating the presence of the condition (Charlson et al., 1987). Carotid atherosclerosis (CAS) was determined based on the carotid

intima-media thickness (CIMT) measured by color Doppler ultrasound diagnostic instrument: when CIMT ≥ 1 mm was determined as carotid atherosclerotic plaque formation (Chambless et al., 2000). Diabetes had been diagnosed by a physician based on the guidelines provided by the Diagnosis and Classification of Diabetes Mellitus of American Diabetes Association (No authors listed, 1997).

All participants underwent comprehensive clinical assessment at baseline, and the clinical data that were collected were screened, assessed, and extracted using predesigned electronic case report forms by at least two medical professionals who were blinded to the patients' PSG results. The categories of covariates are listed in **Supplementary Table S1**.

Assessment of abdominal obesity

Abdominal obesity was defined as WC ≥ 90 cm and ≥85 cm in men and women, respectively, according to the standardized criteria for Chinese individuals (Zhou, 2002). The study cohort in the prospective analysis was subdivided into two groups: (i) a group with AO and (ii) a group without AO, all of whom have completed the median follow-up of 42 months (range 1–72 months).

Follow-up and stroke assessment

All participants were followed-up prospectively for approximately 4 years after the full baseline assessment. Patients or their proxies were contacted initially at 1-, 3-, 6-, and 12-month intervals, and every 6 months thereafter (at least 3 months and up to 1 year) until December 2020 or death *via* telephonic follow-up, a clinic visit, or medical chart review, which was performed independently by at least two investigators who were blinded to the patients' clinical condition, PSG results, and study group.

The predefined endpoint in our study was stroke. Strokes were recorded both at baseline and the median follow-up of 42-month. Older participants who reported two or more stroke events in multiple follow-up notes were uniformly counted as having one relevant event, and we extracted data from the longest follow-up period after the endpoint event. Stroke was defined as both ischemic and hemorrhagic stroke using the Diagnostic Criteria of Cerebrovascular Diseases in China (2019) (Chinese Society of Neurology, and Chinese Stroke Society, 2019; (Su et al., 2021). The prevalence of stroke was defined as the percentage of older patients with OSA who had stroke at baseline. The incidence of stroke was estimated as the percentage of patients who were newly diagnosed with stroke during the follow-up period, excluding patients who reported a history of stroke at baseline. Stroke was preliminarily identified based on the self-reported medical history (shared by patients or their proxies). Next, during a clinic visit or by medical chart review, we obtained the participant's CT or MRI report to verify the diagnosis of stroke. Study events of all participants were adjudicated by the clinical event committee.

Statistical analysis

Continuous variables at baseline are presented as mean ± SD or median (interquartile range 25th and 75th percentiles) in our study, and intergroup differences at baseline were compared using the Mann–Whitney *U* or the chi-square test. Logistic regression analysis was performed to obtain the ORs and 95% confidence intervals (CIs) between AO and stroke risk in total participants and different OSA (mild, moderate, and severe) groups that were stratified according to the AHI. Three models were created to examine the relationship between AO and stroke: Model 1, which was unadjusted; Model 2, adjusted for age and sex; and Model 3, further adjusted for BMI, neck circumference, drinking status, smoking status, WHR, WC, BMI, sleep parameters, and baseline self-reported comorbidities. We used three Cox regression models to examine the association between AO and hazard ratios (HRs) of stroke during a median follow-up of 42 months in the whole cohort as well as in different OSA groups. AO was considered both a continuous and categorical variable during the analysis of all models.

Additionally, all older patients with hypertension received antihypertensive drugs according to Chinese guidelines for the management of hypertension during follow-up (Sun et al., 2017). In this study, patients with hypertension were divided into two categories: treated but with uncontrolled hypertension and hypertension controlled with medication. Forty-seven patients whose blood pressure was not controlled with antihypertensive agents were excluded, whereas we did not exclude patients who had hypertension but whose blood pressure was controlled in the normal range. In a systematic review of stroke risk factors, a history of hypertension or uncontrolled hypertension conferred an increase in stroke risk, but clearly, well-controlled hypertension has a lower risk of stroke compared with uncontrolled hypertension (Gorenek et al., 2017). Three models were created to examine the relationship between AO and stroke: Model 1, which was unadjusted; Model 2, adjusted for age and sex; and we adjusted for as many variables related to stroke as possible in Model 3, adjusted for BMI, neck circumference, drinking status, smoking status, waist–hip ratio, WC, BMI, sleep parameters of $MSpO_2$, $LSpO_2$, TST, TSA90, ODI, AHI, and baseline self-reported comorbidities of CHD, COPD, diabetes, carotid atherosclerosis, atrial fibrillation, and hypertension. All *p*-values were two-tailed, and statistical significance was set at 0.05. SPSS (version 25.0, SPSS Inc., Chicago, IL, United States) was used for all analyses.

Results

Cross-sectional analysis of the association between abdominal obesity and stroke

All 1, 290 participants (age, median 66 [range 66–96] years) who were included in the cross-sectional analysis underwent successful overnight PSG; at baseline, 23.7, 30.1, and 46.2% of the participants had mild, moderate, and severe OSA, respectively. The prevalence of stroke was 6.5, 10.8, and 11.2% for mild, moderate, and severe OSA, respectively, and was 10.0% for all participants. The prevalence of stroke in OSA patients with AO tended to increase compared with those without AO (12.4% *vs.* 6.8%; $P < 0.05$), and this trend was consistent across different OSA groups and became stronger among participants with moderate OSA ($P < 0.05$; Figure 2).

Table 1 presents the baseline characteristics by OSA severity-based groups in participants with and without stroke. Older OSA patients with AO had a higher waist–hip ratio, BMI, and WC in each OSA group (all $P < 0.05$). A statistically significant difference was observed between stroke and non-stroke older participants in the specific OSA subgroup as follows: older OSA patients with stroke had a higher median neck circumference than those without stroke (only in the moderate OSA group); the ratios of AO (in the mild and moderate OSA groups) and the proportion of comorbidities of hypertension (both in the moderate and in the severe OSA groups), CHD (only in the mild OSA group), hyperlipidemia (in the severe OSA group), AF (only in the severe OSA group), and COPD (only in the moderate OSA group) were significantly higher between older participants with stroke compared to those without stroke, whereas no statistically significant difference was noted between the stroke and non-stroke groups in specific OSA groups for all other selected characteristics ($P > 0.05$).

Associations between AO and stroke that were detected in the cross-sectional analysis are shown in Table 2. AO was associated with increased odds of stroke among older patients with OSA in the crude model (OR 2.04, 95% CI 1.36–3.06), the partially adjusted model (OR 2.02, 95% CI 1.35–3.02), and the fully adjusted model (OR 1.96, 95% CI 1.31–32.91). Furthermore, WC as AO judgment criteria with an increased risk of stroke in the overall participants, and the unadjusted, partially adjusted, and fully adjusted ORs (95% CI) were 1.03 (1.02–1.05), 1.03 (1.02–1.04), and 1.02 (1.01–1.04), respectively, per 1 SD increase in WC (Table 3).

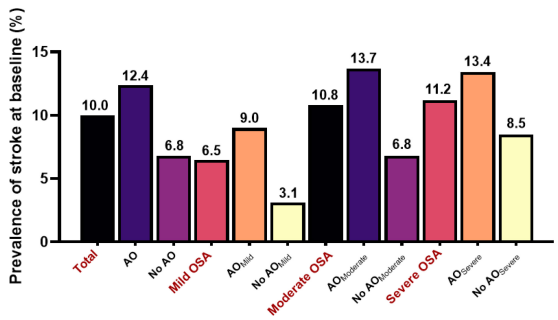

FIGURE 2
Prevalence of stroke at baseline among older patients with OSA.

We observed that these associations between AO and stroke varied with the severity of OSA. A onefold increase in WC was associated with a 2, 3, and 2% increase in the odds of stroke ($P < 0.05$) after adjusting for age, sex, BMI, neck circumference, drinking status, smoking status, waist–hip ratio, WC, BMI, sleep parameters, and baseline self-reported comorbidities in the mild, moderate, and severe OSA groups. The OR of AO for stroke increased significantly (OR 2.16, 95% CI 1.05–4.43) for the moderate OSA group in the fully adjusted model, although there were no significant associations between AO and odds of stroke in the mild and severe OSA groups.

Abdominal obesity increased the risk of stroke in longitudinal analysis

After the exclusion of patients according to predefined criteria, 34 patients were excluded because of a history of myocardial infarction and hospitalization for unstable angina or heart failure; three patients with malignant tumors were excluded; four patients with aphasia mental disorders were excluded; 47 patients were excluded because their blood pressure was not controlled with antihypertensive agents. Next, 17 patients were lost during follow-up due to relocation and non-compliance throughout the follow-up. Furthermore, we excluded 78 patients with stroke at baseline to rule out the reverse causality. Eventually, 1,107 study subjects with OSA aged $\geq$ 60 years were included in the longitudinal analysis (Figure 1). Table 3 presents the intergroup comparison of baseline characteristics between the groups with AO and without AO. The incidence of new stroke was 5.9% in approximately 4 years in the prospectively followed-up older patients with OSA. The mild, moderate, and severe OSA groups had overall cumulative incidence rates of stroke of 5.2, 5.4, and 6.7%, respectively. Patients with AO had a higher cumulative incidence of stroke than those without AO (8.3% vs. 2.4%; $P < 0.05$), and participants with severe OSA and concomitant AO were more likely to have experienced stroke (9.8% *vs.* 2.3%, $P < 0.05$; Figure 3) at the median follow-up of 42 months.

The results of the longitudinal analysis are shown in Table 4. Participants with AO were at greater risk of experiencing stroke than those without AO in the entire cohort ($P < 0.05$). After adjusting for age, sex, BMI, neck circumference, drinking status, smoking status, waist–hip ratio, WC, BMI, sleep parameters,

TABLE 1 Comparisons of participants' characteristics according to the severity of OSA groups and stroke at baseline (n = 1,290).

	Mild OSA (n = 306)			Moderate OSA (n = 388)			Severe OSA (n = 596)		
	Stroke (n = 20)	No stroke (n = 286)	P-value	Stroke (n = 42)	No stroke (n = 346)	P-value	Stroke (n = 67)	No stroke (n = 529)	P-value
Age, y	65.5 (60.5,71)	67.0 (64.0,72.0)	0.152	69.0 (65.0,77.0)	65.0 (62.0,72.0)	0.641	66.0 (64.0,76.0)	65.0 (62.0,69.0)	0.218
Men, %	9 (45.0)	160 (55.9)	0.341	33 (78.6)	200 (57.8)	0.009	52 (77.6)	344 (65.0)	0.040
BMI, kg/m2	27.8 (26.3,29.5)	25.0 (22.6,27.4)	0.003	28.4 (25.66,29.8)	25.5 (23.5,27.7)	0.001	29.7 (26.5,33.8)	27.5 (25.3,30.3)	0.034
NC, mm	39.3 (36.0,43.8)	39.0 (36.0,43.0)	0.397	41.0 (35.0,44.0)	40.0 (37.0,44.0)	0.042	43.0 (38.5,44.0)	42.0 (38.0,45.0)	0.878
WC, mm	99.0 (92.3,117.5)	90.0 (80.0,98.0)	0.001	98.0 (86.0,105.3)	90.0 (78.4,99.0)	0.006	98.0 (82.0,110.0)	90.0 (80.0,99.0)	0.001
Waist-hip ratio, %	1.0 (0.8,1.0)	0.9 (0.8,1.0)	0.015	1.0 (0.8,1.1)	0.9 (0.8,1.0)	0.011	0.9 (0.8,1.1)	0.8 (0.8,1.0)	0.014
Drinking, n (%)	2 (10.0)	28 (9.8)	0.976	4 (9.5)	39 (11.3)	0.733	17 (25.4)	68 (12.9)	0.006
Smoking, n (%)	4 (20.0)	55 (19.2)	0.933	8 (19.0)	73 (21.1)	0.757	14 (20.9)	139 (26.3)	0.342
AHI, events/h	9.7 (7.7,12.0)	9.3 (6.7,11.9)	0.516	21.2 (18.8,25.9)	21.8 (18.1,30.0)	0.978	47.6 (38.1,56.8)	48.8 (37.3,61.6)	0.984
TSA90, min	9.6 (1.8,178.0)	3.4 (0.8,30.1)	0.567	16.3 (2.6,67.2)	9.4 (2.3,26.83)	0.741	42.8 (14.6,87.1)	34.0 (9.7,116.0)	0.805
TST, h	7.3 (6.8,7.4)	7.1 (6.2,7.4)	0.387	7.2 (5.9,7.9)	7.1 (6.3,7.7)	0.609	7.4 (6.3,8.3)	7.2 (6.1,7.8)	0.472
ODI, events/h	10.6 (7.9,15.3)	8.0 (4.6,11.3)	0.314	21.0 (13.1,33.0)	17.3 (12.4,23.0)	0.104	42.0 (33.0,56.4)	41.5 (30.0,55.1)	0.054
MSpO$_2$,%	92.0 (89.0,95.0)	94.0 (92.0,95.0)	0.879	94.0 (90.5,95.0)	94.0 (92.0,95.0)	0.321	93.0 (90.0,94.0)	93.0 (91.0,94.0)	0.617
LSpO$_2$, %	84.0 (74.0,87.0)	84.0 (80.0,87.0)	0.209	80.0 (73.5,86.0)	82.0 (76.5,85.0)	0.798	75.0 (65.0,80.5)	75.0 (67.0,81.0)	0.199
AO, n (%)	16 (80.0)	162 (56.6)	0.041	31 (73.8)	196 (56.6)	0.033	45 (67.2)	292 (55.2)	0.063
Hypertension, n (%)	15 (75.0)	173 (60.5)	0.197	31 (73.8)	299 (57.5)	0.042	51 (76.1)	336 (63.5)	0.042
CHD, n (%)	0 (0.0)	55 (19.2)	0.030	13 (31.0)	84 (24.3)	0.345	20 (29.9)	132 (25.0)	0.386
Hyperlipidemia, n (%)	6 (30.0)	90 (31.5)	0.891	11 (26.2)	92 (26.6)	0.956	25 (37.3)	135 (25.5)	0.040
AF, n (%)	1 (5.0)	20 (7.0)	0.910	6 (14.3)	28 (8.1)	0.176	6 (9.0)	62 (11.7)	0.012
CAS, n (%)	9 (45.0)	87 (30.4)	0.174	16 (38.1)	85 (24.6)	0.059	17 (25.4)	118 (22.3)	0.572
Diabetes, n (%)	3 (15.0)	57 (19.9)	0.591	94 (31.0)	81 (23.4)	0.281	16 (23.9)	149 (28.2)	0.515
COPD, n (%)	1 (5.0)	24 (8.4)	0.592	9 (21.4)	23 (6.6)	0.003	6 (9.0)	30 (5.7)	0.288

TABLE 2 Logistic regression model for stroke according to AO among older patients with OSA at baseline (n = 1,290).

	Model 1		Model 2		Model 3	
	OR (95%*CI*)	P-value	*OR* (95%*CI*)	P-value	*OR* (95%*CI*)	P-value
Total participants						
OR per 1 mm	1.03 (1.02, 1.05)	<0.001	1.03 (1.02, 1.04)	0.001	1.02 (1.01, 1.04)	0.011
Abdominal obesity	2.04 (1.36, 3.06)	0.001	2.02 (1.35, 3.02)	0.015	1.96 (1.31, 2.91)	0.011
Mild OSA						
OR per 1 mm	1.03 (1.01,1.05)	0.006	1.03 (1.02,1.05)	0.001	1.02 (1.01,1.04)	0.010
Abdominal obesity	3.06 (0.99, 9.38)	0.050	2.94 (0.86, 9.05)	0.052	2.89 (0.74,8.96)	0.063
Moderate OSA						
OR per 1 mm	1.03 (1.01, 1.05)	0.004	1.03 (1.01, 1.05)	0.005	1.03 (1.01, 1.05)	0.021
Abdominal obesity	2.45 (1.09, 4.65)	0.029	2.28 (1.10, 4.70)	0.027	2.16 (1.05, 4.43)	0.036
Severe OSA						
OR per 1 mm	1.03 (1.02, 1.05)	0.001	1.03 (1.02, 1.04)	0.010	1.02 (1.01, 1.04)	0.013
Abdominal obesity	1.66 (0.99, 2.83)	0.051	1.64 (0.90, 2.55)	0.054	1.44 (0.70, 1.95)	0.062

OR, odds ratio; CI, confidence interval.
Model 1 was unadjusted.
Model 2 adjusted for age and gender.
Model 3 adjusted for BMI, neck circumference, drinking status, smoking status, waist-hip ratio, waist circumference, BMI, sleep parameters, and baseline self-reported chronic diseases.

and baseline self-reported comorbidities, the differences were moderately attenuated but remained significant (HR 2.16, 95% CI 1.12–4.04). Table 4 shows the results of the risk of stroke resulting from the AO, with and without at baseline, in the multivariate analysis among the three subgroups according to OSA severity. Each 1-mm increase of WC was associated with a 3% (2–5%), 4% (1–7%), 4% (3–6%), and 3% (2–4%) increase in HR for stroke risk in all enrolled older patients with OSA and in the mild, moderate, and severe OSA groups, respectively ($P < 0.05$; Table 4). The crude hazard ratios (HRs) and adjusted

TABLE 3 Comparisons of participants' characteristics according to the severity of OSA groups and AO during follow-up (n = 1,107).

	Mild OSA (n = 305)			Moderate OSA (n = 370)			Severe OSA (n = 432)		
	AO (n = 177)	No AO (n = 128)	P-value	AO (n = 215)	No AO (n = 155)	P-value	AO (n = 255)	No AO (n = 177)	P-value
Age, y	66.0 (63.0,71.0)	67.0 (64.0,72.8)	0.066	65.0 (61.0,71.0)	66.0 (62.0,73.0)	0.098	66.0 (62.0,71.0)	64.0 (61.0,67.0)	0.002
Men, %	88 (49.4)	81 (63.3)	0.016	112 (52.1)	108 (69.7)	0.001	158 (62.2)	127 (71.8)	0.039
BMI, kg/m2	25.6 (23.4,27.5)	24.4 (22.0,27.5)	0.016	25.7 (23.8,18.1)	25.5 (23.4,27.7)	0.454	27.6 (25.4,30.1)	27.6 (25.4,31.5)	0.347
NC, mm	39.0 (36.0,43.0)	38.0 (35.0,42.9)	0.252	40.0 (37.0,45.0)	40.0 (37.0,44.0)	0.727	42.0 (37.4,44.0)	43.0 (38.0,44.0)	0.096
WC, mm	98.0 (92.0,104.0)	78.0 (70.0,83.8)	<0.001	99.0 (93.0,109.0)	78.0 (70.0,80.0)	<0.001	99.0 (92.0,106.0)	79.0 (68.5,81.0)	<0.001
Waist-hip ratio, %	1.0 (0.9,1.1)	0.8 (0.7,0.9)	<0.001	1.0 (0.9,1.1)	0.7 (0.7,0.8)	<0.001	1.0 (0.9,1.1)	0.8 (0.7,0.8)	<0.001
Drinking, n (%)	11 (6.2)	19 (14.8)	0.012	15 (7.0)	23 (14.8)	0.014	22 (8.7)	38 (21.5)	0.004
Smoking, n (%)	31 (17.4)	28 (21.9)	0.329	41 (19.1)	33 (21.3)	0.598	63 (24.8)	57 (32.2)	0.092
AHI, events/h	9.4 (6.9,11.7)	8.9 (6.6,12.3)	0.690	21.7 (17.9,25.4)	21.8 (18.7,26.5)	0.151	49.5 (39.2,64.1)	45.6 (35.3,58.1)	0.007
TSA90, min	3.0 (0.7,19.9)	4.8 (0.9,66.7)	0.084	8.8 (2.1,26.4)	10.3 (2.6,33.0)	0.264	35.6 (10.6,128.7)	34.0 (10.3,92.7)	0.678
TST, h	7.0 (6.2,7.4)	7.2 (6.5,7.4)	0.119	7.0 (6.6,7.5)	7.2 (6.5,7.9)	0.037	7.2 (6.1,7.8)	7.3 (6.2,8.0)	0.123
ODI, events/h	7.8 (4.3,10.6)	9.0 (5.9,13.7)	0.002	17.0 (12.0,23.5)	18.3 (13.2,23.2)	0.415	42.5 (30.4,57.0)	39.7 (30.0,52.2)	0.238
$MSpO_2$, %	94.0 (93.0,96.0)	93.0 (91.0,95.0)	0.002	94.0 (92.0,95.0)	94.0 (92.0,95.0)	0.303	92.5 (90.0,94.0)	93.0 (91.0,95.0)	0.181
$LSpO_2$, %	84.5 (81.0,87.0)	84.0 (79.0,87.0)	0.572	81.0 (76.0,85.0)	81.0 (76.0,85.0)	0.983	74.0 (66.0,81.0)	79.0 (71.0,82.0)	0.601
Hypertension, n (%)	109 (61.2)	79 (61.7)	0.932	131 (60.9)	89 (57.4)	0.497	167 (65.7)	100 (56.5)	0.052
CHD, n (%)	30 (16.9)	25 (19.5)	0.547	51 (23.7)	38 (24.5)	0.860	45 (17.7)	46 (26.0)	0.038
Hyperlipidemia, n (%)	54 (30.3)	42 (32.8)	0.645	56 (26.0)	40 (25.8)	0.959	64 (25.2)	39 (22.0)	0.449
AF, n (%)	7 (4.0)	15 (11.7)	0.012	18 (8.4)	14 (9.0)	0.118	18 (7.1)	24 (13.6)	0.039
CAS, n (%)	42 (23.6)	54 (42.2)	0.001	50 (23.3)	44 (28.4)	0.263	42 (16.5)	22 (12.4)	0.238
Diabetes, n (%)	35 (19.7)	25 (19.5)	0.977	47 (21.9)	39 (25.2)	0.458	71 (28.0)	35 (19.8)	0.019
COPD, n (%)	9 (5.1)	15 (12.5)	0.019	13 (6.0)	17 (11.0)	0.087	14 (5.5)	3 (21.7)	0.045

BMI, body mass index; NC, neck circumference; WC, waist circumference; WHR, waist/hip ratio; AHI, the apnea-hypopnea index; ODI, the oxygen desaturation index; $MSpO_2$, the mean pulse oxygen saturation; $LSpO_2$, the lowest pulse oxygen saturation; TST, total sleep time; TSA90, the duration of time with $SaO_2 < 90\%$; AO, abdominal obesity; CHD, coronary heart disease; AF, atrial fibrillation; CAS, carotid atherosclerosis; COPD, chronic obstructive pulmonary disease.

HRs of the longitudinal association between AO and stroke in both the unadjusted model and the multivariable-adjusted model were statistically significant in the severe OSA group ($P < 0.05$) but not in the mild and moderate OSA groups ($P > 0.05$).

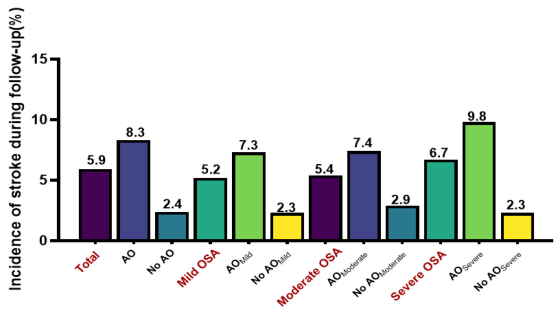

FIGURE 3
Cumulative incidence of stroke during follow-up among older patients with OSA.

Sensitivity analysis

Considering the AO being defined as a WHR ≥ 0.9 for men and ≥0.85 for women, we present the result of WHR as an AO indicator to illustrate the associations between AO and stroke in Supplementary Tables S2, S3, respectively. These associations were approximately consistent across the result confirmed by using the WC as an AO indicator, whether analyzed as a continuous or a categorical variable. Apart from this, we further compared the results of longitudinal analysis by plotting the ROC curves of different obesity measurement parameters included in this study on the ability to identify stroke risk in older patients with OSA. Our results confirm that waist circumference in the AO measure has a higher predictive ability compared to BMI and WHR for the risk of a median incident stroke within approximately 4 years in older patients with OSA (Supplementary Figure S1). Meanwhile, to determine whether CPAP treatment of older patients with OSA has an impact on the results of the stroke outcome during a median follow-up period of 42 months. We divided the 1,107 older OSA patients into three groups, including the

TABLE 4 Cox regression model for stroke according to AO among older patients with OSA at a median follow-up of 42-months (n = 1,107).

	Model 1		Model 2		Model 3	
	HR (95%*CI*)	*P*-value	*HR* (95%*CI*)	*P*-value	*HR* (95%*CI*)	*P*-value
Total participants						
HR per 1 mm	1.05 (1.03, 1.06)	<0.001	1.04 (1.03, 1.06)	0.011	1.03 (1.02, 1.05)	0.013
Abdominal obesity	3.48 (1.82, 6.67)	<0.001	3.46 (1.81, 6.64)	0.015	2.16 (1.12, 4.04)	0.026
Mild OSA						
HR per 1 mm	1.05 (1.02, 1.09)	0.001	1.05 (1.02, 1.08)	0.001	1.04 (1.01, 1.07)	0.001
Abdominal obesity	2.85 (0.81, 10.06)	0.104	2.01 (0.70, 7.77)	0.113	1.84 (0.43, 6.23)	0.214
Moderate OSA						
HR per 1 mm	1.05 (1.03, 1.07)	<0.001	1.04 (1.02, 1.06)	0.002	1.04 (1.03, 1.06)	0.014
Abdominal obesity	2.84 (0.95, 8.51)	0.062	2.24 (0.81, 6.94)	0.073	1.98 (0.73, 6.45)	0.081
Severe OSA						
HR per 1 mm	1.04 (1.02, 1.06)	<0.001	1.04 (1.02, 1.05)	0.016	1.03 (1.02, 1.04)	0.022
Abdominal obesity	4.69 (1.63, 13.51)	0.004	4.01 (1.52, 11.43)	0.021	3.67 (1.41, 9.87)	0.031

HR, hazard ratio; CI, confidence interval.
Model 1 was unadjusted.
Model 2 adjusted for age and gender.
Model 3 adjusted for BMI, neck circumference, drinking status, smoking status, waist-hip ratio, waist circumference, BMI, sleep parameters, and baseline self-reported chronic diseases.

reference group (AHI > 5 event/h; CPAP not used; n = 915), the untreated OSA (AHI > 5 event/h; CPAP compliance < 4 h/day; n = 121), and the CPAP-treated OSA (AHI > 5 event/h; CPAP compliance ≥ 4 h/day; n = 71). A comparative analysis was performed to examine the longitudinal association between AO and stroke among three groups according to the CPAP therapy (**Supplementary Table S4**). Our study found that patients undergoing CPAP therapy for OSA (CPAP compliance ≥ 4 h/day or CPAP compliance<4 h/day) fell short of statistical significance for the risk of stroke compared to patients with OSA without undergoing the CPAP therapy (**Supplementary Table S4**).

Discussion

This is the first study to explore the relationship between AO and stroke among Asian older OSA patients based on a multicentric, observational database. We found that AO was associated with both strokes at the baseline and risk of stroke at the median follow-up of 42 months. Moreover, with AO as a continuous or categorical variable, the association between AO and stroke in older patients varied with the OSA subtype.

The prevalence of AO among older patients with OSA in the present study was 12.4%, which is higher than the prevalence reported in other studies among selected different older general populations (Caspard et al., 2018; Seo et al., 2018; Zhang et al., 2019). Several studies uncovered a specific association between AO and stroke. In one study (Suk et al., 2003) that investigated the relationship between AO and stroke, the main result was that AO is an independent, potent risk factor for stroke among all race-ethnic community-dwelling adults in northern Manhattan, NY, United States. A prospective cohort study among 36,632 adults aged 18–90 was conducted using the China Chronic Disease Risk Factor Surveillance and showed that both normal weight or underweight with AO and overweight or obesity with AO adults had a higher incidence risk of stroke compared to those patients with normal weight, underweight, or obesity without AO during an average follow-up of more than 6 years (Cong et al., 2022). Another study among older participants (mean age 63.0 ± 8.4 years) conducted using the Reasons for Geographic and Racial Differences in Stroke (REGARDS) national cohort demonstrated a significant association between AO and the risk of atrial fibrillation (Kim et al., 2022). Atrial fibrillation is the main risk factor for stroke due to the associated hypercoagulability, leading to arterial embolism (Seiffge et al., 2019). Liu S. et al. (2020) used data from a population-based cohort study comprising more than 26,815 Chinese adults aged ≥ 35 years and found that higher levels of AO consistently predicted an increased risk of stroke during an 11.8-year follow-up.

In contrast, previous studies investigated the relationship directly between general adiposity and stroke but yielded conflicting results. Different methodological approaches, follow-up periods, baseline variables, and study samples might account for discrepancies across studies, as will be discussed later. Abete et al. (2015), based on the data from the 41,020 Spanish EPIC participants aged 26–69 years, confirmed that BMI, an indicator of general adiposity, was not associated with stroke incidence after adjusting for all potential confounders. Moreover, Bodenant et al. (2011) demonstrated that WC, an indicator of AO, is more strongly associated with stroke risk than BMI, which is in concordance with the results of Liu S. et al. (2020). They observed a continuous and positive association between adiposity (regardless of the general or abdominal adiposity) and stroke (Liu S. et al., 2020). However,

considering that AO is associated with an increased risk of stroke, whether AO has a stronger association with stroke among patients with OSA remains unclear, especially the elderly population. Our results may add another piece of evidence to partially support the importance of increasing levels of AO for patients with OSA. We selected the older patients with OSA with a median age in the mid-60s, which confirmed the link between AO and the risk of stroke and provides a better direction for preventive interventions.

Notably, regardless of the BMI categories, the association of AO with a high probability of the prevalence and incidence risk of stroke in older patients with OSA were moderately attenuated but remained after controlling for variables, such as age, sex, BMI, neck circumference, drinking status, smoking status, waist–hip ratio, WC, BMI, sleep parameters, and baseline self-reported chronic diseases at baseline. This indicates that the AO association to stroke does not largely change with the mixture of other factors at baseline in patients with OSA. Additionally, the results of this study confirm the prospective association between AO and stroke in patients with OSA. The subgroup analysis further found that the correlation of this risk was mainly reflected in patients with severe OSA, which suggests that the obesity paradox in older may serve as a certain protective effect on the cerebrovascular system for Chinese older patients with mild to moderate OSA during a prospective median follow-up of 42 months. Furthermore, older patients with OSA are known to have good tolerance to chronic intermittent hypoxia and maintenance of cerebral blood flow through brain ischemic preconditioning in the early stages (Sforza and Roche, 2016). The cross-sectional analysis revealed an association between AO and stroke, which was stronger among participants with moderate OSA only. One potential reason may be the moderate patients with OSA with higher age, which attenuates the self-renewal capacity of the body. Catalan-Serra et al. (2019) found a different association between the severity of OSA and stroke. The age did vary across different groups and the different severity of OSA among older patients concomitant with different chronic diseases at baseline will have different compensatory power to continuous intermittent hypoxia, which might explain the relative difference of AO exerted on the incidence of stroke in different OSA groups. Certainly, this is a significant issue that deserves further exploration and discussion in future works.

However, our study does not show that CPAP treatment has a differential influence on the association between AO and stroke outcome in older patients with OSA. This is likely due to the fact that most of the patients regularly treated with CPAP in this study were patients with mild to moderate OSA, who show modest tolerance to recurrent episodes of intermittent hypoxia during sleep, and also the obesity paradox phenomenon may play a moderate protective role in patients with mild to moderate OSA. This issue deserves further exploration in the future.

Although the exact mechanism remains unclear, there are several potential pathways through which AO can impact the stroke incidence rates of HRs and the prevalence rates of odds in older patients with OSA. First, WC was abnormally elevated and, as a measure that is an indicator of AO, is one of the major chronic complications of metabolic syndrome, as well as hyperglycemia and hypertension. Next, hyperglycemia has also been demonstrated to promote the formation of advanced glycation end products, which can stimulate atherogenic endothelial damage (Francisco et al., 2019; Kang et al., 2020). At the same time, previous studies confirmed that chronic intermittent hypoxia-induced adenosine-triphosphate depletion and lactate accumulation were found to promote atherosclerotic due to the thickening of blood vessel walls (Lee et al., 2017; Liu H. et al., 2020). These processes might be associated with the development of stroke. Second, excessive adipose tissue releases various bioactive and inflammatory mediators that affect the body's metabolism, immune, and thrombolytic pathways that are associated with stroke risk. Most of these factors are overproduced with obesity. Conversely, levels of adiponectin are downregulated during obesity (Tschritter et al., 2003; Lihn et al., 2005; Hajri et al., 2017; Głowinska-Olszewska et al., 2020; Skorepa et al., 2020). Wang et al.'s (2019) results showed that high adiponectin is associated with stroke severity and support the hypothesis that adiponectin can serve as a biomarker of poor outcome after stroke, independent of baseline variables. Thus, the decrease of adiponectin levels caused by AO and the recurrent hypoxia-reoxygenation in patients with OSA may activate oxidative stress, increase sympathetic excitability, and decrease adiponectin levels, both of which might increase the risk of stroke during the follow-up period (Giatti et al., 2021). Third, AO, rather than general obesity, is a major predisposing factor for patients with OSA, especially in the Chinese population (Zhao et al., 2019; Qin et al., 2021). Zhao et al. (2019) revealed a linear dose–response relationship between OSA and AO. In the longitudinal study, the change in WC was significantly correlated with ΔAHI^{12}.

The strengths of this study included its prospective design, the inclusion of subjects who received a gold standard for diagnosis of overnight PSG study, and potential confounding factors controlled by both performing cross-sectional analysis and longitudinal analysis to identify the association between AO and the risk of stroke among totally enrolled older patients with OSA as well as in different OSA groups. However, our study has several limitations that should be acknowledged. First, the main limitation of the present study is that the participant is racially and ethnically homogenous, which is a potential limiting factor to the generalization of our results. Second, the absence of analysis of patients' change dynamically in AO could not account for the longitudinal impact of AO on stroke in this study. Third, some patients did not report the onset of a new-

stroke with regard to a relatively short follow-up period of our study, with a median follow-up of just 42 months. Finally, stroke risk of older patients with OSA is mediated by a complex process and is associated with multiple factors that we did not measure (e.g., disease-specific fears); also, other factors that are potentially affected by AO were not evaluated. Accordingly, future studies taking these issues into account are required to validate and expand the current findings. However, we do not consider that these limitations negate the value of our study.

Conclusion

In this Chinese population-based multicenter study, we provide evidence in support that AO was associated with stroke both at baseline and during a prospective median follow-up of 42 months. Again, considering the specific OSA groups, the relation was varied because of the different categories of variables in AO. Our results showed that the "obesity paradox" cannot be regarded as a major concern in an older population with OSA. Additionally, stroke is associated with increased risks of all-cause mortality and other adverse outcomes; thus, special attention should be paid to the care of Chinese older OSA populations concomitant with AO, and early screening of AO should be scaled up to prevent and reduce the prevalence and incidence of stroke burden.

Data availability statement

The datasets presented in this article are not readily available for confidentiality reasons. Requests to access the datasets should be directed to the authors, without undue reservation.

Ethics statement

The Ethics Committee of Chinese PLA General Hospital (S2019-352-01) approved the study. Written informed consent was obtained from all participants.

Author contributions

YHG, YG, JG, JL, and YY collected and analyzed the data. XS, KL, and LY wrote and participated in all aspects of this research, including the field investigation. LL, JH, and KC designed this study. All authors have read and approved the submitted manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2022.957396/full#supplementary-material

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Benefits and risks of napping in older adults: A systematic review

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A growing body of evidence indicates that napping is common among older adults. However, a systematic review on the effect of napping on the elderly is lacking. The aim of this systematic review was to (i) determine how studies evaluated napping behavior in older adults (frequency, duration and timing); (ii) explore how napping impacts perceptual measures, cognitive and psychomotor performance, night-time sleep and physiological parameters in the elderly (PROSPERO CRD42022299805). A total of 738 records were screened by two researchers using the PICOS criteria. Fifteen studies met our inclusion criteria with a mean age ranging from 60.8 to 78.3 years and a cumulative sample size of $n = 326$. Daytime napping had an overall positive impact on subjective measures (i.e., sleepiness and fatigue), psychomotor performances (i.e., speed and accuracy) and learning abilities (i.e., declarative and motor learning). Additionally, studies showed (i) consistency between nap and control conditions regarding sleep duration, efficiency and latency, and proportion of sleep stages, and (ii) increase of 24 h sleep duration with nap compared to control condition. Based on the findings of the present review, there is minimal evidence to indicate that napping is detrimental for older adults' nighttime sleep. Future studies should consider involving repeated naps during a micro-cycle in order to investigate the chronic effect of napping on older adults.

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KEYWORDS

aging, sleep, napping, psychophysiological measures, cognitive and psychomotor performances, health

Introduction

Daytime napping among older adults has recently attracted the growing attention of researchers and scientists as a behavioral factor that impacts health and performance especially as diurnal napping is more prevalent and more frequent in older adults than in young and middle-aged adults (Furihata et al., 2016; Leng et al., 2016; Faraut et al., 2017; Li et al., 2017; Xiao and Hale, 2018; Yin et al., 2018; Kim et al., 2019; Yang et al., 2020). In this context, research showed that the prevalence of napping is age dependent. While only 9% of children over 5 years of age routinely take daytime naps (Komada et al., 2012). Faraut et al. (2017) reported that 40% of 14–19- year-old (yo) teenagers take daytime naps. For an older population (i.e., ≥20 yo), a Japanese study showed that only 11.7% in the young adult group (20–39 yo) reported taking daytime naps regularly (i.e., ≥4 days/week), 14.4% in the middle-age group (40–59 yo), and 25.8% in the older adult group (i.e., ≥60 yo) (Furihata et al., 2016). In Europe, a study revealed that 57.7% of the participants who reported daytime napping were older than 65 yo (Leng et al., 2016). Participants in this study were drawn from the European Prospective Investigation of Cancer-Norfolk (EPIC-Norfolk) cohort study including a total of 25,639 men and women aged 40–74 years. In addition, several studies revealed that daytime napping is flagrantly more common in middle-aged (50%) and older adults (55%) compared to other age groups among the Chinese population (Zhou et al., 2016; Li et al., 2017; Yin et al., 2018), probably due to a cultural belief, in this country, that napping promotes health (Yang et al., 2020). Similarly, a Korean-based population study reported that out of a sample of 5,427 people, 35.7 to 42.3% of its middle- to old-aged participants (40–69 years) take daytime naps (Kim et al., 2019). Furthermore, more than 300,000 middle-to-old-aged Americans were recruited in six US states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) as part of the National Institutes of Health-AARP Diet and Health Study (Xiao and Hale, 2018). The final analytic cohort included 97,890 women and 110,647 men and 40.3 to 52.6% of them reported regular daytime napping.

Importantly, sleep parameters change with aging (Ohayon et al., 2004). In adults, total sleep time and sleep efficiency decrease with age, while sleep latency and wake after sleep onset increase with age (Ohayon et al., 2004). Thus, the ability to maintain sleep decreases in older adults, which results in a shortened nocturnal sleep duration and an increased number and duration of awakenings during the night (Li et al., 2018b). In addition, the percentage of slow-wave sleep is negatively correlated with age (Ohayon et al., 2004). Therefore, sleep in older adults seems to be less consolidated due to a shortened duration of deep sleep compared to younger adults (Li et al., 2018b). These changes in sleep patterns make older adults more prone to taking naps during the daytime to compensate for the deficit of sleep during the night (Feinsilver and Hernandez, 2017). Napping in older adults is also related to other factors such as excessive daytime sleepiness, comorbidities, and medications (Zhang et al., 2020). All the evidence show that older adults with chronic health conditions (e.g., neurological disease, cardiovascular disease, cognitive impairment, insomnia, immobility, psychiatric disorders) are reported to have a higher prevalence of napping (Furihata et al., 2016; Li et al., 2018b; Liu et al., 2018; Spira et al., 2018). In this context, older adults take naps to counteract daytime sleepiness and fatigue from comorbidities. The prevalence of napping in older adults makes it of great interest to investigate the effect of napping among this population. Interestingly, studies investigating the effect of daytime napping on cognitive performance showed inconclusive results. Some studies reported an improvement of cognitive outcomes with afternoon naps (Keage et al., 2012; Li et al., 2017, 2018a). Nonetheless, other studies suggested that daytime napping may be associated with cognitive decline (Kimura et al., 2019; Leng et al., 2019).

The effect of daytime napping on performance among physically active people has been the topic of several recent studies (Botonis et al., 2021; Lastella et al., 2021; Souabni et al., 2021). Accordingly, a systematic review of the literature on the effect of daytime napping on cognitive and physical performance among older adults is warranted. The primary objectives of this paper are to (1) map out the aspects of the research, (2) outline how napping parameters can influence the potential effect on performance and health, and (3) identify gaps in the current literature.

Methods

Systematic review protocol

This systematic review was conducted and reported in accordance with the updated guidelines of the preferred reporting items for systematic reviews and meta-analysis statement (PRISMA), which is an evidence-based protocol describing a set of items for reporting in systematic reviews and meta-analysis (Page et al., 2021) (See Electronic Supplementary material 1 for PRISMA checklist). The study protocol was prospectively registered (PROSPERO ID: CRD42022299805).

Information sources and search strategy

A comprehensive systematic search of studies was performed electronically in four electronic scholarly databases, namely MEDLINE, Web of Science, SPORDiscus and PubMed, from inception to December 2021. Search strategies were developed in collaboration with an information specialist (KT). Searches identified papers focused on

TABLE 1 Terms used in this review.

Term	Definition
Time in bed (TIB)	The time elapsed between first getting into bed to the final arising.
Total sleep time (TST)	The total amount of time spent asleep whilst in bed.
Sleep efficiency (SE)	TST expressed as a percentage of TIB: TST/TIB x 100. Whether derived from instrumental measures or subjective estimates (of TST), SE provides a sensitive metric for estimating sleep quality.
Sleep inertia	A transient state between sleep to full awake during which performance is temporarily impaired. It disappears ∼1 h after waking.
Post-lunch dip	A phenomenon induced by circadian rhythms characterized by a dip in performance for some variables during mid-afternoon hours.
Excessive daytime sleepiness	Excessive daytime sleepiness was defined as the inability to stay alert and awake during the day accompanied by a feeling of sleepiness.

naps or napping in older-aged populations and contained keywords relating to cognitive and physical performance (See Electronic Supplementary material 2 for Database search strategies).

To identify additional studies not included in these search terms, the reference lists of the included manuscripts were checked, as well as the related citations from other articles *via* Google Scholar and the authors' personal files. Specialists in the field were also contacted for information about possible pending publications. Additionally, target journals (i.e., Sleep, Sleep Medicine, Nature and Science in Sleep, Journal of the American Geriatric Society, Sleep and Biological Rhythms, Journal of Sports Sciences, British Journal of Sports Medicine, Chronobiology International) were hand-searched for relevant accepted studies. Definitions of key terms used in this systematic review are provided in Table 1.

Eligibility criteria/selection criteria

Eligibility was set in accordance with the PICOS criteria [population: older adults (i.e., ≥55 years of age); intervention: acute and/or chronic daytime napping protocol; comparison: napping intervention vs. control and varied frequency and duration of napping interventions; outcomes: cognitive functions and/or physical performances and study design: randomized controlled trials (RCTs)].

Study selection

The process used for selecting articles is outlined in Figure 1. Following the removal of duplicates manually by MS, titles and abstracts of recovered records were reviewed independently by two authors (MS and MJS). Articles were marked "include," "exclude" or "uncertain" according to the prespecified eligibility criteria. Selected papers (i.e., "include" and "uncertain") were then independently read in full by two authors (MS and MJS) to finalize eligibility or exclusion. The reason for excluding an article during the full-text review was recorded (see Electronic Supplementary material 3 for excluded full-text articles). Discrepancies during title/abstract or full-text screening were resolved by a third author (TD) if there was no resolution after discussion between the two screening authors.

Data extraction

Using a standardized form, data were extracted independently by two reviewers (MS and MJS). Any discrepancies were identified and resolved through discussion or by involving a third reviewer (TD). The extracted data included publication details (authors surname, publication year, country), participants' characteristics (number of participants, age, sex, etc.), study design (duration, timing and frequency of daytime napping), napping measurement (actigraphy, polysomnography, self-report), and key outcomes.

Methodological quality and risk of bias

The quantitative assessment tool "QualSyst" (Kmet et al., 2004) was used to assess the risk of bias of each study. QualSyst contains 14 items (Table 2) that are scored depending on the degree to which specific criteria are met (yes = 2, partial = 1, no = 0). Items not applicable to a particular study design were marked as "NA". A summary score was calculated for each article by summing up the total score obtained across relevant items and dividing that by the total possible score. Quality assessments were performed by two authors (MR and MS) independently, and disagreements were solved by consensus or by the intervention of a third reviewer (OH) when necessary. Studies with a score of ≥75% were considered as of strong quality, those rated at 55–75% as of moderate quality, and a score <55% was judged as of weak quality. The percentage of lost points for each item was also calculated.

Results

Study selection

The predefined search strategies yielded a preliminary pool of 738 possible papers, 41 of which remained after duplicates had been excluded and titles and abstracts had been screened.

After a careful review of the 41 full texts, 30 papers were excluded (12 studies with the wrong population, seven in which no control group was included, six in which no physical and/or

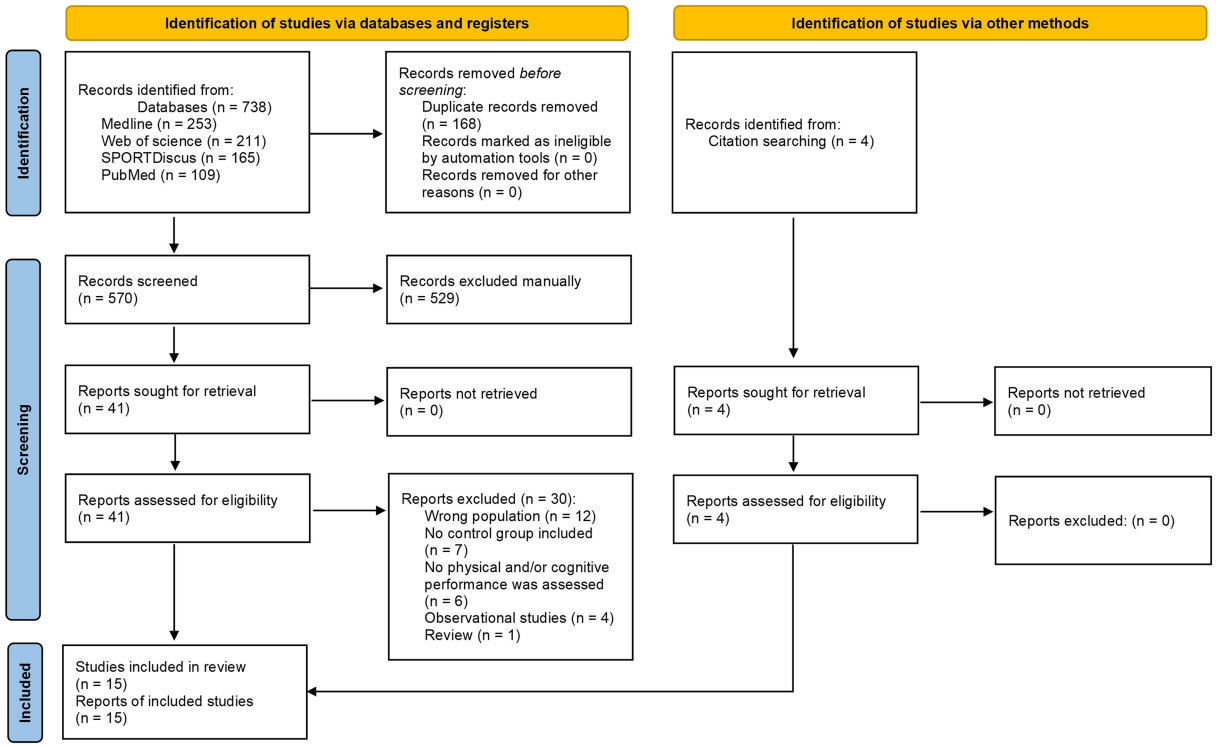

FIGURE 1
PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources.

cognitive performance was assessed, four observational studies and one review). Eleven articles were included, as well as four additional records identified through the screening of the references and related citations from other journals *via* Google Scholar lists of included articles.

In total, 15 studies met our inclusion criteria for determining the effects of napping on cognitive and/or physical performances in older adults.

Study characteristics

Studies characteristics are presented in Table 3. These studies were published between 1995 and 2021, arranged by order of publication date. Five studies were conducted in the USA (Creighton, 1995; Campbell et al., 2005; Baran et al., 2016; Scullin et al., 2017; Fitzroy et al., 2021), five in Canada (Monk et al., 2001; Milner and Cote, 2008; Fogel et al., 2014; King et al., 2017; Fang et al., 2021), two in Japan (Tamaki et al., 1999, 2000), two in Germany (Backhaus et al., 2016; Heim et al., 2017), and one in Israel (Korman et al., 2015). Included studies focused on the effects of napping on perceptual measures [i.e., subjective sleepiness (Creighton, 1995; Tamaki et al., 1999, 2000; Milner and Cote, 2008; Fogel et al., 2014; Backhaus et al., 2016; Fang et al., 2021; Fitzroy et al., 2021), subjective fatigue (Tamaki et al., 1999, 2000; Milner and Cote, 2008) and subjective alertness (Monk et al., 2001)], reaction time (Creighton, 1995; Tamaki et al., 1999; Monk et al., 2001; Milner and Cote, 2008; Backhaus et al., 2016), memory (Milner and Cote, 2008) and psychomotor performance (Monk et al., 2001; Campbell et al., 2005; Fogel et al., 2014), declarative (Backhaus et al., 2016; Baran et al., 2016; Heim et al., 2017) and motor (Fogel et al., 2014; Korman et al., 2015; Backhaus et al., 2016; King et al., 2017; Fang et al., 2021; Fitzroy et al., 2021) learning, nighttime sleep (Monk et al., 2001; Campbell et al., 2005; Korman et al., 2015; King et al., 2017) and physiological parameters (Tamaki et al., 1999; Monk et al., 2001).

Methodological quality and risk of bias

Quality scores for the included studies ranged from 39.2% (weak) to 92.8% (strong). Most studies ($n = 9$) were rated as strong quality, five were of moderate quality and one of weak quality. Causes of lost points included subjects blinded (93.3%), researchers blinded (80%) and random allocation (46.6%) (Table 2).

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TABLE 2 Quality assessment of the studies.

	Question described	Appropriate study design	Appropriate subject selection	Characteristics described	Random allocation	Researchers blinded	Subjects blinded	Outcome measures well defined and robust to bias	Sample size appropriate	Analytic methods well described	Estimate of variance reporter	Controlled for confounding	Results reported in detail	Conclusion supported by results?	Rating (%)	Study quality
Creighton (1995)	Yes	No	Partial	Partial	No	No	No	Yes	No	No	No	Partial	Yes	Yes	39.2	Weak
Tamaki et al. (1999)	Yes	Yes	Yes	Partial	No	No	No	Yes	No	Yes	Partial	Partial	Yes	Yes	60.7	Moderate
Tamaki et al. (2000)	Yes	Yes	Yes	Partial	No	No	No	Yes	No	Yes	Partial	Partial	Yes	Yes	60.7	Moderate
Monk et al. (2001)	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	Yes	Partial	Yes	Yes	Yes	75	Strong
Campbell et al. (2005)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Partial	Partial	Yes	Yes	92.8	Strong
Milner and Cote (2008)	Yes	Yes	Yes	Yes	No	No	No	Yes	No	Yes	Yes	Yes	Yes	Yes	71.4	Moderate
Fogel et al. (2014)	Yes	Yes	Yes	Yes	Partial	No	No	Yes	Yes	Yes	Partial	Yes	Yes	Yes	78.5	Strong
Korman et al. (2015)	Yes	Yes	Yes	Yes	Partial	No	No	Yes	Yes	Partial	Partial	Yes	Partial	Yes	71.4	Moderate
Backhaus et al. (2016)	Yes	Yes	Yes	Partial	Yes	Yes	No	Yes	Yes	Yes	Partial	Yes	Yes	Yes	85.7	Strong
Baran et al. (2016)	Yes	Partial	Yes	Yes	Yes	No	No	Yes	Partial	Yes	Partial	Yes	Yes	Yes	75	Strong
King et al. (2017)	Yes	Yes	Yes	Yes	Partial	No	No	Yes	Yes	Yes	Partial	Partial	Yes	Yes	75	Strong
Heim et al. (2017)	Yes	Partial	Yes	Yes	Yes	No	No	Yes	Partial	Partial	Partial	Partial	Yes	Yes	67.8	Moderate
Scullin et al. (2017)	Yes	Yes	Yes	Yes	Partial	Yes	No	Yes	Yes	Yes	Partial	Yes	Yes	Yes	85.7	Strong
Fang et al. (2021)	Yes	Yes	Yes	Yes	Partial	No	No	Yes	Yes	Yes	Partial	Yes	Yes	Yes	78.5	Strong
Fitzroy et al. (2021)	Yes	Yes	Yes	Yes	Partial	No	No	Yes	Yes	Yes	Partial	Yes	Yes	Yes	78.5	Strong
% of lost points (%)	0	13.3	3.3	13.3	46.6	80	93.3	0	40	13.3	50	20	3.3	0	-	-

TABLE 3 Studies characteristics (population, study design and napping parameters).

Author, year, country	Participants	Experimental design	Nap(s) duration, timing, frequency, assessment method
Creighton (1995) USA	6 (>75 y) (1 M, 5 F) m = NM	Single-subject methodology was used to study the responses of each subject individually. An ABA (reversal) design was applied.	90 min 13:00 h 5 days NM
Tamaki et al. (1999) Japan	6 (66–78 y) m = NM	Subjects participated in both conditions with an interval of 1 week.	30 min 13:00 h 1 day EEG
Tamaki et al. (2000) Japan	10 (66–78 y) m = NM	Ten healthy elderly persons who habitually napped in the afternoon three or more times a week participated in the present study.	30 min 13:00 h 1 day EEG
Monk et al. (2001) Canada	9 (74–87 y) (4 M, 5 F) m = 78.3 y	Order of the two conditions was counterbalanced: 4 subjects experienced nap condition followed by the no-nap condition, 5 the reverse order.	90 min 13:30 h 17 days—14 D Actigraphy (Home)—3 D PSG (Lab)
Campbell et al. (2005) USA	32 (55–85 y) (16 M, 16 F) m = 68.5 y SD = 8.1 y	Two-session, within-subject laboratory design. Order determined by the flip of a coin before the first laboratory visit.	120 min 14:00 h 1 day EEG
Milner and Cote (2008) Canada	12 (56–70 y) (7 M, 5 F) m = 61 y SD = 5 y	Conditions were counterbalanced across participants.	60 / 20 min Timing of naps varied across individuals according to their individual sleep times. 1 day EEG
Fogel et al. (2014) Canada	30 (55–75 y) (10 M, 20 F) m = 62.6 y SD = 5.0 y	15 NAP 15 CON	90 min 13:00 h 1 day PSG
Korman et al. (2015) Israel	21 (60–75 y) (11 M, 10 F) m = 64.8 y SD = 4.3 y	11 NAP 10 CON	90 min NM 1 day PSG
Backhaus et al. (2016) Germany	33 (60–82 y) Sequence learning ($n = 33$) -wake 11 F/M (9/2) m(SD) 73.7(4.5) -short nap: 12 F/M (7/5) m(SD) 69.9(6.1) -long nap: 10 F/M (5/5) m(SD) 71.3(6.0) Motor adaptation ($n = 30$) -wake: 10 F/M (9/1) m(SD) 74.2(4.5) -short nap: 10 F/M (5/5) m(SD) 69.3(6.7) -long nap: 10 F/M (6/4) m(SD) 71.1(5.5)		45/90 min NM 1 day PSG
Baran et al. (2016) USA	13 (60–75 y) (3 M, 10 F) m = 67 y SD = 3.4 y	Conditions were counterbalanced across participants.	120 min NM 1 day PSG

(Continued)

TABLE 3 (Continued)

Author, year, country	Participants	Experimental design	Nap(s) duration, timing, frequency, assessment method
King et al. (2017)	31 (≥55 y) -nap: 15 F/M (13/2) m(SD) 69.9(1.2)		90 min
Canada	-rest: 16 F/M (13/3) m(SD) 63.5(1.4)		13:00 h
			1 day
			PSG
Heim et al. (2017)	30 (50–75 y)		90 min
Germany	-nap: 10		NM
	F/M (6/4) m(SD) 62.6(1.8)		1 day
	-rest: 10		NM
	F/M (7/3) m(SD) 59.9(1.6)		
	-interfering activity: 10		
	F/M (5/5) m(SD) 60.0(1.5)		
Scullin et al. (2017)	45 (58–83 y)		90 min
USA	-nap: 29		14:00 h
	F/M (15/14) m(SD) 69.69(7.1)		1 day
	-rest: 16		PSG
	F/M (10/6) m(SD) 70.13(7.8)		
	Participants were randomly assigned to either the nap or quiet wakefulness conditions, in a 3:2 ratio. The intent of this approach was to increase statistical power for PSG correlational analyses if a significant effect of nap/wake condition was observed.		
Fang et al. (2021)	30 (55–75 y) (9 M, 21 F) m = 62.6 y SD = 5.0 y	15 NAP 15 CON	90 min 13:00 h 1 day PSG
Canada			
Fitzroy et al. (2021)	18 (58–75 y) (10 M, 8 F) m = 65.39 y SD = 5.80 y	Conditions were counterbalanced across participants.	120 min 13:00 h 1 day HD-PSG *High-density polysomnography*
USA			

M, male; F, female; m, mean; NM, not mentioned.

Subjects' characteristics

The studies involved in this systematic review included a total of 326 participants. Except for two studies (Tamaki et al., 1999, 2000) in which gender was not mentioned ($n = 16$), studies included 120 males and 190 females. The number of participants in each trial ranged from 6 (Creighton, 1995; Tamaki et al., 1999) to 45 (Scullin et al., 2017), with a mean sample size of 21.73 (SD 12.08). Mean age ranging from 60.8 (Heim et al., 2017) to 78.3 (Monk et al., 2001) years.

Effect of napping on perceptual measures

Subjective sleepiness

Eight (53.33%) studies (Creighton, 1995; Tamaki et al., 1999, 2000; Milner and Cote, 2008; Fogel et al., 2014; Backhaus et al., 2016; Fang et al., 2021; Fitzroy et al., 2021) have focused on the effects of napping on subjective sleepiness with inconclusive results (Table 4). Four studies showed that sleepiness was not affected by napping opportunities [i.e., 45 (Backhaus et al., 2016), 90 (Fogel et al., 2014; Backhaus et al., 2016; Fang et al., 2021) and 120 min (Fitzroy et al., 2021)]. Otherwise, it has been reported that a 30-min nap opportunity (NAPO) decreased sleepiness compared to the control condition (Tamaki et al., 1999, 2000). Interestingly, Milner and Cote (2008) reported that a 60-min NAPO decreased sleepiness but not a 20-min NAPO. Moreover, Creighton (1995) showed contradictory outcomes between subjects. Out of the six participants, four felt drowsier, with sleepiness scores rising during nap week compared to control week. Nonetheless, a fifth participant displayed the opposite response (Creighton, 1995).

Subjective fatigue

Three (20%) studies (Tamaki et al., 1999, 2000; Milner and Cote, 2008) investigated the effect of napping on subjective fatigue. Results showed that daytime naps had a positive impact

TABLE 4 The effects of napping on perceptual measures.

Measured parameter	Author, year	Nap(s) duration	Nap(s) timing	Nap(s) frequency	Effects of napping
Subjective sleepiness	Creighton (1995)	90 min	13:00 h	5 days	4 ↑
					1 ↓
	Tamaki et al. (1999)	30 min	13:00 h	1 day	↓
	Tamaki et al. (2000)	30 min	13:00 h	1 day	↓
	Milner and Cote (2008)	20 min	See Table 2	1 day	↔
		60 min			↓
	Fogel et al. (2014)	90 min	13:00 h	1 day	↔
	Backhaus et al. (2016)	Short nap 45 min	NM	1 day	↔
		Long nap 90 min			
	Fang et al. (2021)	90 min	13:00 h	1 day	↔
	Fitzroy et al. (2021)	120 min	13:00 h	1 day	↔
Subjective fatigue	Tamaki et al. (1999)	30 min	13:00 h	1 day	↓
	Tamaki et al. (2000)	30 min	13:00 h	1 day	↓
	Milner and Cote (2008)	20 min	See Table 2	1 day	↓
		60 min			↓
Subjective alertness	Monk et al. (2001)	90 min	13:30 h	7 days	↔
				(home)	
				2 days	↔
				(lab)	

NM, not mentioned.

on subjective fatigue. Milner and Cote (2008) reported that participants rated themselves as less fatigued following both a 60- and a 20-min NAPO. Similarly, two studies (Tamaki et al., 1999, 2000) revealed that a 30-min NAPO reduced significantly subjective fatigue.

Subjective alertness and wellbeing

The effect of a 90-min NAPO on alertness and wellbeing was investigated during 17 days (14 days at home and 3 days in the laboratory) (Monk et al., 2001). Nine visual analog scales—yielding scores of global vigor (alertness) and global affect (wellbeing)—were presented to participants four times per day. Results showed a consistency between nap and control conditions in self-rated evening alertness at home (66 vs. 65, $P > 0.25$) which was also evident (71 vs. 70, $P > 0.25$) in the laboratory data.

Effect of napping on cognitive and psychomotor performance

Studies focused on the effect of napping on reaction time (Creighton, 1995; Tamaki et al., 1999; Monk et al., 2001; Milner and Cote, 2008; Backhaus et al., 2016), memory (Milner and Cote, 2008) and psychomotor (Monk et al., 2001; Campbell et al., 2005; Fogel et al., 2014) performance with inconclusive results (Table 5). The effect of a 30-min NAPO on reaction time was investigated using a visual detection task (Tamaki et al., 1999). Results showed that reaction time was shorter in nap conditions than in rest conditions, and that the percentage of correct responses increased after taking a nap, but decreased after taking a rest (Tamaki et al., 1999). Importantly, Campbell et al. (2005) showed that a 120-min NAPO was associated with several significant improvements in cognitive and psychomotor performance using a Walter Reed Performance Assessment Battery. This consists of four tasks: the two-letter visual search task, the Wilkinson four-choice reaction time task, the logical reasoning task and the Stroop congruency task. Output measurements from the performance tasks included accuracy, speed and a summary measure [i.e., throughput = (accuracy x speed)/100]. Overall better performance was observed for the same day (average of 5 p.m. and 7 p.m. trials) results after NAPO. A significant improvement of throughput for Wilkinson four-choice reaction time and Stroop task ($P < 0.05$, $\Delta = 15.5\%$; $P < 0.05$, $\Delta = 9.4\%$, respectively) and speed during Stroop task ($P < 0.03$, $\Delta = 9.2\%$) was reported in the nap condition compared to control condition. Further, the improvement in throughput on the reaction time task was positively correlated with amounts of Stage 4 sleep ($P < 0.03$, $r = 0.41$) and Stages 3 and 4 combined ($P < 0.05$, $r = 0.36$) obtained during the nap. Regarding the Stroop task, enhanced throughput and speed were positively

associated with sleep period time of naps ($P < 0.05$; $r = 0.39$ and 0.40, respectively). Furthermore, next day performance (average of 6 trials from 9 a.m. to 7 p.m.) was measured on the same study (Campbell et al., 2005) and results showed the same improvement for the Stroop task's speed ($P < 0.02$, $\Delta = 6.5\%$) and throughput ($P < 0.02$, $\Delta = 6.6\%$) compared to control condition. In addition, a significantly better performance was reported for the logical reasoning task (i.e., accuracy, $P < 0.03$, $\Delta = 2.5\%$) and the two-letter search task (i.e., throughput, $P < 0.03$, $\Delta = 4.7\%$). Moreover, improvements in speed and throughput on the Stroop were significantly correlated with longer sleep times ($r = 0.44$ and 0.42, respectively; $P < 0.02$). The increased accuracy on the logical reasoning task was positively correlated with nap duration ($r = 0.42$; $P < 0.05$), sleep efficiency ($r = 0.40$; $P < 0.05$), and Stage 2 amounts ($r = 0.56$; $P < 0.01$). It is noteworthy that sex did not affect the outcome of performance measures.

Interestingly, a beneficial effect of naps (90-min NAPO) was observed on objective alertness during a multiple sleep latency test (Monk et al., 2001). Mean sleep latency increased significantly from 11.5 to 15.6 min ($P < 0.01$) indicating a reduction in objective evening sleepiness in the nap condition. However, another study (Fogel et al., 2014) did not report any significant effect on objective sleepiness measured using a psychomotor vigilance task for the same NAPO (90 min). Moreover, a symbol digit modalities test (i.e., a neuropsychological test that measures the ability to concentrate on a cognitive task) was performed following the same NAPO (90 min) and results were inconclusive (Creighton, 1995). Two of the six subjects demonstrated better performance during the nap phase of the study compared to the control phase. In the same study (Creighton, 1995), the nap did not appear to affect performance during the eye-hand reaction time test in which participants were asked to respond as quickly as possible to a flashing red light by pushing a button. Further studies investigated the effect of napping on reaction time using various NAPO [i.e., 20 (Milner and Cote, 2008), 45 (Backhaus et al., 2016), 60 (Milner and Cote, 2008), 90 min (Monk et al., 2001; Backhaus et al., 2016)] but results did not reveal any significant effect of napping on performance.

Only one study (Milner and Cote, 2008) investigated the effect of daytime napping on memory. Milner and Cote (2008) used a 2-back memory test to investigate the effect of a 20- and 60- min NAPO on working memory. Participants were asked to identify target letters (i.e., when the displayed letter matches one seen two letters previously: "a," "R," "a") during three blocks of 60 randomly presented letters on a screen. No significant difference was reported in performance between the nap and control conditions. Therefore, from this perspective, memory performances seem to not be affected by napping of both durations (i.e., 20 and 60 min) in older adults.

Effect of napping on learning

Nine (60%) studies (Fogel et al., 2014; Korman et al., 2015; Backhaus et al., 2016; Baran et al., 2016; Heim et al., 2017; King et al., 2017; Scullin et al., 2017; Fang et al., 2021; Fitzroy et al., 2021) investigated the effect of daytime napping on declarative (Backhaus et al., 2016; Baran et al., 2016; Heim et al., 2017) and motor (Fogel et al., 2014; Korman et al., 2015; Backhaus et al., 2016; King et al., 2017; Fang et al., 2021; Fitzroy et al., 2021) learning capacities in older adults (Table 6). Overall, the selected studies used a range of designs and methodological approaches. It should be noted that Backhaus et al. (2016) examined both declarative and motor learning.

Declarative learning

Four studies (Backhaus et al., 2016; Baran et al., 2016; Heim et al., 2017; Scullin et al., 2017) examined the effect of napping on declarative learning with inconclusive results. Only one of the four studies demonstrated a positive impact of napping on language learning using a pseudo-word learning task (Heim et al., 2017). The task consisted of memorizing monsters' names (a 1- to 3-syllabic pseudo-word in German) that are presented visually (for 10 s each) on the screen and aurally (twice) *via* loudspeakers. Performance was re-tested twice: the first re-test took place on the same day after rest or a nap while the second re-test took place 24 h afterwards. Statistical results revealed a significant increase in language learning scores from test to re-test 1 ($P = 0.01$, $\Delta = +18.1\%$) and re-test 2 ($P = 0.01$, $\Delta = +20.3\%$) following a 90-min NAPO. However, in rest conditions, language learning scores decreased significantly between the test and re-test 1 ($P = 0.003$, $\Delta = -66.3\%$). Baran et al. (2016) used the word pair learning task on a computer (programmed using E-Prime) following a 120-min NAPO to investigate the effect of napping on declarative learning. Stimuli consisted of single-syllable, concrete nouns that were paired to create two lists of 40 semantically unrelated cue-target word pairs (e.g., bath–grass, rail–bag) (Baran et al., 2016). In another study, declarative learning was assessed using two measures (i.e., free recall and recognition tests) (Scullin et al., 2017). For the free recall test, participants were given 5 min to write down all the words they studied. Next, they completed a recognition test on the computer in which they viewed the 100 "old" studied words and 100 "new" lure words. Participants were instructed to indicate which words were old words (i.e., studied words) and which were new words (i.e., non-studied words). On the other hand, a different approach was reported for Backhaus et al. (2016) using only an auditory presentation of 15 words. There, retained knowledge of the list of words was tested twice (i.e., same and next day) (Backhaus et al., 2016). In the last three studies (Backhaus et al., 2016; Baran et al., 2016; Scullin et al., 2017), participants were not found to learn differently as a function of the prescribed sleep condition (i.e., nap or rest).

TABLE 5 The effects of napping on cognitive and psychomotor performances.

Author, year	Measured performances	Nap(s) duration	Nap(s) timing	Nap(s) frequency	Effects of napping
Creighton (1995)	Eye-hand reaction time	90 min	13:00 h	5 days	↔
	Symbol Digit Modalities Test (Subjects are asked to decode a line of symbols according to a key at the top of the worksheet)				2 ↑ 4 ↔
Tamaki et al. (1999)	Reaction time. visual detection task;	30 min	13:00 h	1 day	↑
	Percentage of correct responses. Visual detection task				↑
Monk et al. (2001)	Multiple Sleep Latency Test. As a measure of objective evening sleeping	90 min	13:30 h	2 days (lab)	↑ mean sleep latency (from 11.5 to 15.6 min) → reduced objective evening sleepiness in the nap condition.
	Visual vigilance hits				↔
	Pegboard latency				↔
	Four-choice serial response				↔
	Commission errors made in the response inhibition task				↔
Campbell et al. (2005)	Walter Reed Performance Assessment Battery. -The two-letter visual search task, -The Wilkinson four-choice reaction time task, -The logical reasoning task, -The Stroop congruency task. Output measures from the performance tasks included accuracy, speed and throughput [(accuracy x speed)/100].	120 min	14:00 h	1 day	Session 1 same day (average of 5 p.m. and 7 p.m.) ↑ 15.5% Throughput The Wilkinson four-choice reaction time task. ↑ 9.2% Speed ↑ 9.4% Throughput The Stroop congruency task. Session 2 next day (average of 6 trials from 9 a.m. to 7 p.m.) ↑ 4.7% Throughput The two-letter visual search task, ↑ 2.5% Accuracy The logical reasoning task, ↑ 6.5% Speed ↑ 6.6% Throughput The Stroop congruency task.
Milner and Cote (2008)	Accuracy on simple reaction test	20 min	See Table 2	1 day	↔
	Reaction time on simple reaction test				↔
	Serial addition/subtraction task	60 min			↔
	Working memory				↔
Fogel et al. (2014)	Psychomotor Vigilance Task	90 min	13:00 h	1 day	↔
Backhaus et al. (2016)	Simple reaction time	45 min 90 min	NM	1 day	↔

NM, not mentioned; ↑, better performance compared to control condition; ↔, no significant difference between nap and control condition.

Motor learning

Studies investigating the effect of NAPO on motor learning performance showed inconclusive results (Fogel et al., 2014; Korman et al., 2015; Backhaus et al., 2016; King et al., 2017; Fang et al., 2021; Fitzroy et al., 2021). All the studies used a finger tapping task to assess motor/procedural learning performance with some methodological differences. Additionally, it is important to mention that Fogel et al. (2014) and Fang et al. (2021) are both part of the same large study and presented the same results concerning learning performances.

The positive impact of napping was evident in three of the five studies examining the effects of napping on motor learning performances. In Korman et al. (2015)'s study, participants were trained to generate a given five-element finger-to-thumb opposition sequence (4-1-3-2-4) with their non-dominant left hand. The same protocol was used previously to investigate the

TABLE 6 The effects of napping on learning.

Type of learning	Author, year	Measured performances	Nap(s) duration	Nap(s) timing	Nap(s) frequency	Effects
Declarative learning	Baran et al. (2016)	Word pair learning task. Stimuli consisted of single-syllable, concrete nouns that were paired to create two lists of 40 semantically unrelated cue-target word pairs (e.g., bath–grass).	120 min	See Table 2	1 days	↔
	Backhaus et al. (2016)	An auditory presentation of 15 words. Retained knowledge of the list of words was tested.	45 min 90 min	NM	1 day	↔
	Heim et al. (2017)	Pseudo-word learning task. The task consisted of memorizing monsters' names (a 1- to 3-syllabic pseudo-word in German) while presented visually (for 10 sec each) on the screen and aurally (twice) *via* loudspeakers.	90 min	NM	1 day	↑ 18.1% in re-test 1 vs. test ↑ 20.3% in re-test 2 vs. test
	Scullin et al. (2017)	Declarative learning was assessed using two measures: free recall test (participants were given 5 min to write down all the words they studied) and Recognition test (participants viewed the 100 "old" studied words and 100 "new" lure words).	90 min	14:00 h	1 day	↔
Motor learning	Fogel et al. (2014)	Finger-tapping task. Participants were instructed to perform a five-item sequence (4-1-3-2-4).	90 min	13:00 h	1 day	↔
	Korman et al. (2015)	Finger-tapping task. Participants were trained to generate a given five-element finger-to-thumb opposition sequence (4-1-3-2-4) with their non-dominant left hand.	90 min	13:00 h	1 day	↔ ↑ same day (8-h later) ↑ next day (22-h later)
	Backhaus et al. (2016)	Finger-tapping task. Participants were trained to generate a nine-element sequence using the four fingers of the left hand on a lap top keyboard with covers.	45 min 90 min	NM	1 day	↔
	King et al. (2017)	Finger tapping task. during a test-retest protocol initial learning phase at the pre-nap session, at 11:00 h, and retests were administered 8 and 22 h later.	90 min	13:00 h	1 day	↔ ↑ same day (8-h later) ↑ next day (22-h later)
	Fitzroy et al. (2021)	Serial reaction time task. participants were informed that cues would be sequential during the indicated blocks and instructed to notice and learn any patterns they could.	120 min	13:00 h	1 day	↔ ↑ same day (5-h later)

NM, not mentioned.

effect of daytime napping on motor sequence learning (MSL) in younger adults (Korman et al., 2007). Performance was tested four times; a pre-nap test (learning session) and 3 re-tests (0, 8, and 22 h post-training). The affordance of a 90-min NAPO immediately after training resulted in robust overall gains in speed ($F_{3,30} = 21.1$, $P < 0.001$), within-session ($F_{1,10} = 22.9$, $P = 0.001$) and overnight ($F_{1,10} = 7.97$, $P = 0.018$). There was also no deterioration of performance at 8 h post-training ($F_{1,10} = 0.8$, $P = 0.389$). Nonetheless, for the control condition, an overall improvement in speed performance ($F_{3,27} = 34.35$, $P < 0.001$) was reported, but there was no significant gain in speed overnight and the 8 h post-training performance speed tended to decline from that attained by the end of the training session (0 h, 8 h post-training, $F_{1,9} = 5.39$, $P = 0.072$). Similarly, King et al. (2017) used a finger tapping task during a test-retest protocol (initial learning phase at the pre-nap session, at 11:00 h, and re-tests were administered 8 and 22 h later) to assess the effect of a 90-min NAPO on MSL performance. Importantly, although performance did not differ between control and nap groups during the initial learning phase, a beneficial effect of napping was reported across same and next day re-tests. This beneficial effect was consistent across the two follow-up sessions, and thus the positive impact of the daytime nap lasted for at least 22 h in older adults. In the same way, motor learning was compared prior to the nap and wake intervals in Fitzroy et al. (2021) study using a different task. During a serial reaction time

task, participants were informed that cues would be sequential during the indicated blocks and instructed to notice and learn any patterns they could. Results showed that across-interval performance improvement in older adults was significant for the nap condition but not for the wake condition.

On the other hand, Fogel et al. (2014) and Fang et al. (2021) reported that MSL was not affected by napping (i.e., 90-min NAPO). Results of the study suggest that both nap and control groups had a similar performance during the initial learning phase of the motor skill (at 11:00 h) and re-test session (at 16:00 h). Indeed, performance improved from the training to the re-test session irrespective of the sleep/wake condition. Similarly, Backhaus et al. (2016) reported that both, 45- and 90-min NAPO, did not affect MSL performance.

Effect of napping on nocturnal sleep

Four (26.66%) studies (Monk et al., 2001; Campbell et al., 2005; Korman et al., 2015; King et al., 2017) have focused on the effect of napping on subsequent nighttime sleep (Table 7). The general pattern of results indicates that napping did not negatively impact nocturnal sleep. Three studies (Campbell et al., 2005; Korman et al., 2015; King et al., 2017) compared sleep on the night immediately after a nap with sleep immediately after the control condition. Campbell et al. (2005) revealed that there was no significant difference between both conditions (120-min NAPO/rest) in total sleep time (TST), sleep efficiency (SE) and the minutes or proportion of any sleep stage. However, sleep onset latency (SOL) in the nap condition compared to the control condition was longer: on average, participants took 6.3 min longer to fall asleep. Moreover, when the 24-h period containing the nap was compared with the 24-h control condition, participants averaged more than an hour more in TST (7.4 h vs. 6.2 h). Accordingly, the amount and proportion of stage 1, stage 2 and rapid eye movement sleep (REM) increased significantly when a nap was taken. In the same way, Korman et al. (2015) and King et al. (2017) reported that a 90-min NAPO did not affect the subsequent nighttime sleep; the two experimental groups did not differ in TST, SE, SOL. Additionally, King et al. (2017) reported that there was no difference between conditions in amount and proportion of stage 1, stage 2, REM and slow-wave sleep (SWS). The 24-h TST in the nap condition was not compared with the rest condition for both studies.

Further, Monk et al. (2001) examined the effect of a 90-min NAPO on night-time sleep during 17 days (14 days at home and 3 days in the laboratory). Wrist actigraphy (average of the second week of home study) showed that there was no significant difference between conditions in TST, TIB, SE, sleep quality, bedtime, waketime and wake after sleep onset (WASO). Interestingly, 24 h TST was higher in nap compared

TABLE 7 The effects of napping on nighttime sleep.

Author, year	Nap(s) duration	Nap(s) timing	Nap(s) frequency	Effects of napping
Monk et al. (2001)	90 min	13:30 h	7 days (home)	↔ TST ↔ TIB ↔ SE ↔ SOL ↔ Sleep quality ↔ bedtime ↔ waketime ↔ WASO ↑ 24-h TST
			2 days (lab)	↓ TST ↓ TIB ↓ SE ↔ SOL ↔ bedtime ↓ waketime ↔ WASO ↔ REM
Campbell et al. (2005)	120 min	14:00 h	1 day	↔ TST ↔ SE ↑ SOL ↑ 24-h TST ↔ Minutes/% Stage 1 ↔ Minutes/% Stage 2 ↔ Minutes/% Stage 3 and 4 ↔ Minutes/% REM
Korman et al. (2015)	90 min	13:00 h	1 day	↔ TST ↔ SE ↔ SOL
King et al. (2017)	90 min	13:00 h	1 day	↔ TST ↔ SE ↔ SOL ↔ minutes/% Stage 1 ↔ minutes/% Stage 2 ↔ minutes/% SWS ↔ minutes/% REM

NM, not mentioned; REM, rapid eye movement; SE, sleep efficiency; SOL, sleep onset latency; SWS, slow wave sleep; TIB, time in bed; TST, total sleep time; WASO, wake after sleep onset.

to the control condition (7.3 vs. 6.6 h, respectively). However, the average of nights 2 and 3 in the laboratory (measured *via* polysomnography) revealed a significant decrease in the nap condition compared to the control condition for TST (5.3 vs. 6.1 h, respectively), TIB (7.1 vs. 7.9 h, respectively), SE and waketime. Moreover, no significant difference was reported for WASO, SOL, REM sleep and bedtime.

Effect of napping on physiological parameters

Only two (13.3%) studies examined the effect of daytime napping on physiological parameters. Blood pressure was recorded before and after nap and control condition (Tamaki et al., 1999). Results showed that diastolic blood pressure decreased following NAPO compared to rest. Further, core body temperature was measured continuously in Monk et al. (2001)'s study to analyze the effect of a 90-min NAPO on circadian variations across 24 h. A slight dip in the temperature was reported between 13:30 and 15:00 h due to the nap; however, there was no difference in circadian phases of temperature between the nap and control groups.

Discussion

This systematic review is the first to explore (1) how daytime naps could impact perceptual measures (e.g., sleepiness, fatigue and alertness), cognitive and psychomotor performance, declarative and motor learning, and nighttime sleep in older adults and, (2) how napping parameters (frequency, duration, timing and measurement) could potentially influence the effect of napping. This information is important for older adults and geriatric specialists who provide advice and education to the elderly regarding napping for health improvement.

Why, when and how much older adults nap?

Studies reported a high prevalence of daytime napping in older adults as a result of several factors: health conditions, medications, excessive daytime sleepiness, boredom, lack of physical activity and changes in sleep patterns implying lower night-time sleep quantity and quality. Further, it is well known that diurnal sleepiness induced by circadian rhythms occurs in the afternoon (Mitler et al., 1988; Broughton and Mullington, 1992; Monk, 2005; Waterhouse et al., 2007). This phenomenon is called post-lunch dip and is characterized by a dip in performance for some variables during mid-afternoon hours (Monk, 2005), especially for people who have been partially deprived of sleep (Romdhani et al., 2019). In this context, several studies proposed mid-afternoon as the best time to onset nap (Waterhouse et al., 2007; Romdhani et al., 2021; Souabni et al., 2021). In the same way, all the studies included in the present systematic review initiated the NAPO in the mid-afternoon between 13:00 and 14:00 h. Regarding the nap duration, most studies employed 90 min as a duration for NAPO. This duration was present in 9 (60%) out of the 15 studies included in this systematic review. Three studies (Campbell et al., 2005; Baran et al., 2016; Fitzroy et al., 2021) reported a duration of 120 min for NAPOs and the remaining studies ($n = 3$) reported NAPOs with lower durations [i.e., 20 (Milner and Cote, 2008), 30 (Tamaki et al., 1999, 2000) and 60 min (Milner and Cote, 2008)]. In addition, in a recent systematic review by our team, we suggested 90 min as an optimal NAPO for athletes undergoing chronic sleep deprivation (Souabni et al., 2021). The reason was twofold: for one, it is postulated that rapid eye movement (REM) sleep has a vital role in restorative benefits for cognition (Belenky et al., 2003; Hobson, 2005) and is also associated with memory consolidation and learning of motor skills (Davenne, 2009; Venter, 2012), while non-rapid eye movement (NREM) sleep is when the body actively repairs and restores itself (Davenne, 2009; Venter, 2012). Further, slow wave sleep (SWS)—also known as deep NREM sleep—is thought to play an important role in cerebral restoration and recovery (Dijk, 2009; Wisor et al., 2013). Moreover, a 90-min nap duration allows—in theory—a complete sleep cycle (NREM + REM) to occur (Davies et al., 2010) and consequently could reduce the severity of sleep inertia, since REM sleep is a lighter sleep state and waking up from this sleep stage is easier (Ferrara and De Gennaro, 2000). This could be a possible explanation for the choice of this duration for older adults.

Was performance improved by daytime napping?

Regarding perceptual measures, a positive effect of napping was reported for sleepiness and fatigue. Only Creighton (1995) reported a negative impact of napping on sleepiness. Out of six participants, four felt an increase in sleepiness following a nap and one felt the opposite effect. Further, Monk et al. (2001) revealed that alertness and vigor were not affected by naps. It is important to mention that both studies investigated the chronic effect of naps with participants adopting a napping regimen involving a 90-min NAPO each day (Creighton, 1995; Monk et al., 2001). Thus, the results were taken on an average of 5 (Creighton, 1995) and 7 (Monk et al., 2001) days. As for the study of Creighton (1995), inconsistency in providing the scheduled naps was presented as a possible explanation to the contradictory results.

Interestingly, a positive impact of napping was reported on cognitive and psychomotor performance on the same (Tamaki et al., 1999; Campbell et al., 2005) and the following day (Campbell et al., 2005). There is no evidence to indicate that napping is detrimental to older adults' cognitive and

psychomotor performance. Again, there was great variability in the effect of repeated naps during a micro-cycle. Two of the six subjects demonstrated better performance in attention during the nap phase of the study compared to the control phase (Creighton, 1995). On the other hand, naps did not appear to affect performance during eye-hand reaction time (Creighton, 1995). Similarly, Milner and Cote (2008) reported a beneficial effect of the nap on objective alertness during a multiple sleep latency test, while reaction time was not affected during multiple tasks. The chronic effect of napping is yet unclear, but it was reported that habitual nappers displayed lighter sleep inertia upon awakening compared to non-habitual nappers (Dinges, 1992). By the same reasoning, a possible explanation is that the effect of naps might change with repeated naps every day, and—depending on participants—might gradually decrease. Further studies are needed to bring insight regarding the effect of habitual napping in older adults. Otherwise, work memory performance was tested following two NAPO durations (i.e., 20- and 60-min) in the same study (Milner and Cote, 2008), and the change in performance between napping and not napping did not significantly differ. A plausible explanation could be that both durations were not sufficient to impact memory performance. Future work should investigate the effect of longer nap durations (e.g., 90 min) on working memory performance.

Based on the findings of the present review, daytime napping had an overall positive impact on learning performances. A nap benefitted vocabulary learning in older individuals and this effect persisted to the next day (Heim et al., 2017). Similarly, procedural/motor learning was positively impacted by daytime napping. Although performance did not differ between control and nap groups during the initial learning phase (pre-nap), a beneficial effect of naps was reported across the same (Korman et al., 2015; King et al., 2017; Fitzroy et al., 2021) and next-day (Korman et al., 2015; King et al., 2017) re-tests following a 90-min NAPO. This beneficial effect was consistent across the follow-up sessions and lasted for at least 22 h in older adults (Korman et al., 2015; King et al., 2017). However, this beneficial effect of napping was not observed in the large study of Fogel et al. (2014) and Fang et al. (2021) with the same NAPO duration. Discrepancies between studies could be related to the differences in methodological approaches and protocols used. Indeed, MSL was assessed using the same task for the studies (Fogel et al., 2014; Korman et al., 2015; King et al., 2017; Fang et al., 2021), while learning performance was tested only once (i.e., same day) for Fogel et al. (2014) and Fang et al. (2021), and it was retested twice (i.e., same and next day) for Korman et al. (2015) and King et al. (2017). In addition, same-day re-tests took place at different moments [i.e., 5 (Fogel et al., 2014; Fang et al., 2021) and 8 (Korman et al., 2015; King et al., 2017) h later from the initial learning session]. We believe that if tests took place later in the same day or even the next day, a possible significant effect of napping could be observed in MSL. Also, a different motor learning task was adopted in the Fitzroy et al. (2021) study, where participants performed an explicit variant of the serial reaction time task. Here, they were made aware that there was an underlying pattern in the stimulus sequence, but they were not directly informed what that pattern was. Specifically, participants were only informed that cues would be sequential during the indicated blocks and instructed to notice and learn any patterns they could. This could explain the beneficial effect of napping even when retested 5 h later from the initial learning session. Furthermore, Backhaus et al. (2016) did not reveal any significant effect of daytime napping on MSL performance neither the same nor the next day. It is important to mention that this study aimed to investigate whether sleep-dependent consolidation can be elicited in diurnal settings in MSL using a more difficult task (i.e., 9-item sequence task). Therefore, it could be argued that the beneficial effect of daytime napping—regarding MSL performance—seems to be less effective with difficult tasks.

Was nocturnal sleep affected by daytime napping?

Studies investigating acute (Campbell et al., 2005; Korman et al., 2015; King et al., 2017) and chronic (Monk et al., 2001) effects of daytime napping on nighttime sleep showed consistency between nap and control conditions regarding TST (Monk et al., 2001; Campbell et al., 2005; Korman et al., 2015; Slater et al., 2015), SE (Monk et al., 2001; Campbell et al., 2005; Korman et al., 2015; Slater et al., 2015), SOL (Korman et al., 2015; King et al., 2017) and proportion of sleep stages (Campbell et al., 2005; King et al., 2017). Additionally, 24 h TST was higher in nap compared to control condition (Monk et al., 2001; Campbell et al., 2005; King et al., 2017). Based on the results of the present review, there is minimal evidence to indicate that napping is detrimental for older adults' nighttime sleep. Importantly, it was reported that SOL was 6.3 min longer in the nap condition compared to control condition following a 120-min NAPO (Campbell et al., 2005). Further, Monk et al. (2001) showed a decrease in TST, SE and wake time (in that the participant woke up earlier) following naps. It is important to point out that those results were taken from an average of two nights in the laboratory, which is an unfamiliar place to older adults, compared to the first part of the study which took place in their beds at home. The study also used polysomnography, which can be a complex and uncomfortable technique for the participants (Vlahoyiannis et al., 2020). All these factors might affect older adults' sleep and therefore could explain the decrease of TST in nap condition.

Methodological considerations

Out of 15, only two (13.3%) studies (Creighton, 1995; Monk et al., 2001) reported a napping regimen lasting more than 1 day. Participants adopted a napping regimen (i.e., older adults took a

nap each day) involving a 90-min NAPO lasting 5 (Creighton, 1995) and 17 (Monk et al., 2001) days. Clearly, a tendency toward a great variability in results was observed. Therefore, future investigations may involve repeated naps during a micro-cycle to explore the chronic effect of napping on older adults. Further, all studies investigating motor learning implemented solely hand movements (finger sequence tapping tasks). It would be of interest to investigate the effect of daytime napping on movements implementing the whole body. One of the positive points to mention is that electroencephalography-based devices were used in 13 (86.6%) of the 15 studies included in the present systematic review which—in spite of the fact that it is a complex and uncomfortable technique—gives a clear insight into sleep stages and more precise sleep duration and efficiency (Scott et al., 2020; Vlahoyiannis et al., 2020).

It is well established that adequate sleep is vital for optimal cognitive and physical functioning across the lifespan (Carskadon, 2011; Pace-Schott and Spencer, 2011; Lo et al., 2012). Nonetheless, almost half of older adults reported at least one sleep problem (Neikrug and Ancoli-Israel, 2010). A systematic review and meta-analysis of studies relating to sleep duration and cognition in older adults showed that short ($\leq$5 h) and long ($\geq$9 h) sleep are associated with cognitive impairment (Lo et al., 2016). These associations were found in both cross-sectional and prospective studies, and across multiple cognitive domains (e.g., executive functions, verbal memory, working memory capacity, etc.). Furthermore, a recent study conducted by Wang et al. (2019) included a total of 161,241 participants aged 35–70 years from 21 countries with different income levels in seven geographic regions (North America and Europe, South America, the Middle East, South Asia, Southeast Asia, China, and Africa), confirmed the above-mentioned conclusions. In this study, the authors concluded that (i) estimated total sleep duration of 6–8 h per day is associated with the lowest risk of deaths and major cardiovascular events and (ii) daytime napping is associated with increased risks of major cardiovascular events and deaths in those with >6 h of nighttime sleep but not in those sleeping $\leq$6 h/night (Wang et al., 2019). In the present systematic review, a 90-min duration was adopted as a nap opportunity in 9 (60%) out of the 15 studies. This NAPO has been proved to be the optimal nap duration—in view of the above-mentioned reasons—for athletes carrying sleep debt (Souabni et al., 2021). Similarly for older adults, this nap duration is deemed successful to improve cognitive and psychomotor performance, and declarative and motor learning. However, a longer NAPO (i.e., 120 min) seems to have an impact on subsequent nighttime sleep (i.e., longer sleep latency). Moreover, longer daytime napping was associated with a higher risk for diabetes mellitus, odds ratios were 1.23 for those reporting <60 min and 1.55 for those reporting >60 min of napping compared with individuals who did not nap (Xu et al., 2011). Similarly, another study including a total of 27,009 retired workers reported that longer nap duration (i.e., >60 min) may represent a novel risk factor for diabetes mellitus and higher blood glucose levels (Fang et al., 2013). In addition, a recent study aiming to examine the association between daytime napping and successful aging on 7,469 participants reported that the group having long daytime naps (i.e., >60 min/day) was associated with a lower probability of achieving successful aging compared with the one having no daytime naps (i.e., 0 min/day) (Xin et al., 2020). All those factors should be taken into consideration to draw a firm conclusion regarding the adequate duration of nap for the elderly. A comprehensive recording of sleep duration and quality of older adults seems to be necessary. Specifically, these studies must use objective methods of sleep assessment (e.g., polysomnography, actigraphy and heart rate variability) and consider a duration of at least 7 days for a reliable measure to assess habitual sleep patterns in older adults.

Strengths and limitations

This is the first systematic review of the literature on the effects of napping on older adults' perceptual, cognitive and physical measures. The strengths of the present analysis include a comprehensive coverage of the available literature and a careful appraisal of its quality. The databases PubMed, Web of Science, Scopus, SPORTDiscus and Google Scholar were searched for studies regardless of the time when they were conducted and the languages they were published in. However, this current systematic review has limitations which should be acknowledged. First, the number of articles that include napping regimens ($n = 2$) was low, and there were reservations with compliance with the protocol in one of the studies (Creighton, 1995). Second, both studies did not have sufficient data on nap quality. For example, Creighton (Creighton, 1995) reported neither quantity nor quality of sleep during the nap, and Monk et al. (2001) declared only TST during the nap. It is absolutely necessary for future studies to provide quantitative (e.g., TST and duration and amount of each sleep stage) and qualitative (e.g., sleep efficiency and/or fragmentation indices) data examining napping behaviors of older adults in order to ensure that medical doctors and researchers are able to comprehensively examine the chronic effects of naps in the elderly. Finally, meta-analyses were not able to be conducted owing to the low number of studies of each type of measured variables.

Conclusion

The findings of the present systematic review are meaningful for understanding the impact of daytime napping on the life of older adults. Because short sleep is associated with cognitive impairment in older adults across ages, and given

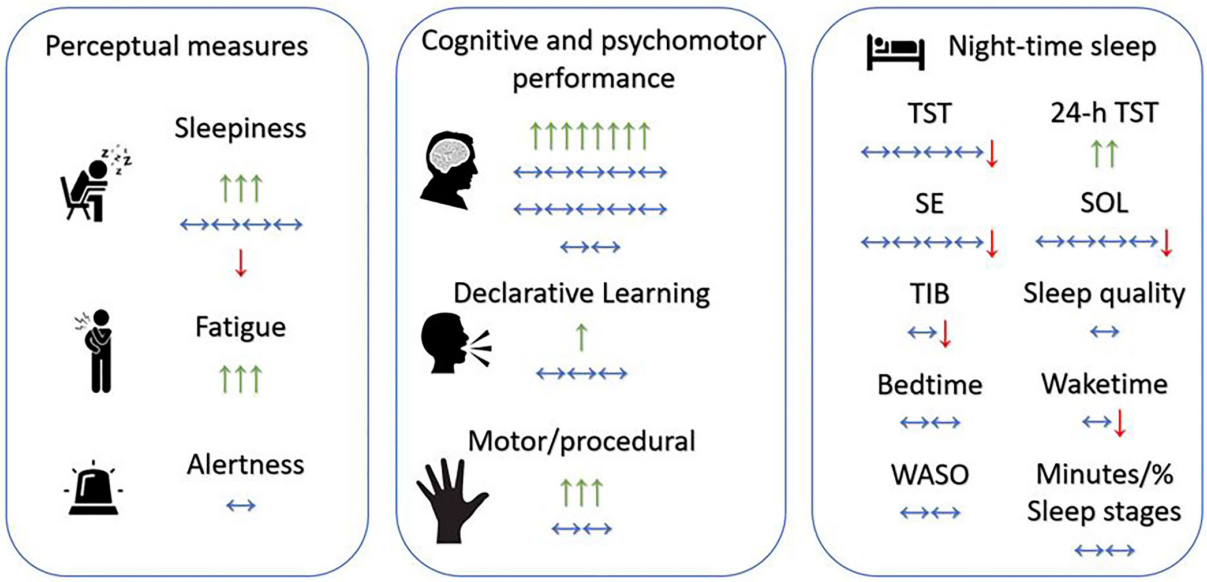

FIGURE 2
Overview of the effects of daytime napping on older adults. Green arrow up ↑, positive significant effect of one study/one nap duration (e.g., positive effect on sleepiness/fatigue means nap reduced sleepiness/fatigue); Red arrow down ↓, negative significant effect of one study/one nap duration (e.g., negative effect on sleepiness means nap increased sleepiness); horizontal-two-edged arrow ↔, no significant effect of one study/one nap duration; SE, sleep efficiency; SOL, sleep onset latency; TIB, time in bed; TST, total sleep time; WASO, wake after sleep onset.

the huge beneficial effect of napping on perceptual measures, cognitive and psychomotor performance, and declarative and procedural learning (Figure 2), a diurnal daytime nap opportunity could be proposed as a solution to improve older adults' health and daily performance. Nonetheless, considering the long-term impact of long sleep on cognitive performance, researchers, geriatric specialists and doctors should be careful about which nap duration to propose to older adults in order to not exceed the recommended duration of sleep. Finally, while napping is a common practice among senior populations, older adults should be aware of the importance of good sleep hygiene so that they could establish good sleep habits and steer clear of extreme sleep durations.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

MS drafted the manuscript. MS, MJS, and TD selected retrieved relevant papers. MR, MS, and OH assessed studies' qualities. OH, MR, KT, AA, and TD critically reviewed the manuscript. AA and TD were the guarantors of the overall content. All authors have read and agreed the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2022.1000707/full#supplementary-material

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Inherent regional brain activity changes in male obstructive sleep apnea with mild cognitive impairment: A resting-state magnetic resonance study

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Obstructive sleep apnea (OSA) is the most common sleep disorder worldwide. Previous studies have shown that OSA patients are often accompanied by cognitive function loss, and the underlying neurophysiological mechanism is still unclear. This study aimed to determine whether there are differences in regional homogeneity (Reho) and functional connectivity (FC) across the brain between OSA patients with MCI (OSA-MCI) and those without MCI (OSA-nMCI) and whether such differences can be used to distinguish the two groups. Resting state magnetic resonance data were collected from 48 OSA-MCI patients and 47 OSA-nMCI patients. The brain regions with significant differences in Reho and FC between the two groups were identified, and the Reho and FC features were combined with machine learning methods for classification. Compared with OSA-nMCI patients, OSA-MCI patients showed significantly lower Reho in bilateral lingual gyrus and left superior temporal gyrus. OSA-MCI patients also showed significantly lower FC between the bilateral lingual gyrus and bilateral cuneus, left superior temporal gyrus and left middle temporal gyrus, middle frontal gyrus, and bilateral posterior cingulate/calcarine/cerebellar anterior lobe. Based on Reho and FC features, logistic regression classification accuracy was 0.87; sensitivity, 0.70; specificity, 0.89; and area under the curve, 0.85. Correlation analysis showed that MoCA scale score in OSA patients was significant positive correlation sleep efficiency and negatively correlation with neck circumference. In conclusion, our results showed that the OSA-MCI group showed decreased Reho and FC in specific brain regions compared with the OSA-nMCI group, which may help to understand the underlying neuroimaging mechanism of OSA leading to cognitive dysfunction and may serve as a potential biomarker to distinguish whether OSA is accompanied by cognitive impairment.

KEYWORDS

obstructive sleep apnea, mild cognitive impairment, rs-fMRI, regional homogeneity, functional connectivity

Introduction

Obstructive sleep apnea (OSA) is a highly common sleep disorder characterized by repeated partial collapse and obstruction of the upper respiratory tract, resulting in intermittent hypoxia, hypercapnia, and sleep fragmentation. OSA affects up to more than 30% of older adults (Peppard et al., 2013), with an incidence rate of ~14% in men and 5% in women (Heinzer et al., 2016). Long-term intermittent hypoxia is not only associated with various complications (hypertension, cardiovascular damage, and chronic kidney disease; Yayan et al., 2017), but can also lead to concomitant cognitive dysfunction, anxiety, and even Alzheimer's disease (Daulatzai, 2015). Studies have also shown that OSA is associated with a variety of cognitive impairments, including deficits in attention, memory, executive function, visuospatial function, and language ability (Olaithe et al., 2018). However, the neuropathological mechanisms underlying cognitive dysfunction in OSA are not fully understood.

Neuroimaging studies to explain these cognitive deficits have revealed functional and structural changes in multiple brain regions in OSA patients (Kumar et al., 2012; Xia et al., 2016). Previous structural magnetic resonance imaging (sMRI) research has shown decreased white matter integrity and volume reduction (Lee et al., 2019) and regional cortical thinning in OSA patients (Joo et al., 2013). A resting-state function MRI (rs-fMRI) study to evaluate brain activity in the spontaneous state also showed that OSA patients had regional homogeneity changes (Santarnecchi et al., 2013) and abnormal global and regional functional connectivity (Park et al., 2016).It involves the default mode network (DMN), saliency network, and central executive network (Prilipko et al., 2011; Khazaie et al., 2017; Chen L. et al., 2018). Changes in the function and structure of these areas are associated with cognition, emotion, autonomic nerves, and sensory control (Chen L. T. et al., 2018; Yu et al., 2019; Kong et al., 2021). However, most previous studies have been limited to comparisons between OSA patients and healthy individuals, and functional differences between OSA patients with and without mild cognitive impairment (MCI) have not been assessed. Thus, how to account for the heterogeneity of concomitant cognitive impairment in the OSA population and the possible mechanisms linking OSA to MCI need to be clarified.

Rs-fMRI is a non-invasive technique that has become a hotspot in neuroimaging research owing to its high spatial and temporal resolution. Regional homogeneity (Reho) is a data-driven local measure of spontaneous neural activity that does not require the onset time of stimulation or prior knowledge and has good test–retest reliability (Xia et al., 2018). Functional connectivity (FC) is an fMRI data processing method used to explore the functional interactions between anatomically separated brain regions (Luo et al., 2021). Reho and FC are considered to be complementary in examining the synchronization of local and remote brain activity (Sun et al., 2018),and the simple computations and reliable representations involved have led to their use in exploring brain diseases with underlying functional alterations, such as epilepsy (Liu et al., 2021), Alzheimer's (Ibrahim et al., 2021), and depression (Chen et al., 2021). Biomarkers obtained by various resting-state MRI techniques [functional connectivity, Reho, amplitude of low-frequency fluctuation (ALFF)] are widely used in disease classification (Hojjati et al., 2017, 2019; Ju et al., 2019; Wang et al., 2021). Long et al. used ALFF, regional uniformity, and gray matter density as classification features to improve the efficiency of MCI diagnosis by distinguishing between MCI patients and healthy controls. The classification model obtained high accuracy (sensitivity, 93.1%; specificity, 100%, area under the curve, 0.97; Long et al., 2016).

This study aimed to determine whether there are differences in regional consistency and FC across the brain between OSA patients with MCI (OSA-MCIs) and those without MCI (OSA-nMCIs) and whether such differences can be used to distinguish the two groups. We hypothesized that compare with OSA-nMCI, OSA-MCI would showed abnormal spontaneous functional activity and connectivity change. To test this hypothesis, the voxel-level Reho method was used to explore local spontaneous brain activity in OSA-MCI patients, while exploring functional connectivity with the whole brain using significantly different Reho brain regions as seed points. Then, logistic regression was used to evaluate whether Reho and FC values could be used as neuroimaging markers to distinguish whether MCI was associated with OSA.

Materials and methods

As a descriptive cross-sectional study, we conducted an function analysis using Gpower software. The specific settings were: Effect size $d = 0.8$, $\alpha = 0.05$, $1 - \beta = 0.8$. The total sample size was required to be 52. In this study, we recruited a total of 95 OSA patients diagnosed in the sleep monitoring room of the Respiratory Department of the First Affiliated Hospital of Nanchang University between August 2017 and August 2022. Diagnosis was jointly determined by experienced respiratory physicians according to the American Society of Sleep Medicine 2017 Clinical Practice Guidelines for adult obstructive sleep apnea (Kapur et al., 2017). The inclusion criterion was male with apnea-hypopnea index (AHI) > 15/h. The exclusion criteria were as follows: (1) sleep disorders other than OSA (e.g., insomnia, somnolence, and circadian dysrhythmicity sleep disorder); (2) respiratory diseases, cardiovascular diseases, diabetes mellitus, hypothyroidism, central nervous system diseases, metabolic diseases, and tumors; (3) alcohol or illicit drug abuse or current use of psychotropic substances; (4) contraindications for MRI, such as claustrophobia and various internal stents; and (5) image artifacts (motion, metal). All participants were right-handed, native Chinese speakers, and aged 20–60 years.

This study was approved by the Medical Ethics Committee of the First Affiliated Hospital of Nanchang University [2020(94)] and was conducted according to the principles of the Declaration

of Helsinki. Written informed consent was obtained from all participants.

Polysomnography and neuropsychological assessment

All subjects were instructed to abstain from alcohol, coffee, and hypnotics prior to polysomnography monitoring. All participants underwent an overnight polysomnography (from 10 p.m. to 6 a.m. the next day) using a Respironics LE series physiological monitoring system (Alice 5 LE, Respironics, Orlando, FL, United States). Polysomnography monitoring included standard electrocardiogram, electroophthalmogram, electromyogram, electrocardiogram, oral and nasal airflow, chest and abdomen breathing movement, and snoring. Blood oxygen saturation (SaO2), sleep latency, total sleep time, sleep efficiency, sleep stage, arousal and respiratory events were also recorded.

Obstructive apnea was described as a sustained 90% reduction in airflow for ≥10 s with significant dyspnea. Hypopnea was defined as a ≥30% decrease in airflow for ≥10 s accompanied by an oxygen saturation of ≥4%. AHI was determined as the sum of apnea and hypopnea events per hour during sleep and was classified as mild (5–15), moderate (15–30), or severe (≥30; Berry et al., 2017). Cognitive function was assessed using the 11-item Montreal Cognitive Assessment (MoCA) scale (Chinese version) with the area under the ROC (AUC) of 0.930 (95%CI: 0.894; 0.965), a sensitivity of 92%, and a specificity of 85% (Hu et al., 2013). All MoCA scale assessments were performed by one senior experienced psychologists. Briefly, the MoCA scale examines eight cognitive domains, including executive functioning, language, attention, computation, abstraction, naming, memory, and orientation. A total MoCA score of <26 indicates cognitive impairment (Chen et al., 2016).

MRI data acquistion

All patients underwent MRI using a 3.0 Tesla MRI scanner with an 8-channel phased array head coil (Siemens, Munich, Germany) at our hospital. Foam pads and earplugs were used to reduce head movement and noise. Before the scan, the patients were instructed to close their eyes, stay awake, and not engage in specific thinking. First, a routine MRI scan was performed. The conventional T1-weighted imaging parameters were as follows: repetition time (TR) = 250 ms, echo time (TE) = 2.46 ms, thickness = 5 mm, gap = 1.5 mm, field of view (FOV) = 230 × 230 mm. For T2-weighted imaging, they were: TR = 4,000 ms, TE = 113 ms, thickness = 5 mm, gap = 1.5 mm, FOV = 230 × 230 mm, slice = 19. Then, high-resolution T1-weighted MRI images of brain structures were obtained using sagittal brain volume sequences (TR = 1,900 ms, TE = 2.26 ms, thickness = 1.0 mm, gap = 0.5 mm, FOV = 250 × 250 mm, Matrix = 256 × 256, turning angle = 9°, slice = 176). Finally, the rs-fMRI data were collected in the echo plane imaging sequence (TR = 2,000 ms, TE = 30 ms, flip angle = 90°, thickness = 4.0 mm, gap = 1.2 mm, FOV = 230 × 230 mm2, matrix size = 64 × 64, slice = 30). A total of 240 rs-fMRI images were obtained. Two experienced radiologists read the images to exclude macroscopic lesions (demyelinating encephalopathy, brain tumors) and motion artifacts.

Data preprocess

Imaging data were examined using MRIcro software[1] to discard suboptimal data, such as the presence of deflected or missing images, etc. Data processing is based on Data Processing & Analysis for Brain Imaging 6.0 (DPABI6.0, Chinese Academy of Sciences, Beijing, China, http://rfmri.org/dpabi), which is based on statistical parameter mapping (SPM12, http://www.fil.ion.ucl.ac.uk/spm/software/spm12/), and in MATLAB2018b (Math Works, Natick, MA, United States). Firstly, the file format was converted from Digital Imaging and Communications in Medicine to Neuroimaging Informatics Technology Initiative. Secondly, The first 10 time points are removed to ensure signal stability. Then, time layer correction and 3D head motion correction were performed. Patients whose frame displacement exceeded 2.5 standard deviations were excluded (Van Dijk et al., 2012). Structural images were co-registered with functional images for each subject using a linear transformation. Thus, the new segmentation in SPM12 was used to segment the structural images of all subjects into grey matter, white matter and CSF. Then, the image space was normalized to the Montreal Neurological Institute (MNI) template and resampled to 3 × 3 × 3 mm voxels. Finally, the Friston 24 parameters, white matter signals, and cerebrospinal fluid signals were regressed from the time series of all voxels using linear regression, after filtering with a temporal filter (0.01–0.08 Hz). The data preprocessing is described in detail in our previous study (Li et al., 2021).

The Reho value was generated using Kenndall's consistency coefficient to generate a separate Reho map (in a given voxel and its 26 nearest time series; Zang et al., 2004). The calculation formula is as follows:

$$\mathrm{ReHo} = \frac{\Sigma\left(R_i\right)^2 - n\left(\bar{R}\right)^2}{K^2\left(n^2 - n\right)/12}$$

where Reho is the consistency coefficient of Kenndall in a given voxel, and the range is 0–1; K is the voxel number of the time series in the measurement cluster, $k = 27$; n is the rank number; and Ri is the total rank of the ith time point, where $\bar{R} = (n+1)K/2$ is the average value of Ri. When a given cluster is consistent with

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its neighbors in the time series, the consistency coefficient is close to 1. Then, to reduce the global effect of subject variability, we divided the Reho plot by the Reho value of the global tie and spatially smoothed with a gaussian kernel (half-height full-width = 6 mm). Reho plots were generated using Fisher's r-to-z normalization, and szReho plots were used for final statistical analyses.

Functional connectivity analysis

Functional connectivity analysis was calculated using DPABI 6.0. The brain areas that exhibited significantly different Reho values between the OSA-MCI and OSA-nMCI groups were set as regions of interest (ROIs). First, the time series of each region (i.e., the average of the fMRI sequences of all voxels in that region) were extracted. Then, Pearson's correlation coefficients between the time series and all other voxels in the brain were calculated to obtain a whole-brain FC map of the subject. Finally, Fish R-to-z changes were used to transform the correlation maps into Z-value maps.

Logistic regression

Logistic regression (LR) is a multivariable technique that requires a functional relationship between a number of predictor variables and a single output to predict the likelihood of a target variable. Reho and FC values, which were significantly different between OSA-MCI and OSA-nMCI groups, were used as features to construct LR models. First, we calculated the Pearson correlation coefficient between the characteristics of each group, with a 0.75 cutoff for the related absolute threshold. Given that the characteristics of correlation is greater than the threshold after comparing the mean absolute correlation, the mean absolute correlation variable was deleted. To weaken the multicollinearity at the expense of the smaller variable, the most valuable predictor variable was retained. Mesh optimization was used to optimize the hyperparameters, and leave-one-out cross validation and permutation test (5,000 times) were used to verify the model performance. The accuracy, sensitivity and specificity of the model were calculated, and the predictive performance of the model was evaluated according to the receiver operating characteristic curve and the area under the curve. The heterogeneity of the test results was evaluated by Kappa.

Statistics

For demographic and clinical evaluation data, we first processed the data using SPSS 23.0 software and tested the normality of the data by Kolmogorov–Smirnov. Then, two-sample *t*-test was performed on the data conforming to normal distribution, and Mann–Whitney *U* test was performed on the data not normally distributed. $p < 0.05$ was considered statistically significant.

Voxel-based comparisons of all Reho maps and functional connections were performed using DPABI6.0. Two-sample *t*-tests were performed to analyze differences in the Reho and FC maps among the groups. Multiple comparisons were corrected using the Gaussian random field method (voxel level, $p < 0.005$; cluster level, $p < 0.05$).

Furthermore, Pearson correlation analysis was performed to evaluate the relationship between clinical variables, MoCA scale scores and the abnormal signal value in Reho and FC with significant group differences. All statistical analyses were performed using SPSS 23.0 with a statistical significance level of $p < 0.05$, and the analyses were corrected for multiple comparisons using the Bonferroni correction.

Results

Demographic and clinical characteristics

There were significant differences in neck circumference ($p = 0.018$) and MoCA scale score ($p < 0.001$) between the OSA-MCI and OSA-nMCI groups. Meanwhile, there were no between-group significant differences in age, education, BMI, waist circumference, AHI, LSaO2, MSaO2, SaO2 < 90%, sleep efficiency, oxygen index reduction, and AI (all $p > 0.05$; Table 1).

TABLE 1 General clinical scale.

	OSA-MCI $n = 48$	OSA-nMCI $n = 47$	Value of p
Age[a], years	38.37 ± 8.06	35.48 ± 8.86	0.100
education[b]	13.06 ± 2.31	13.59 ± 3.13	0.347
BMI[a]	27.35 ± 3.08	26.91 ± 4.13	0.561
Neck circumference[b]	41.47 ± 2.92	40.10 ± 2.60	0.018
Waistline[b]	99.66 ± 6.79	97.59 ± 18.78	0.383
AHI[a]	54.38 ± 23.26	50.29 ± 18.78	0.349
$LSaO_2$[b]	70.77 ± 12.46	68.00 ± 12.38	0.280
$MSaO_2$[b]	92.21 ± 3.58	91.71 ± 5.13	0.580
Sleep efficiency%[b]	78.91 ± 22.63	84.86 ± 12.04	0.114
AI[b]	30.52 ± 17.75	33.59 ± 21.78	0.453
Oxygen index reduction[b]	47.40 ± 23.09	43.34 ± 23.43	0.825
$SaO_2 < 90\%$[b]	24.94 ± 19.88	23.67 ± 16.25	0.728
MoCA[b]	22.4 ± 2.36	27.27 ± 1.17	<0.001

AHI, apnea hypopnea index; $LSaO_2$, minimum blood oxygen saturation; $MSaO_2$, average blood oxygen saturation; $SaO_2 < 90\%$, percentage of total sleep time with oxygen saturation <90.
[a]Student, *t*-test.
[b]Mann–Whitney *U*-test.

Group differences in Reho maps

The group means of the Reho plots for OSA-MCI and OSA-nMCI are shown in Figure 1. Two-sample *t*-test was performed to compare Reho data between OSA-MCI group and OSA-nMCI group. Differences between groups are shown in Table 2 and Figure 2. Compared with OSA-nMCI, OSA-MCI group showed significant abnormalities in bilateral lingual gyrus and left superior temporal gyrus.

Group differences in functional connectivity maps

Patients with OSA-MCI showed decreased FC between left superior temporal gyrus (STG) and left middle temporal gyrus (MTG), left middle frontal gyrus (MFG), bilateral posterior cingutate (PC) /Calcarine/left cerebellum anterior lobe (CAL), and decreased FC between bilateral lingual gyrus and bilateral Cuneus (Table 3; Figure 3).

Correlational analysis

In patients with OSA, the MoCA scale scores showed a significant positive correlation with sleep efficiency ($r = 0.272$, $p = 0.008$) and a negative correlation with neck circumference ($r = -0.243$, $p = 0.018$; Figure 4). No significant correlation was found between clinical variables, MoCA scale scores and the abnormal Reho and FC value in OSA-MCI or OSA-nMCI groups.

Logistic regression

The screened features (Reho of bilateral lingual gyrus, left STG, FC between left STG and B PC/B Calcarine/L CAL) were optimized with hyperparameters and left cross validation to obtain the performance of LG machine learning model, as shown in Figure 4. The AUC was 0.85, the accuracy was 0.87, the sensitivity was 0.70, the specificity was 0.89, the Kappa coefficient was 0.60, and the *p*-value was 0.0014 after 5,000 permutation tests (Figure 5).

Discussion

In this study, voxel-based Reho and secondary FC were used to explore the abnormal brain activity in OSA-MCI and OSA-nMCI groups. Consistent with our hypothesis, compared with OSA-nMCI group, OSA-MCI group showed significantly lower Reho value in the bilateral lingual gyri and left STG. Decreased FC value was observed between left STG and MTG, left MFG, bilateral PC, calcarine cortex, left ACL, and between bilateral lingual gyrus and bilateral cuneus,which DMN, visual network (VN), and cerebellar networks were mainly involved. These findings indicating that the functional changes of such brain networks may be related to mild cognitive impairment. Secondly, based on the Reho and FC characteristics of significantly different brain regions, we can effectively distinguish whether OSA patients are accompanied by MCI, and provide more evidence for early clinical intervention.

Our study found that in OSA-MCI group, the Reho value of left STG was decreased, the FC value between left STG and left MTG, MFG, and bilateral PC was decreased, and these abnormal brain functional regions were mainly involved in DMN. The DMN

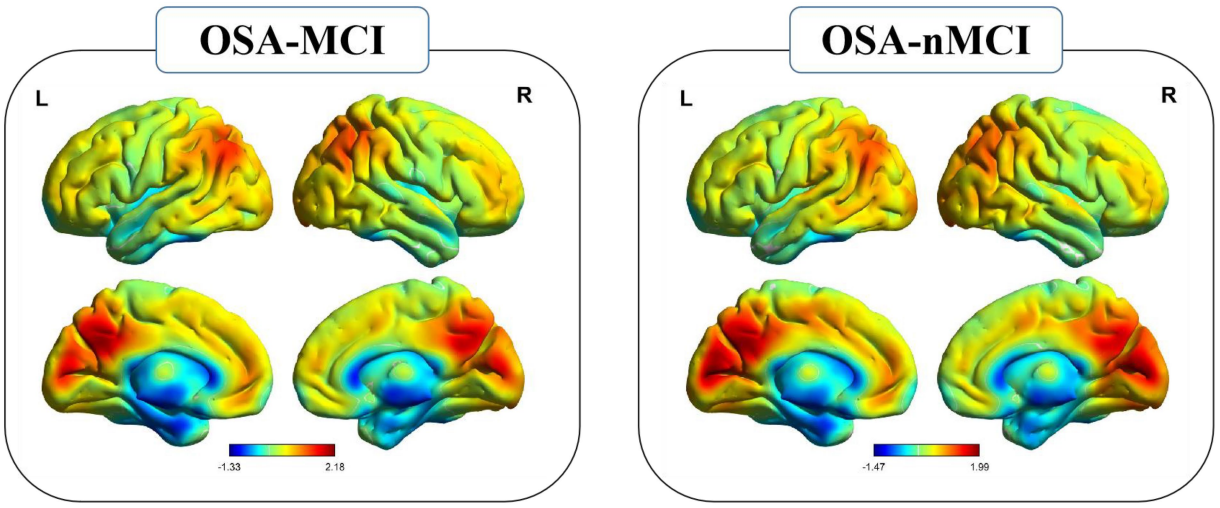

FIGURE 1
Reho spatial patterns at the group mean level of the OSA-MCI and OSA-nMCI groups.

is a group of brain regions, including the anterior and medial frontal cortex, bilateral temporal lobes, precuneus, and lateral parietal cortex, that are associated with social behavior, emotional control, memory, learning, and task execution (Raichle, 2015). Ya-ting Chang et al. showed that reduced functional connectivity in the DMN was associated with nocturnal hypoxemia rather than sleep rhythms (Chang et al., 2020). Our previous studies have shown that decreased FC between the DMN and the central executive network and decreased functional connectivity between brain networks are associated with delayed memory (Li et al., 2016). DMN was further divided into aDMN and pDMN (Yang et al., 2017; Wang et al., 2018), aDMN is related to social cognitive functions (emotional self-referential processing and inferential mental states of others), and pDMN is related to cognitive processes (temporal episodic memory and thinking). Zhang et al. (2013) found that FC in the anterior DMN of OSA patients decreased, while FC in the posterior DMN increased compensatively. Similar to previous studies, we found changes in FC values in multiple brain functional areas in the MCI group, which may be related to long-term intermittent hypoxia in OSA patients. In addition, compared with the nMCI group, the FC changes in multiple brain regions (aDMN and pDMN) were decreased, indicating that MCI patients may have more obvious brain function changes, and the possible disruption of compensatory mechanism in the DMN may be the potential cause of MCI.

TABLE 2 Altered Reho regions between OSA-MCI and OSA-nMCI groups.

Brain regions	MNI			Voxels	*T* value
	X	*Y*	*Z*		
B Lingual Gyrus	12	−69	−12	229	−4.945
L Superior Temporal Gyrus	−54	−9	−3	126	−4.433

MNI, montreal neurological institute; L, left; B, bilateral.

In our study, we found that the Reho value of bilateral lingual gyrus and FC of left STG and calcarine were decreased in MCI group. The lingual gyrus is mainly involved in the processing of visual memory (Menon and Uddin, 2010) and is an important region of visual perception (Yang et al., 2015). The calcarine is a component of the primary visual cortex and is associated with spatial working memory response time (Valenzuela et al., 2015). Both lingual gyrus and calcarine cortex are involved in the visual network, and the functional changes of visual network are related to MCI (Amaefule et al., 2021). In patients with Alzheimer's disease, task-state and resting-state MRI studies found that decreased FC of visual network function was significantly associated with cognitive impairment, and changes in visual network integrity were associated with the progression of MCI (Huang et al., 2021). Yang et al. (2022) showed that compared with healthy people, OSA patients took longer to process visual information, which reflected impaired visual perception from the perspective of electrophysiology, and suggested that impaired visual perception may be the potential mechanism of cognitive impairment. In our study, compared with the OSA-nMCI group, the function of brain areas related to visual network was impaired in the MCI group, which may be related to hypoxemia and oxidative stress (Archer and Pepin, 2013). However, reduced Reho

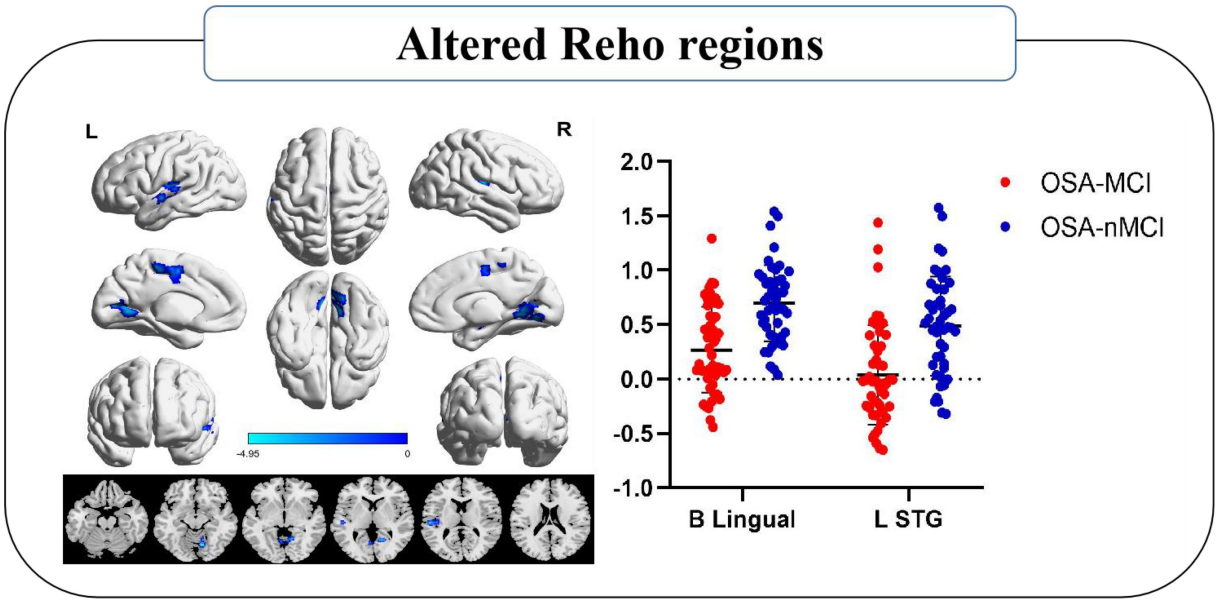

FIGURE 2
Significantly different Reho was observed between the OSA-MCI and OSA-nMCI groups. Reho values decreased significantly in the MCI group compared to the nMCI group (blue). B, bilateral; L, left; STG, superior temporal gyrus.

in the bilateral lingual gyrus and FC in the left STG and talus were not associated with cognitive scales. Therefore, the potential causal relationship between changes in the visual network and cognitive dysfunction needs further investigation.

The cerebellum is a key module not only in the motor control system, but also in cognitive and emotional processing (Stoodley et al., 2012). Ping Xiao's study showed that cerebellar gray matter thinning and decreased blood flow in OSA patients and found that structural changes in cerebellum and changes in blood circulation were associated with cognitive impairment (Xiao et al., 2022). Several other studies have shown that the cerebellum is vulnerable to hypoxia and ischemia, and that sleep deprivation is also an important factor affecting cerebellar function (Gazes et al., 2012; Kim et al., 2016). In a study of healthy people, small-world properties of the cerebellum and brain-cerebellum functional coupling were shown (Chen et al., 2022). A resting-state function-based study found that intermittent hypoxia resulted in impaired cerebellar network integration and cerebellar functional connectivity and was associated with cognitive impairment (Park et al., 2022). In this study, our results showed that FC decreased in the anterior cerebellar lobe and left STG, and this decreased functional connectivity in the cerebellum may be related to hypoxia or ischemia. Therefore, we hypothesized that hypoxia or sleep disturbance may lead to the disruption of functional connectivity between cerebellum and brain, which may be one of the causes of cognitive impairment.

TABLE 3 Functional connectivity between ROIs and the whole brain.

ROIs	Brain regions	MNI coordinates			Voxels	Value of *p*
		X	*Y*	*Z*		
L STG	L MTG	−66	−30	−9	209	−5.101
	L MFG	−6	39	−12	341	−5.067
	B PC/B Calcarine/L CAL	−21	−36	−21	1,044	−5.479
B Lingual	B Cuneus	6	−81	33	254	−4.500

ROIs, regions of interest; MNI, montreal neurological institute; L, left; B, bilateral; STG, superior temporal gyrus; MTG, middle temporal gyrus; MFG, middle frontal gyrus; PC, posterior cingutate; CAL, cerebellum anterior lobe.

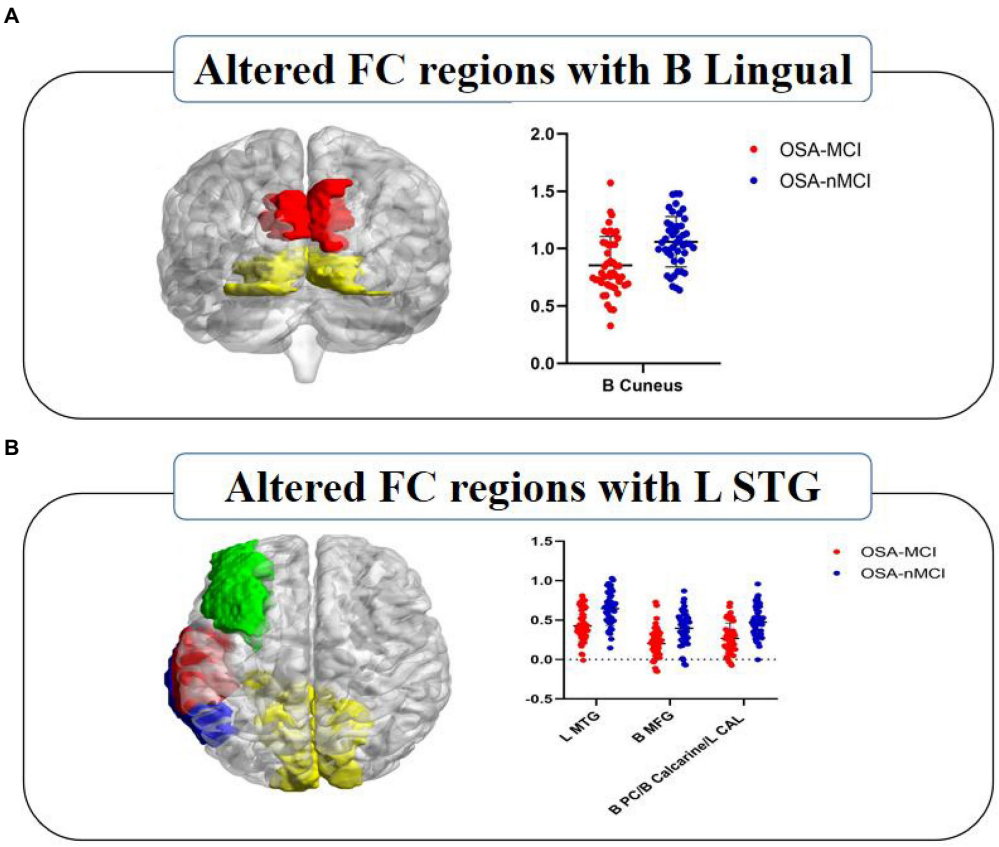

FIGURE 3
Significantly different FC values seeded as ROI in B-Lingual **(A)** and L-STG **(B)**. In figure **(A)**, red represents the lingual gyrus and yellow represents the cuneus; In figure **(B)**, red represents the left superior temporal gyrus, green represents the left middle frontal gyrus, blue represents the left middle temporal gyrus, and yellow represents the bilateral posterior cingulate/calcarine/left cerebellum anterior lobe. The FCs between significantly different regions and ROIs in OSA-MCI group was significantly reduced compare with OSA-nMCI group. L, left; B, bilateral; ROI, region of interest; FC, functional connectivity; STG, superior temporal gyrus; MTG, middle temporal gyrus; MFG, middle frontal gyrus; PC, posterior cingutate; CAL, cerebellum anterior lobe.

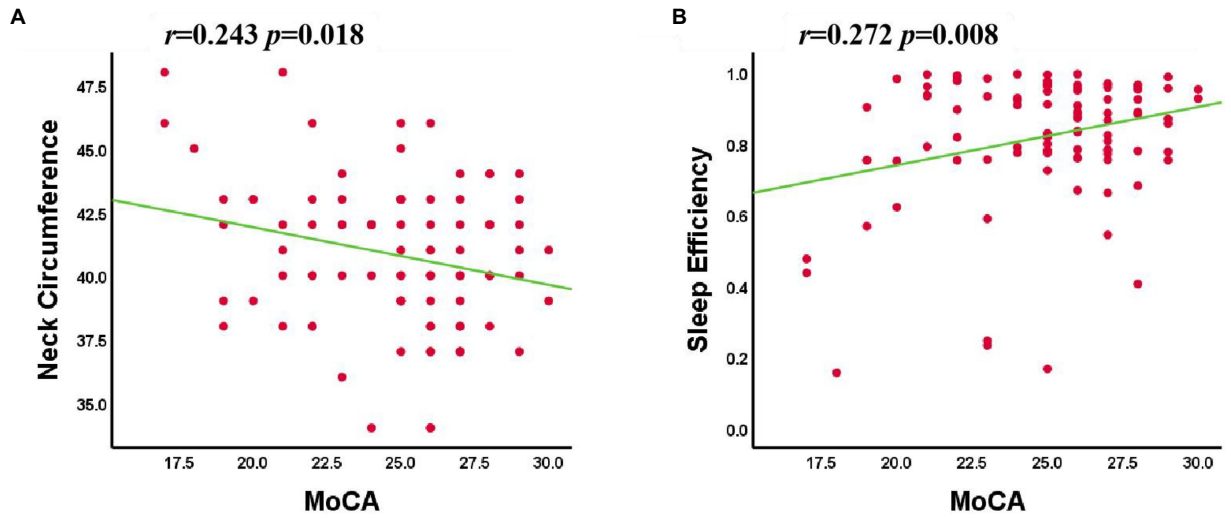

FIGURE 4
The MoCA scale scores was negatively correlated with neck circumference **(A)** and positively correlated with sleep efficiency **(B)**.

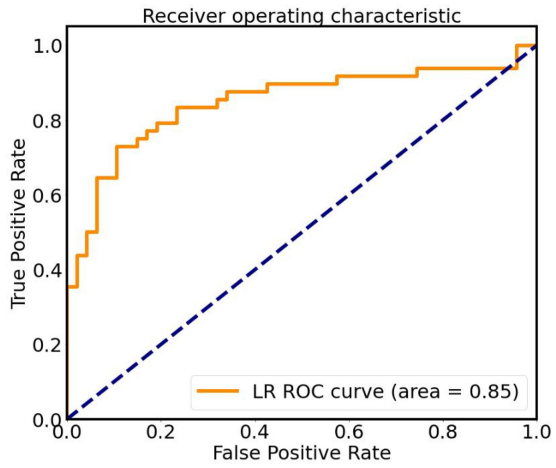

FIGURE 5
ROC curve of classifier based on altered Reho and FC values, AUC is 0.85. LR, logistic regression; ROC, receiver operating characteristic.

In addition, we found that MoCA scale scores were associated with neck circumference and sleep efficiency. Increased neck circumference is associated with obesity, which is one of the risk factors for OSA. Obesity plays an important role in the pathogenesis of apnea syndrome by altering the caliber of the upper airway during breathing in subjects and thus in the pathogenesis of apnea syndrome (Kim et al., 2014). An arterial MRI study showed that the posterior palatal airway was narrower in obese subjects during respiratory arousal and was associated with OSA severity (Feng et al., 2018). Our results showed that the range of neck circumference was significantly different between the OSA-MCI and OSA-nMCI groups. Therefore, we hypothesized that the increase of neck circumference may imply changes in airway anatomy, which may be related to the severity of OSA, although no significance difference was found in BMI or AHI indices between the two groups. Characteristics of sleep disorders include decreased sleep duration and quality, reduced sleep efficiency, fragmented sleeping and sleepiness all day (Casagrande et al., 2022). Previous studies have also shown that sleep disorders are associated with declined cognitive level (Bubu et al., 2020), particularly impairements showed in attention, memory and executive. Our study showed a positive correlation between sleep efficiency and cognitive performance, suggesting that the decline in sleep efficiency may be associated with cognitive impairment.

At last, based on Reho and FC features, LR was used to distinguish OSA-MCIs and OSA-nMCIs. Khatri and Kwon (2022) showed that an efficient classification model was established based on various rs-fMRI and structural MRI, combined with machine learning, indicating that rs-fMRI can be used as a neuroimaging marker to solve prediction and classification. In this study, LR models with excellent classification accuracy (AUC = 0.85, accuracy rate 0.87, sensitivity 0.70, specificity 0.89) were constructed, which suggests that LR may be an effective tool to identify OSA-MCI from OSA patients.

Limitation

First, our subjects were male with severe OSA, and the results may not be generalizable to patients with mild OSA or women with OSA. Second, we only analyzed abnormal functional change and ignore potential morphological and microstructural changes, which may help us to deepen our understanding of OSA with

cognitive impairment. Therefore in the future, we will combine other fMRI features (e.g., cortical thickness, white matter fiber) to improve the classification efficiency of the model. Finally, the sample size was small. Larger samples will be needed in future studies.

Conclusion

Our results show that OSA patients with MCI have spontaneous brain activity changes and decreased functional connectivity in multiple brain regions, mainly related to DMN, VN, and the cerebellar network. These provide additional information about the underlying neural mechanisms of OSA-related cognitive impairment. At the same time, our results demonstrate that an effective machine learning method can efficiently distinguish whether OSA patients are accompanied by MCI and provide potential imaging markers for clinical treatment.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Medical Ethics Committee of the First Affiliated Hospital of Nanchang University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

YS and XL wrote, reviewed, and revised the manuscript. DP guided and designed the MRI experiment. HL analyzed the resting-state fMRI data. YS and HL analyzed and discussed the ideas of the paper. PY analyzed machine learning. WD, KL, YZ, and WX collected resting-state fMRI data and applied for the ethics approval. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Development of an age-dependent cognitive index: relationship between impaired learning and disturbances in circadian timekeeping

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Preclinical quantitative models of cognitive performance are necessary for translation from basic research to clinical studies. In rodents, non-cognitive factors are a potential influence on testing outcome and high variability in behavior requires multiple time point testing for better assessment of performance in more sophisticated tests. Thus, these models have limited translational value as most human cognitive tests characterize cognition using single digit scales to distinguish between impaired and unimpaired function. To address these limitations, we developed a cognitive index for learning based on previously described scores for strategies used by mice to escape the Barnes maze. We compared the cognitive index and circadian patterns of light-dark entrainment in young (4–6 months), middle-aged (13–14 months), and aged (18–24 months) mice as cognitive changes during aging are often accompanied by pronounced changes in sleep-wake cycle. Following continuous analysis of circadian wheel-running activity (30–40 days), the same cohorts of mice were tested in the Barnes maze. Aged mice showed significant deficits in the learning and memory portions of the Barnes maze relative to young and middle-aged animals, and the cognitive index was positively correlated to the memory portion of the task (probe) in all groups. Significant age-related alterations in circadian entrainment of the activity rhythm were observed in the middle-aged and aged cohorts. In middle-aged mice, the delayed phase angle of entrainment and increased variability in the daily onsets of activity preceded learning and memory deficits observed in aged animals. Interestingly, learning-impaired mice were distinguished by a positive relationship between the extent of Barnes-related cognitive impairment and variability in daily onsets of circadian activity. While it is unclear whether changes in the sleep-wake cycle or other circadian rhythms play a role in cognitive impairment during aging, our results suggest that circadian rhythm perturbations or misalignment may nevertheless provide an early predictor of age-related cognitive decline.

KEYWORDS

Barnes maze, entrainment, activity rhythm, aging, middle aged, mice, cognitive index

Introduction

Cognitive decline is the clinical hallmark of age-related dementia and Alzheimer's disease (AD). The hippocampus, the region of the brain responsible for spatial memory (Gallagher, 1997; Foster et al., 2012), is severely affected in AD, and behavioral assessments which can probe the integrity of this region have been historically used in diagnosis. However, most patients are in late stages of the disease when they receive this diagnosis. With continued characterization of age-related dementia, it has become clear that the hallmark cognitive decline is often preceded by atypical behavioral symptoms, including pronounced alterations in circadian rhythms, and that this combination of functional impairments reflect degeneration in multiple systems. Thus, the development of preclinical models to identify specific behavioral changes that occur early in the progression of age-related cognitive impairment could yield a better index and advance diagnosis of dementia.

Rodents and humans share correlative similarities between brain structures and their functions in learning and memory. As such, aged rodent models have been useful in preclinical studies, exhibiting similar hippocampal deficits and performance variability to those observed in humans (Gallagher and Rapp, 1997). More specifically, during normal aging, cognitive decline is observed in part of the aged population, while others may show no significant cognitive change and perform within the range of their younger counterparts. To characterize behavior and improve translation of findings from these animal models to humans, Gallagher et al. (1993) developed the Spatial Learning Index (SLI) for the water maze. This quantitative index scores animals based on their hippocampal performance and allows for individual variability to be represented within study cohorts, thereby facilitating the separation of better learners from learning-impaired in the aged cohort (Tomás Pereira and Burwell, 2015). Although the water maze has significant utility in behavioral studies, there are limitations with its use as a cognitive assessment in mice (Harrison et al., 2009). For example, some mouse models show low motivation for swimming and searching for an escape in water (Whishaw and Tomie, 1996). In addition, the water maze may not be ideal for rodent models involving significant motor deficits, such as models of spinal cord or traumatic brain injury and stroke (Leconte et al., 2020; Panta et al., 2020). The Barnes maze is also less stressful than the water maze and animals may habituate quicker to the maze requiring less trials to reach ceiling performance (Harrison et al., 2009). Thus, the development of similar indices for other tasks is necessary for the advancement of research on age-related changes in cognitive function.

The Barnes maze represents a suitable alternative for the water maze. There are many variations of this task, but in general, there is a learning phase in which mice learn how to find the escape route and a probe trial (or trials) in which memory of the escape position can be assessed (Barnes, 1979; O'Leary and Brown, 2013). Here we focus on the development of a single cognitive index for the learning phase of the Barnes, based on strategy scoring first devised by Illouz et al. (2016). Multiple variables can be assessed during this task for cognitive (learning and memory of spatial-dependent navigation) and non-cognitive behaviors (speed, mobility). Distance and latency have been often used to demonstrate proficiency in finding the escape (Pitts, 2018; Rees et al., 2020). Quantification of latency may show level of efficiency to find the goal, but this variable is affected by age-dependent speed differences (Bizon et al., 2009). Although these measures are useful for determining group differences, distance and speed do not consider the efficacy of the different strategies that mice use to find the escape hole, and thus the aforementioned parameters only provide limited information on cognitive capacity. Rodents use multiple approaches to navigate the Barnes maze, including non-hippocampal strategies, such as serial search, that often result in large distances as mice search systematically until reaching the goal. By identifying different navigation strategies with validated scores, we are able to quantify the extent of efficiency on the learning acquisition without relying solely in hippocampal strategies (National Sleep Foundation, 2003; Illouz et al., 2016). Furthermore, quantification of performance with single numerical value allows for direct comparisons with other biomarkers, and also for within group comparisons to detect impairment in aging rodent models. Using the validated scores for each type of strategy, we created a single summed cognitive index for the learning phase of the task to evaluate Barnes performance across the aging spectrum of C57Bl/6 mice. Additionally, the cognitive index from the learning phase of the Barnes task was correlated with the probe (memory) trial, showing that this score provides a useful descriptor of cognitive performance even if its derivation is not solely from hippocampal-dependent performance.

To gauge the potential of the cognitive index as an indicator and/or predictor of cognitive impairment during aging, the same cohort of mice was analyzed for parallel changes in the circadian regulation of sleep-wake rhythms, especially with regard to their entrainment to the light-dark cycle. The prevalence of sleep disorders, especially those affecting the circadian regulation of the sleep-wake cycle, increases with advancing age (National Sleep Foundation, 2003). These sleep disorders and circadian rhythm disturbances occur during healthy aging but some are distinctive and more pronounced in age-related dementia and AD (Homolak et al., 2018). In contrast to the circadian and sleep-wake disturbances typically observed in healthy elderly individuals, delayed sleep-wake patterns in which both bedtime and wake times occur later in the day and irregular sleep-wake rhythm disorder with high variability in the timing of sleep onset and wakefulness are commonly observed in patients with mild to severe dementia

(Wang et al., 2015; Canevelli et al., 2016; Homolak et al., 2018; Leng et al., 2019). Based on the link between distinctive circadian rhythm alterations and cognitive impairment in aging (Devan et al., 2001; Craig and McDonald, 2008) and AD (Wulff et al., 2010), we explored the relationship between changes in cognition and light-dark entrainment of the circadian activity rhythm across the lifespan of the C57Bl/6 mouse model. Marked alterations in the light-dark entrainment of the activity rhythm were observed early in middle-aged mice prior to any age-related deficits in Barnes maze performance, demonstrating their potential predictive value for further cognitive decline. The correlation between the cognitive index of learning-impaired mice in Barnes maze and circadian variables suggests that there may be a relationship between cognition deficits and circadian disturbances across all age groups. Our cognitive index, used in combination with correlative changes in circadian behavior, thus offers a putative model for early diagnostic and detection of age-related cognitive impairment.

Materials and methods

Animals

Wild type male and female C57Bl/6 were obtained from a breeding colony from breeding pairs purchased from the Jackson Laboratory (stock #014548). The breeding colony was maintained by the Comparative Medicine Program at Texas A&M and new breeder pairs were purchased and introduced accordingly as per Jackson Laboratory's protocols for breeding. Based on comparisons with our published data (Bang et al., 2021), there were no signs of any strain variability or variability in behavioral and physiological measures due to crossbreeding. All mice were maintained under controlled conditions (22°C–25°C) on a standard 12 h light:12 h dark cycle (LD 12:12; lights-on at 0700 h) in the AAALAC-accredited vivarium at the Texas A&M University Health Science Center. All animal experiments were performed in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals. Animal procedures used in this study were conducted in compliance with Animal Use Protocol 2019-0265 as reviewed and approved by the Institutional Animal Care and Use Committee at Texas A&M University.

Mice used for analysis of the circadian rhythm of wheel-running behavior were: young (4–6 months, n = 21, 12 males and nine females), middle-aged (13–14 months, n = 20, nine males and 11 females) and aged (18–22 months, n = 29, 14 males and 15 females). These mice were housed individually in cages equipped with running wheels to provide for continuous analysis of wheel-running activity during the analysis of circadian behavior, which lasted 30 days. Two weeks after the analysis of circadian behavior, mice were habituated and tested in the Barnes maze (**Figure 1A**). Mice used for Barnes maze analysis were: young (n = 21, 12 males and nine females), middle-aged (n = 21, 10 males and 11 females) and aged (n = 29, 14 males and 15 females). Only mice with values for both circadian and Barnes behavior analyses were used in the correlational comparisons (shown in **Figure 5**).

Barnes maze

The Barnes circular platform maze is a 66 cm diameter circular platform on a 1.4 m stand with 20 evenly spaced 5.08 cm diameter holes around the circumference, where a black box (escape tunnel) was placed underneath one of the holes (San Diego Instruments, San Diego, CA, USA). Four bright lights were positioned above the maze as an aversive stimulus. Between each trial, the platform and escape tunnel were cleaned with 70% ethanol and water, and video was acquired using a Color GigE camera (model: acA1300-30gc). Data were quantified using Ethovision XT 16 video tracking software (Noldus, Leesburg, VA, USA).

The protocol consists of habituation, acquisition training (learning) and probe (**Figure 1B**; Rees et al., 2020).

Habituation

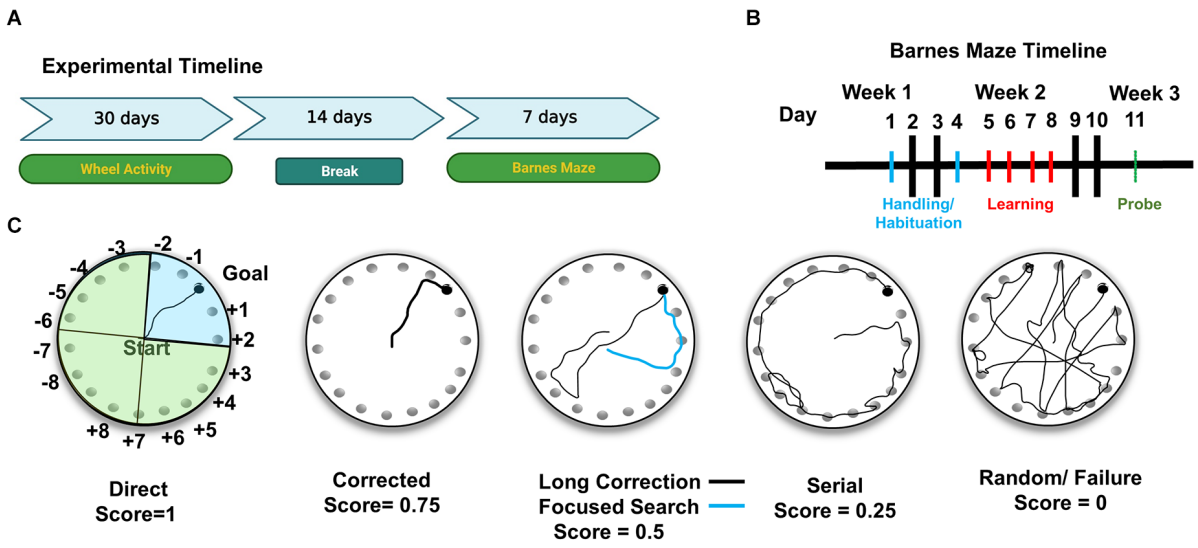
During habituation day 1, mice were placed on the table for 5 min and allowed to explore the maze without an escape box, under dim lighting. In day 2, mice were placed in a 2 L transparent glass beaker under aversive lighting, and then after 1 min were gently guided to the escape hole and lights were turned off.

Learning trials

In all subsequent days (3–6), the mice were individually placed in the center of the table under a dark container for 30 s before the container was lifted and the mouse was allowed to navigate the maze. Each mouse was allowed 180 s to locate and enter the escape box per trial. If the mouse was unable to locate the escape hole after 180 s, it was gently guided to the correct hole location and allowed to enter the escape tunnel. Once the mouse entered the escape tunnel (either guided or on their own), it remained in the tunnel for 1 min before returning to its home cage. Each day, the mice received four trials spaced 15 min apart for a total of 16 learning training trials over 4 days.

Probe trial

A probe trial was done 72 h after the last day of the learning phase. During this single trial, on day 7, mice were placed on the table as described for the learning trials, but the escape box was



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	Trial 1	Trial 2	Trial 3	Trial 4	Day1
Strategy	Fail	Random	Serial	Corrected	1
Cognitive Index	0	0	0.25	0.75	

FIGURE 1
Experimental design for cognitive and circadian behavior analysis. **(A)** For the experimental timeline, mice were first analyzed for circadian wheel-running activity, followed by Barnes maze testing. **(B)** Barnes maze testing consisted of 7 days of behavioral analysis, including habituation to the apparatus in days 1 and 2, training/learning of the position of escape hole (days 3–6), and a 72 h probe on day 7. **(C)** Schematic representation of the Barnes maze shows faux escape boxes (numbered) and goal location (escape box). For illustration purposes, maze is divided into four quadrants. Blue shaded quadrant is the target quadrant used for Probe analysis. Representative strategies are shown in each circular depiction of the Barnes. Spatial strategies include direct, corrected, long correction (black trace), focused search (blue trace). **(D)** Example of scoring of trials in Day 1 for a mouse. Cognitive indices are calculated per mouse by adding the scores from each trial for all 4 days.

not available. After 180 s, the mouse was removed and placed back into their holding cage.

Search strategies and development of the cognitive index

In order to analyze Barnes maze performance, each trial was scored using a modified scale created by Illouz et al. (2016). From left to right, representative paths of the possible strategies that a mouse can choose to find the escape are shown in Figure 1C. The hippocampal-dependent strategies are: direct (no error; score = 1), corrected (searched + or – 1 immediate hole, score = 0.75), focused (searched + or – 3 immediate holes, score = 0.5), and long correction (mouse searches across the target and immediately corrects toward correct hole, score = 0.5). Non-hippocampal strategies include the serial search (animal methodically searches holes one by one, score = 0.25), random (search without a clear strategy and target hole identified by chance, score = 0), and failure (animal searches but does not find the target, score = 0). Trials are scored by a blinded investigator. Each trial receives a single score, and scores are summed for each day as shown in the example in Figure 1D. The cognitive index was created by summing the scores of all 4 days.

Wheel-running activity

The circadian rhythm of wheel-running activity was continuously recorded for at least 30 days. Wheel-running activity was stored in 10-min bins, graphically depicted in actograms, and analyzed using ClockLab data collection and analysis software (ActiMetrics, Evanston, IL, USA). Entrainment and qualitative parameters of the activity rhythm were measured over the same interval for all animals. During entrainment to LD 12:12, the onset of activity for a given cycle was identified as the first bin during which an animal attained 10% of peak running-wheel revolutions (i.e., intensity). To measure phase angle of entrainment (φ), least squares analyses was used to establish a regression line through the daily onsets of activity during the period of entrainment (30 days), and then the number of minutes before (positive) or after (negative) the time of lights-off in the LD cycle (1,800 h) was determined for each

animal. Total daily activity was calculated by averaging the number of wheel revolutions per 24 h over the 30-day interval of analysis.

Statistical analysis

In each case, differences in behavior were considered significant at $p < 0.05$ (GraphPad, San Diego, CA, USA). Statistical analyses were performed on the raw data using one or two-way (age alone, or age and sex) repeated measures ANOVA to determine the significance of age-related differences when the data was analyzed across days for significance. One-way ANOVAs were performed on all other comparisons.

For probe trials, the percent of the time in the target quadrant is used to quantify the animal's insistence about the escape hole's location. Quadrants contain five possible locations for escape, and the escape hole is in the middle of the target quadrant (blue shaded quadrant in Figure 1C). Only data from the first 30 s are analyzed because mice typically give up searching after approximately 30 s. Group means from the probe trial were analyzed with one-way ANOVAs. Newman-Keuls *post hoc* analysis were applied when necessary to determine the significance of age-related differences in circadian entrainment and quantitative parameters of the activity rhythm. Tukey/Kramer (or Tukey's for multiple comparisons) *post hoc* analysis was used for more comprehensive Barnes maze analysis. Correlations were analyzed by Spearman's correlation with significance $p < 0.05$.

Results

Aged mice, but not middle-aged, are impaired in the Barnes maze

Many Barnes maze measures can be used to measure learning and memory. In our analysis of distance traveled to the target (Figure 2A), aged mice took longer paths (distance in cm) to find the escape box than the middle-aged and young mice ($F_{(2,65)} = 8.903$, $p < 0.001$). *Post-hoc* analysis of distance traveled further demonstrated that the aged group was statistically different from young ($p < 0.01$) and also from middle-aged cohorts ($p < 0.01$), with no difference observed between young and middle-aged mice ($p = 0.27$). Mice of all ages performed better across time ($F_{(3,195)} = 32.893$, $p < 0.0001$), with all age groups demonstrating less distance to reach the goal across days. There was no overall effect of sex in the distance measure ($F_{(1,65)} = 0.109$, $p = 0.74$). Speed changes as the animals learn the position of the platform and can vary depending on the strategy. On the first day when mice are naïve and untrained, the average speed was significantly different ($F_{(2,68)} = 7.401$, $p < 0.001$) between young, middle-aged, and aged mice (Figure 2B). The young cohort moved around faster than middle-aged and aged mice. Speed on day 1 did not differ between the middle-aged and aged groups but was significantly decreased (Tukey's multiple comparison; $p < 0.01$) in comparison with the young cohort. We did not observe a sex difference on speed on day 1 ($F_{(1,68)} = 3.219$, $p = 0.077$).

During the first 30 s of the probe trial, shown in Figure 2C, when the escape box was not available, we tested whether mice used their learning experience and concentrated their search in the target quadrant. Age was a significant factor in this measure of memory ($F_{(2,68)} = 4.425$, $p < 0.05$). Young and aged mice were the only group comparison with significant differences (Tukey's multiple comparison; $p < 0.05$) in this measure, such that the percent of path in the target quadrant was greater in young animals than in the aged cohort. There was no effect of sex on this measure ($F_{(1,68)} = 1.050$, $p = 0.31$).

Aged mice show more failures and less preference for spatial strategies

Hippocampal-dependent performance was observed to change as mice aged (Figure 3A). Aged mice preferred nonspatial (failures or serial) strategies (about 50% of the time) to spatial (about 25%) and showed more failures (25%) than their middle-aged and young (about 5%) counterparts. We then summed the cognitive scores for each animal for all learning days and compared the mean cognitive index scores for each group with a one-way ANOVA (Figure 3B). Higher scores indicate that spatial strategies were used more often than serial strategies and that fewer failures were detected. Age had a significant effect on escape strategy preference ($F_{(2,68)} = 14.66$, $p < 0.0001$), but the difference was only due to the aged group as the young and middle-aged cohorts were characterized by similar cognitive indexes. Both the young and middle-aged groups had significantly higher (Tukey's multiple comparison; $p < 0.001$) cognitive indices than aged mice. No effect of sex was observed in the cognitive index measure ($F_{(1,68)} = 0.12$, $p = 0.73$). Young and middle-aged groups showed similar range and variability within their cognitive indices, ranging from 4.25 to 10, whereas the scores in aged mice were lower and ranged between 1.75 and 7.75. The minimum CI score was 4.25, representing the lowest performer in the young cohort. To further evaluate the relationship between cognitive index scores and other variables, we used this score as a differential to specifically identify and separate low performers (learning-impaired) on this task in each age cohort. The dashed line in Figure 3B delineates this separation of learning-impaired (at CI = 4.25).

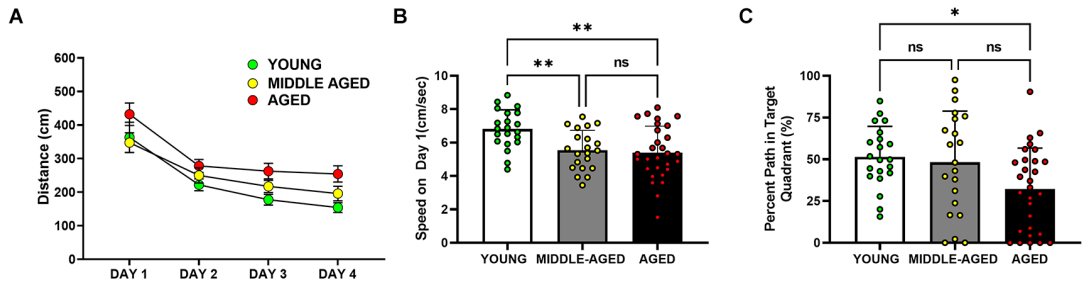

FIGURE 2
Cognitive performance of aged mice (18–22 months) is impaired in the Barnes maze, but not in middle-aged mice (13–14 months) relative to the young cohort (4–6 months). **(A)** Analysis of the distance traveled by mice to locate the escape box. Aged mice showed longer distance traveled to the escape than young and middle-aged mice (*), such that distance traveled in young and middle-aged mice was significantly decreased in comparison with the values observed in aged mice (*, *post hoc* Tukey/Kramer, $p < 0.05$). **(B)** Speed on the first day of Barnes performance, pre training. Young mice moved faster than the middle-aged and aged cohorts (**, *post hoc* Tukey's multiple comparison, $p < 0.01$; middle-aged vs. aged, ns = non-significant, $p > 0.05$). **(C)** Percent of the path localized in the target quadrant (i.e., quadrant in which the escape was localized during training trials, during the first 30 s of the trial). Only the young and aged groups are marked by significant differences (*, Tukey's multiple comparison; $p < 0.05$). In **(B)** and **(C)**, bars depict Mean ± SEM values of the corresponding age group. Circles indicate individual scores of each mouse.

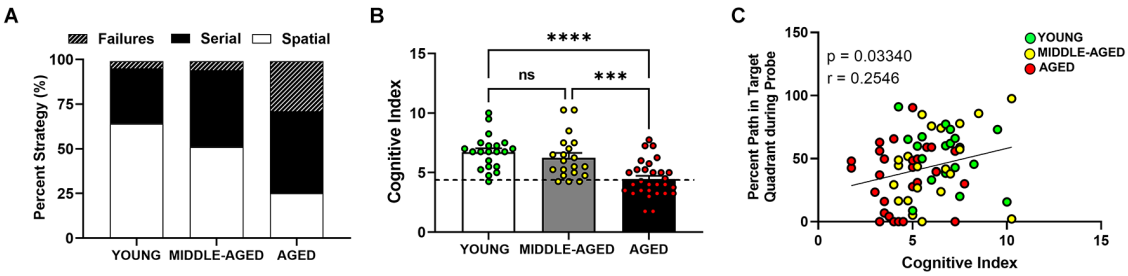

FIGURE 3
Aged mice (18–22 months) show lower hippocampal-dependent performance in Barnes maze. **(A)** Representative between-group comparison of profiles of strategy selection by each age group for entire training session (prior to probe). **(B)** Summed cognitive index comparison for training trials showed an age effect due to lower use of spatial strategies. Mean ± SEM value of the corresponding age group is shown and dashed line represents the cut off for division between high and low performers (i.e., learning-impaired mice). Young and middle-aged cohorts are not different, but aged mice have significant lower scores (Tukey's multiple comparison; young vs. aged, ****$p < 0.0001$; middle-aged vs. aged; ***$p < 0.001$; young vs. middle-aged, ns = non-significant, $p > 0.05$). **(C)** Correlation between cognitive index and probe analysis of Barnes performance. Circles indicate individual scores of each mouse and are color coded as in **(B)**. Cognitive index was positively correlated with the percent path values from the probe trial (Person correlation $p < 0.05$).

Cognitive score from learning trials correlates with memory score from probe

Further analysis using Pearson correlations revealed a significant positive correlation between the cognitive index and the percent path values from the probe trial (Figure 3C; Pearson correlation $p < 0.05$, $r = 0.25$). Based on comparisons within individual age cohorts (data not shown separately), there was no correlation between cognitive index and this variable in the young (Pearson correlation, $p = 0.32$, $r = 0.053$), middle aged (Pearson correlation, $p = 0.17$, $r = 0.32$), or aged (Pearson correlation, $p = 0.58$, $r = 0.107$) mice. The lack of correlation within individual age cohorts provides evidence that the overall correlation is age-dependent. The overall correlation also is consistent with age-related differences in the distance data because the effect of age is the main driver of the changes in cognitive performance. This relationship further confirms that the cognitive index is a reliable score to grade the level of cognition (spatial/hippocampal) during the learning or training phase of the Barnes maze.

Altered entrainment of the circadian rhythm activity occurs as early as middle-age and persists through aging

During exposure to LD 12:12, entrainment of the activity rhythm was observed in all young, middle-aged, and aged

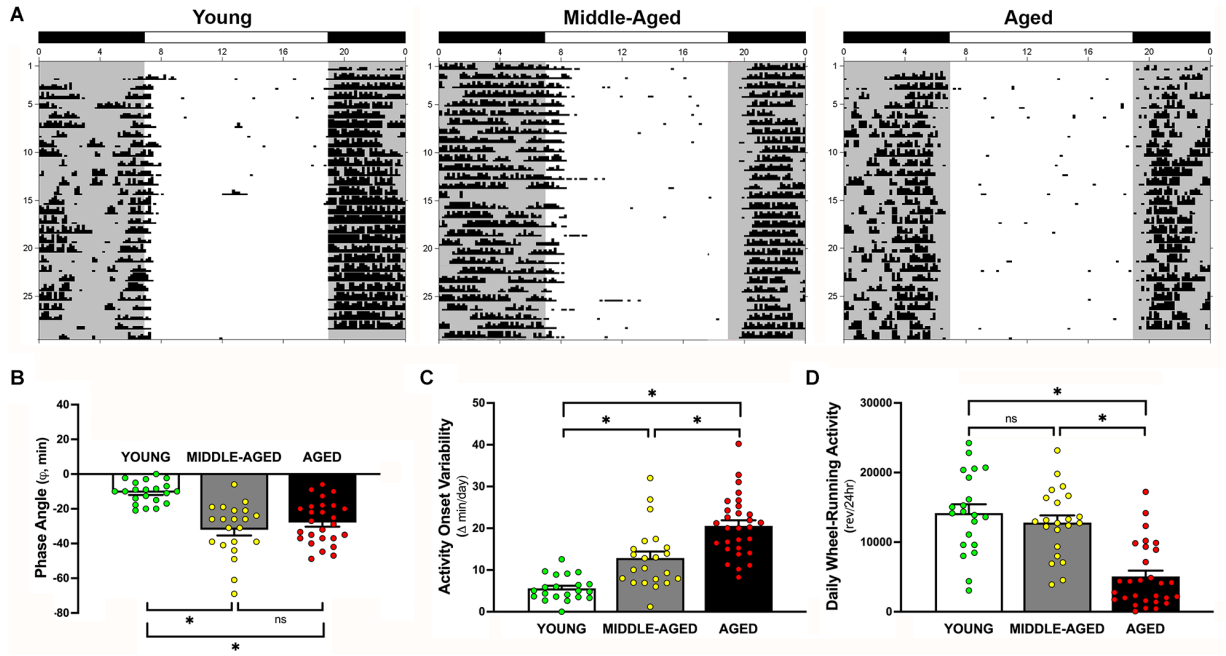

FIGURE 4
Effects of aging on light-dark entrainment and other properties of the circadian rhythm of wheel-running activity in mice. **(A)** Representative records of circadian wheel-running behavior in young (left), middle-aged (center), and aged (right) mice during entrainment to LD 12:12. Actograms are plotted over a 24-h period. The closed bars at the top and shading on the records signify the timing of the dark phase in the LD 12:12 cycle. Comparisons of **(B)** the phase angle (φ) between daily activity onsets and lights-off, **(C)** absolute day-to-day variability, and **(D)** total daily wheel-running activity (wheel revolutions/24 h) in young, middle-aged, and aged mice during entrainment to LD 12:12. In panel **(B)**, negative phase angle values (in minutes) indicate that daily onsets of activity occur after lights-off whereas positive values denote that activity onsets precede the end of the light phase. Bars (in **B–D**) depict Mean ± SEM values in young, middle-aged, and aged mice. Circles indicate individual scores of each mouse (*, Tukey's multiple comparison; $p < 0.0001$; young vs. aged; middle-aged vs. aged; young vs. middle-aged, ns = non significant, $p > 0.05$).

mice. Representative actograms of mice from each age group are shown in Figure 4A. Comparisons of young mice with the middle-aged and aged cohorts revealed clear differences in their patterns of circadian entrainment (overall effect of age; $F_{(2,69)} = 19.67$, $p < 0.0001$). In young mice, their daily onsets of activity occurred shortly after lights-off such that the average phase angle (φ) between the daily onset of activity and the offset of the photoperiod was −10.7 ± 1.4 min (Figure 4B). In contrast, the activity rhythms of middle-aged and aged mice were distinguished by an altered phase angle of entrainment to LD 12:12 such that their daily onsets of activity were delayed and occurred at later times relative to young animals, commencing up to 30–70 min after lights-off for some animals. The average values for φ between activity onsets and lights-off in middle-aged mice (−32.6 ± 3.4 min) and in aged animals (−27.5 ± 2.2 min) were significantly different ($p < 0.001$) from that observed in young mice. However, no significant difference in φ was observed between middle-aged and aged groups ($p = 0.46$). In conjunction with the delayed onsets of daily activity, middle-aged and aged mice showed unstable patterns of entrainment to LD 12:12 in which the timing of their activity onsets was highly variable between successive days (effect of age; $F_{(2,69)} = 34.13$, $p < 0.0001$). During exposure to LD 12:12, the activity onsets in individual middle-aged and aged mice occurred at (earlier or later) times that differed on average by 12.9 min and 20.6 min, respectively from the preceding day, whereas the average day-to-day variability in activity onset times of young animals was only 5.6 min (Figure 4C). The absolute day-to-day variation in the onsets of activity in middle-aged and aged animals were significantly greater ($p < 0.001$ and $p < 0.0001$, respectively) than that observed in young mice. Daily activity onset variability was also significantly greater in aged mice than in the middle-aged cohort ($p < 0.001$). Coupled with the differences in φ and the variability in the daily onsets of activity, young, middle-aged, and aged mice were characterized by marked disparities in the total amount of daily wheel-running activity (overall effect of age; $F_{(2,69)} = 24.58$, $p < 0.0001$). During entrainment to LD 12:12, daily activity levels (wheel revolutions/24 h) in young mice and middle-aged were not different from each other ($p = 0.65$) but were significantly ($p < 0.0001$) and approximately 280% and 250% greater (Figure 4D) than in aged mice, respectively.

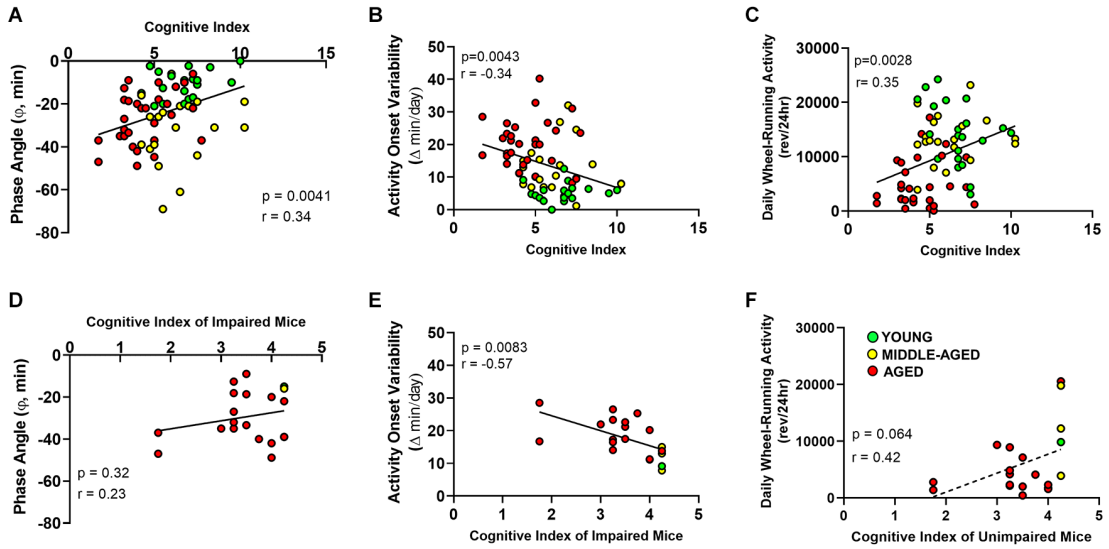

FIGURE 5
Relationship between cognitive index acquired from Barnes maze and circadian entrainment properties of the activity rhythm. **(A)** The phase angle (φ) between daily activity onsets and lights-off; **(B)** absolute day-to-day variability in onsets of activity; and **(C)** total daily wheel-running activity (wheel revolutions/24 h) are correlated with Cognitive Index for young, middle-aged, and aged mice. Panels **(D–F)** show the same circadian measures as in **(A–C)**, however only for learning-impaired. Circles indicate individual scores of each mouse (young n = 1, middle-aged n = 3 and aged n = 16). Activity onset variability, but not phase angle of entrainment or total wheel-running activity, of learning-impaired mice are negatively correlated (r = −0.57) with cognitive index.

Relationship between entrainment activity and cognition

Next, we examined the relationship between changes in cognition and circadian entrainment of the activity rhythm. In this regard, Pearson correlations were used to compare the cognitive index based on the escape strategies used by mice during training trials with three parameters of the activity rhythm characterized by changes during aging: variability in the daily onsets of activity, pattern of light-dark entrainment, and daily activity levels. The phase angle of circadian entrainment to LD 12:12 was correlated with cognitive index when all ages were analyzed as a group (Figure 5A, Pearson correlation, $p < 0.01$, $r = 0.3384$). When learning-impaired mice were analyzed separately, no correlation between CI and phase angle (Figure 5D, Pearson correlation, $p = 0.32$, $r = 0.23$) was observed. The complement group of unimpaired mice with better CI scores also did not show a correlation between the two variables (Pearson correlation, $p = 0.071$, $r = 0.26$).

For young, middle-aged and aged mice, the day-to-day variability in daily onsets of activity was negatively correlated with the Barnes maze cognitive index (Figure 5B; Pearson correlation, $p < 0.01$, $r = -0.340$). When we analyzed only learning-impaired mice, the variability in the daily onsets of activity was significantly and negatively correlated with the cognitive index (Pearson correlation, $p < 0.01$, $r = -0.57$). In this comparison, when activity onset variability was lower, the scores were higher and thus performance was better in the Barnes maze (Figure 5E). The unimpaired mice with better CI performance scores did not show a correlation between these measures (data not shown; Pearson correlation $p = 0.2403$, $r = -0.1692$). The total daily wheel-running activity was similarly correlated with the cognitive index (Figure 5C, Pearson correlation, $p < 0.01$, $r = 0.351$). A non-significant trend toward a correlation between total daily wheel-running activity and cognitive index was observed in learning-impaired mice (Pearson correlation, $p = 0.06$, $r = 0.42$), but not in unimpaired mice (Pearson correlation, $p = 0.6770$, $r = 0.06$). The significant correlations when all ages are analyzed together, but not separately for individual age cohorts again demonstrates that the observed changes in circadian properties and their relation to cognitive index are age-dependent.

Conclusion

Quantification of cognitive performance in preclinical studies is necessary in order to achieve higher translational power from basic studies to clinical observations. Learning curves are useful for demonstrating performance and change over time, but the lack of a standardized scoring system for aging mouse models presents some difficulty in comparing behavioral performances across cognitive domains. Thus, new methods of cognitive scoring are necessary for optimizing assessment in rodent models. The new index described in this report was designed to provide information about the cognitive

performance of individual animals and also to allow for a better distribution of the cognitive strategies used for learning and remembering the escape box location in the Barnes maze. Similar to the spatial learning index (SLI) for the water maze (Gallagher et al., 1993; LaSarge et al., 2007; Bizon et al., 2009), where aged rodents can be sub-divided into "low performers" and "high performers" groups, our score provides a continuous scale for measuring severity of cognitive impairment in Barnes maze. This subgrouping allowed us to investigate if C57Bl/6 mice with lower cognitive indices also exhibited changes in circadian behavior such as light-dark entrainment of the activity rhythm (**Figure 5**). Thus, the results of the present study are significant in establishing cognitive index scores that can be used to probe the relationship between cognitive impairment and other age-related biological markers in mice.

The different search strategies used by rodents in the Barnes maze test influence the latency and distance, and these measures may not be interpreted as absolute quantification of spatial learning and memory. Our novel cognitive index standardizes quantification of performance regardless of strategy selection and motor proficiency, creating a way to measure overall cognitive performance in aging, and negates the need for a true hippocampal-dependent measure. The baseline scores defined by Illouz et al. (2016) indeed reflect the animal's strategy choice based on spatial conceptualization of the Barnes maze on each individual trial. Spatial strategies demonstrating that the rodent is purposefully directed toward the goal, either directly running toward the escape, focusing its search in the proximity of the escape or correcting itself, indicate the animal has established a spatial reference map. As testing continues, we observe that the mice become less sensitive to the noxious stimulus, the drive to escape into the dark box diminishes, and the more naturalistic serial search approach becomes as prominent as the spatial search (or more prominent in some cases; Illouz et al., 2020). Modifications to the protocol, such as minimizing the number of trials, allow for focus on the time period prior to this habituation, but by summing the scores, we automatically normalized the quantification without losing the differences as the higher scores from the spatial strategies drive the difference between groups. After learning the task, spatial memory can be tested using probe trials. We observed the aged mice in our study showed less percent amount of the path in the target quadrant, and we interpret this result as a lower memory or certainty for the location of the goal. The positive relationship between the cognitive index and the probe measure in cohorts of all ages further indicates that the cognitive index reflects the severity of learning impairment regardless of influence of additional non-hippocampal mediated behaviors. Thus, our cognitive index is of value for comparisons between experimental groups in aging studies.

Circadian rhythm alterations and related disturbances of the sleep-wake cycle are commonly observed with aging and often precede or accompany the disease progression in AD (Cipriani et al., 2015; Canevelli et al., 2016), thus providing a potential diagnostic tool for assessment of early onset cognitive impairment. The fragmented sleep patterns precede, and thus are thought to contribute to, the decline in learning and memory performance in AD. In conjunction with other studies characterizing circadian rhythm misalignment in mice during aging (Bang et al., 2021), our results demonstrate that aged mice show irregular sleep-wake patterns similar to those observed in the elderly. As we are interested in modeling age-related changes that can be used as biomarkers of early decline in dementia, we also tested middle-aged C56Bl/6 mice. During entrainment to LD 12:12, the sleep-wake rhythms of middle-aged and aged mice showed delayed onsets of activity commencing at later times (by 20–60 min) relative to the young cohort. In addition to the delayed onsets of daily activity, the sleep-wake patterns of these middle-aged and aged mice were marked by fragmented bouts of activity throughout the night and by unstable patterns of entrainment to LD 12:12 as indicated by high variability in the timing of their activity onsets between successive days.

It is interesting that in the low performers group on the Barnes maze, the cognitive index was correlated with key measures of light-dark entrainment, such that lower cognitive index scores were associated with delayed and more unstable patterns of entrainment. The implications of these altered patterns of circadian entrainment in cognitive impairment during aging are unknown. Because age-related changes in circadian rhythms are not restricted to patients with cognitive decline or dementia, comparisons distinguishing two groups of animals based on cognitive performance (i.e., impaired vs. unimpaired) raises a variety of interesting questions about the mechanism of neurodegeneration during aging. The observed relationship between altered circadian rhythmicity and impaired learning suggests that there is a shared mechanism of neural dysfunction for age-related changes in circadian entrainment and cognition, but perhaps some mice are differentially protected from these changes. Consequently, it is possible that these circadian alterations may be "driving" further age-related deficits in cognition, again illustrating the utility of our model in isolating resilience factors that may differentiate unimpaired from impaired learners. These observed changes in the sleep-wake patterns of middle-aged animals also suggest that the brain circuitry responsible for circadian rhythm entrainment may be impaired earlier in the aging process than areas of the brain that mediate cognition.

In summary, the present results indicate that the cognitive index maintains a strong relationship with the memory portion of the Barnes maze and thus provides a sensitive, efficient, and valid approach to assess age-related cognitive deficits. The paired analysis of Barnes maze-acquired cognitive index and circadian entrainment may provide a valuable model within the context of age-related cognitive decline. Our findings that circadian timekeeping disturbances present before cognitive

impairment illustrate how alterations in the sleep-wake cycle might fit into the overall progression of the cognitive decline during aging and even in AD. As such, the altered and unstable patterns of circadian entrainment may be used as an early predictor of age-related cognitive impairment. In addition, this information may lead to the development of potential therapeutic strategies based on the mitigation of sleep-wake cycle disturbances/misalignment to at least slow cognitive impairment during aging and its progression in AD.

Data availability statement

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

Ethics statement

The animal study was reviewed and approved by Texas A&M University accredited AAALAC committee.

Author contributions

KS: conceptualization, formal analysis, data acquisition, analysis and curation, visualization, original writing, review and editing. AP: data acquisition. GA: data acquisition, writing—review and editing. DE: conceptualization of circadian behavior study, data analysis, curation and visualization, original writing—review and editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Longitudinal associations between sleep duration and cognitive impairment in Chinese elderly

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Background: Age-associated cognitive decline has become a major threat to both personal welfare and public health and can further develop into Dementia/Alzheimer's disease. Sleep is significantly correlated with cognitive function, but both cognitive impairment and sleep problems increase with normal aging. This study explored how sleep duration affects cognitive performance among older adults in China.

Methods: Using data from the Chinese Longitudinal Healthy Longevity Survey (CLHLS) in 2014 and 2018, cognitive function was assessed *via* the Mini-Mental State Examination (MMSE), which included five domains: orientation, registration, attention or calculation, recall, and language. Logistic regression was used to examine whether the change in sleep duration was a risk factor for cognitive impairment. We also used multinomial logistic regression to study the impact of sleep duration and the changes in sleep duration on cognitive changes during the follow-up period.

Results: The empirical study showed a U-shaped relationship between sleep duration and increased risk of cognitive impairment. Short (< 6 hours) and long (> 8 hours) sleep durations were positively associated with cognitive impairment. Tests of interactions between sleep duration and sleep quality showed that short sleep durations with fair sleep quality had an increased risk of cognitive impairment. Further, the participants were divided into three groups: normal cognition (MMSE > 24), mild cognitive impairment (MCI, 18 $\leq$ MMSE score $\leq$ 24), and severe cognitive impairment (MMSE < 18). First, of the participants with normal cognition at baseline, those who sleeping > 7 h at follow-up and > 7 h at both baseline and 4-year follow-up assessments could increase the risk of cognitive impairment. Second, for individuals with MCI at baseline, those who transitioned to sleeping > 7 h at follow-up period

and > 7 h at both baseline and 4-year follow-up assessments had a lower chance of reverting to normal cognition.

Conclusion: Excessive sleep may be a major risk for cognitive impairment among older adults. Furthermore, a moderate amount of sleep could be a possible strategy to prevent cognitive impairment.

KEYWORDS

sleep duration, cognitive impairment, U-shaped association, changes in sleep duration, cognitive changes, Chinese population

Background

Cognitive ability is the capacity of the human brain to process, store and extract information (Hunter, 1986). Cognitive decline is a progressive neurodegenerative disease associated with increasing age among the elderly (Li et al., 2019; Kioussis et al., 2021; Liu et al., 2021). The aggravation of cognitive decline is likely to lead to Alzheimer's disease, dementia, and death (Backman et al., 2005; Prince et al., 2015). By 2018, the number of Alzheimer's patients in China has increased from about 3.68 million in 1990 to nearly 10 million, ranking first in the world (Liu and Guo, 2022), posing huge pressure on informal care costs and health resources. Moreover, the cognitive health of elderly people is a very important part of healthy aging (Mei et al., 2017).

Moderate sleep duration is particularly important for optimal cognitive function. Aging also leads to changes in the sleep patterns of the elderly. And shorter or longer sleep duration was associated with a higher risk of cognitive decline. Multiple studies have assessed longitudinal associations between sleep duration and cognitive function in the elderly. However, to date, the results of these associations have been contradictory. For example, studies have shown that short (6 h or less/day) and long (9 h or more/day) durations of sleep are associated with a risk of cognitive impairment (Kronholm et al., 2009; Virta et al., 2013), whereas other studies did not find a "U-shaped" association. For example, some illustrated that only longer sleep was associated with the risk of poorer cognitive function in the elderly (Faubel et al., 2009; Loerbroks et al., 2009; Ramos et al., 2013). The inconsistent results may be due to differences in methodology and sample data.

Recently, although many studies have started to pay attention to changes in sleep duration, their results are still inconsistent. Several studies found that increased sleep durations at follow-up were associated with greater cognitive decline (Benito-León et al., 2009; Gildner et al., 2019), or all-cause dementia (Benito-León et al., 2009). Hua et al. (2020) found that an increase in sleep duration from short to moderate was significantly associated with better global cognition scores among the Chinese elderly. Ferrie et al. (2011) demonstrated participants who moved from a regular pattern of 6–8 h per night to shorter and longer durations of sleep were associated with poorer cognitive function. Moreover, few studies have focused on the association between changes in sleep duration and cognitive change over time. The absence of baseline cognitive performance data implies that the associations would lead to reverse causality, the participants with baseline cognitive impairment being more likely to develop adverse sleep patterns during the follow-up period (Xu et al., 2014).

Although considerable studies have focused on the associations between sleep duration and cognitive function, the results are still inconsistent. In addition, few studies have tested how changes in sleep duration over time in association with cognitive impairment. Thus, our purpose was to clarify how changes in sleep patterns might impact age-related cognitive deficits among Chinese elderly people. Based on longitudinal data from the Chinese Longitudinal Healthy Longevity Survey (CLHLS) in 2014 and 2018 follow-up data, this current study enriches and expands previous research in three aspects. **Firstly,** several studies targeting Chinese older adults (Gu et al., 2010; Lee et al., 2018; Wang et al., 2020) were based on a cross-sectional design, but we provided a perspective on changes in sleep duration by using a large study sample with longitudinal data. **Secondly,** in comparison with the earlier studies, we evaluated the impact of sleep duration and the changes in sleep duration on cognitive impairment. **Thirdly,** we explored the impact of sleep duration and the changes in sleep duration on cognitive changes over 4 years.

Materials and methods

Participants

The data used in the study are selected from a publicly accessible database of the CLHLS, conducted by the Chinese Center for Disease Control and Prevention and Peking University. The baseline survey of the CLHLS program is officially launched in 1998 and followed-up every 2–3 years since, which covers 23 provinces/cities/autonomous regions in mainland China. The CLHLS adopts a multi-stage unequal proportion target random sampling method (Wu et al., 2021),

which represents 85% of the total population in China. As a nationwide and comprehensive longitudinal tracking survey, the CLHLS provides high-quality longitudinal data for academic/scientific investigation and policy research in important areas such as Chinese society, population, and health. The present study included individuals who had data in 2014 as a baseline and 2018 as a follow-up for data analysis (the latest datasets we could obtain when this study was carried out).

A total number of 15,874 participants were enrolled in CLHLS (2018). We used 2 waves of CLHLS data conducted in 2014 and 2018 to analyze how sleep duration influenced cognitive function. In 2018, 1,525 were lost to follow-up and 2,226 older adults died before the re-interview. After excluding respondents with missing values and under 60 years old, 2,195 out of 7,192 eligible participants were included for analyses. Details about the sample selection and preprocessing are shown in **Figure 1**.

Cognitive function

As a classic cognitive function assessment tool, the Mini-Mental State Examination (MMSE) is widely used to assess cognitive function worldwide (Zhang et al., 1990; König et al., 2017). The Chinese versions of the MMSE was developed and validated in Chinese populations (Chen et al., 2021). In CLHLS, the MMSE includes five aspects of cognitive functioning: orientation, registration, attention or calculation, recall, and language. More details about MMSE are shown in **Table 1**.

The MMSE is a frequently used 24-item assessment of cognitive functioning. Referring to Zhang (2006), the results of item-6 were evaluated by scoring point for each food and 7 points for those who name 7 or more foods. For the other 23 questions, participants who got the correct answer received a score of 1 (otherwise 0). The total score for the MMSE ranges from 0 to 30, with higher scores indicating better cognitive ability. In this study, cognitive impairment was defined as an MMSE score ≤ 24, whereas scores > 24 indicate no cognitive impairment (Ganguli et al., 2004). Cronbach's coefficient alpha of scales testing orientation, registration, attention or calculation, recall, and language were 0.756, 0.769, 0.732, 0.754, and 0.729, respectively. The total Cronbach's coefficient alpha was 0.789, indicating good internal consistency of the items in the scale.

Sleep measures

To measure sleep duration, we used the following question: "How many hours of actual sleep did you get at night (average hours for one night)?" To further examine any association between sleep duration ranges and cognitive function, participants were divided into short (<6 h), moderate (6–8 h; reference group), and long (>8 h) groups (Li et al., 2022; Ding et al., 2020). According to the results of restricted cubic spline (RCS), we recoded sleep duration as a dichotomous variable (≤ 7 h vs. > 7 h) to better understand the relationship between change in sleep duration and cognitive change.

Covariates

Referring to Zhang et al. (2021) and Lin et al. (2022), the covariates included sociodemographic variables and risk factors for cognitive function. The sociodemographic variables are age (years), sex (male or female), body mass index (BMI), marital status (married, separated/divorced, and single), household income (RMB), residential area (rural or urban), living arrangement (live with families or live alone), smoking status (non-smoker or smoker), drinker status (non-drinker or drinker), and ADL disability (yes or no). A respondent was defined as ADL disabled if any difficulty in one or more of the above six activities was reported. For each of the following items, score "1" if the respondent had no difficulty in finishing it, or "0" if the respondent had difficulty completing the following tasks: (1) bathing; (2) dressing; (3) toileting; (4) indoor transferring; (5) continence; (6) eating.

Referring to Iizuka et al. (2019) and Han et al. (2022), the risk factors for cognitive function are sleep quality (poor, fair, and good), regular physical activity (yes or no), social activities (never, irregular, and regular), and cultural activities (never, irregular, and regular).

Statistical analysis

We described the characteristics of participants based on two groups according to the respondent's MMSE score (cognitively impaired group, cognitively normal group). Basic characteristics are shown as the frequencies and percentages (*N*, %) for categorical variables and mean values for continuous variables. The differences between the two groups were investigated through the Chi-squared test for categorical variables and the *t*-test for continuous variables. The descriptive statistical analysis of all variables is shown in **Table 2**.

We adopted the logistic model to explore the association between sleep duration and the risk of cognitive impairment. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated to estimate the effects of sleep duration on the risk of cognitive impairment. In addition, further analyses were performed to examine the association between the changes in sleep parameters and cognitive changes. **First,** we examined whether the combination at two-time points affected the risk

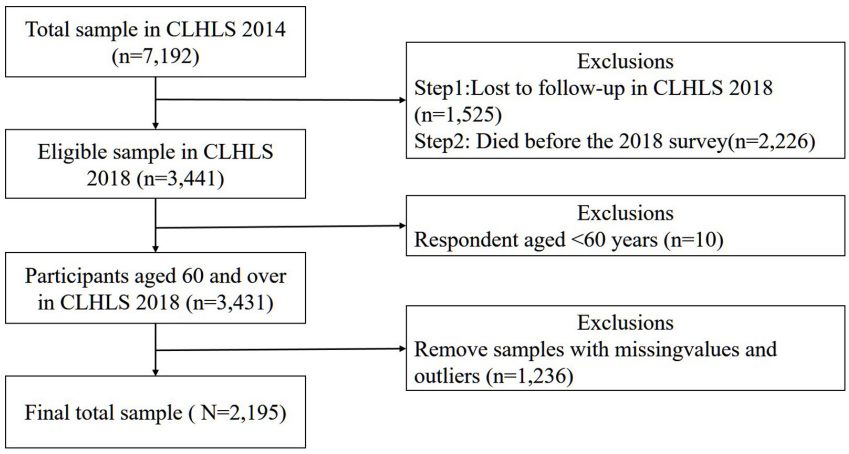

FIGURE 1
Flowchart of sample selection and preprocessing (*n* represents sample size).

TABLE 1 Details about the Chinese version of the modified mini-mental state examination.

Dimensions	Item	Scores
Orientation	1. What time of day is it now (morning, afternoon, evening)?	1
	2. What is the animal year of this year?	1
	3. What is the date (day and month) of the mid-autumn festival?	1
	4. What is the season now (spring, summer, fall, or winter)?	1
	5. What is the name of this county or district?	1
	6. Please name as many kinds of food as possible in 1 min (1 point for each food and 7 points for those who name 7 or more foods).	7
Registration	7–9. Please repeat these three objects: table, apple, clothes.	3
Attention and calculation	10–14. I will ask you to spend $3 from $20, then you must spend $3 from the number you arrived at and continue to spend $3 until you are asked to stop.	5
	15. I want you to draw the figure on B Card.	1
Recall	16–18. Repeat the three objects learned a little while ago (table, apple, clothes).	3
Language	19–20. Naming pen and watch.	2
	21. Repeat the following sentence: what you plant, what you will get.	1
	22–24. I will give you a piece of paper. You must take the paper using your right hand, fold it in the middle using both hands, and place the paper on the floor.	3

of cognitive impairment. **Second,** we performed a multinomial logistic regression analysis to estimate the association between sleep duration and cognitive changes over 4 years. Specifically, for the MCI in CLHLS (2014), we classified the outcome at follow-up (CLHLS, 2018) into 3 categories: (1) remained as MCI ($18 \leq$ MMSE score ≤ 24), (2) reverted to normal cognition (MMSE > 24), and (3) progressed to severe cognitive impairment (MMSE < 18) (Wang et al., 2010). **Third,** we investigated the association between the change in sleep parameters (7 h as cutoff points) and cognitive changes over 4 years. Statistical analysis was conducted using the R software version 4.1.0.

Results

Characteristics of samples

Table 2 represented the comparison between cognitively impaired (MMSE score ≤ 24) and cognitively normal (MMSE scores > 24) by covariates. Among the 2,195 participants, 417

TABLE 2 Baseline characteristics of study participants in the CLHLS 2018.

Variables	Total	Cognitive impairment	Normal cognition	*P*-value[a]
	(*n* = 2,195)	(*n* = 544)	(*n* = 1,651)	
Sleep duration (hours/per day)				
Short	417 (19.0%)	119 (21.9%)	298 (18.1%)	0.05
Moderate	1,266 (57.7%)	247 (45.4%)	1,019 (61.7%)	0.001
Long	512 (23.3%)	178 (32.7%)	334 (20.2%)	0.001
Age, years	83.89 ± 9.63	89.15 ± 8.27	82.16 ± 8.03	0.001
≤ 80	848 (38.6%)	87 (16.0%)	761 (46.1%)	0.05
> 80	1,347 (61.4%)	457 (84.0%)	890 (53.9%)	0.001
Sex (males)	1,108 (50.5%)	177 (32.5%)	931 (56.4%)	0.001
BMI (kg/m^2)	23.18 ± 12.50	22.22 ± 8.38	23.49 ± 13.58	0.001
Marital status (married)	1,212 (55.2%)	392 (72.1%)	820 (49.7%)	0.001
Household income (RMB)	9.83 ± 1.79	9.74 ± 1.95	9.86 ± 1.74	0.001
Residential area (urban)	449 (20.5%)	84 (15.4%)	365 (22.1%)	0.001
Living arrangement (live alone)	414 (18.9%)	101 (18.6%)	313 (19.0%)	0.83
Sleep quality				
Poor	317 (14.4%)	92 (16.9%)	225 (13.6%)	0.05
Fair	739 (33.7%)	199 (36.6%)	540 (32.7%)	0.09
Good	1139 (51.9%)	253 (46.5%)	886 (53.7%)	0.001
Smoking status	393 (17.9%)	83 (15.3%)	310 (18.8%)	0.06
Drinker status	378 (17.2%)	60 (11.0%)	318 (19.3%)	0.001
ADL disability	312 (14.2%)	184 (33.8%)	128 (7.8%)	0.001
Regular physical Activity	709 (32.3%)	123 (22.6%)	586 (35.5%)	0.001
Social activity				
Never	736 (33.5%)	268 (49.3%)	468 (28.3%)	0.001
Irregular	731 (33.3%)	158 (29.0%)	573 (34.7%)	0.05
Regular	728 (33.2%)	118 (21.7%)	610 (36.9%)	0.001
Cultural activity				
Never	1781 (81.1%)	521 (95.8%)	1260 (76.3%)	0.001
Irregular	204 (9.3%)	14 (2.6%)	190 (11.5%)	0.001
Regular	210 (9.6%)	9 (1.6%)	201 (12.2%)	0.001

[a] *T*-test for continuous variables and a chi-square test for categorical variables.

participants (19.0%) slept for less than 6 h, 1,266 participants (57.7%) slept for 6–8 h, and 512 participants (23.3%) slept for 8 h or more. The majority (75.2%) had an MMSE score between 25 and 30 (normal cognition), with the remainder (24.8%) having an MMSE score ≤ 24 (cognitive impairment).

Of all the respondents, there were 1,087 (49.5%) females and 1,108 (50.5%) males. The majority of the participants lived in rural areas (79.5%) and lived with their household members to share in their later years (81.1%). More than half of the elderly had good self-reported sleep quality (51.9%). Few older people reported being current smokers or drinkers, accounting for 17.9 and 17.2%, respectively. Most Chinese seniors didn't participate in physical activity (67.7 %) or cultural activities (81.1%).

In total, 61.7% of participants with moderate sleep have normal cognition, while only 45.4% of participants with moderate sleep experienced cognitive impairment; this difference is significant ($P < 0.001$). Respondents who suffered from cognitive impairment were more likely to be female, older, married, living in rural areas, living with family, smoker or drinker, have ADL difficulties, and never participate in leisure activities (physical activity, social activity, and cultural activity).

Associations between sleep duration and cognitive impairment

Results from the unadjusted and covariate-adjusted multilevel models are presented in Table 3. Model 1 was a crude model. Model 2 was adjusted for sociodemographic variables. Model 3 was further simultaneously adjusted by sleep quality, regular physical activity, social activities,

TABLE 3 Impact of sleep duration on the risk of cognitive impairment at follow-up (CLHLS, 2018)[a] (*N* = 2,195).

Variables	Model 1	Model 2	Model 3	Model 4
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Sleep duration				
Short (< 6 h)	1.64 (1.27–2.12)***	1.54 (1.16–2.04)**	1.39 (1.01–1.92)*	0.67 (0.24–1.61)
Moderate (6–8 h)	Ref	Ref	Ref	Ref
Long (>8 h)	2.19 (1.74–2.76)***	1.86 (1.44–2.41)***	1.97 (1.50–2.58)***	1.75 (1.26–2.43)***
Duration × Quality				
Short*Fair				2.91 (1.08–8.63)*
Short*Bad				1.70 (0.57–5.49)
Long* Fair				1.38 (0.74–2.56)
Long* Bad				1.35 (0.42–4.43)
Age (> 80)		3.12 (2.39–4.12)***	2.87 (2.18–3.81)***	2.89 (2.20–3.84)***
Sex (males)		0.44 (0.34–0.56)***	0.51 (0.40–0.67)***	0.52 (0.40–0.67)***
BMI (kg/m^2)		0.99 (0.97–1.00)	0.99 (0.97–1.00)	0.99 (0.97–1.00)
Marital status (married)		1.39 (1.06–1.81)*	1.37 (1.05–1.80)*	1.36 (1.04–1.78)*
Household income (RMB)		0.96 (0.90–1.02)	0.97 (0.91–1.03)	0.97 (0.91–1.03)
Residential area (urban)		0.49 (0.36–0.66)***	0.62 (0.44–0.86)**	0.61 (0.44–0.85)**
Living arrangement(live alone)		0.80 (0.59–1.07)	0.84 (0.62–1.14)	0.85 (0.62–1.14)
Smoking status		1.43 (1.03–1.97)*	1.46 (1.04–2.03)*	1.47 (1.05–2.05)*
Drinker status		0.81 (0.57–1.04)	0.84 (0.58–1.18)	0.83 (0.58–1.18)
ADL disability		4.74 (3.59–6.03)***	3.92 (2.92–5.29)***	4.01 (2.98–5.41)***
Sleep quality				
Poor			1.18 (0.83–1.68)	0.85 (0.23–3.20)
Fair			Ref	Ref
Good			0.86 (0.66–1.22)	0.26 (0.07–0.80)*
Regular physical activity			0.91 (0.70–1.19)	0.92 (0.70–1.20)
Social activity				
Never			Ref	Ref
Irregular			0.87 (0.66–1.14)	0.87 (0.66–1.14)
Regular			0.56 (0.42–0.75)***	0.56 (0.42–0.75)***
Cultural activity				
Never			Ref	Ref
Irregular			0.31 (0.16–0.54)***	0.31 (0.16–0.54)***
Regular			0.21 (0.09–0.41)***	0.21 (0.09–0.41)***

[a]Multiple logistic regression.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

and cultural activities. Model 4 was the same as model 3 plus the interaction term between sleep duration and sleep quality.

In Model 3, short or long sleep duration was significantly associated with a higher risk of cognitive impairment, with moderate sleep durations as the reference (column 4 of Table 3). In Model 4, short sleep durations with fair sleep quality had a higher risk of cognitive impairment (OR = 2.91, 95% CI: 1.08–8.63). The subgroup analyses show that the elderly who are older, female, married, smoking, live in the rural area, have ADL difficulties, and never participate in social activities or cultural activities predict an increased risk of cognitive decline than their counterparts (column 4 of Table 3).

We further evaluated the relationship between sleep duration and cognitive impairment by RCS. The results showed a U-shaped relationship between sleep duration and risk of cognitive impairment (Figure 2).

Table 4 presents the adjusted associations between sleep duration and cognitive impairment of persons with normal cognition at baseline. Those who slept > 7 h at follow-up (OR, 1.28; 95% CI, 1.00–1.71) were at an increased risk of cognitive impairment, whereas baseline sleep duration had shown insignificant effects. The individual's sleep duration > 7 h at both baseline and follow-up period (OR, 1.50; 95% CI, 1.00–2.31) had an approximately 1.5 times higher risk of cognitive decline.

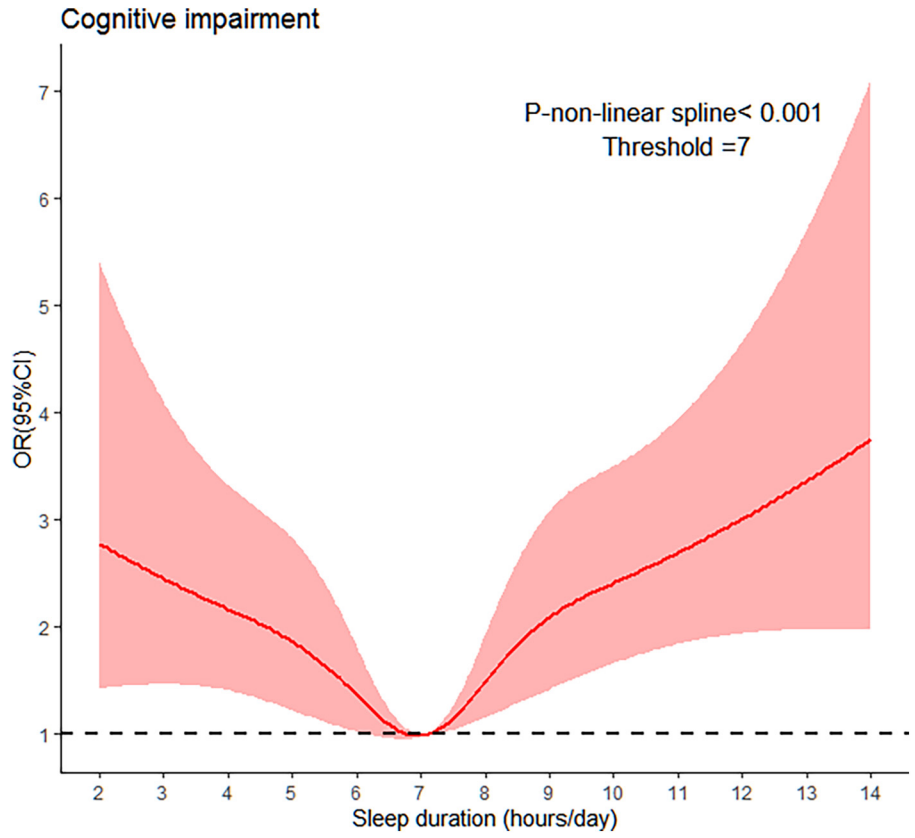

FIGURE 2
Associations between sleep duration and cognitive impairment using a RCS regression. Using logistics regression to get the odds ratio after adjusting for age, sex, body mass index (BMI), marital status, household income (RMB), residential area, living arrangement, smoking status, drinker status, ADL disability, sleep quality, regular physical activity, social activities, and cultural activities.

TABLE 4 Associations between changes in sleep duration across 2014 and 2018 and cognitive impairment[a].

Normal cognition at baseline (n = 1,851)	Cognitive impairment	
	No. Events/Total	OR (95% CI)
Sleep duration at baseline, h		
≤ 7	175/953	Ref
> 7	170/898	1.16 (0.89–1.52)
Sleep duration at follow-up, h		
≤ 7	180/1045	Ref
> 7	165/806	1.28 (1.00–1.71)*
Changes in sleep duration over 4 years, h		
≤ 7 at both baseline and follow-up	107/610	Ref
Changed from ≤ 7 to > 7	68/343	1.09 (0.72–1.64)
Changed from > 7 to ≤ 7	73/435	0.66 (0.43–1.01)
>7 at both baseline and follow-up	97/463	1.50 (1.00–2.31)*

[a]Multiple logistic regression analysis adjusted for age, sex, body mass index (BMI), marital status, household income (RMB), residential area, living arrangement, smoking status, drinker status, ADL disability, sleep quality, regular physical activity, social activities, and cultural activities.
*$p < 0.05$.

TABLE 5 Impact of change of sleep parameters on the cognitive changes over 4 years[a].

MCI at baseline (n = 259)	Reverted to normal cognition		Progressed to severe cognitive impairment	
	No. Events/Total	OR (95% CI)	No. Events/Cognitive Total	OR (95% CI)
Sleep duration at baseline, h				
≤ 7	72/133	Ref	24/133	Ref
> 7	54/126	0.54 (0.28–1.03)	28/126	0.98 (0.45–2.15)
Sleep duration at follow-up, h				
≤ 7	79/140	Ref	21/140	Ref
> 7	47/119	0.46 (0.22–0.96)*	31/119	1.26 (0.51–3.07)
Changes in sleep duration over 4 years, h				
≤ 7 at both baseline and follow-up	46/80	Ref	13/80	Ref
Changed from ≤ 7 to >7	26/53	0.54 (0.20–1.50)	11/53	0.85 (0.24–3.03)
Changed from >7 to ≤ 7	33/60	0.62 (0.25–1.46)	8/60	0.65 (0.20–2.11)
>7 at both baseline and follow-up	21/66	0.25 (0.09–0.66)**	20/66	1.12 (0.36–3.47)

[a]Multinomial logistic regression analysis adjusted for age, sex, body mass index (BMI), marital status, household income (RMB), residential area, living arrangement, smoking status, drinker status, ADL disability, sleep quality, regular physical activity, social activities, and cultural activities.
*$p < 0.05$, **$p < 0.01$.

TABLE 6 Sensitivity analyses including the interpolated missing values of covariates[a] (N = 2,635).

Variables	Model 1	Model 2	Model 3	Model 4
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Sleep duration				
Short (< 6 h)	1.71 (1.35–2.15)***	1.58 (1.22–2.04)***	1.37 (1.02–1.83)*	0.53 (0.21–1.19)
Moderate (6–8 h)	Ref	Ref	Ref	Ref
Long (> 8 h)	2.21 (1.35–2.15)***	1.80 (1.43–2.27)***	1.94 (1.52–2.48)***	1.71 (1.28–2.30)***
Duration × Quality				
Short*Fair				3.69 (1.49–10.02)**
Short*Bad				2.21 (0.81–6.51)
Long* Fair				1.40 (0.79–2.45)
Long* Bad				1.16 (0.40–3.37)

[a]Models were adjusted as we did in Table 3.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

Associations between changes in sleep duration and cognitive changes over 4 years

Among the 259 participants with MCI (18 ≤ MMSE score ≤ 24) at baseline, 126 individuals transitioned to normal cognition and 52 into severe cognitive impairment. As shown in Table 5, those sleeping > 7 h at follow-up (OR, 0.46; 95% CI, 0.22–0.96) had about a 54% lower chance of reverting to normal cognition. In addition, those who sleeping > 7 h at baseline and 4-year follow-up assessments (OR, 0.25; 95% CI, 0.09–0.66) had about a 75% lower chance of reverting to normal cognition, respectively (Table 5). However, sleep duration at baseline had no association with cognitive change during 4-year period.

Sensitivity analyses

Referring to Xiong et al. (2022), this study uses a machine learning method, the Random Forest (RF) algorithm, to interpolate all the missing values of covariates. As shown in Table 6, the estimation results of sleep duration on cognitive impairment are similar to the results of Table 3, indicating that this study has good robustness.

Discussion

In this study, we explored the influence of sleep duration on cognitive impairment, as well as the longitudinal association

between the changes in sleep duration and cognitive change with a 4 years follow-up from 2014 to 2018. Older adults with cognitive impairment and normal cognition were 24.8 and 75.2%, respectively. Compared with moderate sleep duration between 6 and 8 h, short (<6 h) and long (>8 h) sleep durations had a stronger association with cognitive impairment. Similar associations were also found in other studies (Ma et al., 2020; Fu et al., 2021). Several possible explanations for their relationship can be suggested. First, short durations of sleep would lead to elevated stress hormones (Reynolds et al., 2010), which had been linked with cognitive decline. Second, longer sleep durations could contribute to elevated levels of inflammatory markers (Irwin et al., 2016) and psychiatric disorders (i.e., either anxiety or depression) (Zhai et al., 2015; Dong et al., 2022), which in turn can lead to cognitive decline. Also, short sleep durations with fair sleep quality were detrimental to cognitive performance. Short sleep duration will lead to circadian dysfunction, and circadian dysfunction was associated with cognitive decline (Xiong et al., 2021a).

In our study, participants living in rural areas have an increased risk of cognitive decline than participants living in urban areas. The result was in line with some previous existing literature (Jia et al., 2014; Xiong et al., 2021b). This may be because, under the urban-rural dual structure, rural areas have relatively few entertainment products and local services compared with urban areas. Participation in social activities and cultural activities might significantly contribute to prevention of cognitive decline and dementia, this was consistent with the study of Fancourt et al. (2018). Probably because social activities could not only reduce perceived isolation but minimize the negative impacts of sedentary behaviors by encouraging older adults to leave their homes. Cultural participation (i.e., reading activities) activated several cognitive processes, such as working memory capacity (Baddeley, 2003), executive functioning (Swanson and O'Connor, 2009), and the ability of decoding (Perfetti, 1985).

Few previous studies have focused on the relationship between the changes in sleep duration and cognitive changes. In this longitudinal study, we explored the association between changes in sleep duration and cognitive change. Our findings unveiled that sleeping > 7 h at follow-up period was associated with cognitive impairment in both those with normal cognition and MCI at baseline. However, Westwood et al. (2017) demonstrated that prolonged sleep duration was only associated with the risk of cognitive decline in persons with MCI, but not with normal cognition. Amyloid β, a key mechanism in the development of Alzheimer's disease pathology, begins to accumulate before an individual is diagnosed with MCI (Holth et al., 2017). Those with MCI would have some psychiatric disorders such as anxiety and depression (Gabryelewicz et al., 2004), which are closely related to sleep disturbances. This might explain our findings.

In addition, sleeping > 7 h at both baseline and 4-year follow-up assessments was associated with cognitive impairment in both those with normal cognition and MCI at baseline. Several previous studies supported our findings. For example, Suh et al. (2018) conducted a cross-sectional study and found that long sleep duration at both the baseline and 4-year follow-up assessments had a high risk of cognitive decline among the Korean elderly, while no significant association was detected between an increase sleep duration from short to long and cognitive change.

However, our study also had certain limitations that should be mentioned. Firstly, the measures of sleep duration were calculated based mainly on self-reported and single-item, which could be biased. Nevertheless, plenty of large cohorts confirmed the identified relationship between self-reported sleep duration and objectively ascertained health outcomes, making our research more reliable and convincing (Jike et al., 2018; Kwok et al., 2018). Secondly, of all the respondents, 1,525 were lost to follow up and 2,226 died in CLHLS (2018), which accounted for 21.2 and 31.0% of the total included participants, respectively. This might affect our result. Thirdly, the CLHLS did not collect the sleep-related parameters that might impact cognitive performance, such as sleep efficiency, midsleep time, sleep latency, and sleep efficiency. Therefore, further research is necessary to confirm the relationship between sleep-related parameters and cognitive function to find more effective ways to prevent sleep problems and cognitive impairment.

Conclusion

The identified relationship in this study would provide further evidence to determine the optimal sleep duration in the elderly. For those with long sleep durations, policies and interventions that target cognitive impairment should emphasize the importance of normal sleep durations and avoid excessively long sleep durations. This would be important to offset the increasing burdens to individuals and society arising from late-life dementia and cognitive impairment in our rapidly aging populations.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://opendata.pku.edu.cn/.

Author contributions

W-CC conceptualized the manuscript and designed the methodology and writing—original draft preparation. W-CC and X-YW contributed to the data analysis and writing—review and editing. Both authors have read and agreed to the published version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Instability of non-REM sleep in older women evaluated by sleep-stage transition and envelope analyses

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Study objective: Traditionally, age-related deterioration of sleep architecture in older individuals has been evaluated by visual scoring of polysomnographic (PSG) recordings with regard to total sleep time and latencies. In the present study, we additionally compared the non-REM sleep (NREM) stage and delta, theta, alpha, and sigma wave stability between young and older subjects to extract features that may explain age-related changes in sleep.

Methods: Polysomnographic recordings were performed in 11 healthy older (72.6 ± 2.4 years) and 9 healthy young (23.3 ± 1.1 years) females. In addition to total sleep time, the sleep stage, delta power amplitude, and delta, theta, alpha, and sigma wave stability were evaluated by sleep stage transition analysis and a novel computational method based on a coefficient of variation of the envelope (CVE) analysis, respectively.

Results: In older subjects, total sleep time and slow-wave sleep (SWS) time were shorter whereas wake after sleep onset was longer. The number of SWS episodes was similar between age groups, however, sleep stage transition analysis revealed that SWS was less stable in older individuals. NREM sleep stages in descending order of delta power were: SWS, N2, and N1, and delta power during NREM sleep in older subjects was lower than in young subjects. The CVE of the delta-band is an index of delta wave stability and showed significant differences between age groups. When separately analyzed for each NREM stage, different CVE clusters in NREM were clearly observed between young and older subjects. A lower delta CVE and amplitude were also observed in older subjects compared with young subjects in N2 and SWS. Additionally, lower CVE values in the theta, alpha and sigma bands were also characteristic of older participants.

Conclusion: The present study shows a decrease of SWS stability in older subjects together with a decrease in delta wave amplitude. Interestingly, the decrease in SWS stability coincided with an increase in short-term delta, theta, sigma, and alpha power stability revealed by lower CVE. Loss of electroencephalograms (EEG) variability might be a useful marker of brain age.

KEYWORDS

delta power, sleep transition, envelope analysis, K-complexes, SWS, older

Introduction

Epidemiologic studies indicate that sleep disorders are associated with chronic diseases such as obesity, diabetes heart disease as well as poor mental health (Foley et al., 2004, 1995). Older adults voice more complaints about sleep than young adults (Wolkove et al., 2007; Ministry of Health, Labor and Welfare, 2019), and over 50% of older adults express chronic sleep complaints (Ancoli-Israel, 2009). With advancing age, the characteristic sleep experience changes are as follows: (1) advanced sleep phase (e.g., go to bed early and rise early), (2) longer sleep onset latency, (3) shorter overall sleep duration, (4) increased sleep fragmentation, (5) reduced amount of slow-wave sleep (SWS), and (6) increased number of wake events and time spent awake (Prinz et al., 1990; Ohayon et al., 2004).

Age-related changes in sleep can be viewed as the effect of aging on homeostatic and circadian sleep processes (Borbély, 1982; Borbély et al., 2016). The magnitude of the delta power in the electroencephalograms (EEG) depends on the awake time before sleep onset, and is considered an index of a homeostatically regulated process, i.e., Process S of the two-process model of sleep (Borbély, 1982). Previous studies targeting various age groups showed an attenuation of delta power with aging (Carrier et al., 2001; Gaudreau et al., 2001; Landolt and Borbély, 2001; Darchia et al., 2007). The effect of aging on the circadian process of sleep is reflected as an advanced sleep phase. Indeed, the circadian rhythm of body temperature also shows a phase advance as well as a decreased amplitude (Weitzman et al., 1982; Van Someren et al., 2002). Although sleep is conventionally classified into discrete stages every 30 s, the aggregated deterioration in the sleep architecture of older subjects is most commonly assessed as total time in each sleep stage and sleep onset latency; few studies have evaluated differences in the stability of sleep stages and their transitions. Given the homeostatic and circadian components of sleep regulation, it is important to evaluate the time course of the sleep stages and delta power throughout the entire sleeping period.

Hypnograms showing sleep stages as a function of time could provide insight into sleep quality, such as the number and duration of different sleep stages, and sleep stage transitions (Laffan et al., 2010). For example, it is well known that exercise performed during the day increases the probability of transitions from N1 to N2 and decreases transitions from N1 to waking (Kishi et al., 2013). Comparisons of hypnograms between young and older subjects are limited, however, and the sleep stage durations have not been considered (Schlemmer et al., 2015).

A novel computational analysis method of EEG, termed the envelope analysis, was proposed by Díaz et al. (2018), as a complement to classic spectral analysis. The EEG is band-pass filtered for the desired frequency range—for example, the delta band (0.5–4 Hz), and the envelope of this signal is obtained. The amplitude of the envelope can be thought of as the instantaneous energy in the respective band with its time course revealing the temporal stability of the oscillation in this band. The coefficient of variation of the envelope (CVE) of the given EEG band provides a scale-independent measure of its temporal stability. In human sleep, low delta-CVE values were associated with the stable oscillations characterizing SWS, while high delta-CVE values were a sign of the irregular phasic processes associated with shallow non-rapid eye movement (NREM) sleep, stages N1 and N2 (Díaz et al., 2018; Park et al., 2021).

In the present study, polysomnographic (PSG) recordings were performed in young and older subjects. First, we confirmed previously reported age-related changes in sleep architecture, such as longer wakefulness and shorter SWS, in older subjects. Second, we assessed the stability of NREM sleep, particularly SWS, by comparing the number of episodes and their duration, and by analyzing sleep stage transitions; detecting more transitions in older subjects. Third, after Fourier transform of EEG signals, delta power was compared between age groups, with older subjects exhibiting lower EEG delta power values. Lastly, CVE analysis of the delta, theta, alpha and sigma bands showed significant differences between young and older subjects. Older participants showed lower CVE values, which indicate less short term variability of EEG power in the respective bands.

Materials and methods

Participants

All participants were recruited through advertisements, and 11 older women (68–76, average 72.1 years old) and 9 young women (21–25, average 22.3 years old) participated in the study.

Inclusion criteria were standard body size (BMI < 30 kg/m^2), and absence of the following: subjective sleep complaints, use of sleeping pills, exercising habit more than twice a week, smoking habit, and shift work or trans meridian travel within 1 month before the study. In addition, young women with a regular menstrual cycle were selected. Before beginning the study, the nature, purpose, and risks of the study were explained to all subjects and informed written consent was obtained. All study protocols were approved by the local Ethics Committee of the University of Tsukuba (Ref No., Tai 29-29 and Ref No., 30-134), and conducted in accordance with the Helsinki Declaration.

Protocol

To accustom the subjects to the experimental environment, the experiment was preceded by an adaptation night in the laboratory within 7 days before the experiment, during which electrodes of the PSG recording system were attached to the subjects. For 1 week before the experiment, subjects were instructed to follow their own regular sleep-wake schedule and this was confirmed by a wrist-worn actigraph (GT3X-BT, AMI, VA, USA).

On the experiment day, subjects ate dinner 5 h before bedtime, and then reported to the laboratory. After attaching the PSG electrodes, subjects entered the environment-controlled room where the temperature and humidity of incoming fresh air were maintained at 25.0 ± 0.5°C and 55.0 ± 3.0%, respectively (Fuji Medical Science, Chiba, Japan). Subjects were instructed to maintain a sedentary posture and stay awake till bedtime, which was individually determined based on their habitual bedtime, and sleep time was set 8 h. As for young subjects, their experimental day was set during the follicular phase to eliminate the effects of menstrual cycles on sleep architecture.

Polysomnography

Sleep was recorded polysomnographically (PSG-1100, Nihon Kohden, Tokyo, Japan). EEG electrodes were placed at six sites (F3/M2, F4/M1, C3/M2, C4/M1, O1/M2, and O2/M1), and two electro-oculograms and one submental electromyogram were adopted and recorded during an 8-h sleep period. The recordings were scored every 30 s for classification into the five sleep stages: wakefulness (W), rapid eye movement (R), NREM sleep stage 1 (N1), NREM sleep stage 2 (N2), and SWS according to the standard criteria (Silber et al., 2007). Sleep efficiency is calculated as sum of Stage N1, Stage N2, Stage N3, and REM sleep, divided by the total time in bed and multiplied by 100. K-complexes are well delineated, sharp negative waves followed by a positive component standing out from the background EEG with a total duration $\geq$0.5 s. They are usually maximal in amplitude when recorded using frontal derivations (American Academy of Sleep Medicine [AASM], 2010). We identified K complexes through a machine-learning algorithm using the EEG directly as an input. The number of K-complex was normalized as % of 5 s segment in the entire N2, in which K-complexes was detected. The number of sleep episodes, defined as the time interval of consecutive sleep stages, and the length of each episode were calculated for each subject. The C3-A2 EEG recording was analyzed using discrete fast Fourier transformation. The fast Fourier transformation was conducted on an EEG record length of 5 s to obtain a frequency resolution of 0.2 Hz (Park et al., 2017). Each 5-s segment of the EEG signal was first windowed with a Hanning tapering window before computing the power spectrum. The power content of the delta band for each 30-s epoch of sleep was determined as the average delta power across the 6 consecutive 5-s segments of the EEG (expressed as μV^2).

The CVE for the different EEG bands was calculated for the C3-A2 EEG recordings at 30-s intervals. To minimize aliasing effects, the epochs had a 50% overlap, which means the epoch length was 60 s. First, every epoch was digitally bandpass-filtered (delta: 0.5–4.0 Hz, theta: 4–8 Hz, alpha: 8–12 Hz, sigma 13–17 Hz) with a fourth-order IIR implementation of a Butterworth filter using the "signal" package for the R language[1] as filt_EEG. The envelope of the filt_EEG (Filt_EEG_env) was obtained using its Hilbert transform (Ht) according to the standard relation:

$$\text{Filt\_EEG\_env} = \sqrt{(\text{Filt\_EEG}^2 + \text{Ht}(\text{filt\_EEG})^2)}$$

Both the filter and envelope calculations usually produce artifacts at the border of each epoch. To avoid this problem, the samples of each epoch were collected with a 10% excess (i.e., 66 s in total, 3 s per side). Once the envelope was obtained, the time excess was removed. The mean and standard deviation (SD) of the envelope were calculated and a normalized version of the CVE was obtained: SD/(mean $\times$ 0.523); with 0.523 being the value for the CVE of Gaussian waves (Díaz et al., 2018). As a consequence, CVE values larger than 1 indicate processes more phasic than Gaussian waves, while CVE values below 1 indicate more sinusoidal processes. For each epoch, the coefficient of variation of the corresponding envelope was stored as a relevant feature (Díaz et al., 2018). As CVE is a scale independent metric, it is useful to complement the information provided by delta CVE with delta amplitude. The density maps shown in **Figure 5** were calculated following the algorithms described in Díaz et al. (2018).

Statistics

To compare the time course of delta power changes, a two-way ANOVA with repeated measures and Bonferroni's

1 http://r-forge.r-project.org/projects/signal/

correction for *post-hoc* pair-wise tests were used. An independent *t*-test was used to compare average PSG parameters. A Mann–Whitney *U*-test was used to compare the average sleep episode duration distribution. Data in the figures are presented as means ± SE or means ± SD, which is denoted in the figure legend. All statistical analyses were performed using IBM SPSS statistical software Version 27.0 (IBM Japan, Ltd., Tokyo, Japan). Statistical significance was set at 5% (two-tailed).

Results

Subjects

Table 1 shows the participants' characteristics. Although the older and young groups exhibited a statistically significant height difference, their heights and weights were comparable to mean values by age, as shown in "Statistics Japan."[2] The mean habitual bedtime of the older group was approximately 2 h earlier than that of the young group and their wake time was 2.5 h earlier ($p < 0.001$).

Conventional sleep parameters

Overall sleep architecture is summarized in Table 2. Compared with the young subjects, total sleep time and SWS were significantly shorter and wake after sleep onset and N1 were longer in the older subjects. Accordingly, the sleep efficiency was significantly lower in the older group than in the young group. Changes in dominant sleep stage were observed in both age groups; SWS was observed during the first 2 h, and was gradually replaced with N2 and REM in both age groups (Figure 1). The occurrence of K-complexes was calculated in N2 as expressed by the proportions (young subjects: 30.5 ± 6.9% vs. older subjects: 11.2 ± 5.8%, $p < 0.0001$).

Duration and number of sleep episodes in non-REM sleep stages

Duration and number of NREM sleep episodes were calculated, and statistically significant differences in episode duration were detected between the two age groups in the SWS stage (p = 0.230, 0.080, <0.001 for N1, N2, and SWS, respectively) (Figure 2A). Although the duration of most of the SWS episodes was shorter than 10 min in both groups. It was noticeable that younger subjects had episodes longer than that (up to 50 min), while older participants did not have any episodes longer than 16 min (Figure 2B).

2 https://www.stat.go.jp/data/nihon/back15/21.html

TABLE 1 Characteristics of the study participants.

		Young	Older	*P*-value
Age	Year	23.3 ± 1.1	72.6 ± 2.4	<0.001*
Height	cm	161.8 ± 5.5	152.9 ± 5.0	0.001*
Weight	kg	53.9 ± 9.3	51.5 ± 6.0	0.504
BMI	kg/m^2	20.5 ± 2.6	22.1 ± 3.0	0.230
PSQI		5.7 ± 2.3	6.1 ± 2.3	0.686
Habitual bedtime	hh: mm ± min	0: 04 ± 65	22: 07 ± 40	<0.001*
Habitual waketime	hh: mm ± min	8: 38 ± 52	5: 56 ± 23	<0.001*

Values are mean ± SD. Statistically significant differences are indicated by*. SD, standard deviation; PSQI, Pittsburgh sleep quality index.

TABLE 2 Sleep parameters.

		Young	Older	*P*-value
Total bedtime	min	480	480	–
Total sleep time	min	451 ± 27	396 ± 58	0.019*
Wakefulness	min	19 ± 20	72 ± 42	0.003*
Sleep latency	min	11 ± 14	13 ± 19	0.817
Sleep efficiency	%	94 ± 6	82 ± 12	0.019*
N1	min	42 ± 28	73 ± 19	0.008*
N2	min	240 ± 42	224 ± 62	0.507
SWS	min	92 ± 27	36 ± 27	<0.001*
REM sleep	min	77 ± 15	63 ± 29	0.193
REM sleep latency	min	108 ± 36	122 ± 58	0.527
SWS latency	min	26 ± 17	37 ± 25	0.287
N1 ratio in NREM	%	11 ± 8	23 ± 10	0.009*
N2 ratio in NREM	%	64 ± 7	66 ± 12	0.650
SWS ratio in NREM	%	25 ± 8	11 ± 8	0.001*

Values are mean ± SD. Statistically significant differences are indicated by*.

Sleep stage transition

We analyzed sleep stage transitions between all neighboring 30-s epochs. Transition numbers between stages are shown in Figure 3. Transitions from wake to wake, wake to N1, wake to SWS, N1 to wake, N1 to N2, and N2 to N1 were more frequent in older subjects. On the other hand, staying in stage SWS, i.e., SWS to SWS, was significantly less frequently found in older subjects (Figure 3).

Delta power

The time course of EEG delta power showed significant effects of age group, time, and interaction. Delta power gradually decreased as sleep time increased in both age groups, and delta power was significantly lower in the older group than in the young group ($p < 0.001$) (Figure 4A). The distribution of the delta power was skewed toward lower values for both groups in all NREM stages. Of note, the tendency was even more pronounced for older subjects, especially in SWS. Delta power

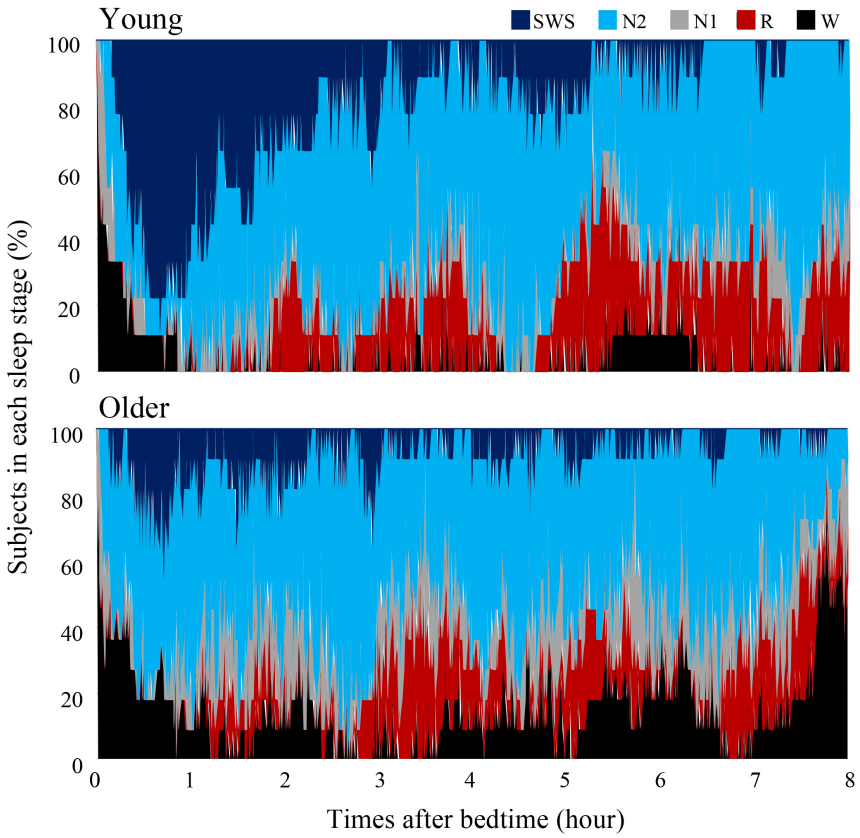

FIGURE 1
Cumulative display of sleep architecture. Distribution of sleep stages of 9 subjects in the young group and 11 subjects in the older group. The percentage of subjects in each sleep stage is shown; Wake (black), REM sleep (red), NREM Stage 1 (gray), NREM Stage 2 (light blue), and NREM Stage SWS (blue). Data of young group was presented in our previous study to compare sleep architecture of follicular and luteal phase (Zhang et al., 2020).

in each NREM sleep stage and the distribution of delta power for all epochs (30 s) of NREM sleep were also compared. In all NREM stages, mean delta power was significantly lower in the older group than in the younger group ($p < 0.001$, 0.002, and < 0.001 for N1, N2, and SWS, respectively) (Figures 4B–D).

Delta amplitude vs. delta coefficient of variation of the envelope density maps

Scatter plots between the delta power amplitude and delta power CVE are shown as a heatmap-like presentation (Figure 5). Different clusters in NREM were clearly observed between the young and older subjects (Figures 5A,B). When separately analyzed in each NREM stage, a lower CVE and amplitude were observed in older subjects compared with young subjects in N2 and SWS (Figures 5E–H). The ascending order of amplitudes of delta waves was N1, N2, and SWS in both age groups. The delta wave amplitudes of N2 and SWS were clearly separated in young subjects, whereas there was an overlap in older subjects. The lower SWS delta power amplitudes in older subjects explain the difference in the cluster of NREM epochs with a higher amplitude (> 2.4) and lower CVE (< 1.2) between age groups. The cluster along the X-axis in N2 was more spread out in young subjects compared with older subjects; this is related to the presence of prominent non-Gaussian (i.e., phasic) delta activity in younger subjects, which is absent in older participants.

Coefficient of variation of the envelope in the other bands

For all analyzed bands (delta, theta, alpha, and sigma band), younger subjects showed CVE distributions significantly biased to high values compared to older subjects. Remarkably, these distributions were more extreme for delta and sigma bands, respectively, matching frequency bands of the main features of NREM sleep: Delta waves and sleep spindles (Figure 6).

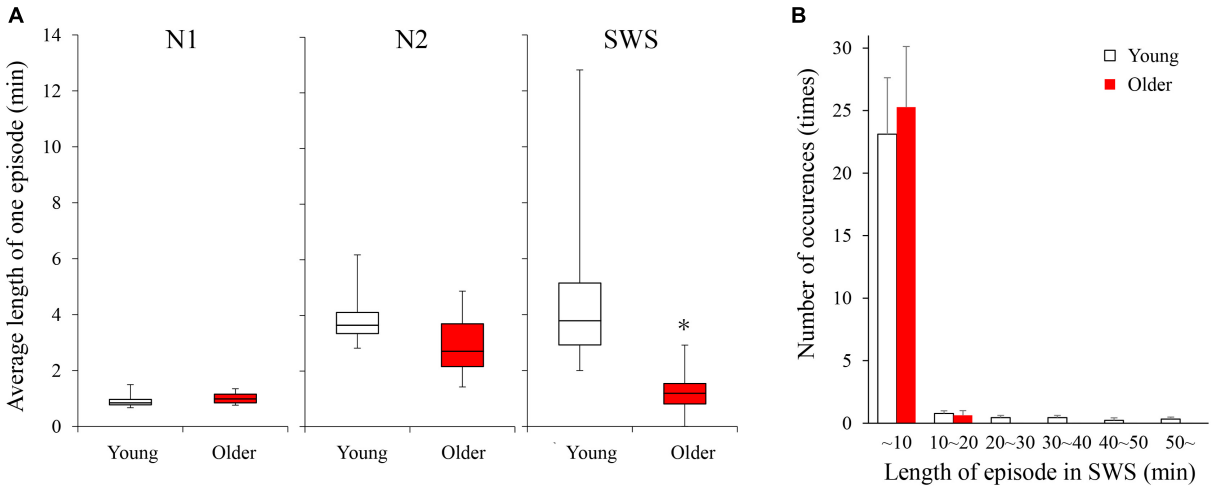

FIGURE 2
Average length of 1 continuous episode of each NREM stage **(A)** and distribution of SWS sleep episode duration **(B)**. **(A)** A statistically significant difference between older and young groups was detected in the SWS stage with the Mann–Whitney *U*-test ($p < 0.001$). **(B)** Although total numbers of SWS episodes were identical between the 2 age groups, older subjects did not have any episodes longer than 16 min. Asterisk represents a statistically significant difference between the older and young subjects ($p < 0.05$).

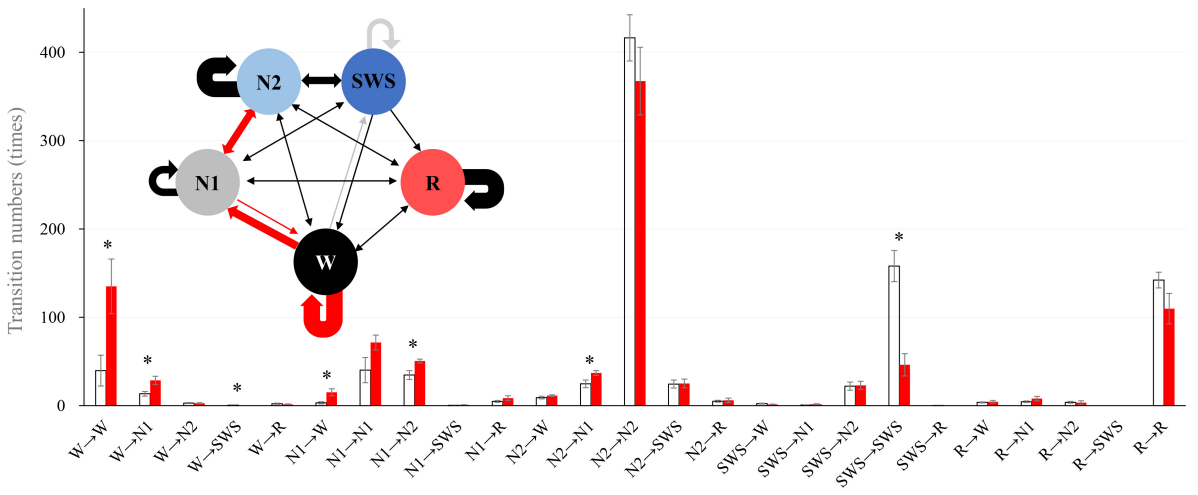

FIGURE 3
Intra-stage transition numbers and transition probability. Stage transition numbers and diagram during the 8-h experiment night. The young group is shown in white, and the older group in red in the bar graph. Asterisks represent statistically significant differences between older and young groups ($p < 0.05$). In the diagram, the thickness of the arrows indicates the number of transitions (bold line: >100, semi-bold line: >20, thin line ≤20; red and gray arrows indicate statistical significance (red: older >young, and gray: young >older). The I-bar shows SE.

Discussion

Conventional analysis of sleep architecture

The present study revealed a lower delta power and distinct sleep architecture in older women compared with younger women; reduced SWS, TST, and sleep efficiency, with increased N1 and wakefulness. These results are consistent with reported features of sleep in older subjects, both men and women (Landolt et al., 1996; Li et al., 2018; Ye et al., 2020). In accordance with previous studies (Brezinová, 1975; Schlemmer et al., 2015), the numbers of SWS episodes were comparable between the two age groups, whereas the SWS duration was shortened in older subjects. Stage transition analysis revealed a decreased ability to maintain SWS, and an increased probability of remaining in wake state; i.e., transitions from wake to wake. Sleep fragmentation is a common symptom of poor sleep quality

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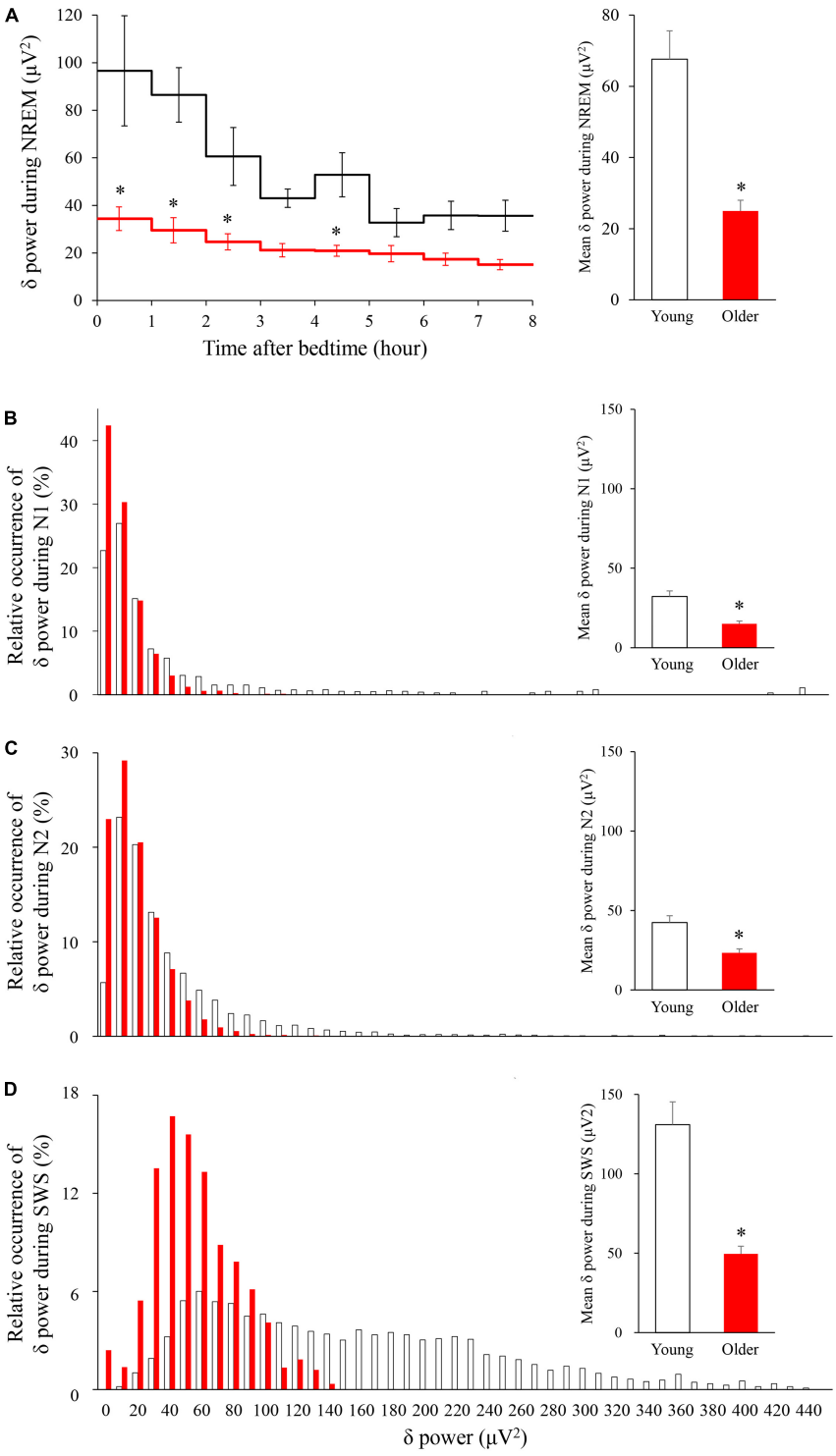

FIGURE 4
Time course of delta power of NREM sleep EEG **(A)** and relative occurrence of delta power in each NREM stage **(B–D)**. **(A)** An hourly mean ± SE of delta power of the two groups is shown as a line graph and mean delta power during NREM is shown as a bar graph. Hourly mean ± SE is shown for young women (white) and older women (red). The main effect of age, main effect of time, and interaction *p*-values of two-way repeated measures ANOVA were all $p < 0.001$. Asterisks represent statistically significant difference between the two age groups by *post-hoc* pair-wise comparisons using the Bonferroni's correction ($p < 0.05$). Relative occurrence distribution of 5-s delta power and mean delta power during N1 **(B)**, N2 **(C)**, and SWS **(D)**. Asterisk represents a statistically significant difference between the older and young subjects by an independent *t*-test ($p < 0.05$), and error bars denote the standard error.

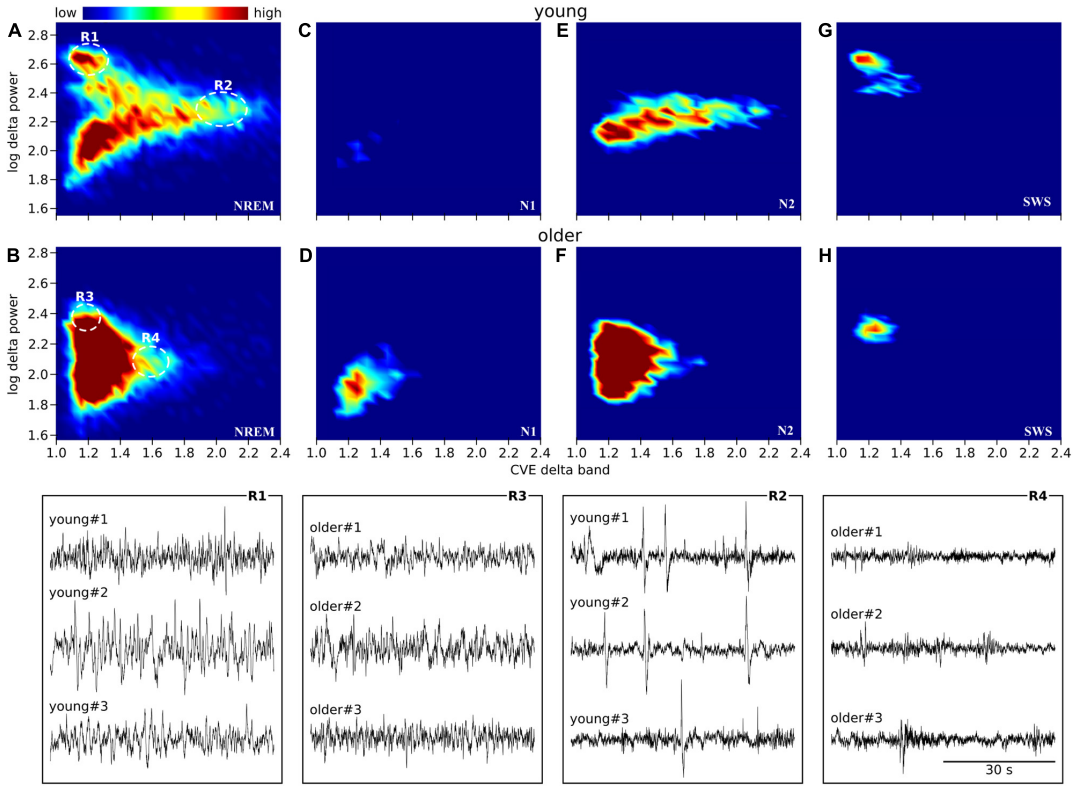

FIGURE 5
Envelope characterization space (ECS) of EEG delta band during NREM sleep. Upper panels **(A–H)** show the ECS -i.e., CVE vs. amplitude- of the EEG delta band as density plots (2D histograms) of pooled young subjects (first row) and older subjects (second row). Panels **(A,B)** correspond to the ECS considering all NREM epochs. Panels **(C,D)** only N1 epochs. Panels **(E,F)** only N2 epochs. Panels **(G,H)** only SWS (N3) epochs. Notice that while in older subjects all epochs are condensed in a single cluster **(B)**, younger subjects generate rich clustering patterns with evident local densities and a long tail pointing to high CVE values. Bottom traces correspond to representative EEG epochs from three young and three older subjects taken from regions 1 to 4 as indicated in panels **(A,B)**. In young subjects, SWS is an objectively isolated cluster of high amplitude delta waves (R1 vs. R3). In young subjects, high amplitude transients (K complexes) are observed while in the older subjects, the expected amplitude of transient delta activity is greatly diminished (R2 vs. R4).

observed in older women (Lu et al., 2000; Lim et al., 2014). The occurrence of K-complexes during N2 was significantly decreased in older subjects compared with young subjects, consistent with findings from previous studies (Wauquier, 1993; Crowley et al., 2002a,b). Delta wave and K-complexes are thought to be generated by the same mechanisms (Crowley et al., 2002b), and the effects of age on K-complex production can be interpreted as reflecting an age-related change in thalamocortical regulatory mechanisms to induce delta waves (Crowley et al., 2002b). K-complexes may be useful biologic markers of the changes in the nervous system that occur with aging (Crowley et al., 2002b).

Sleep stage transition

In a fine-grained epoch-by-epoch analysis of sleep stability, the present study revealed differences in the sleep stage transitions between older and young individuals. The significantly more frequent transitions from wake to N1, N1 to wake, N1 to N2, N2 to N1 in older subjects are consistent with findings from a previous study (Schlemmer et al., 2015) in which sleep episode transitions were analyzed at lower resolution. Stage transition analysis in the present study further revealed a lower number of transitions to maintain SWS and a higher probability of remaining awake in older subjects compared with young subjects, i.e., older subjects stayed in SWS for a shorter duration, and in a wake stage for a longer duration of time. These findings indicate a general decrease in stability of sleep architecture and corroborate the loss of SWS in older individuals.

Delta power and envelope analysis

Interestingly at high temporal resolution, EEG patterns were significantly more homogeneous and less varied in older compared to young subjects. This reduced variability was

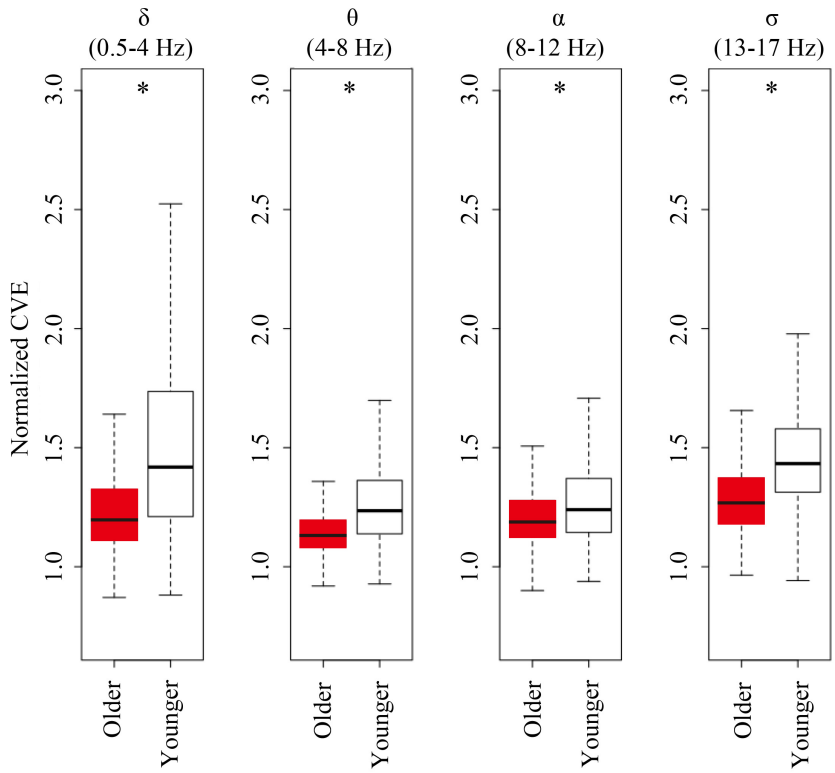

FIGURE 6
Envelope analysis of all major spectral bands. Box and whisker plots for each band of envelope analysis. The older group is shown in red, and young group is shown in white in the box. A black line in the box to indicate the mean value, a box to indicate variability (± SE), and whiskers around the box to indicate the 95% normal confidence interval for mean. Asterisks represent statistically significant differences between older and young groups ($p < 0.05$).

accompanied by a reduction in EEG delta power in older participants. The amplitude of delta waves depends on the NREM stage. In contrast to the clearly separated amplitudes between N2 and SWS in young subjects, we found an overlap in older subjects, likely underlying the unstable SWS. To assess oscillatory stability, we used CVE analysis to determine the instantaneous power in different EEG spectral bands. Envelope analysis, in particular CVE analysis, is gaining a relevant role among various analysis tools for its specific ability to account for morphological aspects of the signal that are outside the reach of traditional techniques based on Fourier analysis (Díaz et al., 2018; Segning et al., 2022). From early theoretical development in the analysis of local field potentials in animal models (Díaz et al., 2007) to recent applications in the analysis of the human alpha rhythm (Hidalgo et al., 2022), this methodology has shown diverse applications including its use as a clinical diagnostic tool (Díaz et al., 2014; Qian et al., 2021). Regarding the particular goals of this study, we have previously used CVE with the same objective, namely, as a scale-independent measure of the stability of delta waves, with high CVE values indicating unstable oscillations (Park et al., 2021). In general, clinical EEG studies can benefit from CVE analysis, as it provides an alternative approach to classical spectral analysis, much-needed for information extraction from complex EEG morphology not strictly sinusoidal as the basis of Fourier analysis (Cole and Voytek, 2017).

Decreased sleep state stability in older subjects is thus paired with delta oscillations that are less varied and more Gaussian in their temporal energy distribution. This was particularly visible in the lower CVE of delta waves during N2 in older subjects. The difference in CVE in N2 between the age groups may be related to different frequencies of K-complexes, which increase the CVE as abrupt huge slow oscillations in EEG (Li et al., 2018). In the present study, CVE values were positively correlated with K-complexes ($r = 0.89$; $p < 0.001$). Although there is some controversy regarding the role of K-complexes to trigger transitions from N2 to SWS, previous studies provided strong evidence that K-complexes induce neuronal silence ("down-states") and are the forerunner of delta sleep (De Gennaro et al., 2000; Cash et al., 2009). We expanded the CVE analysis to other EEG bands that are relevant for sleep. We found reduced CVE values in older subjects in all of these bands, indicating that this is a general feature and not restricted to the delta band. This more monotonous EEG of elderly participants indicates that

some of the richness of EEG features that can be found in young subjects is lost in aged subjects. The underlying causes for this reduced EEG repertoire obviously need further investigation. As it stands CVE analysis can provide an easily visualized measure of oscillatory stability and the reduced values observed here might provide a general measure of brain aging.

Potential mechanisms of age-related changes in sleep

Age-related changes in sleep may be related to age-related changes in lifestyle or age-related changes in physiology. Physical activity during the daytime is significantly reduced in older subjects compared with that in young subjects (Husu et al., 2021). The physiologic mechanisms underlying fragmented and suppressed SWS in older subjects are elusive. The number of galanin neurons in the ventrolateral preoptic nucleus, which play a critical role in the regulation of NREM sleep, is reduced in older subjects (Lim et al., 2014). The number of galanin neurons at the time of death is negatively correlated with sleep fragmentation monitored before death. The relation between galanin neurons, and the delta power and stability of SWS remains to be clarified. Another possibility is age-related changes in the sensitivity to corticotropin-releasing hormone, which stimulates the secretion of adrenocorticotropic hormone and cortisol, and suppresses SWS (Vgontzas et al., 2001). Pyramidal neurons in the cerebral cortex fire synchronously in deep sleep or SWS, and the intensity of their synchronous firing correlates with sleep depth (Neske, 2016). Pyramidal cell density decreases with age in all four hippocampal sectors (CA1 through C4), with maximal loss in sector C4. The age-related loss of pyramidal cells is most overt after age 65 (Mani et al., 1986).

Limitation of the study

In this study, we examined NREM sleep of older (≥62 years of age) women without sleep disorders compared with younger women in their 20 s. To generalize our findings on SWS sleep changes as a characteristic of older people, it will be critical to conduct the same experiment targeting females with sleep disorders as well as males with or without sleep disorders. In addition, it is important to examine sleep in middle-aged subjects to determine the age at which the changes occur.

Conclusion

In older subjects, although the number of transitions into SWS was almost the same as that in young subjects, the SWS stage was less stable and the duration of SWS over the entire night was shorter. The CVE of delta waves, an index of delta wave stability, was similar between age groups. In older subjects, the delta power amplitude during SWS was lower, and its distribution overlapped with that of N2, which underlies less stable SWS.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The study protocols were approved by the Ethics Committee of the University of Tsukuba (Ref Nos., Tai 29-29 and 30-134), and conducted in accordance with the Helsinki Declaration. The patients/participants provided their written informed consent to participate in this study.

Author contributions

IP, JS, TO, and KT designed the experiment. CK, JS, SZ, AU, and HO performed polysomnographic recording of sleep. IP, RM, KH, CS, YS, JD, and KV performed the sleep analysis. JS performed the statistical analysis. IP, CK, AI, JD, KV, and KT interpreted the results and wrote the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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A bibliometric analysis of the application of imaging in sleep in neurodegenerative disease

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Objective: The purpose of this study was to examine the current state of the application of imaging in sleep research in degenerative disease, as well as hotspots and trends.

Materials and methods: A search was conducted on the Web of Science Core Collection (WoSCC) between 1 September 2012, and 31 August 2022 for literature related to sleep imaging. This study analyzed 7,679 articles published in this field over the past 10years, using CiteSpace to analyze tendencies, countries, institutions, authors, and hotspots.

Results: There were 7,679 articles on the application of imaging to sleep research published by 566 institutions located in 135 countries in 1,428 journals; the number of articles was increasing on a yearly basis. According to keyword analysis, the research direction of the application of imaging in sleep research focused on the effects of degenerative diseases on sleep, such as Parkinson's disease, Alzheimer's disease, and small vessel disease. A literature evaluation found that Parkinson's disease, insomnia, sleep quality, and rapid eye movement sleep behavior disorder were the top research trends in this field.

Conclusion: A growing body of research has focused on sleep disorders caused by degenerative diseases. In the application of imaging to sleep research, magnetic resonance functional brain imaging represents a reliable research method. In the future, more aging-related diseases may be the subject of sleep-related research, and imaging could provide convenient and reliable evidence in this respect.

KEYWORDS

sleep, imaging, bibliometrics, CiteSpace, degenerative disease

1. Introduction

Humans sleep most of their lives, but the functional role of sleep remains mysterious. The importance of sleep for the maintenance of many physiological functions, including cognitive function, has become increasingly apparent over the last few decades (Malkani and Zee, 2022). Current studies illustrate that sleep disorders constitute a health burden for all societies (Spaggiari et al., 2022; Xu et al., 2022); many diseases are associated with sleep disorders, including high blood pressure, mental illness, neurodegenerative diseases, and cardiovascular disease, and sleep disorders affect 40–50% of the world's population (Bin Heyat et al., 2021). Therefore, it is essential to study sleep. Sleep cannot be attributed to any one specific organ, unlike other physiological functions; thus, the study of the functional role of sleep is a systematic and complex task requiring different

techniques to reveal its underlying mechanisms. With the development of the disciplines of physiology and psychology, as well as increasing understanding of the structure and function of the nervous system, sleep research has become increasingly objective. Electroencephalography (EEG) became the central monitoring tool in sleep research in the 1930s, to observe the sleeping brain with high temporal resolution (Schulz, 2022). With the rapid development of brain imaging technology, functional imaging has made it possible to image brain activity during sleep at a high spatial resolution (Ferini-Strambi et al., 2019). Compared with functional magnetic resonance imaging, magnetoencephalography is not affected by age-related changes in vascular factors and allows simpler and more powerful methods to correct head motion artifacts (Tibon and Tsvetanov, 2021). Polysomnography is a procedure for evaluating the root causes of sleep disorders using electroencephalogram, electro-oculogram, electrocardiogram, pulse oximeter, airflow, and breathing efforts (Rundo and Downey 3rd, 2019). It is an authoritative and objective tool for studying sleep. Currently, neuroimaging methods play a crucial role in sleep research, both in basic research and clinical fields (Bourgouin et al., 2019).

With the aggravation of the aging population, the problem of sleep to human beings is becoming more and more serious. Sleep imaging research develops over time, and it is vital to explore the hotspots and trends of future applications. Summarizing the experience of prior researchers is helpful to promote more in-depth and valuable research in the future. Bibliometrics is a visual analysis tool that permits quantitative analysis of the literature using mathematical and statistical methods (Glanzel, 2015). It identifies influential and valid areas of scientific research, knowledge bases, and emerging topics (Hou et al., 2018).

This study used CiteSpace (Hou et al., 2018; Chen and Song, 2019) to analyze the literature related to sleep. Cataloged in the Web of Science Core Collection (WoSCC) database, to explore the research status, hotspots, and trends in the application of imaging to sleep in degenerative disease and to provide new perspectives and paths for the study of the application of imaging in sleep research in degenerative disease using imaging.

2. Materials and methods

2.1. Data retrieval strategy

This was a retrospective cross-sectional study regarding imaging of sleep disorders in degenerative disease. Data retrieval was based on the Web of Science Core Collection (WoSCC) database. The WOSCC is a standardized online database that is considered to be the most suitable for bibliometric analysis (Schulz, 2022). To ensure the accuracy of the data, the literature search was completed in 1 day (22 September 2022), with 1 September 2012, to 31 August 2022, selected as the time frame for this study. Since the set time span did not include the literature for the first 8 months of 2012 and the last 4 months of 2022, the data for 2012 and 2022 are incomplete; the analysis does not represent the whole of these 2 years. The primary type of literature selected in this study was articles, and English was the primary language. To identify any possible selection differences, two researchers independently searched the raw data. Figure 1 shows the detailed filtering process.

The search terms were as follows: (TS) = (imaging OR "magnetic resonance imaging" OR MRI OR "functional magnetic resonance imaging" OR fMRI OR "diffusion tensor imaging" OR DTI OR "single-photon emission computed tomography" OR SPECT OR "positron emission tomography" OR PET OR "structural neuroimaging" OR neuroimaging) AND TS = ("insomnia disorder" OR insomnia OR "REM behavior sleep disorder" OR "excessive daytime sleepiness" OR sleep).

2.2. Data export and extraction

CiteSpace[1] was used to analyze collaborative networks (country/region, institution, author, and journal), co-citations (author, journal, and reference), and co-occurrence bursts of keywords. CiteSpace (Chen and Song, 2019) 6.1.R2 parameters were set as follows: time slice, August 2012 to September 2022, 1 year per slice; text processing, title, abstract, author, keywords; node type, from country/region, institution, author, keyword, co-cited journal, co-cited author, and co-cited literature; link strength, cosine; link range, within slices; selection criteria, *g*-index, $k = 25$; pruning, pathfinding network method and pruning slices, integrated network; using the pathfinding network algorithm. Statistics were imported into Microsoft Office Excel 2019[2] for graphing.

In CiteSpace, the "*g*-index" is used as a selection criterion. This index is defined as the largest number whose sum of citations is at least *g*-squared. If papers are listed in descending order of their citations, highly cited articles are more accurately reflected by this index than by the H-index (Abbas, 2012). In CiteSpace, *k* is a scale factor that is added to the *g*-index calculation and adjusted to include or exclude more nodes (Abbas, 2012). "Burst detection" and "betweenness centrality" are features of the software that allow researchers to identify new trends, research frontiers, and abrupt changes in a research area. Betweenness centrality is a measure of the importance of nodes in a network and is guided by tree hole theory (Assenov et al., 2008; Chen et al., 2014). Additionally, literature co-citation refers to the relationship that exists between two (or more) papers that are cited simultaneously by one or more subsequent papers (Ding et al., 2021). In this study, the algorithm was used to extract noun phrases (Chen and Song, 2019). During the analysis, we assessed network structure and network homogeneity based on modules (Q-value) and profiles (S-value). Q-values greater than 0.3 indicate significant clustering structure, while S-values greater than 0.7 indicate high clustering confidence (Sabe et al., 2022). By examining these parameters, we determined the state of the research and trends in the field.

3. Results

3.1. Publication outputs and trends

Over the 10 years from 31 August 2012 to 31 August 2022, there were 7,679 publications relevant to imaging in sleep disorders, with a mean of 76.79 publications per year. There was an increasing trend in the number of publications per year from 2013 to 2021 (Figure 2).

1 https://sourceforge.net/projects/citespace/

2 https://www.microsoft.com/en-us/microsoft-365/previous-versions/microsoft-office-2019

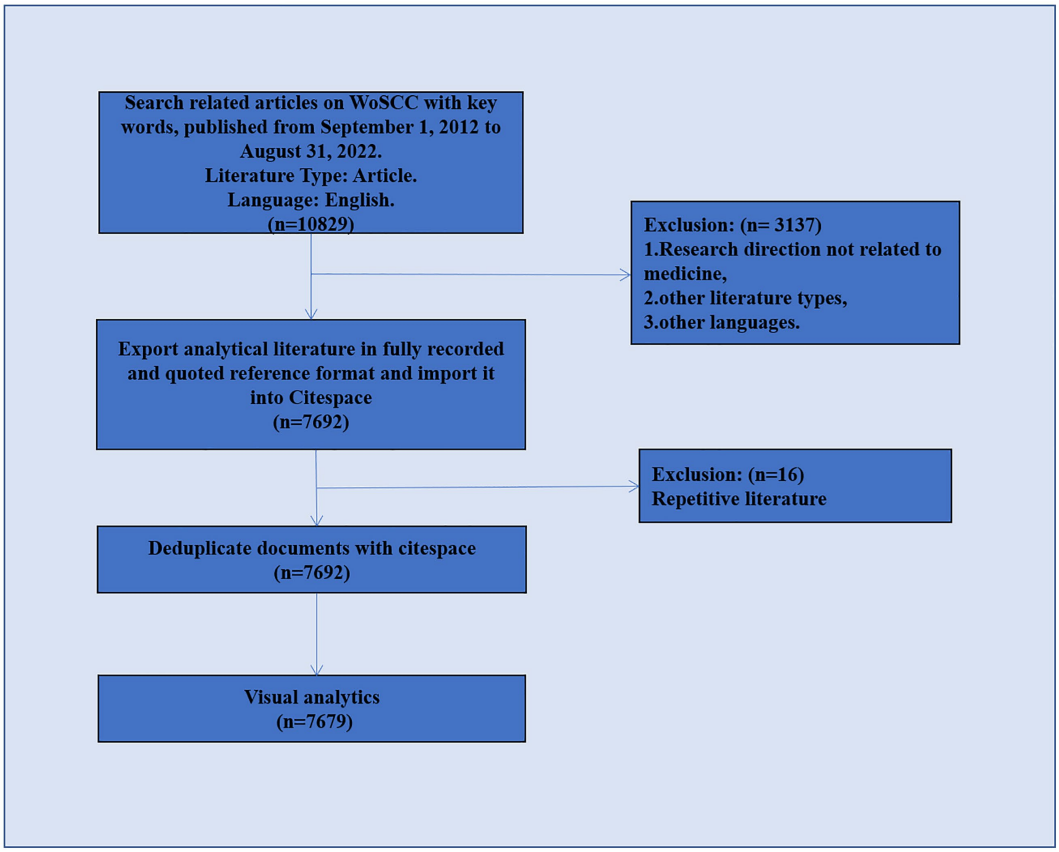

FIGURE 1
Flow chart of data preparation.

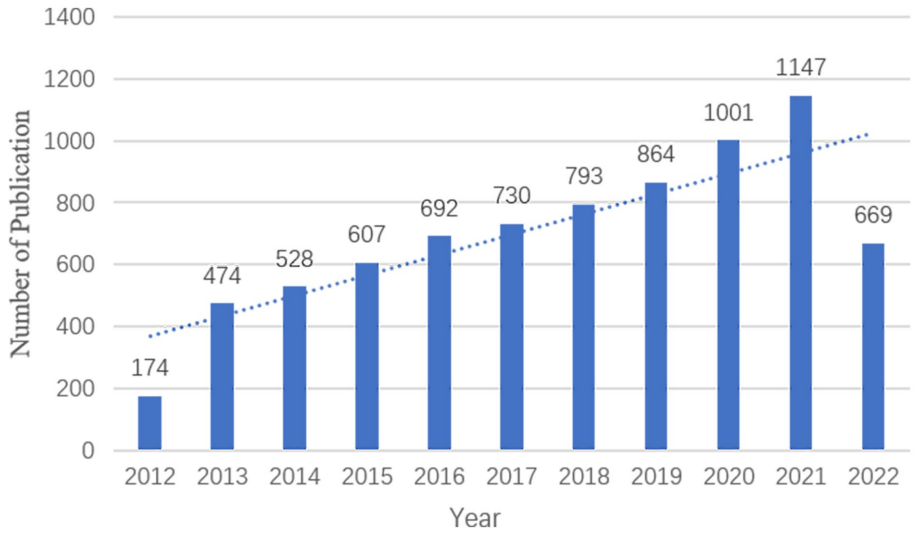

FIGURE 2
Distribution of annual publications.

3.2. Countries and institutions

A total of 566 institutions from 135 countries published literature on imaging in sleep problems over the past decade. As measured by the number of publications, Table 1 provides a list of the top 10 countries/regions and institutions in the world. The United States (2,993/37.56%) and China (1,064/13.35%) had the most publications, accounting for more than half of the total. Among the top 10 institutions with the most publications, seven were in the United States (Table 1). Among the top 10 countries/regions and institutions in

TABLE 1 Top 10 countries/regions and institutions in terms of number of articles issued.

Ranking	Country/Region	Documents (%)	Centrality	Institution (country/region)	Documents (%)	Centrality
1	United States	2,993 (38.78%)	0.03	Harvard University (United States)	279 (3.63%)	0.19
2	China	1,064 (13.86%)	0.00	Birmingham Women's Hospital (United Kingdom)	200 (2.60%)	0.16
3	United Kingdom	782 (10.18%)	0.03	University of Pennsylvania (United States)	183 (2.38%)	0.01
4	Germany	721 (9.39%)	0.03	University of California, Los Angeles (United States)	164 (2.14%)	0.00
5	Canada	557 (7.25%)	0.12	Stanford University (United States)	159 (2.07%)	0.01
6	Italy	545 (7.10%)	0.00	Harvard University (United States)	153 (1.99%)	0.19
7	Australia	537 (6.99%)	0.00	University of Sydney (Australia)	153 (1.99%)	0.05
8	France	475 (6.19%)	0.03	McGill University (Canada)	141 (1.84%)	0.04
9	Japan	438 (5.70%)	0.00	University of Pittsburgh (United States)	140 (1.82%)	0.01
10	Netherlands	350 (4.56%)	0.00	Johns Hopkins University (United States)	140 (1.82%)	0.01

terms of volume, only Canada (0.12) and Harvard University (0.19) showed high centrality, as shown in Figure 3. There was less cooperation between countries, and regional cooperation between institutions appeared vital (Countries are represented by country co-authorship, and institutions are represented by institution co-authorship.).

3.3. Visual analysis of authors and co-cited authors

Seven hundred seventy-seven authors and 927 co-cited authors contributed to the study of imaging in sleep disorders. Among them, author Lee, J and co-citation authors Buysse, DJ (677); Smith, SM (403); Johns, MW (375); and Postuma, RB (289) had high centrality. Figure 4 shows communication and collaboration networks among the authors and co-cited authors in this study field, with collaborative exchanges increasing in recent years (Authors are represented by author co-authorship; Table 2)

3.4. Journal analysis

There were 7,679 articles from 1,428 journals, among which *Sleep* was the journal with the largest number of publications ($n = 265$) and the most cited journal. Table 3 shows the top 10 journals and co-cited journals in the field of sleep-related imaging.

3.5. Keyword analysis

From the keyword co-occurrence map obtained by CiteSpace, we extracted a total of 662 keywords. The top 20 keywords with the highest frequency are shown in Table 4, indicating the hotspots of imaging applications in the field of sleep. The diseases most frequently studied were obstructive sleep apnea, Parkinson's disease, and Alzheimer's disease. Clustering of keywords revealed a cluster Q value of 0.8342 ($Q > 0.3$) and S value of 0.9352 ($S > 0.5$), showing that the clustering structure was significant and reasonable. Based on keyword clustering analysis, 22 clusters were formed (Figure 5A), from which we extracted the top 10 clusters in size for timeline analysis (Figure 5B). Imaging studies of sleep predominately use magnetic resonance imaging. The keyword has been popular since 2012, including functional imaging, white matter visualization, and body imaging. Memory consolidation is the function of greatest concern to researchers, and the condition of greatest concern is Alzheimer's disease. While interest in sleep deprivation has waned in recent years, research on emotion has received increasing attention. Among the keywords in the top 50 strongest citation burst (Figure 6), those representing the frontiers of research were machine learning, people, rating scales, criteria, decline, images, gray matter volume, case reports, perfusion, and small vessel disease, with machine learning having the highest emergent intensity.

3.6. Co-cited reference analysis

The clustering structure was significant and the clustering content was convincing. Seven thousand six hundred seventy-nine citing articles were analyzed to identify homogeneous clusters of highly cited literature on sleep-related imaging studies. Table 4 shows the top 10 most co-cited references out of 225,108 co-cited references. "*The sleep-deprived human brain*" (Krause et al., 2017) published by Adam J. Krause in the journal Nature Reviews Neuroscience in 2017, was the most frequently cited publication, with 80 citations. The co-cited literature was subjected to cluster analysis, which generated a cluster Q value (module value) of 0.9051 ($Q > 0.3$) and an S value (mean profile value) of 0.9597 ($S > 0.7$), signifying a significant cluster structure and convincing cluster content (Figure 7; Table 5).

4. Discussion

In this study, WOSCC was searched for publications related to imaging in sleep disorders in the past 10 years. The search results were

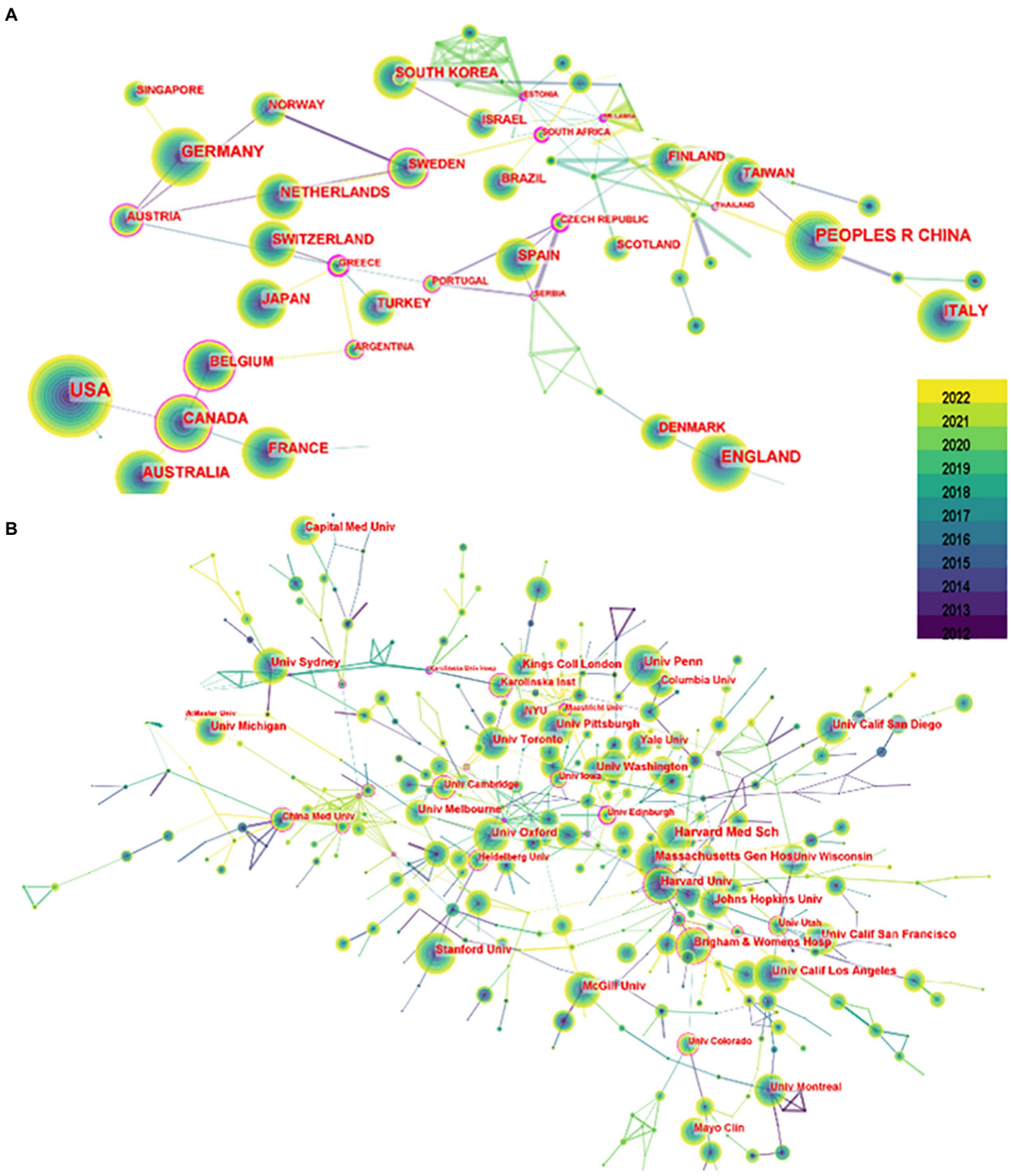

FIGURE 3
Mapping of issuing countries and institutions. **(A)** Shows the country/region from which publications issued, and **(B)** shows the issuing institution. Each circle in the figure represents a country, with the circle's size indicating that country's publication output. The lines connecting the circles represent international cooperation: the thicker the line, the closer the cooperation. The purple outer circle in the figure indicates centrality ≥0.10.

analyzed using CiteSpace software. The number of articles published in the past 10 years has increased on a yearly basis, and imaging has received increasing attention in sleep research. The top international publications have been from developed nations in Europe and the United States, particularly the latter. European and American research institutions, headed by Harvard University, have conducted more in-depth research and made more significant contributions to this field than other locations or institutions. Developing countries have not paid sufficient attention to this field, lack influential institutions, and there is room for their development. Cooperation among institutions shows regionalization, with relatively less international multi-center cooperation. International cooperation could be strengthened and more meaningful research could be carried out in the future. China had the second largest number of published articles, and Chinese persons authored the most articles in this field, which may be because China has a large population. The author analysis of CiteSpace is not based on the

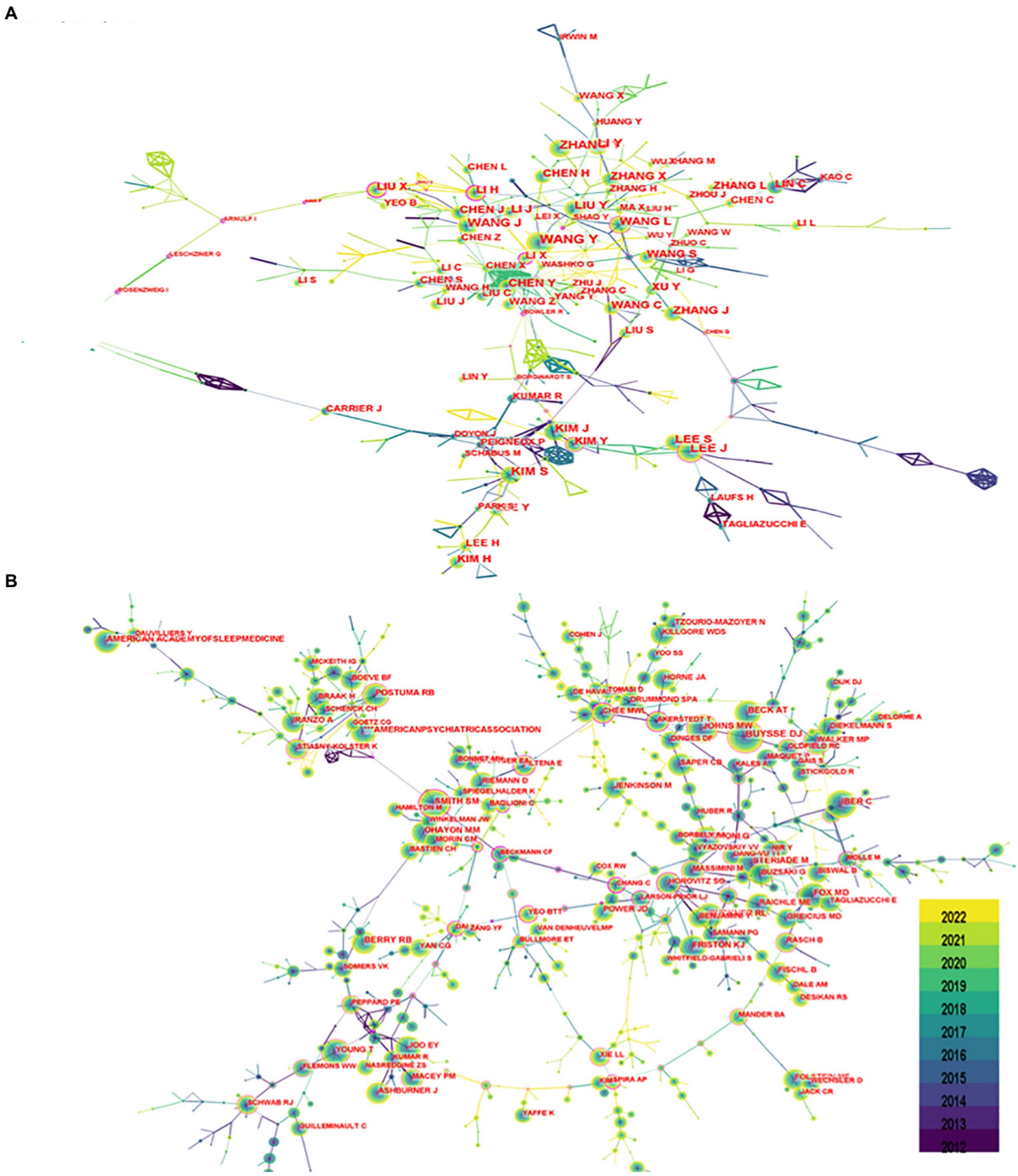

FIGURE 4
Author chart. **(A)** Shows the author graph, and **(B)** shows the co-cited author graph. The node size indicates the number of studies published or co-cited by the author, and a larger node suggests that the author has published more papers or co-cited more times. The closer the collaboration between two authors, the shorter the distance between the two nodes.

first author but on all participating authors. However, there is a considerable problem for Chinese researchers: they have published many articles, but have received few citations. That is, their research results relatively lack international recognition. For Chinese scholars, it is crucial to conduct more valuable, high-quality research. Increasing international influence is essential. In the analysis of co-citations of journals, *Sleep* had the largest number of articles and co-citations in this field and is the most influential journal, which is of guiding significance for researchers when reading the literature and publishing results. As can be seen from the keyword time chart, with the development of imaging technology and computer technology, the research on sleep is becoming more and more elaborate, and the computer post-processing technology brings great changes to the research, so we can make a quantitative analysis of imaging indicators. And the research extends from organic pathological changes to psychological cognition, from macro to micro.

TABLE 2 Top 10 authors and co-cited authors.

Ranking	Author	Documents	Centrality	Co-cited Authors	Citations	Centrality
1	Wang Y	125	0.02	Buysse DJ	677	0.14
2	Zhang Y	101	0.00	Iber C	405	0.00
3	Li Y	93	0.04	Smith SM	403	0.19
4	Lee J	90	0.12	Johns MW	375	0.14
5	Kim S	83	0.06	Berry RB	352	0.00
6	Wang J	82	0.03	Beck AT	297	0.00
7	Liu Y	78	0.08	Steriade M	293	0.08
8	Kim J	78	0.01	Fox MD	292	0.08
9	Lee S	76	0.00	Postuma RB	289	0.17
10	Wang L	71	0.06	Buckner RL	288	0.00

TABLE 3 Top 10 journals in terms of number of articles and citations.

Rank	Journal	Documents	JCR	Impact Factor	Cited Journal	Citations	JCR	Impact Factor
1	Sleep	265	Q1	6.316	Sleep	3,005	Q1	6.316
2	Scientific Reports	218	Q2	4.996	Plos One	2,995	Q2	3.752
3	Plos One	212	Q2	3.752	Neuroimage	2,634	Q1	7.400
4	Neuroimage	186	Q1	7.400	Proc Natl Acad Sci USA	2,504	Q1	12.779
5	Sleep Medicine	144	Q2	4.842	Journal of Neuroscience	2,471	Q1	6.709
6	Journal of Sleep Research	101	Q2	5.296	Neurology	2,057	Q1	11.800
7	Frontiers in Neurology	98	Q2	4.086	Brain	2,002	Q1	15.255
8	Frontiers in Neuroscience	97	Q2	5.152	Science	1,896	Q1	63.714
9	Journal of Neuroscience	89	Q1	6.709	Neuron	1,760	Q1	18.688
10	Cranio	86	Q4	1.670	Sleep Medicine	1,759	Q2	4.842

TABLE 4 Top 20 keywords in terms of frequency of appearance.

Rank	Keywords	Frequency	Rank	Keywords	Frequency
1	Sleep	764	11	Disease	327
2	Obstructive sleep apnea	639	12	Alzheimer's disease	325
3	Brain	522	13	Diagnosis	300
4	Functional connectivity	486	14	Performance	299
5	Children	420	15	Cortex	259
6	Risk	395	16	Network	257
7	Prevalence	384	17	Magnetic resonance imaging	256
8	Association	366	18	Sleep deprivation	253
9	Parkinson disease	343	19	Dementia	253
10	Disorder	340	20	Memory	248

According to keyword analysis, research has focused on the effects of degenerative diseases on sleep, such as Parkinson's disease (Postuma et al., 2015; Krause et al., 2017; McKeith et al., 2017; Postuma et al., 2019), Alzheimer's disease (Mizrahi-Kliger et al., 2022; Sun et al., 2022), and small vessel disease (Semyachkina-Glushkovskaya et al., 2020; Li et al., 2022). We speculate that this may be related to the aging of the population and the fact that the elderly are more likely to develop sleep disorders. It is reported that insomnia is a common sleep disorder in the elderly, of which up to 50% report insomnia symptoms, and according to the diagnostic guidelines used, up to 20% of patients

meet the criteria for insomnia (Sexton et al., 2020). The incidence and prevalence of sleep disorders continues to in older persons, especially those with neurodegenerative diseases. A recent study clarified the mechanisms of neurodegeneration exacerbated by poor sleep quality and circadian rhythm disorders (Standlee and Malkani, 2022). Small vessel disease exists in both Parkinson's and Alzheimer's diseases (Paolini Paoletti et al., 2021); this refers to the dominant injury of arterioles and capillaries, resulting in reduced or interrupted perfusion of the affected organs, primarily affecting organs that receive most of the cardiac output, such as the brain, kidney, and retina (Hakim, 2019). Sleep disorders can adversely affect the regulation of gene expression or protein production, resulting in pathological protein changes. The accumulation of toxic proteins in Parkinson's and Alzheimer's diseases, such as alpha-synuclein, TDP-43, A, β, and tau, has been shown to disrupt the sleep-awakening cycle (Dong et al., 2019). Sleep disorders promote the development of neurodegenerative symptoms (Lucey et al., 2018), increasing the risk of Parkinson's and Alzheimer's disease and aggravating the symptoms of these diseases. Such symptoms include muscle stiffness, tremor, motor dysfunction, and cognitive impairment, among which researchers are most concerned with the patient's cognitive ability, especially memory ability (Figure 6). This may be due to the effect of sleep on cognitive ability has been proved by several studies (Dzierzewski et al., 2018; Ma et al., 2020). For the elderly, the decline of memory ability leads to a serious decline in the quality of life, which is the most easily detected symptom in life.

Symptom assessment is very important for diagnosing and treating neurological diseases, not only in clinical practice but also in basic

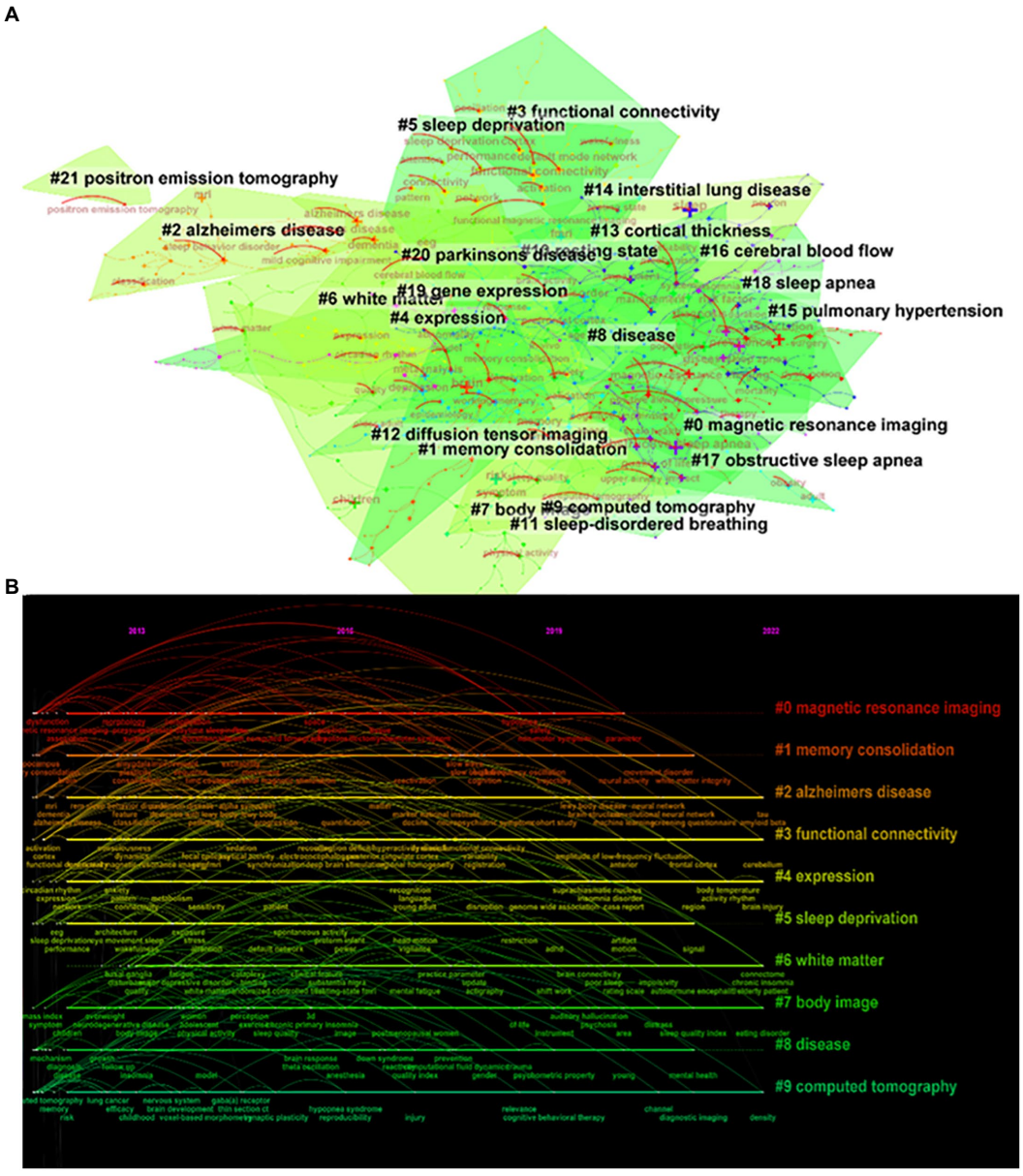

FIGURE 5
Keyword clustering analysis. **(A)** Keyword clustering mapping, **(B)** Keyword clustering timeline mapping.

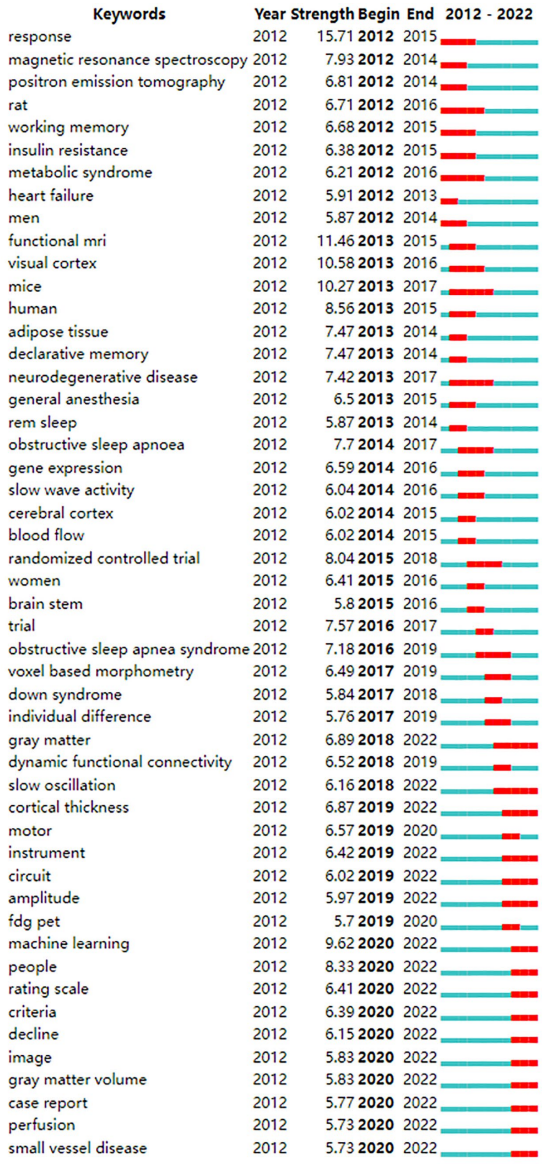

FIGURE 6
Keyword strongest citation bursts map.

research. It is usually necessary to observe the severity of neurological diseases and use appropriate methods to evaluate the effectiveness of specific treatments (Asakawa et al., 2019). There is a growing demand for cognitive assessment tools in the field of sleep imaging; accordingly, assessment scales and criteria have become popular keywords in the previous 2 years. Magnetic resonance functional brain imaging (De Havas et al., 2012; Tagliazucchi and Laufs, 2014; Yan et al., 2016) and the development of image processing software provide objective and quantitative evaluation tools for application in sleep research. The development of MRI techniques and data processing technologies that have emerged in the previous decade have permitted accurate assessment of brain structure, function, and metabolism for sleep research, and imaging has provided new tools for the development of this field. As the keyword with the strongest citation bursts after 2020, machine learning is both a subfield of artificial intelligence and a method for artificial intelligence research and development. It uses a combination of mathematical, statistical, probabilistic, and information-theoretic methods to learn and tune performance on specific tasks, using large, and real-world data sets. Artificial intelligence is rapidly advancing in the field of imaging, with a wide range of applications in the screening, staging, diagnosis, and treatment of sleep disorders (Watson and Fernandez, 2021).

The most recent four clusters cited in the literature encompass Parkinson's disease, insomnia, sleep quality, and REM sleep behavior disorder (Figure 5), namely these topics were cited the most. In the field of sleep research, Parkinson's disease is the condition of greatest concern among diseases that cause sleep disorders. Conditions of most concern are insomnia and REM sleep behavior disorder, a type of abnormal sleep considered to be the precursor to α-synaptophysin disease, such as Parkinson's disease; such disordered sleep affects more than 50% of patients with Parkinson's disease (Valli et al., 2022). In addition, insomnia is one of the most common sleep disorders in Parkinson's disease and is significantly associated with poor quality of life (Diaconu and Falup-Pecurariu, 2022).

Recent studies have revealed that the neural mechanisms responsible for these sleep disorders may be related to abnormalities and interhemispheric interactions in brain regions associated with excessive arousal and sensorimotor and cognition. Imaging in such cases is characterized by topological organization disorder of functionally connected brain groups, which may lead to decreased cognitive, emotional, and memory function (Fasiello et al., 2022). Further, sleep disorders are associated with various changes in magnetic resonance functional brain imaging, such as gray matter volume (Paulekiene et al., 2022), cortical thickness (Babu Henry Samuel et al., 2022), and white matter function (Bai et al., 2022; Yang et al., 2022). These indexes reflect changes in brain structure, function, and metabolism, and provide a qualitative and quantitative basis for the study of sleep disorders, and guidance for disease prediction and future treatment target selection, thus may provide suggestions as to how to relieve patients' pain and provide early diagnosis and treatment of related diseases.

The primary deficiency of this study is that the scope of literature was limited to the WOS database, with the exclusion of PubMed, Embase, and other databases. As the relationship between co-citations is analyzed, only the citation database WoSCC can be selected, which may limit the inclusion of literature. This may have permitted bias in the results, but the WOS database, as the most cited database, cover most of the high-quality sleep imaging literature. And CiteSpace software evaluates countries, institutions, and authors based on all co authored countries, co-authored institutions, and co-authors, hence it is unable to differentiate between the first author and other authors.

Overall, the analysis using CiteSpace software showed that the focus of research attention is the impact of degenerative diseases on sleep. With population aging, sleep disorders and diminished sleep quality caused by degenerative diseases are receiving increasing attention. Sleep efficiency, slow wave sleep volume, REM sleep, and REM sleep latency all decrease with increasing age (Etholén et al., 2022). With the rapid development of magnetic resonance software and hardware technology, sleep imaging will likely continue to provide strong support for research into sleep disorders caused by aging. The current research is becoming increasingly detailed. This study shows a trend in imaging of sleep in degenerative disease research from symptoms to changes in brain structure and function in diseases that cause sleep disorders and changes in sleep quality, with the primary goal of predicting the occurrence of sleep disorders in degenerative disease patients.

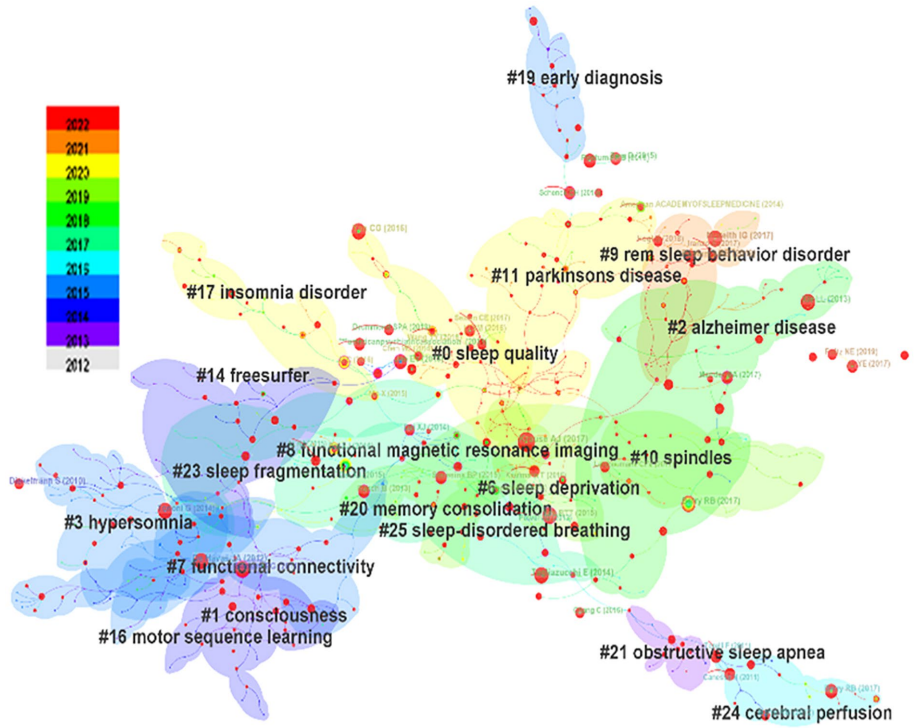

FIGURE 7
Co-citation clustering map of the literature.

TABLE 5 Top 10 literature in terms of total citations.

Rank	Cited reference	Journal	Author	citations	Centrality	Year
1	The sleep-deprived human brain	Nat Rev. Neurosci	Adam J. Krause	80	0.05	2017
2	Decoding wakefulness levels from typical fMRI resting-state data reveal reliable drifts between wakefulness and sleep	Neuron	Enzo Tagliazucchi	69	0	2014
3	Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium	Neurology	Ian G. McKeith	65	0.01	2017
4	Risk and predictors of dementia and Parkinsonism in idiopathic REM sleep behavior disorder: a multicenter study	Brain	Ronald B. Postuma	63	0.03	2019
5	Sleep deprivation reduces default mode network connectivity and anti-correlation during rest and task performance	Neuroimage	Jack A. De Havas	60	0.09	2012
6	DPABI: Data Processing and Analysis for (Resting-State) Brain Imaging	Neuroinformatics	Chao-Gan Yan	59	0	2016
7	Sleep drives metabolite clearance from the adult brain	Science	Lulu Xie	57	0.02	2013
8	AASM Scoring Manual Updates for 2017 (Version 2.4)	J Clin Sleep Med	Richard B. Berry	56	0.01	2017
9	The memory function of sleep	Nat Rev. Neurosci	Susanne Diekelmann	52	0.04	2010
10	MDS clinical diagnostic criteria for Parkinson's disease	Movement Disorder	Ronald B. Postuma	50	0	2015

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

ML and ZJ mainly focused on data collection, data analysis, and writing. CL and RW contributed to manuscript revision. JW and CL contributed to manuscript reviewing and suggestion and contributed to

the conception, supervision, and reviewing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The relationship between sleep quality, snoring symptoms, night shift and risk of stroke in Chinese over 40 years old

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Objectives: To analyze the relationship between sleep quality, snoring symptoms, night shift and risk of stroke in Chinese population over 40 years old.

Methods: Based on the national screening and intervention program for high-risk population of stroke in 2016, 15,016 people completed the study of "the association between sleep and stroke," 58,696 people completed the snoring questionnaire, and 58,637 people completed the night shift questionnaire.

Results: The proportion of coronary heart disease, hypertension, hyperlipidemia, diabetes, snoring, atrial fibrillation, stroke and high-risk group of stroke risk rating were higher in the group with poor sleep quality ($p < 0.05$). The proportion of high blood pressure, hyperlipidemia, diabetes, atrial fibrillation, transient ischemic attack (TIA), or high-risk group of stroke risk rating was higher in snoring group ($p < 0.05$). The body mass index (BMI), waist circumference, neck circumference, fasting blood glucose, triglyceride (TG), total cholesterol (TC), low density lipoprotein (LDL) and homocysteine (Hcy) levels in snoring group were higher than the non-snoring group, and high density lipoprotein (HDL) levels were lower ($p < 0.05$). People with TIA, high risk for stroke, and high blood pressure were higher in night shift workers than non-night shift workers ($p < 0.05$). The levels of BMI, fasting blood glucose, 2 h postprandial blood glucose, glycated hemoglobin, TG, TC, LDL, HDL and Hcy in night shift group were lower than the non-night shift group ($p < 0.05$).

Conclusion: Sleep quality, snoring and night shift might be related to the risk factors of stroke.

KEYWORDS

sleep quality, snoring symptoms, night shift, stroke, old

Introduction

One third of human life is spent in sleep and sleep is important for everyone. Up to 150 million people in the word suffer from sleep problems that can affect their quality of life and make them vulnerable to other adverse consequences (Lawes et al., 2008). Stroke is a common cerebrovascular disease. There were about 16 million people in the world experienced their first stroke every year, among which about 5.7 million people died and about 5 million people were left with disabilities.

Sleep quality is associated with a variety of factors, including diabetes, high blood pressure, stroke, myocardial infarction, chronic kidney disease, depression, cognitive impairment, pain, and lifestyle habits such as alcohol use, smoking, and certain physical activities. Sleep quality is associated with stroke, hypertension and so on. In a meta-analysis of 16 prospective studies, a "J" shaped trend was observed between total sleep time and

stroke and the lowest risk of stroke was found in people who slept for 7 h at night (He et al., 2017). A prospective study of 1,268 patients with hypertension in 2010 found that the risk of stroke in hypertensive patients with total sleep time <7.5 h is two times higher than that in hypertensive patients with total sleep time ≥7.5 h (Eguchi et al., 2010).

Snoring is a form of sleep-disordered breathing, and snoring can lead to decreased sleep quality. Snoring may have adverse effects on healthy. One study showed that habitual snorers had a 26% increased risk of stroke and a 15% increased risk of coronary heart disease (Li et al., 2014). In a case-control study of 400 patients hospitalized for stroke, snorers are 3.2 times more likely to have a stroke than non-snorers (Spriggs et al., 1992). In a case-control study of 177 stroke patients and 177 age—and sex-matched patients, habitual snoring was found to be an independent risk factor for stroke with an OR of 2.1 (Palomäki, 1991).

Night shift can disrupt circadian rhythm, impair sleep quality, affect the balance between work and life, and is closely related to the occurrence of coronary heart disease and stroke. A report from the Nurses' Health Study showed that night nurses had a 4% increased risk of ischemic stroke (Brown et al., 2009). A prospective cohort study of ~500,000 Finnish men showed that night work was associated with an increased risk of death from cerebrovascular disease compared with normal day work (Virtanen and Notkola, 2002). Another study showed that the relative risk of cardiovascular disease among night shift workers was 1.4 times that of non-night shift workers (Bøggild and Knutsson, 1999). Night shift workers have a higher incidence of hypertension and a higher incidence of high triglyceride (Ruidavets et al., 1998).

Previous studies have linked sleep quality, snoring symptoms and night shifts to stroke, coronary heart disease, hypertension and metabolic syndrome. The purpose of this study is to investigate the sleep quality, snoring symptoms and night shift of people over 40 years old in Chinese community, to analyze the risk factors of stroke among people with poor sleep quality, snoring symptoms and night shift, and to explore the relationship between sleep quality, snoring symptoms, night shift and risk of stroke. May be in the future, the diagnosis and treatment of sleeping disorders should be considered as a prevention and intervention of stroke.

Subjects and methods

All data were from the National Major Public Health Service Project-2016 Annual Screening and Intervention Program for Stroke Patients at High Risk (CN-2016F0007). The data were extracted from the database platform of "Chinese Stroke Center," and the use consent of the data center was obtained. A total of

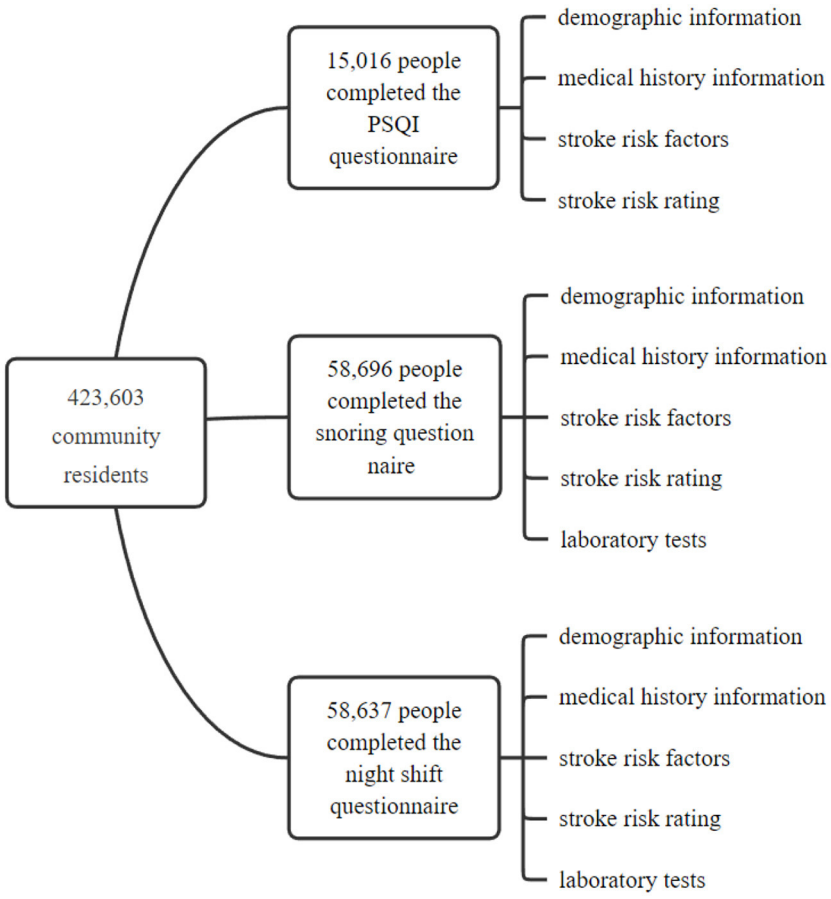

FIGURE 1
The flow chart of the research method.

TABLE 1 Comparison of low sleep quality and high sleep quality.

	High sleep quality	Low sleep quality	*p* value
	n (%)	*n* (%)	
Gender			<0.001*
Male	5,392 (42.7)	813 (34.0)	
Female	7,233 (52.3)	1,578 (66.0)	
Age (year)	60.85 ± 11.01	64.18 ± 10.35	<0.001*
Marital status			<0.001*
Unmarried	86 (0.7)	12 (0.5)	
Married	12,022 (95.2)	2,176 (91)	
Widowed	385 (3.0)	192 (8.0)	
Divorce	34 (0.3)	7 (0.3)	
Other	97 (0.8)	4 (0.2)	
Education			<0.001*
Primary school or below	3,542 (28.1)	991 (41.4)	
Junior high school	6,009 (47.6)	1,050 (43.9)	
High school education	2,034 (16.1)	260 (10.9)	
Undergraduate	1,031 (8.2)	88 (3.7)	
Master or above	8 (0.1)	2 (0.1)	
Drinking			0.594
No drinking	11,458 (90.8)	2,182 (91.3)	
Heavy drinking	156 (1.2)	26 (1.1)	
Drinking habit, no heavy drinking	901 (7.1)	158 (6.6)	
Used to drink, but no longer	110(0.9)	25(1.0)	
Exercise			<0.001*
Exercise regularly	9,387 (74.4)	1,444 (60.4)	
Lack of exercise	3,238 (25.6)	947 (39.6)	
Coronary heart disease			<0.001*
Yes	457 (3.6)	190 (8.0)	
No	12,168 (96.4)	2,201 (92.0)	
Hypertension			<0.001*
Yes	1,995 (15.8)	594 (24.8)	
No	10,628 (84.2)	1,797 (75.2)	
Dyslipidemia			<0.001*
Yes	1,231 (9.8)	494 (20.7)	
No	11,394 (90.2)	1,897 (79.3)	
Diabetes			<0.001*
Yes	679 (5.4)	207 (8.7)	
No	11,946 (94.6)	2,184 (91.3)	
Snoring			<0.001*
Yes	704 (5.6)	294 (12.3)	
No	11,921 (94.4)	2,097 (87.7)	
Atrial fibrillation			<0.001*
Yes	63 (0.5)	34 (1.4)	
No	12,562 (99.5)	2,357 (98.6)	
Smoking			0.973
Yes	1,545 (12.2)	292 (12.2)	
No	11,080 (87.8)	2,099 (87.8)	
Overweight			<0.001*
Yes	3,063 (24.3)	670 (28.0)	
No	9,562 (75.7)	1,721 (78.0)	
History of stroke			<0.001*
Yes	333 (2.6)	141 (5.9)	
No	12,292 (97.4)	2,250 (94.1)	
History of TIA			0.306
Yes	148 (1.2)	34 (1.4)	
No	12,477 (98.8)	2,357 (98.6)	
Stroke risk rating			<0.001*
Low-risk	9,961 (82.0)	1,591 (71.7)	
Medium-risk	1,223 (10.0)	316 (14.2)	
High risk	969 (8.0)	312 (14.1)	

TIA, transient ischemic attack; *$p < 0.05$.

31 provinces, autonomous regions, municipalities and Xinjiang Production and Construction Corps were included and a total of 423,603 community residents over 40 years of age completed the program screening from April 2016 to May 2017.

Among the 423,603 community residents, 15,016 people completed the PSQI questionnaire, 58,696 people completed the snoring questionnaire, and 58,637 people completed the night shift questionnaire. In this study, demographic information, medical history information, stroke risk factors and stroke risk rating (high-risk, medium-risk and low-risk) were analyzed based on the questionnaire survey results of these three groups of people. Laboratory tests were carried out on night shifts and snorers. The flow chart of the research method was shown in Figure 1.

All participants in this study were trained strictly, and qualified physicians served as investigators or auditors. The investigators were responsible for all those who met the inclusion criteria. Auditors strictly reviewed all the input data, and checked the data according to the original files after finding extreme data, unreasonable data and deviation data. The quality control experts would conduct the quality control spot check on the data.

Sleep quality was assessed according to the PSQI questionnaire. PSQI≥5 was considered to have poor sleep quality. Snoring was defined as snoring at least 3 nights a week. Night shift was referred

to regular evening or night work, lasting at least six months. Retirees were subject to their pre-retirement state.

Statistics

In this study, descriptive analysis was used to compare the differences in demographic characteristics, lifestyle, stroke risk factors and other aspects between low and high sleep quality groups, snoring and non-snoring groups, night shift and non-night shift groups.

Enumeration data was expressed as percentage and measurement data was expressed as mean ± standard deviation ($\bar{x} \pm s$). Rates were compared using χ^2 test. The non-parametric test method was used for the data with non-normal distribution and heterogeneity of variance. Levene test for homogeneity of variance was conducted for the comparison of the mean values between the two groups. If the variance was homogeneous, t test was used; if the variance was not homogeneous, t 'test was used. SPSS 21.0 statistical software was used for analysis and processing. $p < 0.05$ was considered statistically significant.

Result

A total of 15,016 people were included in the "Sleep and Stroke Related Study" and received the PSQI questionnaire survey, among which 12,625 people (84.1%) had high sleep quality and 2,391 people (15.9%) had low sleep quality. The comparison between low and high sleep quality groups was shown in Table 1 and Figure 2. The proportion of low sleep quality was higher in women, older, widowed, people with low education (primary school or below), and people who was lack of exercise ($p < 0.05$). The analysis of stroke risk factors showed that compared with the group with high sleep quality, the proportion of coronary heart disease, hypertension, hyperlipidemia, diabetes, stroke, snoring, atrial fibrillation, overweight and stroke risk assessment as high risk were higher in the group with low sleep quality ($p < 0.05$).

There were 58,696 people completed the snoring questionnaire. There were 37,703 non -snorers (64.2%) and 20,993 snorers (35.8%). The analysis of snorers and non-snorers was shown in Table 2 and Figure 3. Compared with non-snorers, snorers were more likely to be male, low education (primary school level and below), older, long working hours, smoking, drinking, and lack of exercise ($p < 0.001$). Compared with non-snoring group, the levels of BMI, waist circumference, neck circumference, systolic blood pressure, TG, TC, LDL and Hcy were higher in snoring group ($p < 0.001$). The levels of diastolic blood pressure, pulse, fasting blood glucose, glycated hemoglobin and HDL were lower in the snoring group ($p < 0.05$). The snoring group had higher rates of hypertension, hyperlipidemia, diabetes, atrial fibrillation, overweight, history of TIA, and stroke risk assessment ($p \leq 0.001$).

There were 58,637 people completed the night shift questionnaire. There were 55,161 people (94.1%) without night shift and 3,476 people (5.9%) on the night shift. The analysis of night shift and non-night shift population was shown in Table 3 and Figure 4. Compared with the group without night shift, the proportion of male, middle school education, working more than 40 h per week and lack of exercise was higher in the group with night shift ($p \leq 0.001$), and the proportion of primary and middle school education or less, working 8 h per day or less and no-drinking was lower in the group with night shift ($p < 0.001$). Compared with the group without night shift, the waist circumference, neck circumference and diastolic blood pressure of night shift group were higher ($p < 0.05$). The levels of BMI index, pulse, fasting blood glucose, 2 h postprandial blood glucose, glycated hemoglobin, TG, TC, LDL and Hcy in night shift group

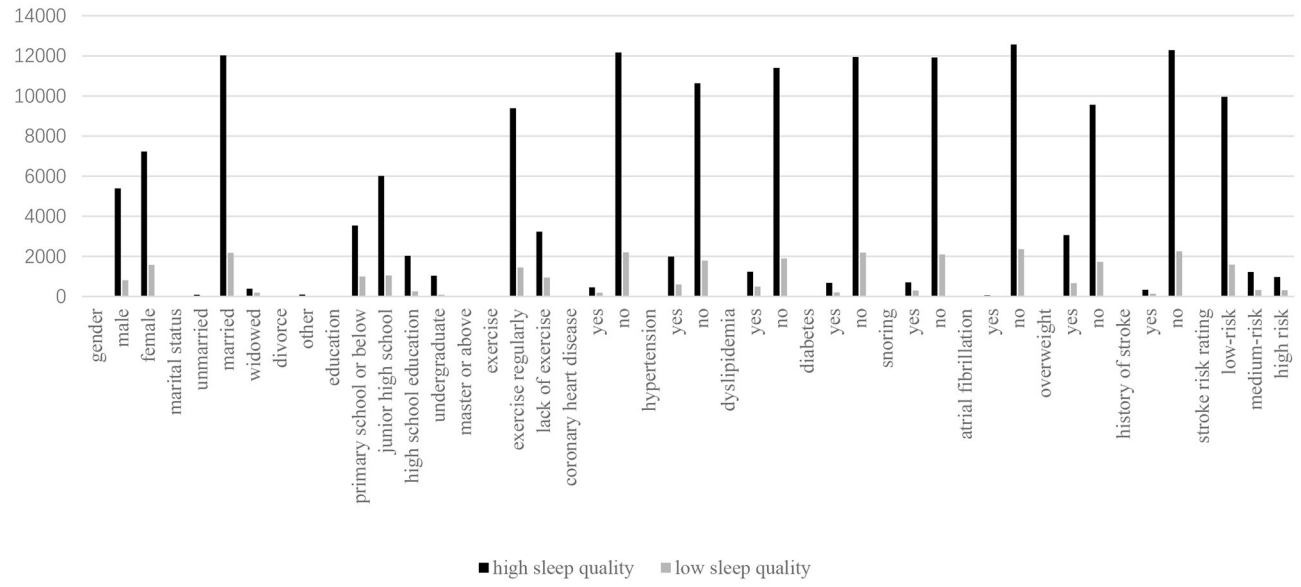

FIGURE 2
Comparison of low sleep quality and high sleep quality.

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TABLE 2 The analysis of snoring patients.

	Non-snoring	Snoring	*p*
	n (%)	*n* (%)	
Gender			<0.001*
Male	15,274 (40.5)	10,125 (48.2)	
Female	22,429 (59.5)	10,868 (51.8)	
Age (year)	60.36 ± 11.50	61.17 ± 11.09	<0.001*
Marital status			0.055
Unmarried	184 (0.5)	114(0.5)	
Married	36,667 (97.3)	20,451 (97.5)	
Others	821 (2.2)	399 (2.0)	
Education			<0.001*
Primary school or below	14,202 (37.7)	8,513 (40.6)	
Junior high school	15,120 (40.1)	7,575 (36.1)	
Others	8,350 (22.2)	4,876 (23.3)	
Working hours			<0.001*
≤8 h/day	32,059 (85.1)	18,138 (86.5)	
>55 h/week	2,361 (6.3)	1,475 (7.0)	
40–55 h/week	3,251 (8.6)	1,351 (6.5)	
Night shift			0.615
Yes	2,247 (6.0)	1,229 (5.9)	
No	35,424 (94.0)	19,735 (94.1)	
Smoking			<0.001*
Yes	4,087 (10.8)	3,662 (17.4)	
No	32,778 (87.0)	16,711 (79.6)	
Passive smoking	838 (2.2)	620 (3.0)	
Drinking			<0.001*
No drinking	35,559 (94.3)	18,546 (88.3)	
Heavy drinking	281 (0.7)	320 (1.5)	
Drinking habit, no heavy drinking	1,704 (4.5)	1,952 (9.3)	
Used to drink, but no longer	159 (0.5)	175 (0.9)	
Exercise			<0.001*
Exercise regularly	30,827 (81.8)	15,880 (75.6)	
Lack of exercise	6,876 (18.2)	5,113 (24.4)	
Hypertension			<0.001*
Yes	8,914 (23.6)	6,730 (32.1)	
No	28,787 (76.4)	14,261 (67.9)	
Dyslipidemia			<0.001*
Yes	6,999 (18.6)	5,593 (26.6)	
No	30,702 (81.4)	15,398 (73.4)	
Diabetes			<0.001
Yes	5,376 (14.3)	4,107 (19.6)	
No	32,325 (85.7)	16,884 (80.4)	
Atrial fibrillation			0.001*
Yes	337 (8.9)	248 (1.2)	
No	37,364 (99.1)	20,743 (98.8)	
Overweight			<0.001*
Yes	8,408 (22.3)	6,269 (29.9)	
No	29,292 (77.7)	14,722 (70.1)	
History of stroke			<0.001*
Yes	945 (2.5)	850 (4.0)	
No	36,756 (97.5)	20,143 (96.0)	
History of TIA			<0.001*
Yes	551 (1.5)	440 (2.1)	
No	37,150 (98.5)	20,553 (97.9)	
Stroke risk rating			<0.001*
Low-risk	24,551 (67.7)	11,324 (57.4)	
Medium-risk	7,515 (20.7)	4,317 (21.9)	
High risk	4,193 (11.6)	4,097 (20.8)	
BMI	24.35 ± 3.40	25.01 ± 3.31	<0.001*
Waistline (cm)	84.66 ± 9.08	86.35 ± 9.66	<0.001*
Neck circumference (cm)	33.77 ± 3.48	34.38 ± 3.94	<0.001*
Systolic pressure (mmHg)	130.45 ± 15.04	132.26 ± 16.32	<0.001*
Diastolic blood pressure (mmHg)	89.75 ± 9.31	81.46 ± 10.40	<0.001*
Pulse	74.43 ± 8.22	72.67 ± 6.63	<0.001*
Fasting blood-glucose (mmol/L)	5.35 ± 1.17	5.17 ± 1.37	<0.001*
Postprandial blood glucose at 2 h (mmol/L)	6.06 ± 1.61	6.18 ± 1.49	0.162
Glycated hemoglobin (%)	6.34 ± 2.50	6.12 ± 1.15	0.003*
TG (mmol/L)	1.55 ± 0.97	1.66 ± 1.07	<0.001*
TC (mmol/L)	4.33 ± 1.14	4.59 ± 1.15	<0.001*
LDL (mmol/L)	2.50 ± 0.86	2.61 ± 0.91	<0.001*
HDL (mmol/L)	1.50 ± 0.58	1.45 ± 0.51	<0.001*
Hcy (umol/L)	13.83 ± 9.86	15.47 ± 12.67	<0.001*

TG, triglyceride; TC, total cholesterol; LDL, low density lipoprotein; HDL, high-density lipoprotein; Hcy, homocysteine; *p < 0.05.

were lower, and the proportion of overweight was lower ($p < 0.01$). The night shift group had a higher risk of hypertension, history of TIA and stroke ($p < 0.001$).

Discussion

In this study, we used the PSQI questionnaire, which is recognized as a reliable, effective and standardized global sleep quality measurement questionnaire and have previously been

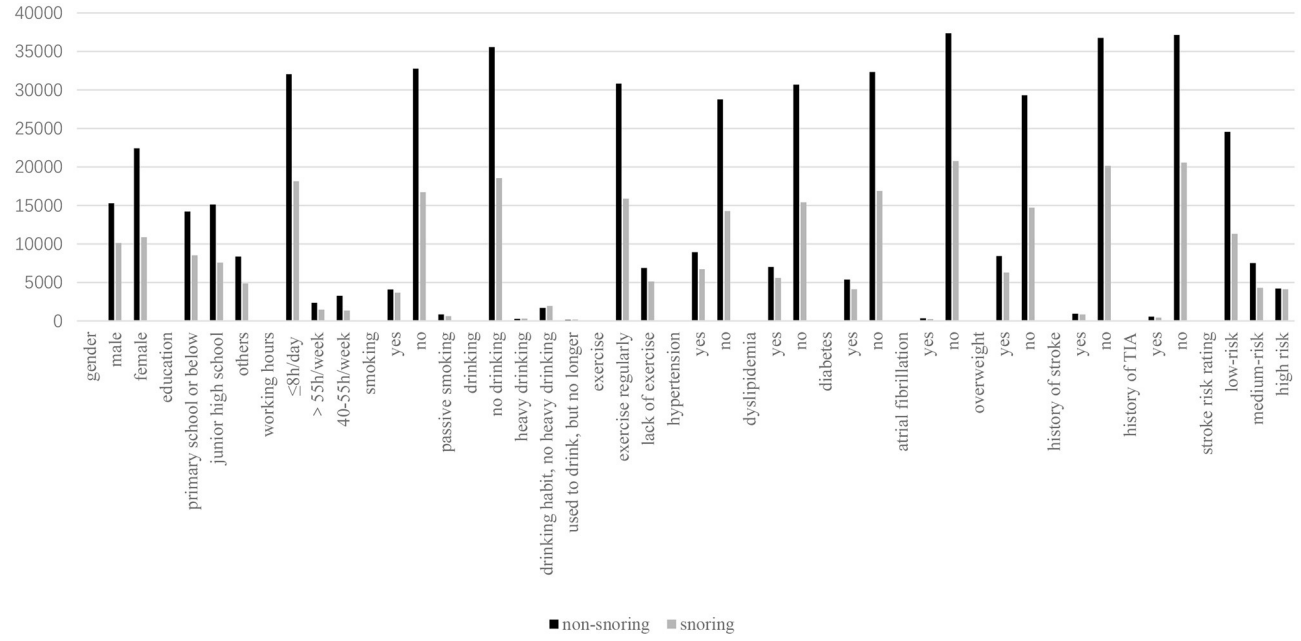

FIGURE 3
The analysis of snoring patients.

confirmed for its accuracy. PSQI was developed in 1989 by Dr. Buysse, a psychiatrist at the University of Pittsburgh. It was used to evaluate sleep quality in clinical and basic research. Liu Xianchen translated the scale into Chinese in 1996 and conducted a study on its reliability and validity. The results showed that the scale also had high reliability and validity when applied to China. The PSQI is a self-reported questionnaire used to assess sleep quality. It contains 19 questions which indicate overall sleep quality. Each question weighed on a 0–3 interval scale in 7 components. PSQI < 5 indicates high sleep quality, and PSQI ≥ 5 indicates low sleep quality. In this study, 15,016 people were surveyed by PSQI questionnaire, and 2,391 people had poor sleep quality, accounting for 15.9% of the community population over 40 years old.

Individuals who lack support from spouses and families may have difficulty controlling their anxiety and loneliness, causing sleep disorders. Consistent with this, sleep quality was lower in the widowed population in our study. Some studies had shown that the sleep quality of female population is lower (Da Rocha et al., 2013). This study showed that the lower sleep quality of female patients was related to the more trivial life and the lower stress resistance of female patients. In addition, consistent with previous studies, our study also found that people with lower education level had lower sleep quality, which was considered to be related to cognitive level, life stress, health literacy, stress resistance, and psychological factors. Physical activity may affect sleep quality in adults (Kredlow et al., 2016). Regular non-competitive physical activities can lower body temperature, increase parasympathetic activity, down-regulate hypothalamic-pituitary-adrenal secretion, increase melatonin secretion, regulate the release of inflammatory cytokines, reduce psychological stress, and improve sleep quality (Chennaoui et al., 2015). Our study showed that people who were physically inactive had higher rates of poor sleep quality. Therefore, people with poor sleep quality can improve their sleep with aerobic exercise or intensive exercise. Large waist circumference and neck circumference may cause sleep-disordered breathing (Ng et al., 2015; Baltzis et al., 2016). Our research showed that people who were overweight had lower sleep quality.

Our study shows that people with hypertension have lower sleep quality. A study on hypertension in rural adults in northeast China (Liu et al., 2016) found that the prevalence of hypertension was significantly increased in people with low sleep quality. However, some studies have reported that the PSQI score was not correlated with hypertension (Sforza et al., 2014). Decreased sleep quality is an important risk factor for hypertension, possibly due to increased sympathetic nervous system activity.

Sleep disorders have been reported to be associated with elevated glycated hemoglobin in type 2 diabetes (Knutson et al., 2006). A meta-analysis showed that the risk of diabetes due to sleep deprivation increased with the extension of follow-up time (Cappuccio et al., 2010). However, an earlier study of 6,509 Japanese workers aged 19–69 found no significant association between sleep deprivation and the development of diabetes (Hayashino et al., 2007). Our study shows that people with diabetes have lower sleep quality. Sleep deprivation leads to the increase of various inflammatory markers and the decrease of immune level, thus promoting the occurrence and development of diabetes (Wang et al., 2013).

The relationship between sleep quality and lipid levels remains controversial. Studies have shown that lipid levels are only related to sleep duration, not self-reported sleep quality (Petrov et al., 2013). However, some studies have shown that hyperlipidemia is independently associated with decreased subjective sleep quality (Cappuccio et al., 2010). Studies have shown that higher LDL and TG levels are also associated with higher PSQI

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TABLE 3 Analysis of night shift population.

	No night shift	Night shift	*p* value
	n (%)	*n* (%)	
Gender			<0.001*
Male	23,719 (43)	1,657 (47.7)	
Female	31,442 (57)	1,819 (52.3)	
Age (year)	60.64 ± 11.37	60.62 ± 11.05	0.913
Marital status			0.084
Unmarried	284 (0.5)	14(0.4)	
Married	53,733 (97.4)	3,373 (97)	
Others	1,131 (2.1)	89 (2.6)	
Education			<0.001*
Primary school or below	21,659 (39.3)	1,055 (30.4)	
Junior high school	21,070 (38.2)	1,625 (46.7)	
Others	12,432 (22.5)	796 (22.9)	
Working hours			<0.001*
≤8 h/day	48,875 (88.6)	1,324 (38.1)	
>55 h/week	2,259 (4.1)	1,577 (45.4)	
40–55 h/week	4,027 (7.3)	575 (16.5)	
Smoking			0.718
Yes	7,294 (13.2)	446 (12.8)	
No	46,498 (84.3)	2,939 (84.6)	
Passive smoking	1,367 (2.5)	91 (2.6)	
Drinking			<0.001*
No drinking	50,949 (92.4)	3,096 (89.1)	
Heavy drinking	522 (0.9)	79 (2.3)	
Drinking habit, no heavy drinking	3,392 (6.1)	263 (7.6)	
Used to drink, but no longer	296 (0.5)	38 (1.1)	
Exercise			<0.001*
Exercise regularly	44,083 (79.9)	2,596 (74.7)	
Lack of exercise	11,076 (20.1)	880 (25.3)	
Hypertension			<0.001*
Yes	14,584(26.4)	1,016 (29.2)	
No	40,573 (73.6)	2,460 (70.8)	
Dyslipidemia			0.202
Yes	11,851 (21.5)	715 (20.6)	
No	43,306 (78.5)	2,761 (79.4)	
Diabetes			0.190
Yes	8,923 (16.2)	533 (15.3)	
No	46,234 (83.8)	2,943 (84.7)	
Atrial fibrillation			0.441
Yes	545 (1.0)	39 (1.1)	
No	54,612 (99)	3,437 (98.9)	
Overweight			0.001*
Yes	13,875 (25.2)	788 (22.7)	
No	41,282 (74.8)	2,688 (77.3)	
History of stroke			0.028*
Yes	1,666 (3.0)	128 (3.7)	
No	53,492 (97)	3,348 (96.3)	
History of TIA			<0.001*
Yes	868 (1.6)	123 (3.5)	
No	54,290 (98.4)	3,353 (96.5)	
Stroke risk rating			0.003*
Low-risk	33,787 (61.3)	2,079 (59.8)	
Medium-risk	11,195 (20.3)	626 (18)	
High risk	7,723 (14)	530 (15.2)	
BMI	24.36 ± 3.41	22.02 ± 3.32	<0.001*
Waistline (cm)	85.30 ± 9.33	86.35 ± 9.66	0.015*
Neck circumference (cm)	32.94 ± 3.70	34.77 ± 3.13	<0.001*
Systolic pressure (mmHg)	131.07 ± 15.56	131.396 ± 15.12	0.224
Diastolic blood pressure (mmHg)	80.25 ± 9.72	82.01 ± 10.09	<0.001*
Pulse	74.43 ± 8.22	72.67 ± 6.63	<0.001*
Fasting blood-glucose (mmol/L)	5.35 ± 1.18	5.18 ± 1.38	<0.001*
Postprandial blood glucose at 2h (mmol/L)	6.27 ± 1.59	5.54 ± 1.29	<0.001*
Glycated hemoglobin (%)	6.28 ± 2.31	6.00 ± 0.94	<0.001*
TG (mmol/L)	1.60 ± 1.00	1.42 ± 1.14	<0.001*
TC (mmol/L)	4.45 ± 1.15	4.03 ± 1.17	<0.001*
LDL (mmol/L)	2.56 ± 0.86	2.27 ± 1.10	<0.001*
HDL (mmol/L)	1.49 ± 0.56	1.30 ± 0.44	<0.001*
Hcy (umol/L)	14.68 ± 11.44	12.61 ± 6.79	<0.001*

TG, triglyceride; TC, total cholesterol; LDL, low density lipoprotein; HDL, high-density lipoprotein; Hcy, homocysteine; *p < 0.05.

scores (Geovanini et al., 2019). However, some studies showed no significant correlation between PSQI score and blood lipid (Petrov et al., 2013). Our study showed that people with poor sleep quality have higher rates of hyperlipidemia. Decreased sleep quality leads to increased activity of hypothalamic-pituitary-adrenal axis and increased cortisol secretion, resulting in increased cholesterol level (Zhan et al., 2014).

Studies have found that decreased sleep quality and shorter sleep duration are independently associated with the risk of coronary heart disease events in adults 40 years and older (Lao et al., 2018). Everding et al. (2016) used PSQI to evaluate sleep quality and found a significant correlation between sleep quality and risk factors of cardiovascular disease. Our study also showed

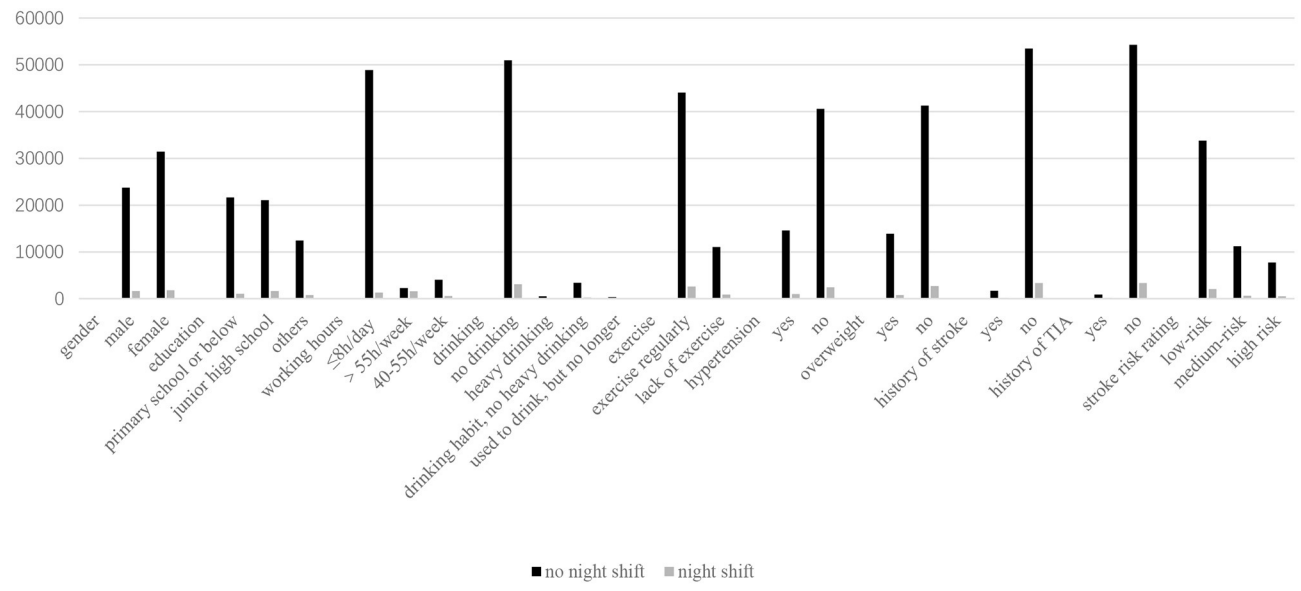

FIGURE 4
Analysis of night shift population.

that poor sleep quality was associated with coronary heart disease. The mechanisms by which sleep disorders affect cardiovascular disease include: first, sleep deprivation leads to changes in leptin and ghrelin levels, which promote the development of obesity, and elevated blood sugar levels; second, sleep disorders can lead to changes in growth hormone metabolism and increased cortisol secretion; finally, mild inflammation caused by sleep disorders can increase the hypothalamic-pituitary-adrenal axis stress response, resulting in increased blood pressure, blood flow blockage, and increased risk of cardiovascular disease (Klop et al., 2013).

Stroke patients are prone to sleep disorders and may relapse several years after stroke (Jönsson et al., 2006). One research found that participants who slept for <6 h had a 0.97 times increased risk of stroke compared to those who slept for 6–7 h and participants with sleep disorders had 0.71 times the risk of stroke compared with those without sleep disorders (Wang and Ren, 2022). Our study found that people with a history of stroke and who were assessed to be at high risk of stroke had lower sleep quality. Sleep disorders are associated with a variety of chronic diseases, including hypertension, diabetes, dyslipidemia and so on, all of which are the causes of stroke. Sleep and stroke also affect each other.

The majority of snoring people are male, and this sex difference may be related to the difference of pharynx collapse and central respiratory drive. The incidence of snoring in males was higher than that in females. In addition, habitual snoring is associated with high BMI (Svensson et al., 2006). In this study, the BMI, waist circumference and neck circumference of snoring people were higher than the none snoring people. Our study also found that people with low education (primary school level or below) and working more than 55 h per week were more likely to snore. These factors and high psychological stress could indirectly lead to higher rates of smoking and drinking.

This study showed that people with hypertension, hyperlipidemia, coronary heart disease, atrial fibrillation and diabetes had a high proportion of snoring. The fasting blood glucose, TG, TC, LDL and Hcy of snoring people were higher than those of non-snoring people, and the HDL level of snoring people was lower than that of non-snoring people. Snoring has been linked to hypertension, type 2 diabetes and metabolic syndrome, all of which can increase the risk of coronary heart disease and stroke. Severe snoring is associated with increased plaque and atherosclerosis (Drager and Lorenzi-Filho, 2008). This study showed that the proportion of snoring was higher in TIA or the high-risk group of stroke. A study showed that habitual snoring was associated with a 26% increased risk of stroke and a 15% increased risk of coronary heart disease (Li et al., 2014). Habitual snoring has been identified as an independent risk factor for stroke (Partinen, 1995). This study showed that the snoring group had lower fasting blood glucose and glycated hemoglobin, but a higher incidence of diabetes, possibly because the diabetic patients had normal levels of fasting blood glucose and glycated hemoglobin under the control of medication.

Sleep insufficiency is a common problem in the night shift population. Our study showed that the proportion of working <8 h and sleeping more than 8 h in night shift population was significantly smaller than that in non-night shift population. Sleep insufficiency can adversely affect carbohydrate metabolism and levels of endocrine hormones such as insulin, cortisol and leptin, which can lead to changes in appetite and glucose metabolism, accelerating the development of obesity and diabetes. Sleep restriction in adult males who sleep normally leads to increased sympathetic, norepinephrine, and pro-inflammatory cytokines (interleukin-1, interleukin-6, and C-reactive protein) activity, which are independently associated with coronary heart disease and death (Dettoni et al., 2012).

Night shift work disrupts circadian rhythm and is associated with increased risk factors for vascular disease and catecholamine secretion (Costa et al., 1997). The association between night shift work and cerebrovascular disease has not been fully established. A report from the Nurses' Health Study showed that night nurses

had a 4% increased risk of ischemic stroke (Brown et al., 2009). Studies have also pointed out that people who work at night have a higher risk of dyslipidemia, metabolic syndrome, hypertension and diabetes, and even one overnight shift can lead to increased blood pressure and impair heart rate variability (Lo et al., 2010).

A characteristic of night shift work is its susceptibility to metabolic syndrome (Sookoian et al., 2007). Some studies have shown that night shift workers have an elevated BMI, however, some studies have shown a decrease in BMI after a short time of night shift while no change in BMI after a long time of night shift (van Amelsvoort et al., 2004). These studies show that adaptability increases after long time of night shifts. Our study showed that BMI index, pulse, fasting blood glucose, 2 h postprandial blood glucose, glycosylated hemoglobin, TG, TC, LDL, HDL and Hcy levels of night shift population were lower than those of non-night shift population, which was different from the results of previous studies showing that night shift population was prone to metabolic disorders. The reason may be that the subjects of this study are the people who have worked at night for more than half a year, and their adaptability is enhanced after working at night for a long time. Secondly, some of the subjects have retired and are not disturbed by night work, so their metabolic status tends to be stable. Further prospective studies are needed to confirm this.

Conclusion

1. Women, the widowed, low education, and the elderly are more likely to have poor sleep quality. Compared with high sleep quality, low sleep quality may be associated with hypertension, hyperlipidemia, diabetes, snoring, coronary heart disease, atrial fibrillation and other risk factors of stroke.
2. The Chinese community over 40 years old have a higher proportion of snoring. A higher proportion of risk factors of stroke and lower sleep quality were found in snore population. Snoring may be related to the risk factors of stroke.
3. Night shift may be associated with risk factors of stroke. After a long time of night shift, the adaptability increased, and the metabolic situation tended to be stable. The levels of BMI, pulse, fasting blood glucose, 2 h postprandial blood glucose, glycosylated hemoglobin, TG, TC, LDL, HDL and Hcy in the night shift population were lower than those in the non-night shift population.

Limitation

1. Sleep quality and snoring were obtained by questionnaire, and there was no objective measurement, which could produce potential bias.
2. This is a cross-sectional study and cannot determine a definitive cause-and-effect relationship.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The ethical approval and consent was obtained from the Ethics Committee of Tianjin Huanhu Hospital. All methods were carried out in accordance with relevant guidelines and regulations. All experimental protocols were approved by Tianjin Huanhu Hospital Licensing Committee. Informed consent was obtained from all subjects.

Author contributions

YZ was responsible for writing the article. TZ, XX, YH, CZ, RL, YY, XL, and WY are responsible for collecting and organizing data. WY was responsible for reviewing the articles. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Gender differences in the modifying effect of living arrangements on the association of sleep quality with cognitive function among community-dwelling older adults: a cross-sectional study

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Background: Sleep quality is considered to be associated with cognitive function for older adults, but little is known about whether living with others can buffer mild cognitive impairment in older adults with poor sleep quality. The objective of this study was to examine the role of living arrangements in sleep quality and cognitive function among older adults aged 65 and over.

Methods: 2,859 older adults over 65 years old were selected by using multi-stage stratified sampling method. Cognitive function and sleep quality were measured using Mini-Mental State Examination (MMSE) and Pittsburgh Sleep Quality Index (PSQI). Binary logistic regression was performed to examine the relationship between sleep quality and mild cognitive impairment, and the interaction effects of sleep quality and living arrangements on mild cognitive impairment stratified by gender.

Results: Poor sleep quality was associated with mild cognitive impairment among men and women regardless of living arrangements. The significantly protective role of living with others in reducing the incidence of mild cognitive impairment was found in men with poor sleep quality, but not in women.

Conclusion: Targeted support for older adults with poor sleep quality may be effective in preventing mild cognitive impairment, and gender differences should be taken into account when promoting cohabitations.

KEYWORDS

mild cognitive impairment, sleep quality, living arrangements, gender differences, older adults

1. Introduction

One of the most pressing concerns facing most nations is the aging of their populations, and China began to experience this trend at the close of the 20th century (1). Data from China's seventh National Census showed that nearly 200 million people were aged over 65, accounting for 13.5% (2). It is estimated that by 2050, China will have 400 million people over 65, accounting for approximately 25% of the total population (3). There is no doubt that older individuals are often vulnerable to chronic physical and mental illness. With the aging of population, numerous serious health-related problems are in urgent need of attention (4). Dementia is one of the most common and serious diseases among older adults, which has been the top 10 leading causes of disability in low- and middle-income countries (5). China is now carrying a heavy burden of prevention and management due to having the most dementia sufferers in the world, accounting for about 25% of the global total (6). The early stages of dementia can be marked by some kinds of impairment in cognitive function, hence mild cognitive impairment (MCI) is an essential screening indicator and the best period of window to delay dementia for early recognition and intervention (7, 8).

MCI refers to impairment in one or more cognitive function domains, a state of possible transition between normal aging and dementia (7). MCI poses a serious threat to the quality of life among older adults, which may result in functional dependence and premature mortality (9). The prevalence of cognitive impairment rises along with the population's aging trend and the rising life expectancy. Previously, it has been reported that the prevalence of cognitive impairment among Chinese community-dwelling older adults ranged from 10.2% (10) to 31.5% (11). One recent research showed a rate of cognitive impairment in the older adults over 65 even reached 54.9% (7), with a higher prevalence in women than men (12). The severe consequences and high prevalence of cognitive impairment will place enormous challenges to healthcare systems and hinder the advancement of successful and active ageing (13–15). In order to provide pertinent information for the prevention of dementia, it is important to investigate the associated risk and protective factors affecting cognitive impairment. Numerous studies have examined the causes of MCI in recent years, with an increasing focus on the relationship between sleep and cognitive function or dementia. A number of systematic reviews and meta-analyses have managed to ascertain whether the existing evidence supports the proposed risk contribution of sleep complaints to the developing process of cognitive impairment and dementia (16–19).

Sleep, a habitual behavior that takes a significant portion of lives, is crucial for preserving human health (20, 21). But sleep problem has increasingly become one of the main health issues affecting older people (22, 23). A national survey found that about 35% of Chinese older people reported poor sleep quality among 15,638 individuals (24). Meanwhile, higher odds of sleep problems among women than men in India, China, Russia, and South Africa were found according to data from the WHO Study on global aging and adult health survey (25). A growing body of research has linked low sleep quality to MCI. One study conducted among female older adults showed that those with sleep disorders of breathing were more likely to experience cognitive decline (26). Sleep disturbance is also prevalent and predictive of cognitive decline in older people (27). Following sleep disturbance or sleep loss, deficiencies in attention, learning and memory, emotional reactivity, and higher-order cognitive processes have all been observed (28). There have also been a number of clinical and physiological studies that have attempted to understand the mechanisms by which poor sleep quality is associated with cognitive impairment (16, 29).

However, few studies have examined the role of environmental conditions, such as living arrangements, in the relationship between sleep quality and cognitive function in older adults. Living arrangements matter to the health and well-being of the older adults, as the home is a significant factor of establishing social roles and providing older persons with social support and contact (30). The incidence of living alone is higher among older persons, despite the fact that it has increased for younger and middle-aged adults (31). With more than 50% of China's old population living alone, living arrangements have become a social concern that cannot be disregarded (32). Some studies supported that living alone was associated with poor health and mental consequences such as decreased physical and cognitive function, loneliness, and suicidal ideation among older adults (33–36). What's more, the degree to which living arrangements impact health varies across men and women (37–39). The stress-buffering model indicated that the moderator can reduce the likelihood of adverse health outcomes by buffering stress before it has an effect on health outcomes (40). Therefore, we speculate that living with others, generating a stable and intimate companionship as support resources, may buffer the stress from sleep disorders to reduce the impairment of cognitive function.

In light of the disparities between men and women in MCI, sleep and the health effects of living arrangements, it would be wise to consider gender differences when probing into the associations between them. Previous research has shown that there existed gender differences in the relationship between sleep disorders and MCI since sex hormones play a key role in regulating these conditions (41). Besides, the association between living alone and cognitive impairment seems to be distinctly different among males and females. Evidence from longitudinal study suggested that men who lived alone were at a higher risk of cognitive impairment whereas there is not such trend among women (39).

To our knowledge, no study has examined the buffering effect of living with others in the relationship between sleep quality and cognitive function. Therefore, the aims of this study were as follows: (1) to analyze the relationship between poor sleep quality and MCI among older adults, (2) to investigate whether there is a buffering effect of living with others on the relationship between poor sleep quality and MCI among older adults, and (3) to explore whether gender influences such effect.

2. Methods

2.1. Data and sample

Data were gathered from the 2020 Household Health Interview Survey, which sought to investigate inhabitants' health state, demand for, and use of, healthcare services. This cross-sectional survey was performed in Taian City, Shandong Province, China. Participants were chosen using stratified multi-stage random sampling from each of the six administrative districts (4 counties and 2 districts). Three or four sub-districts or towns were randomly chosen from each district or county in Taian City in the first stage using the probability proportionate to size sampling method (PPS), based on the level of

socioeconomic development and geographic location, for a total of 20 sub-districts or towns. Eight villages and eight residency committees were chosen independently (PPS) from each town and subdistrict in the second stage, for a total of villages and committees. Lastly, an average of 50 families was randomly chosen from each village or residency committee (simple random sampling). 7,920 out of a total of 7,945 selected homes completed the entire survey. Finally, 2,859 older persons aged 65 and over who had not been diagnosed with dementia by doctors made up the research sample out of the 8,542 participants in the survey. A paper-based questionnaire was used to administer to every participant face-to-face by trained interviewers in their homes.

2.2. Measures

2.2.1. Mini-mental state examination

Cognitive function was assessed by Mini-Mental State Examination. A total of 30 items evaluates orientation (0–10), immediate recall (0–3), delayed recall (0–3), attention or concentration capacity (0–5), and language ability (0–9) (42). Given that cognitive function and educational attainment are correlated, the cut-off value for MCI was adjusted to account for this relationship; it was set at ≤17 for illiteracy, ≤20 for primary school, and ≤24 for junior high school and above (43, 44).

2.2.2. Pittsburgh sleep quality index

Sleep quality was measured by using Pittsburgh Sleep Quality Index (PSQI) (45). 19 items and 7 dimensions consist of the whole scale, which measures subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, usage of sleep medication, and daytime dysfunction. Each subdimension drops score into 0, 1, 2, and 3 based on the entries it contains, the total score of the scale is the sum of the seven dimensions, with a higher score indicating the severe sleep problem. Participants with a score of >5 were considered to be with poor sleep quality (46), and correspondingly, those who scored ≤5 were thought to be with good sleep.

2.2.3. Living arrangements

Living arrangements were collected by asking "How many persons have lived in your home in the past 6 months," and the answer "only me" was defined as living alone.

2.2.4. Covariates

We included as covariates confounding factors that may influence cognitive function according to previous studies. Sociodemographic characteristics included gender (male/female), age, residence (village/city or town), education (illiteracy or low literacy/primary school/junior high school and above), marital status (with spouse/ without spouse) (47). Life behaviors including, smoking (yes/no), drinking (yes/no), taking exercise (yes/no), and drinking tea (yes/no) were collected (48, 49). In addition, we also collected some health-related variables. By conducting physical measurement, body mass index (BMI) was calculated as weight (kg) by the square of height (m^2) (50). The number of chronic diseases was categorized to 3 statuses: 0 represented no chronic disease, 1 represented single chronic disease, and ≥2 represented multimorbidity (50). Additionally, it was demonstrated that cognitive performance was related to hearing and vision difficulty (51). Self-perceived difficulty in hearing was obtained by asking participants to "in the past 6 months, whether (1) you hardly heard clearly, (2) or needed others to raise their voice, or (3) hear clearly," answer (1) and (2) were classified as difficulty in hearing. Self-perceived difficulty in vision was obtained by asking "How difficult it was for you to recognize an acquaintance 20 m away within the past 6 months," and the person who reported difficulty was considered as a case of vision impairment.

2.3. Statistical analysis

IBM SPSS statistical software (version 26.0) was used to conduct all statistical analyses. Firstly, classified variables were provided as frequency and percentage, and continuous variables (age and BMI) were presented as mean and standard deviation (SD). Differences in MCI among older adults in sociodemographic characteristics, life behaviors, and health-related variables were analyzed using chi-square test of independence and two independent-sample *t*-test according to gender. Secondly, the associations between poor sleep quality and cognitive impairment in men and women were analyzed by using logistic regression model on the basis of gradually adjusting the control variables. Thirdly, according to the status of sleep quality and living arrangements, the participants were stratified into four groups (see details in Tables 1, 2) to investigate the interaction effects of sleep quality and living arrangements on MCI by using binary logistic regression. Statistical significance was defined as a two-tailed *p*-value less than 0.05.

3. Results

3.1. Sample description

Table 3 shows descriptive statistics for the participants. Among 2,859 older adults, 41.4% were men and 58.6% were women. The rates of MCI were 22.9 and 29.7% in men and women, respectively. Compared with participants without MCI, both men and women with MCI were more likely to be older, living in small town, uneducated, without spouse, have a lower intake of tea, with slightly lower BMI value, and have difficulty in hearing and vision, poor sleep quality and live alone. In addition, the proportion of women with MCI of smokers was significantly higher than non-smokers.

3.2. Association between sleep quality and MCI

Table 4 shows the results of binary logistic regression for association between sleep quality and MCI among older adults. In model 1, poor sleep quality was a risk factor for MCI among both men (OR: 1.640, 95% CI: 1.234–2.712) and women (OR: 1.510, 95% CI: 1.211–1.884). After controlling for sociodemographic, behavioral, and health-related variables, the effect still existed in men (OR: 1.565, 95%CI: 1.168–2.097) and women (OR:1.387, 95%CI: 1.168–2.097).

3.3. Interaction effects analyses

Table 1 summarizes the combined effects of sleep quality and living arrangements on MCI in men. In Model 4, men with poor sleep

TABLE 1 Interaction effects of sleep quality and living arrangement on MCI in men.

	Model 4	Model 5	Model 6
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Sleep quality + Living arrangements (ref: Good sleep quality + Living with others)			
Poor sleep quality + Living with others	1.591 (1.172, 2.161)**	1.567 (1.151, 2.133)**	1.499 (1.092, 2.057)*
Good sleep quality + Living alone	1.312 (0.671, 2.569)	1.286 (0.653, 2.529)	1.191 (0.600, 2.362)
Poor sleep quality + Living alone	2.640 (1.218, 5.723)*	2.640 (1.211, 5.750)*	2.519 (1.138, 5.576)*
Age	1.068 (1.040, 1.097) ***	1.069 (1.040, 1.099) ***	1.053 (1.023, 1.083) ***
Residence (ref: Village)			
City or town	0.705 (0.516, 0.964)*	0.714 (0.520, 0.979)*	0.820 (0.593, 1.124)
Education (ref: Illiteracy or low literacy)			
Primary school	0.688 (0.459, 1.031)	0.709 (0.472, 1.066)	0.742 (0.490, 1.123)
Junior high school and above	1.912 (0.836, 1.701)	1.252 (0.873, 1.795)	1.441 (0.994, 1.087)
Marital status (ref: With spouse)			
Without spouse	1.059 (0.611, 1.837)	1.048 (0.601, 1.827)	1.067 (0.608, 1.874)
Smoking (ref: No)			
Yes		1.039 (0.756, 1.427)	0.978 (0.707, 1.353)
Drinking (ref: No)			
Yes		0.861 (0.639, 1.159)	0.850 (0.627, 1.153)
Having tea (ref: No)			
Yes		0.610 (0.452, 0.824)**	0.612 (0.450, 0.831)**
Taking exercise (ref: No)			
Yes		0.737 (0.314, 1.731)	0.658 (0.276, 1.570)
BMI			0.955 (0.913, 0.999)*
Number of chronic diseases (ref: 0)			
1			0.964 (0.665, 1.396)
≥2			0.742 (0.512, 1.074)
Self-perceived difficulty in hearing (ref: No)			
Yes			2.166 (1.599, 2.935)***
Self-perceived difficulty in vision (ref: No)			
Yes			1.154 (0.854, 1.559)

BMI, body mass index; OR, odds ratio; CI, confidence interval.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

TABLE 2 Interaction effects of sleep quality and living arrangement on MCI in women.

	Model 7	Model 8	Model 9
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Sleep quality + Living arrangements (ref: Good sleep quality + living with others)			
Poor sleep quality + living with others	1.489 (1.155, 1.918)**	1.474 (1.143, 1.901)*	1.362 (1.048, 1.770)*
Good sleep quality + living alone	0.911 (0.583, 1.423)	0.896 (0.571, 1.405)	0.906 (0.572, 1.434)
Poor sleep quality + living alone	1.443 (0.948, 2.197)	1.420 (0.931, 2.168)	1.332 (0.861, 2.062)
Age	1.085 (1.061, 1.111)***	1.087 (1.062, 1.112)***	1.074 (1.048, 1.100)***
Residence (ref: Village)			
City or town	0.558 (0.442, 0.704)***	0.574 (0.454, 0.726)***	0.582 (0.457, 0.742)***
Education (ref: Illiteracy or low literacy)			
Primary school	0.437 (0.317, 0.604)***	0.442 (0.320, 0.611)***	0.449 (0.333, 0.625)***
Junior high school and above	0.856 (0.600, 1.221)	0.869 (0.609, 1.241)	0.975 (0.676, 1.405)
Marital status (ref: With spouse)			
Without spouse	1.156 (0.846, 1.578)	1.152 (0.842, 1.576)	1.070 (0.775, 1.478)
Smoking (ref: No)			
Yes		1.764 (0.794, 3.918)	1.745 (0.767, 3.969)
Drinking (ref: No)			
Yes		1.059 (0.622, 1.805)	1.010 (0.585, 1.745)
Having tea (ref: No)			
Yes		0.792 (0.632, 0.993)*	0.867 (0.686, 1.096)
Taking exercise (ref: No)			
Yes		0.563 (0.322, 0.983) *	0.524 (0.296, 0.928) *
BMI			0.986 (0.945, 1.018)
Number of chronic diseases (ref: 0)			
1			1.004 (0.736, 1.371)
≥2			1.111 (0.826, 1.495)
Self-perceived difficulty in hearing (ref: No)			
Yes			2.427 (1.912, 3.082) ***
Self-perceived difficulty in vision (ref: No)			
Yes			1.239 (0.970, 1.581)

BMI, body mass index; OR, odds ratio; CI, confidence interval.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

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TABLE 3 Characteristics of the older adults aged 65 and over.

Variables	Total (n =2,859)	Men (n =1,184)			Women (n =1,675)		
		Mild cognitive impairment			Mild cognitive impairment		
		No[a] (n =913)	Yes[b] (n =271)	p	No[a] (n =1,178)	Yes[b] (n =497)	p
Age, mean ± SD	71.29 ± 5.04	70.77 ± 4.719	72.45 ± 5.95	<0.001[c]	70.72 ± 4.54	72.95 ± 5.75	<0.001[c]
Residence				0.049[d]			<0.001[d]
Village	1,718 (60.1)	588 (75.4)	192 (24.6)		607 (64.7)	331 (35.3)	
City or town	1,141 (39.9)	325 (80.4)	79 (19.6)		571 (77.5)	166 (22.5)	
Education				0.031[d]			<0.001[d]
Illiteracy or low literacy	1,393 (48.7)	197 (74.1)	69 (25.9)		737 (65.4)	390 (34.6)	
Primary school	666 (23.3)	272 (82.2)	59 (17.8)		280 (83.6)	55 (16.4)	
Junior high school and above	800 (28.0)	444 (75.6)	143 (24.4)		161 (75.6)	52 (24.4)	
Marital status				0.010[d]			<0.001[d]
With spouse	2,089 (73.1)	786 (78.4)	216 (21.6)		800 (73.6)	287 (26.4)	
Without spouse	770 (26.9)	127 (69.8)	55 (30.2)		378 (64.3)	210 (35.7)	
Smoking				0.452[d]			0.011[d]
Yes	408 (14.3)	295 (78.5)	81 (21.5)		16 (50.0)	16 (50.0)	
No	2,451 (85.7)	618 (76.5)	190 (23.5)		1,162 (70.7)	481 (29.3)	
Drinking				0.086[d]			0.406[d]
Yes	864 (30.2)	614 (78.6)	167 (21.4)		55 (66.3)	28 (33.7)	
No	1,995 (69.8)	299 (74.2)	104 (25.8)		1,123 (70.5)	469 (29.5)	
Having tea				0.001[d]			0.021[d]
Yes	1,906 (66.7)	684 (79.7)	174 (20.3)		758 (72.3)	290 (27.7)	
No	953 (33.3)	229 (70.2)	97 (29.8)		420 (67.0)	207 (33.0)	
Taking exercise							
Yes	88 (3.1)	21 (72.4)	8 (27.6)	0.542[d]	35 (59.3)	24 (40.7)	0.060[d]
No	2,771 (96.9)	892 (77.2)	263 (22.8)		1,143 (70.7)	473 (29.3)	
BMI, mean ± SD	24.34 ± 3.49	24.08 ± 3.31	23.43 ± 3.24	0.002[c]	24.83 ± 3.50	24.12 ± 3.78	<0.001[c]
Number of chronic diseases				0.402[d]			0.092[d]
0	662 (23.2)	212 (76.0)	67 (24.0)		280 (73.1)	103 (26.9)	
1	999 (34.9)	319 (75.6)	103 (24.4)		415 (71.9)	162 (28.1)	
≥2	1,198 (41.9)	382 (79.1)	101 (20.9)		483 (67.6)	232 (32.4)	
Self-perceived difficulty in hearing				<0.001[d]			<0.001[d]
Yes	1,063 (37.2)	345 (68.3)	160 (31.7)		304 (54.5)	254 (45.5)	
No	1796 (62.8)	568 (83.7)	111 (16.3)		874 (78.2)	243 (21.8)	
Self-perceived difficulty in vision				0.002[d]			<0.001[d]
Yes	1,641 (57.4)	471 (73.6)	169 (26.4)		663 (66.2)	338 (33.8)	
No	1,218 (42.6)	442 (81.2)	102 (18.8)		515 (76.4)	159 (23.6)	
Living arrangements				0.012[d]			0.004[d]
Alone	513 (17.9)	97 (68.8)	44 (31.2)		239 (64.2)	133 (35.8)	
With others	2,346 (82.1)	816 (78.2)	227 (21.8)		939 (72.1)	364 (27.9)	
Poor sleep quality				<0.001[d]			<0.001[d]
Yes	914 (68.0)	290 (71.1)	118 (28.9)		563 (65.9)	291 (34.1)	
No	1,945 (32.0)	623 (80.3)	153 (19.7)		615 (74.9)	206 (25.1)	

SD, standard deviation; BMI, body mass index.
[a]Without MCI.
[b]With MCI.
[c]t-test.
[d]Chi-square test.

TABLE 4 Binary logistic regression for association between sleep quality and MCI.

	Men	Women
	AOR (95% CI)	AOR (95% CI)
Model1		
Good sleep quality	Ref	Ref
Poor sleep quality	1.640 (1.234, 2.172) **	1.510 (1.211, 1.884) ***
Model 2		
Good sleep quality	Ref	Ref
Poor sleep quality	1.628 (1.224, 2.166)**	1.500 (1.201, 1.873)***
Model 3		
Good sleep quality	Ref	Ref
Poor sleep quality	1.565 (1.168, 2.097)**	1.387 (1.168, 2.097)**

Model 1: adjusted for age, residence, education and marital status.
Model 2: adjusted for age, residence, education, marital status, smoking, drinking, having tea, taking exercising, and living arrangements.
Model 3: further adjusted for BMI, number of chronic disease, self-perceived hearing difficulty, self-perceived vision difficulty.
AOR, adjusted odds ratio; CI, confidence interval.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

quality who lived with others (OR = 1.591, 95% CI: 1.172, 2.161) were more likely to have MCI in comparison with those with good sleep who lived with others, and so did those with poor sleep quality who lived alone (OR = 2.640, 95% CI: 1.218–5.723). Model 5 shows similar results with approximate OR values. After further controlling for health-related variables (Model 6), the estimates aforementioned were attenuated but remained significant despite the significant effects of BMI and hearing difficulties on MCI. Men with poor sleep quality who lived with others (OR = 1.499, 95% CI: 1.092–2.057) as well as those with poor sleep quality who lived alone (OR = 2.519, 95% CI: 1.138–5.576) were both more likely to have MCI in comparison with those with good sleep who lived with others. Table 2 shows that women with poor sleep quality who lived with others had a significantly higher risk of MCI (OR = 1.489, 95% CI: 1.155–1.918) in Model 7. In the fully adjusted model (Model 9), the effect was diminished but still significant (OR = 1.362, 95% CI: 1.048–1.770). The results highlight the important buffering role of living with others on MCI in males with poor sleep quality, but not in females.

4. Discussion

This study investigated the relationship between sleep quality and cognitive function among male and female older adults aged 65 and over, and then further considered the interaction effect of poor sleep quality and living arrangements on MCI. Our main findings can be summarized as follows: (1) both men and women who had poor sleep quality were more likely to suffer from MCI and (2) the significantly protective role of living with others in reducing the incidence of MCI was found in men with poor sleep quality, but not in women.

In this study, the overall rate of cognitive impairment among older adults aged over 65 was 23.4%, which was in line with the prevalence of one study conducted among Chinese community-dwelling older adults (52). Besides, consistent with the literature, women reported a higher rate of MCI than men (8, 12). One possible explanation can be that women have a longer life expectancy than men (53), and cognitive impairment is associated with age-related neurodegenerative diseases (50), the incidence of cognitive impairment increases as they age. The findings further indicated that the prevention of cognitive impairment should not ignore gender differences.

After controlling sociodemographic characteristics, life behaviors and health-related variables, male and female older adults with poor sleep quality tend to experience higher risks of MCI. This result supports the viewpoint from previous observations that older adults with sleep problems were more likely to report severer subjective cognitive decline and poor cognitive performance in longitudinal and cross-sectional studies (54, 55). As one of the sleep problems, sleep-disordered breathing has been shown to cause early potentially reversible alterations in Alzheimer's disease biomarkers (56), which may predict individual risk to develop Alzheimer's disease (18). A network of state-modulating neurons in the hypothalamus and brain stem participates in the dynamic process of sleep, which interacts with the circadian and homeostatic systems to produce stable sleep and awake cycles every day (57). Due to the lack of continuous sleep or sleep duration, they may need to nap during the daytime, and this lack of wakefulness can cause problems with cognitive function including domains of memory, orientation, or concentration (58).

We observed that living with others had a buffering effect on cognitive impairment in male participants with sleep problems. There is a wide range of supporting ideas or evidence that living with others can directly or indirectly improve cognitive performance in older adults. To begin with, in traditional Chinese norms, it is a symbol of happiness for older adults to live with their spouse or children to enjoy the joys of family life (39). Older adults who lived with a spouse had much better objectively measured physical functions due to better support and motivation for exercise (50). It can be reasonably speculated that older adults are more likely to go for walks or visit friends and relatives by following their co-residents like spouse or children. This gentle form of walking has been suggested to be associated with the maintenance of cognitive function (51). In terms of the supportive environment created by living with others, the benefits of emotional support on older adults' cognitive function do matter, as well. Generally, living with other people can benefit cognitive reserve in older adults by expanding their social networks and creating more stable social bonds through family ties (59). The positive emotions that older adults experience from high perceived social support are predictors of good cognitive function (52).

In the present study, our finding is partially consistent with previous longitudinal research, which found that living alone only negatively affected cognitive function in men (30). Males may experience limitations as a result of worries about the physical or emotional well-being of others, whether they live with spouse or children and grandchildren (60). Therefore, men are more likely to avoid or abstain from unhealthy habits such as smoking and drinking that have been shown to be risk factors of cognitive decline (61). Besides, men often rely on their partners more often than women as their main source of emotional and social support for confidence (62). What's more, living with others is itself a predictor of better sleep quality (63). Hence, men are more likely to gain a better sense of well-being, physical activity motivation, and emotional support, thereby obtaining a lower risk of cognitive impairment. On the contrary, no cushioning effect of cohabitation on MCI was found in women. This may result from that women often take on prominent dedication tasks in family, taking care of not only their spouse but also their children

and grandchildren (63). In this case, women who have sleep complaints are still burdened with trivia rather than seeking an outlet for relaxation or relief. As has been proposed by Jeon, living alone seems to be advantageous to women (64).

Conversely, the state of empty-nesters is easily associated with poorer physical, mental, and social interactions in men (65). As we mentioned earlier, older adults with sleep problems are at a cognitive disadvantage, and living alone can exacerbate this vulnerability with negative effects on physical, psychological, and social interactions. In a comparative study, male adults aged 70 and over who lived alone in the community were associated with lower physical function scores than those living with a spouse or partner (66), which may predict poor cognitive performance (67). Emotionally, living alone has been proven to be associated with severe depression and wide psychological distress (68, 69). As we know, psychological risk factors influence people's cognitive trajectories, depression, anxiety, and decreased psychological resilience are somewhat contributors to cognitive decline (70, 71). Additionally, people who live alone were more likely to feel more socially isolated and had fewer social networks, both of which have been linked to cognitive decline (72, 73). And men were more prone than women to feel disconnected from society when they lived alone (74). Therefore, paying attention to the dual effects of sleep problems and living alone in men is a key point in preventing cognitive decline. But for women, we should not stereotype that living alone, loneliness, and isolation are always interrelated and simultaneous, or just conflate them (75). Living alone does not mean less social engagement and decreased psychological well-being, especially among older female adults (69). Though they have difficulty sleeping a comfortable and intact night, they can arrange more time to participate in physical activities and intellectually stimulating activities like square dancing or playing cards with friends to maintain better cognitive performance (76–78).

The findings on living with others being buffer of association between poor sleep quality and MCI might have essential implications for older adults. It is suggested that health managers like family doctors have the responsibility to understand and improve sleep quality in older people to promote their cognitive reserve. In addition, it is advocated for adult children to live with their older parents in order to create a more supportive environment with a caring, emotional, and behavioral assistant. Moreover, to better target MCI prevention, more gender-specific measures should be proposed on the basis of mastering health-related information including the physical, psychological, and social state.

There are several limitations that need to be stated here in this study. Firstly, given the cross-sectional design of the present study, we were unable to determine the causal association between sleep quality and cognitive function. Secondly, we have some concerns about using PSQI to measure sleep quality, as it only measures sleep in the month preceding the evaluation and lacks sufficient information about sleep breathing disorders (although including snoring) which may limit the comprehensive assessment of sleep quality and its relationship with MCI; meanwhile, the lack of assessment of mood may lead to insufficient inclusion of control variables. Thirdly, the population in this study was merely from Taian, Shandong Province, which is not conducive to generalizing the conclusion to the wider population of older adults, a representative sample from more geographical areas will be needed in the future. Finally, information about living arrangements was collected only as living alone and not alone, it is crucial to understand whom the older adults are living with to analyze its effect on MCI in more detail in the future.

5. Conclusion

Our results indicate that MCI was positively associated with poor sleep quality among older adults. The research further demonstrates the protective role of living with others on the relationship between sleep quality and MCI in only men. For men with poor sleep quality, living with others creates a more supportive environment that buffers the negative impact of poor sleep quality on cognitive function. These results suggest that more support and intervention strategies for cognitive function improvement should be provided for older adults with poor sleep quality, and gender differences should be taken into account when promoting cohabitations.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethical Committee of the Centre for Health Management and Policy Research, Shandong University (approval number: LL20191220). The patients/participants provided their written informed consent to participate in this study.

Author contributions

HY designed the study, reviewed the literature, and wrote the manuscripts. LX provided the datasets and revised the draft. WQ refined the ideas and interpreted the results. FH contributed to data collection. LL, CC, and WT contributed to statistical analysis. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Relation between sleep disorders and post-stroke cognitive impairment

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Objective: To investigate the effects of sleep disorders on post-stroke cognitive impairment (PSCI) and other factors affecting post-stroke cognitive impairment.

Methods: A total of 1,542 first-ever stroke inpatients in department of neurology of Tianjin Huanhu Hospital from 2015.6.1 to 2016.12.31. We recorded the personal history of patients. The MMSE (mini-mental state examination), MoCA (Montreal Cognitive Assessment), HAMD (Hamilton Depression Scale), BI (Barthel index), mRS (Modified Rankin Scale), PSQI (Pittsburgh Sleep Quality Index), ESS (Epworth Sleepiness Scale), Berlin questionnaire, nocturnal TST (total sleep time) were assessed before discharge. All patients were followed up at 3 months, 6 months, and 4 years (2019–2020) after stroke. During follow-up, the above scales should be evaluated again to assess the sleep status and cognitive function of patients at that time.

Results: Nocturnal TST (>8 h) (OR 3.540, 95% CI 1.692–7.406, $P = 0.001$) was a risk factor for cognitive impairment 3 months after stroke. Nocturnal TST (<7 h) (OR 6.504, 95% CI 3.404–12.427, $P < 0.001$) was a risk factor for cognitive impairment 6 months after stroke. Low sleep quality (OR 2.079, 95% CI 1.177–3.672, $P = 0.012$), sleepiness (OR 3.988, 95% CI 1.804–8.818, $P = 0.001$), nocturnal TST (<7 h) (OR 11.334, 95% CI 6.365–20.183, $P < 0.001$), nocturnal TST (>8 h) (OR 4.096, 95% CI 1.682–9.975, $P = 0.002$) were risk factors for cognitive impairment 4 years after stroke. The prevalence of cognitive impairment with TIA were 79.3% at admission, 68.1% at 3-months follow-up, 62.1% at 6-months follow-up and 52.2% at 4-year follow-up.

Conclusion: Long or short nocturnal TST (<7 h or >8 h) was a risk factor for cognitive impairment after stroke (3 months, 6 months and 4 years). Poor sleep quality and sleepiness were shown to be risk factors for cognitive impairment at 4-year follow-up. Cognitive impairment was very common in patients with TIA.

KEYWORDS

sleep disorders, post-stroke cognitive impairment, nocturnal total sleep time, sleepiness, OSA

Introduction

Stroke can lead to death and disability. The number of stroke cases is increasing globally, as is the number of post-stroke disabilities. While current research on stroke has focused on physical disability, an important aspect of cognitive impairment in stroke survivors has been neglected. The prevalence of post-stroke cognitive impairment (PSCI) will increase

in the future as the incidence of stroke increases and the mortality in the elderly declines. PSCI cannot only cause physical disability, but also reduce the quality of life. As a result, PSCI has become one of the most serious public health problems in the world. Due to the high prevalence of stroke, it is necessary to assess the risk of PSCI in stroke patients so that preventive measures and rehabilitation can be targeted at high-risk groups. The direct effect of stroke events on cognition remains unclear. After stroke, the damage to the body tends to improve more or less, however, for unknown reasons, the cognitive impairment gradually worsened.

Sleep is a modifiable factor, and sleep disorders are common in elderly stroke patients. There is more and more evidence that stroke and sleep are correlated. Stroke can damage the central nervous system, leading to changes in brain activity, function and sleep structures. Sleep is regulated by a number of complex interacting mechanisms located in the brain stem, hypothalamus, preoptic region and thalamus (Scullin and Bliwise, 2015), so 20–40% of stroke patients will have sleep disorders, and 50–70% of stroke patients will have sleep-related breathing disorders. The current focus is on improving sleep in stroke patients.

Sleep disorders are associated with inflammation, metabolism, and vascular disease, affecting about 5% of the Chinese population (Ng et al., 2015). In post-stroke patients, the following disorders can be observed: sleep-disordered breathing, insomnia, sleepiness, and circadian rhythm disturbances. Sleep disorders are underdiagnosed in China. Increasing evidence also suggests that sleep is associated with cognitive function (Yaffe et al., 2014). Sleep disorders also play a role in the development of cognitive impairment, and poor sleep is a risk factor for dementia (Landry and Liu-Ambrose, 2014). The purpose of this study was to investigate sleep related factors and potential other risk factors in patients with post-stroke cognitive impairment (PSCI).

Research object

A total of 1,542 first-ever stroke in patients, including cerebral infarction, TIA and cerebral hemorrhage, were hospitalized in department of neurology of Tianjin Huanhu Hospital from 2015.6.1 to 2016.12.31. The patients were all admitted within 72 h after onset. (1) Inclusion criteria: ① According to international diagnostic standards (Easton et al., 2009; Jauch et al., 2013; Hemphill et al., 2015), patients were diagnosed with cerebral infarction, TIA, and cerebral hemorrhage.② Patients who can provide written informed consent and are willing to follow the 4-year follow-up protocol. (2) Exclusion criteria: ① Patients with obvious liver and kidney dysfunction, heart failure, specific genetic diseases, severe infection, malignant disease or brain disease including cerebral infarction, cerebral hemorrhage, intracranial tumor, severe head trauma, or neurosurgery; ② Patients previously diagnosed with cognitive impairment. The cognitive status of patients before stroke was assessed by asking their close relatives through the Chinese version of Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE), which had previously been validated in the Chinese population (Fuh et al., 1995), in order to exclude patients with pre-stroke cognitive impairment. ③ Patients under 18 years of age; ④ Patients with aphasia, apraxia, disturbance of consciousness, visual and hearing impairment and other reasons who have difficulty to perform functional tests and cannot accurately provide reliable information.

Research method

All enrolled patients underwent a detailed medical history, prior history, and personal history, as well as a detailed neurological examination, magnetic resonance imaging (MRI), transcranial doppler, cervical ultrasound, magnetic resonance angiography (MRA), or CT angiography (CTA).

According to MRI results, the lesion of the patients were divided into dominant hemisphere and non-dominant hemisphere; large lesion, brain stem lesion, critical sites lesion and other lesions; multiple infarcts and non-multiple infarcts; microbleeds and non-microbleeds.

Medial temporal lobe atrophy Rating Scale (MTA) and Fazekas scale were performed. Homocysteine (Hcy), fasting blood glucose (FBG), triglycerides (TG), cholesterol (TC), high density lipoprotein (HDL), and low density lipoprotein (LDL) were recorded.

The educational level of the patients was recorded in detail. Patients with less than 6 years of education (illiterate and primary school) were in the low level of education group, and those with more than 6 years of education were in the high level of education group.

Patients were given the detailed mini-mental state examination (MMSE) score, Montreal Cognitive Assessment (MoCA score), Hamilton Depression Scale (HADM) score, National Institutes of Health Stroke Scale (NIHSS) score, Modified Rankin Scale (mRS) score, Barthel index (BI),Pittsburgh Sleep Quality Index (PSQI) score, Epworth Sleepiness Scale (ESS) score, Berlin Questionnaire (BQ), and nocturnal total sleep time (TST) before discharge, 3 months after discharge, 6 months after discharge and 4 years after discharge (2019–2020). The end point was the end of follow-up and the secondary end point was death.

The total score of MMSE is 0–30 points, and the normal value is divided into illiteracy >17 points, primary school >20 points, junior high school and above >24 points. MMSE has good clinical value for dementia screening (Mitchell, 2009; Blackburn et al., 2011; Velayudhan et al., 2014). The total score of MoCA is 0–30 points (Nasreddine et al., 2005). Patients with less than 12 years of education added one point to their MoCA score (Nasreddine et al., 2005). Cognitive impairment was defined as MoCA < 26 because this boundary produces the optimal balance between sensitivity and specificity in detecting cognitive impairment (Nasreddine et al., 2005). The combined application of MMSE and MoCA makes up for their disadvantages and improves the accuracy of screening for cognitive impairment. PSCI includes post-stroke dementia (PSD) and post-stroke cognitive impairment non-dementia (PSCIND). The diagnosis of PSD includes cognitive decline, impairment in 2 or more cognitive areas of attentional or executive function, memory, language, and visuospatial function, affecting the patient's daily living function, which should be independent of the impaired motor and sensory function after stroke. The diagnosis of PSCIND also includes cognitive decline, impairment in at least one of the cognitive areas of attentional or executive function, memory, language, and visuospatial function,

and normal or mildly affected daily living function, which should be independent of the impaired motor and sensory function after stroke. The diagnosis of PSCI is based on the patient's clinical presentation, combined with the MoCA and MMSE scores. The diagnosis of PSCI is made by an expert panel composed of clinically experienced neuropsychiatrists, psychologists and neurologists.

Hamilton Depression Scale score >7 is considered depression. PSQI < 5 indicates high sleep quality, and PSQI ≥ 5 indicates low sleep quality. The total score of ESS is 0–24 and an overall score of ≥10 indicates sleepiness. The Berlin Questionnaire (BQ) consists of 10 questions divided into three categories: severity of snoring, daytime sleepiness, and a history of hypertension or obesity. Patients with two or more positive categories were classified as "high-risk obstructive sleep apnea (OSA) patients," and patients with one category of positive or asymptomatic groups were classified as "low-risk OSA patients" (Kang et al., 2013).

A total of 1,542 stroke patients were enrolled and 188 patients were lost to follow-up. Among the 188 patients, 56 patients went to other places and could not cooperate with the follow-up, 103 patients withdrew from the follow-up, and 29 patients could not be contacted because their contact information was changed.

In order to reduce the rate of lost to follow-up, patients were followed up by telephone every 3–5 months, and patients were instructed to timely inform the doctors if they changed their contact information. Patients who were unable or unwilling to the hospital for follow-up will be followed up at their homes with the consent of their families. A total of 1,354 patients, including 144 who died, completed follow-up. The mortality rate was 0.9% at 3 months after stroke, 2.0% at 6 months after stroke and 10.6% at 4 years after stroke.

All data were collected by trained neurologists and nurses through standard face-to-face questionnaires. Before the follow-up, all the investigators were given special training. The training included the purpose of the study, questionnaire management methods, questionnaire testing methods and research procedures. After the training, we conducted a strict assessment, and only those who were excellent in the assessment could become investigators. Investigators were given adequate guidance and assistance during data collection.

This study had passed the ethical approval of Tianjin Huanhu Hospital. The purpose of the study had been explained to all participants and confidentiality had been promised, and participants had been informed of their right to withdraw.

PSCI includes PSD and PSCIND. The diagnosis of PSCI, PSD, and PSCIND was based on "expert consensus on the Management of Post-stroke cognitive impairment" (Wang et al., 2021), combined with MMSE and MoCA scores. The diagnosis of PSCI, PSD, PSCIND was made by a team of clinically experienced neuropsychiatrists, psychologists and neurologists. Cognitive impairment occurring within 3–6 months after stroke was defined as early-onset cognitive impairment, and cognitive impairment occurring after 6 months after stroke was defined as late-onset cognitive impairment (Mok et al., 2017). mRS ≤ 2 indicated good prognosis of neurological function and mRS > 2 indicated poor prognosis of neurological function.

Statistics

Statistical product and service solutions (SPSS) software (version 17.0) was used for data processing and analysis. The distribution of categorical variables is expressed as a percentage. Logistic univariate regression analysis was used to analyze the factors affecting the cognitive function of patients at 3 months, 6 months and 4 years after stroke, and binary logistic regression analysis was performed for the factors with statistical significance in Logistic univariate regression analysis ($P < 0.05$). Logistic univariate regression analysis was used to analyze the factors affecting the early and late onset cognitive impairment, and binary Logistic regression analysis was performed for statistically significant factors ($P < 0.05$).

The stepwise forward method was used to select the variables that were eventually included in the model. Among the covariables, stroke was classified into TIA, cerebral hemorrhage and cerebral infarction, with cerebral hemorrhage as the reference category. TIA and cerebral infarction were combined as ischemic cerebrovascular disease. Nocturnal TST was divided into 7–8 h, <7 h, and >8 h, with 7–8 h as the reference category (Li et al., 2018). The lesions were divided into large lesion, brainstem lesion, key sites lesion, other lesions and other lesions were used as reference.

Results

The proportion of sleep quality in each stage after stroke was shown in Table 1. The proportion of low sleep quality was 52.5% at admission, 46.8% at 3 months after stroke, 40.9% at 6 months after stroke, and 40.2% at 4 years after stroke.

The proportion of nocturnal TST in each stage after stroke is shown in Table 2. The proportion of nocturnal TST (<7 h) was 50.8% at admission, 49.3% at 3 months after stroke, 46.6% at 6 months after stroke, and 43.9% at 4 years after stroke. The proportion of nocturnal TST (>8 h) was 13.9% at admission, 12.9% at 3 months after stroke, 7.6% at 6 months after stroke, and 12.6% at 4 years after stroke.

TABLE 1 Proportion of sleep quality in each stage after stroke.

	Low sleep quality	High sleep quality
At admission	711 (52.5%)	643 (47.5%)
3 months after stroke	627 (46.8%)	713 (53.2%)
6 months after stroke	542 (40.9%)	782 (59.1)
4 years after stroke	486 (40.2%)	724 (59.8%)

TABLE 2 Proportion of nocturnal TST in each stage after stroke.

	Nocturnal TST (<7 h)	Nocturnal TST (>8 h)	Nocturnal TST (7–8 h)
At admission	688 (50.8%)	188 (13.9%)	478 (35.3%)
3 months after stroke	661 (49.3%)	173 (12.9%)	506 (37.8%)
6 months after stroke	617 (46.6%)	101 (7.6%)	606 (45.8%)
4 years after stroke	531 (43.9%)	152 (12.6%)	527 (43.5%)

TABLE 3 Proportion of sleepiness in each stage after stroke.

	Sleepiness	Non-sleepiness
At admission	290 (21.4%)	1,064 (78.6%)
3 months after stroke	292 (21.8%)	1,048 (78.2%)
6 months after stroke	295 (22.3%)	1,029 (77.7%)
4 years after stroke	261 (21.6%)	949 (78.4%)

TABLE 4 Proportion of OSA in each stage after stroke.

	High-risk OSA	Low-risk OSA
At admission	1,011 (74.7%)	343 (25.3%)
3 months after stroke	1,015 (75.8%)	325 (24.2%)
6 months after stroke	1,033 (78%)	291 (22%)
4 years after stroke	937 (77.4%)	273 (22.6%)

The proportion of sleepiness in each stage of stroke was shown in Table 3. The proportion of sleepiness was 21.4% at admission, 21.8% at 3 months after stroke, 22.3% at 6 months after stroke, and 21.6% at 4 years after stroke.

The proportion of OSA in each stage after stroke was shown in Table 4. The proportion of high-risk OSA was 74.7% at admission, 75.8% at 3-month follow-up, 78% at 6-month follow-up, and 77.4% at 4-year follow-up.

Three months after stroke, there were 288 patients without PSCI, 1,056 patients with PSCI, and 10 patients with death. The prevalence of PSCI was 78%. Univariate and multivariate logistic analyses of cognitive impairment at 3 months after stroke are shown in Table 5 (PSCI was coded as 1, non-PSCI was coded as 0).

Logistic univariate analysis showed gender, age, education, stroke type, multiple lesions, MTA score, Fazekas score, microbleeds, drinking, smoking, HDL, depression at 3 months, neurological function recovery, sleep quality, sleepiness, OSA, nocturnal TST were statistically significant ($P < 0.05$). In logistic multivariate analysis, low level of education (≤6 years) (OR 2.075, 95% CI 1.332–3.232, $P = 0.001$), cerebral infarction (OR 2.858, 95% CI 1.175–6.949, $P = 0.021$), high Fazekas score (OR 1.585, 95% CI 1.284–1.957, $P < 0.001$), depression (OR 2.243, 95% CI 1.033–4.870, $P = 0.041$), poor neurological recovery (mRS > 2) (OR 3.154, 95% CI 1.416–7.023, $P = 0.005$), nocturnal TST (>8 h) (OR 3.540, 95% CI 1.692–7.406, $P = 0.001$) were risk factors for cognitive impairment at 3 months after stroke.

Six months after stroke, there were 980 patients (72.4%) with PSCI, 354 patients (26.1%) without PSCI, and 20 dead patients (1.5%). The prevalence of PSCI was 72.4%. Univariate and multivariate logistic analyses of cognitive impairment at 6 months after stroke are shown in Table 6.

Logistic univariate analysis showed gender, age, education, lesion, multiple lesions, MTA score, Fazekas score, microbleeds, drinking, smoking, TG, depression at 6 months, neurological function recovery, sleep quality, sleepiness, OSA, nocturnal TST were statistically significant ($P < 0.05$).

Logistic multivariate analysis showed large lesion (OR 20.112, 95% CI 2.248–179.936, $P = 0.007$), critical lesion (OR 2.383, 95% CI 1.291–4.399, $P = 0.005$), high Fazekas score (OR 1.532, 95% CI 1.133–2.073, $P = 0.006$), nocturnal TST (<7 h) (OR 6.504, 95% CI 3.404–12.427, $P < 0.001$) were risk factors for cognitive impairment at 6 months after stroke.

Four years after stroke, there were 840 patients (62.0%) with PSCI, 370 patients (27.4%) without PSCI and 144 patients (10.6%) with death. The prevalence of PSCI was 62%. Univariate and multivariate logistic analyses of cognitive impairment at 4 years after stroke are shown in Table 7.

Logistic univariate analysis showed gender, age, education, stroke type, lesion, multiple lesions, MTA score, Fazekas score, microbleeds, diabetes, drinking, smoking, TG, depression at 4 years, neurological function recovery, sleep quality, sleepiness, OSA, nocturnal TST were statistically significant ($P < 0.05$).

Logistic multivariate analysis showed that low level of education (OR 2.581, 95% CI 1.490–4.470, $P = 0.001$), large lesion (OR 5.087, 95% CI 1.486–17.408, $P = 0.01$), brain-stem lesion (OR 1.885, 95% CI 1.005–3.535, $P = 0.048$), critical lesion (OR 3.389, 95% CI 1.918–5.990, $P < 0.001$), multiple lesions (OR 1.870, 95% CI 1.054–3.317, $P = 0.032$), high Fazekas score (OR 2.116, 95% CI 1.584–2.827, $P < 0.001$), depression (OR 7.851, 95% CI 3.314–18.599, $P < 0.001$), low sleep quality (OR 2.079, 95% CI 1.177–3.672, $P = 0.012$), sleepiness (OR 3.988, 95% CI 1.804–8.818, $P = 0.001$), nocturnal TST (<7 h) (OR 11.334, 95% CI 6.365–20.183, $P < 0.001$), nocturnal TST (>8 h) (OR 4.096, 95% CI 1.682–9.975, $P = 0.002$), were risk factors for cognitive impairment 4 years after stroke.

Four years after stroke, among the 840 patients with PSCI, there were 806 patients (59.5%) with early onset cognitive impairment and 34 patients (2.5%) with late onset cognitive impairment. Univariate and multivariate logistic analyses of early and late onset cognitive impairment 4 years after stroke are shown in Table 8.

Logistic univariate analysis showed gender, depression at 4 years, OSA and nocturnal TST were statistically significant ($P < 0.05$). Logistic multivariate analysis showed depression (OR 3.410, 95% CI 1.513–7.689, $P = 0.003$) were risk factors for late onset cognitive impairment 4 years after stroke.

The prevalence of cognitive impairment in patients with TIA was shown in Table 9.

The prevalence of cognitive impairment in patients with TIA was 79.3% at admission (PSD 8.9%, PSCIND 70.4%) and 68.1% at 3-month follow-up (7.4% for PSD, 60.7% for PSCIND). The prevalence of cognitive impairment in patients with TIA was 62.1% at 6 -month follow-up (7.5% for PSD, 55.6% for PSCIND) and 52.2% at 4-year follow-up (8.7% for PSD, 43.5% for PSCIND).

Discussion

The study showed that the proportion of poor sleep quality decreased from 52.5% at admission to 40.2% at 4-year follow-up. The proportion of nocturnal TST (<7 h) decreased from 50.8% at admission to 43.9% at 4-year follow-up. The proportion of nocturnal TST (>8 h) decreased from 13.9% at admission to 12.6% at 4-year follow-up. It showed that sleep quality and sleep duration improved over time after stroke. The proportion of sleepiness ranged from 21.4% at admission to 21.6% at 4-year follow-up, suggesting that post-stroke sleepiness leveled off

TABLE 5 Univariate and multivariate logistic analyses of cognitive impairment at 3 months after stroke.

		Univariate analysis		Multivariate analysis	
		OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Population information	Gender (male)	0.523 (0.384–0.712)	<0.001*	0.672 (0.417–1.083)	0.103
	Age	1.053 (1.039–1.067)	<0.001*	0.997 (0.974–1.020)	0.792
	Low level of education	3.143 (2.227–4.436)	<0.001*	2.075 (1.332–3.232)	0.001
Stroke type	TIA	0.348 (0.175–0.692)	0.003*	2.509 (0.816–7.715)	0.109
	Cerebral infarction	0.622 (0.340–1.137)	0.123	2.858 (1.175–6.949)	0.021
Lesion characteristics	Dominant hemisphere	1.269 (0.964–1.670)	0.089	NA	
	Large lesion	0.777 (0.378–1.597)	0.492	NA	
	Brain-stem lesion	0.934 (0.597–1.461)	0.764	NA	
	Critical sites lesion	0.959 (0.654–1.407)	0.832	NA	
	Multiple lesions	2.009 (1.480–2.727)	<0.001*	0.831 (0.556–1.241)	0.365
	MTA score	2.374 (2.007–2.807)	<0.001*	1.348 (0.972–1.871)	0.074
	Fazekas score	2.128 (1.87–2.410)	<0.001*	1.585 (1.284–1.957)	<0.001
	Microbleeds	4.752 (3.190–7.080)	<0.001*	1.043 (0.580–1.875)	0.888
Risk factors	Hypertension	1.016 (0.755–1.367)	0.918	NA	
	Coronary heart disease	1.342 (0.962–1.872)	0.083	NA	
	Diabetes	1.015 (0.761–1.353)	0.920	NA	
	Drinking	0.677 (0.519–0.884)	0.004*	0.982 (0.623–1.547)	0.936
	Smoking	0.663 (0.508–0.866)	0.003*	0.832 (0.523–1.323)	0.437
Laboratory examination	Hcy	1.000 (0.990–1.011)	0.944	NA	
	TG	0.934 (0.837–1.043)	0.224	NA	
	TC	0.993 (0.983–1.003)	0.185	NA	
	HDL	2.107 (1.184–3.752)	0.011*	1.209 (0.756–1.933)	0.428
	LDL	1.073 (0.914–1.259)	0.388	NA	
Patients status at 3 months after stroke	Depression	4.107 (2.250–7.498)	<0.001*	2.243 (1.033–4.870)	0.041
	mRS > 2	8.928 (4.651–16.949)	<0.001*	3.154 (1.416–7.023)	0.005
	Low sleep quality	3.052 (2.318–4.019)	<0.001*	0.650 (0.410–1.031)	0.067
	Sleepiness	2.011 (1.427–2.833)	<0.001*	1.433 (0.792–2.594)	0.234
	Nocturnal TST (<7 h)	8.214 (6.021–11.206)	<0.001*	0.616 (0.294–1.291)	0.199
	Nocturnal TST (>8 h)	5.157 (3.331–7.983)	<0.001*	3.540 (1.692–7.406)	0.001
	High risk OSA	2.508 (1.782–3.530)	<0.001*	1.075 (0.666–1.733)	0.768

*$p < 0.05$, items with statistical significance in univariate analysis were included in the multivariate logistic regression analysis.

over time. The proportion of high risk OSA ranged from 74.7% at admission to 77.4% at 4-year follow-up, indicating that the high risk of OSA did not improve significantly after stroke over time, but increased.

An increased incidence of sleep disorders in dementia is associated with neurodegeneration and current research is focusing on whether sleep disorders can lead to cognitive decline and dementia. In a cross-sectional study of middle-aged adults (mean age 47 ± 15 years), insomnia was associated with cognitive decline (Fortier-Brochu et al., 2012). Some studies had shown a link between insomnia and decreased brain volume, including the hippocampus, frontal and parietal gray matter. Whether insomnia is a risk factor for cognitive decline and dementia, or an early marker of these conditions, is unclear. Most studies using polysomnography (PSG) had supported the link between low sleep quality and cognitive impairment. In a cross-sectional study of older women (≥65 years), sleep disturbances detected using PSG were associated with an increased risk of cognitive impairment (Blackwell et al., 2006). Prospective studies of elderly people living in communities had shown that increased sleep fragmentation was associated with increased incidence of Alzheimer's disease and decreased cognitive function (Lim et al., 2013). More than one third of adults sleep less or more than the 7–9 h a day, and there is a lot of evidence that sleep duration can predict cognitive function in older adults. A cross-sectional study (Schmutte et al., 2007) found that self-reported long sleep duration was associated with decreased cognitive function. Another study (Xu et al., 2011) showed that both long and short sleep duration were associated with decreased cognitive function when compared to normal sleep duration (usually 7–8 h). A study of nurses (Tworoger et al., 2006)

TABLE 6 Univariate and multivariate logistic analyses of cognitive impairment at 6 months after stroke.

		Univariate analysis		Multivariate analysis	
		OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Population information	Gender (male)	0.559 (0.422–0.739)	<0.001*	0.738 (0.378–1.441)	0.374
	Age	1.057 (1.044–1.070)	<0.001*	1.005 (0.971–1.040)	0.776
	Low level of education	3.016 (2.212–4.111)	<0.001*	1.666 (0.905–3.067)	0.101
Stroke type	TIA	0.630 (0.354–1.124)	0.118	NA	
	Cerebral infarction	1.090 (0.676–1.758)	0.725	NA	
Lesion characteristics	Dominant hemisphere	1.166 (0.905–1.502)	0.234	NA	
	Large lesion	16.534 (3.998–68.381)	<0.001*	20.112 (2.248–179.936)	0.007
	Brain-stem lesion	1.712 (1.209–2.426)	0.002*	1.851 (0.886–3.866)	0.101
	Critical sites lesion	2.672 (1.945–3.671)	<0.001*	2.383 (1.291–4.399)	0.005
	Multiple lesions	2.364 (1.772–3.154)	<0.001*	0.918 (0.506–1.667)	0.779
	MTA score	2.759 (2.343–3.249)	<0.001*	1.542 (0.966–2.463)	0.070
	Fazekas score	2.353 (2.081–2.660)	<0.001*	1.532 (1.133–2.073)	0.006
	Microbleeds	7.856 (5.163–11.953)	<0.001*	1.648 (0.702–3.868)	0.251
Risk factors	Hypertension	1.037 (0.786–1.368)	0.798	NA	
	Coronary heart disease	1.315 (0.969–1.786)	0.079	NA	
	Diabetes	1.039 (0.795–1.357)	0.780	NA	
	Drinking	0.596 (0.465–0.763)	<0.001*	0.784 (0.407–1.509)	0.466
	Smoking	0.668 (0.522–0.856)	0.001*	1.150 (0.586–2.256)	0.685
Laboratory examination	Hcy	1.003 (0.992–1.014)	0.595	NA	
	TG	0.877 (0.790–0.972)	0.013*	1.016 (0.806–1.281)	0.893
	TC	0.994 (0.983–1.004)	0.223	NA	
	HDL	1.097 (0.767–1.570)	0.611	NA	
	LDL	1.015 (0.939–1.098)	0.700	NA	
Patients status at 6 months after stroke	Depression	4.434 (2.615–7.517)	<0.001*	1.522 (0.515–4.499)	0.447
	mRS > 2	9.524 (4.975–18.182)	<0.001*	1.495 (0.522–4.280)	0.453
	Low sleep quality	5.020 (3.756–6.711)	<0.001*	1.117 (0.603–2.070)	0.724
	Sleepiness	2.599 (1.607–4.202)	<0.001*	1.188 (0.504–2.800)	0.694
	Nocturnal TST (<7 h)	12.063 (8.821–16.497)	<0.001*	6.504 (3.404–12.427)	<0.001
	Nocturnal TST (>8 h)	5.715 (3.800–8.593)	<0.001*	1.383 (0.537–3.562)	0.502
	High risk OSA	4.055 (2.902–5.667)	<0.001*	1.824 (0.918–3.626)	0.086

*$p < 0.05$, items with statistical significance in univariate analysis were included in the multivariate logistic regression analysis.

found that older women with short sleep duration were at increased risk of cognitive impairment. These studies suggested a "U-shaped" relationship between sleep duration and cognitive function, with both short and long sleep duration increasing the risk of dementia and cognitive impairment. In this study, we found that long or short nocturnal TST (<7 h or >8 h) was a risk factor for cognitive impairment after stroke (3 months, 6 months and 4 years). Poor sleep quality was a risk factor for cognitive impairment 4 years after stroke.

Sleepiness is a common symptom in adults and sleepiness is estimated to be 20–30% of the total population (Young, 2004). Sleepiness can be caused by a variety of reasons, including sleep disordered breathing (SDB), poor sleep habits, obesity, cardiovascular disease (CVD) and depression, all of which can increase the risk of cognitive impairment. Some studies had shown an independent link between daytime sleepiness and cognitive impairment. In a cross-sectional study of elderly people (≥60 years) living in a community (Ohayon and Vecchierini, 2002), after controlling for a range of confounders, older adults with daytime sleepiness were more likely to have cognitive impairment than those without daytime sleepiness. Another cross-sectional study in older adults (Merlino et al., 2010) found that, after controlling for potential confounders, daytime sleepiness was the only sleep indicator associated with dementia. Daytime sleepiness had been linked to an increased risk of cognitive decline and dementia. In this study, sleepiness was shown to be a risk factor for cognitive impairment at 4-year follow-up. A limitation of this study was that sleepiness was measured using a self-reported questionnaire, and future studies need to combine subjective and objective sleepiness measures.

TABLE 7 Univariate and multivariate logistic analyses of cognitive impairment at 4 years after stroke.

		Univariate analysis		Multivariate analysis	
		OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Population information	Gender (male)	0.620 (0.470–0.818)	0.001*	0.777 (0.420–1.435)	0.419
	Age	0.050 (1.052–1.081)	<0.001*	1.020 (0.989–1.052)	0.217
	Low level of education	2.936 (2.160–3.989)	<0.001*	2.581 (1.490–4.470)	0.001
Stroke type	TIA	0.491 (0.274–0.880)	0.017*	0.498 (0.102–2.420)	0.387
	Cerebral infarction	1.119 (0.696–1.798)	0.643	0.908 (0.290–2.846)	0.869
Lesion characteristics	Dominant hemisphere	1.029 (0.798–1.327)	0.825	NA	
	Large lesion	3.618 (1.668–7.848)	0.001*	5.087 (1.486–17.408)	0.010
	Brain-stem lesion	1.809 (1.270–2.578)	0.001*	1.885 (1.005–3.535)	0.048
	Critical sites lesion	2.831 (2.052–3.906)	<0.001*	3.389 (1.918–5.990)	<0.001
	Multiple lesions	3.160 (2.329–4.288)	<0.001*	1.870 (1.054–3.317)	0.032
	MTA score	3.551 (2.956–4.267)	<0.001*	1.372 (0.891–2.113)	0.151
	Fazekas score	3.255 (2.796–3.789)	<0.001*	2.116 (1.584–2.827)	<0.001
	Microbleeds	15.481 (8.913–26.890)	<0.001*	2.013 (0.798–5.079)	0.138
Risk factors	Hypertension	1.176 (0.894–1.549)	0.247	NA	
	Coronary heart disease	1.224 (0.894–1.675)	0.207	NA	
	Diabetes	1.338 (1.014–1.765)	0.039*	1.171 (0.710–1.932)	0.537
	Drinking	0.570 (0.444–0.731)	<0.001*	0.760 (0.417–1.383)	0.369
	Smoking	0.666 (0.520–0.855)	0.001*	0.958 (0.531–1.728)	0.886
Laboratory examination	Hcy	1.012 (0.999–1.026)	0.073	NA	
	TG	0.829 (0.744–0.924)	0.001*	1.041 (0.840–1.290)	0.714
	TC	0.957 (0.857–1.069)	0.440	NA	
	HDL	1.016 (0.730–1.416)	0.924	NA	
	LDL	1.007 (0.987–1.027)	0.493	NA	
Patients status at 4 years after stroke	Depression	13.831 (8.447–22.647)	<0.001*	7.851 (3.314–18.599)	<0.001
	mRS > 2	9.213 (4.807–17.655)	<0.001*	0.484 (0.193–1.217)	0.123
	Low sleep quality	10.380 (7.403–14.556)	<0.001*	2.079 (1.177–3.672)	0.012
	Sleepiness	9.554 (5.824–15.675)	<0.001*	3.988 (1.804–8.818)	0.001
	Nocturnal TST (<7 h)	18.665 (13.384–26.03)	<0.001*	11.334 (6.365–20.183)	<0.001
	Nocturnal TST (>8 h)	33.556 (17.188–65.51)	<0.001*	4.096 (1.682–9.975)	0.002
	High risk OSA	4.509 (3.188–6.378)	<0.001*	1.721 (0.921–3.214)	0.089

*$p < 0.05$, items with statistical significance in univariate analysis were included in the multivariate logistic regression analysis.

OSA is more common in older adults and men. The proportion of cognitive impairment in OSA population is high. A study on elderly women showed that OSA was associated with cognitive decline (Spira et al., 2008), and APOE4 carriers were more significant. Mild to moderate OSA was associated with cognitive decline in older men who were followed up for more than 3 years and OSA patients had an 85% increased risk of mild cognitive impairment or dementia in older women followed up for 5 years (Yaffe et al., 2011). Compared with healthy controls, OSA patients showed decreased white matter integrity and decreased gray matter volume associated with memory and executive function (Joo et al., 2010). Cohort studies in older men had also shown an association between reduced oxygen saturation and cognitive decline (Blackwell et al., 2011). In this study, no relationship was found between OSA and cognitive impairment after stroke, which was related to OSA assessment by questionnaire and objective indicators such as PSG should be used for further study.

Our study showed that other factors affecting cognitive impairment after stroke included depression, low level of education, poor neurological recovery, high Fazekas score, large lesion, brain stem lesion, key site lesion. Although PSCI has received increasing attention, its risk factors have not been fully recognized. A review of PSCI risk factors showed that age, education, history of stroke, diabetes, hypertension, stroke type, stroke focus, size and location of focus, depression, and neurological function can affect the cognitive function of stroke patients (Mohd Zulkifly et al., 2016). Depression is common among stroke patients. Up to 38% of stroke patients are depressed. Depression is a risk factor for poor prognosis after stroke and is negatively associated with cognitive function. This study showed

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TABLE 8 Univariate and multivariate logistic analyses of early and late onset cognitive impairment 4 years after stroke.

		Univariate analysis		Multivariate analysis	
		OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Population information	Gender (male)	2.466 (1.009–6.028)	0.048*	2.150 (0.870–5.316)	0.097
	Age	1.005 (0.971–1.041)	0.763	NA	
	Low level of education	0.710 (0.335–1.506)	0.372	NA	
Stroke type	Ischemic cerebrovascular disease	0.583 (0.199–1.712)	0.326	NA	
Lesion characteristics	Dominant hemisphere	1.555 (0.739–3.272)	0.245	NA	
	Multiple lesions	1.103 (0.531–2.293)	0.793	NA	
	MTA score	0.719 (0.489–1.058)	0.094	NA	
	Fazekas score	0.965 (0.741–1.256)	0.792	NA	
	Microbleeds	0.695 (0.328–1.474)	0.343	NA	
Risk factors	Hypertension	1.174 (0.523–2.633)	0.698	NA	
	Coronary heart disease	1.214 (0.540–2.731)	0.640	NA	
	Diabetes	0.901 (0.424–1.912)	0.785	NA	
	Drinking	1.377 (0.692–2.741)	0.363	NA	
	Smoking	1.650 (0.821–3.313)	0.159	NA	
Laboratory examination	Hcy	1.009 (0.993–1.024)	0.264	NA	
	TG	0.847 (0.564–1.271)	0.422	NA	
	TC	0.838 (0.611–1.148)	0.270	NA	
	HDL	0.812 (0.228–2.888)	0.748	NA	
	LDL	0.840 (0.556–1.268)	0.406	NA	
Patients status at 4 years after stroke	Depression	3.607 (1.702–7.645)	0.001*	3.410 (1.513–7.689)	0.003
	mRS $\leq$ 2	1.156 (0.471–2.839)	0.752	NA	
	Low sleep quality	1.271 (0.620–2.604)	0.512	0.867 (0.385–1.953)	0.730
	Sleepiness	1.888 (0.947–3.762)	0.071	1.124 (0.499–2.529)	0.778
	Nocturnal TST (<7 h)	2.863 (0.661–12.390)	0.159	1.719 (0.378–7.814)	0.483
	Nocturnal TST (>8 h)	5.840 (1.285–26.547)	0.022*	3.464 (0.708–16.946)	0.125
	High risk OSA	1.712 (1.220–2.402)	0.002*	0.993 (0.442–2.230)	0.987

*$p < 0.05$, items with statistical significance in univariate analysis were included in the multivariate logistic regression analysis.

that depression was a risk factor for cognitive impairment at 3 months and 4 years after stroke, as well as a risk factor for late onset cognitive impairment.

Cognitive reserve refers to the ability of the brain to maintain the same cognitive function in the presence of disease, which is influenced by factors such as age, education and lifestyle (such as participation in intellectual activities and regular exercise) (Ballard et al., 2003; Pendlebury, 2012). Low cognitive reserve caused by low level of education may lead to higher incidence of cognitive impairment after stroke. This study showed that low level of education was a risk factor for cognitive impairment at 3 months and 4 years after stroke. PSCI was affected by stroke site and stroke severity. Leukodystrophy is an important risk factor for early onset PSCI. Leukodystrophy can lead to disruption of fronto-subcortical connections and cholinergic fiber bundle connections (Tuladhar et al., 2016), resulting in secondary cortical or subcortical regional-specific atrophy (such as medial temporal lobe atrophy), cognitive decline, and eventually dementia.

Many patients with TIA continue to have cognitive problems long after the focal neurological symptoms have been resolved. However, the prevalence and causes of post-TIA cognitive impairment remain unclear. Because cognitive function assessments are not routine for patients with TIA, cognitive impairment is often overlooked. Studies have shown that post-TIA cognitive impairment is relatively common, with 29–68% of patients with mild cognitive impairment (MCI) and 8–22% of patients with severe cognitive impairment (van Rooij et al., 2016). The higher incidence of cognitive impairment after TIA suggests that the non-local symptoms may not be as transient as local

TABLE 9 Prevalence of cognitive impairment in patients with TIA.

	Non-PSCI	PSD	PSCIND
At admission	28 (20.7%)	12 (8.9%)	95 (70.4%)
3 months after TIA	43 (31.9%)	10 (7.4%)	82 (60.7%)
6 months after TIA	49 (36.8%)	10 (7.5%)	74 (55.6%)
4 years after TIA	55 (47.8%)	10 (8.7%)	50 (43.5%)

neurological symptoms. The incidence of cognitive dysfunction after TIA is lower than that after stroke. The severity and location of stroke are the major determinants of cognitive impairment after stroke (Pendlebury and Rothwell, 2009). Whether these features apply to TIA is unclear. Ischemic impairment after TIA may be the basis of cognitive impairment. The presence of vascular risk factors in patients with TIA increases the risk of white matter progression, which is also associated with cognitive decline. In addition, anxiety, depression, and delirium following TIA may affect cognitive function.

The prevalence of cognitive impairment in patients with TIA was 79.3% at admission (PSD 8.9%, PSCIND 70.4%) and 68.1% at 3-month follow-up (7.4% for PSD, 60.7% for PSCIND). The prevalence of cognitive impairment in patients with TIA was 62.1% at 6 -month follow-up (7.5% for PSD, 55.6% for PSCIND) and 52.2% at 4-year follow-up (8.7% for PSD, 43.5% for PSCIND). This study shows that cognitive impairment is very common in patients with TIA, and it should be noted that patients with TIA have persistent cognitive impairment after the complete resolution of their neurological symptoms.

Sleep disorders are common in stroke patients and are a risk factor for cognitive impairment after stroke. The sleep-wake cycle plays an important role in brain aging, which offers a potential way to improve cognitive function. Pathological changes in cognitive impairment can be present in the brain years to decades before clinical symptoms appear and it is not clear whether sleep disorders appear as an early marker of this pathology or as a risk factor for disease initiation or progression. Further prospective studies, using structural MRI and biomarkers, are needed to document the biological changes associated with sleep disorders and to investigate the mechanism of cognitive function changes after stroke.

Conclusion

In the 4-year follow-up of patients with stroke, it was found that sleep quality and TST were improved over time after stroke, the change of sleepiness after stroke was not obvious and the high risk of OSA did not improve significantly after stroke, but showed an upward trend. Long or short nocturnal TST (<7 h or >8 h) was a risk factor for cognitive impairment after stroke (3 months, 6 months and 4 years). Poor sleep quality was a risk factor for cognitive impairment 4 years after stroke. Sleepiness was shown to be a risk factor for cognitive impairment at 4-year follow-up. Cognitive impairment is very common in patients with TIA, and we should pay attention to cognitive impairment after TIA.

Limitation

Sleep quality, sleepiness, and OSA were measured using questionnaires, without objective measurements, which may be potentially biased. However, large studies using objective methods such as PSG are not feasible in the general population, especially in stroke patients. The PSQI questionnaire, ESS questionnaire and Berlin questionnaire are reliable screening methods for sleep disorders. Previous studies have demonstrated that sleep parameters monitored by PSG are highly correlated with subjective assessment. Importantly, our investigators were trained to conduct comprehensive interviews with patients about their sleep status and the study also conducted longitudinal follow-up on sleep status, which may lead to more accurate sleep results.

Data availability statement

The original contributions presented in this study are included in this article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

YZ: conceptualization, methodology, software, and writing—original draft preparation. XX and TZ: data curation and writing—original draft preparation. CZ: visualization and investigation. RL: supervision. YY and SL: software and validation. WY and XL: writing—review and editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Association of sleep disorders with clinical symptoms and age in Chinese older adult patients with and without cognitive decline

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Objective: To investigate correlation between cognitive function, age, and sleep disturbances.

Methods: This retrospective clinical study enrolled 78 patients with sleep disorders who were divided into three groups: a group of 24 patients with sleep disorders accompanied by cognitive decline (SD-CD); 54 patients with sleep disorders and no cognitive decline (SD-nCD) was divided into two groups, one of 30 patients aged between 60 and 70 years and another of 24 patients aged >70 years. Polysomnography was used to record patients' sleep indicators throughout night; these included total sleep duration, sleep efficiency (SE), sleep latency, sleep structure and percentage of N1, N2, and N3 stages, rapid eye movement (REM) stage, as well as apnea hypopnea index (AHI), and oxygen saturation (OS). Analysis of variance (ANOVA) for continuous variables and chi-square test for categorical variables were used to analyze variables between different groups. Pearson's correlation was used to analyze correlation between sleep parameters and mini-mental state examination (MMSE). Blood samples were used to determine their Aβ, $A\beta_{40}$, $A\beta_{42}$, total tau, phosphorylated tau protein (ptau), $ptau_{181}$, $ptau_{217}$, the inflammatory factor IL-1β, vitamin B12 (VB12), and melatonin levels.

Results: In the SD-CD group, there was a significant decrease in SE and an increase in N1 stage sleep in older patients and a significant increase in AHI, REM stage AHI, and non-REM stage AHI. In patients with SD-nCD, the minimum OS, minimum OS in the REM period, and minimum OS in the non-REM period were significantly reduced. OS was significantly correlated with cognitive level, as evaluated by the MMSE. The addition of sleep parameters can significantly improve the accuracy of dementia diagnosis. Dementia biomarkers of Aβ and tau proteins in blood showed cognition-related differences, while ptau181 was associated with both cognition and age-related differences. Regression models revealed that age was related to higher levels of cognitive decline before ($\beta = -0.43$, $P < 0.001$) and after ($\beta = -0.38$, $P < 0.001$) adjustment of gender, BMI, and education level. There was a significant mediation effect

of relationship between aging and cognitive function by sleep efficiency and N1 stage sleep.

Conclusion: Sleep disorders and low OS are associated with a higher incidence of cognitive decline and dementia.

KEYWORDS

sleep disorders, cognitive decline, aging, dementia, oxygen saturation

1. Introduction

Aging is associated with a decline in sleep quality and cognitive function. Sleep architecture changes with age; for example, there is a decrease in the slow wave sleep (SWS/N3) stage as well as a reduction in rapid eye movement (REM) periods (Mander et al., 2017). These changes are divided into normal aging, which generally does not affect cognitive function, and pathological changes, which can affect cognitive function to some extent. However, there is also a correlation between reduced sleep quality and cognitive decline. This correlation is commonly observed in older adults with normal sleep, insomnia, or sleep breathing disorders, as well as in those with normal cognition or dementia (Dzierzewski et al., 2018). The age factor should also be considered because of the prevalence of both sleep-disordered breathing and cognitive changes that increase with age (Ayalon et al., 2010; Peppard et al., 2013).

Aside from aging, previous studies have found that a proportion of patients with sleep disorders experience cognitive decline (Cricco et al., 2001). Older adults with long-term insomnia and long-term use of hypnotics had a two-fold higher risk of developing dementia during a 3-year follow-up period than healthy controls (Chen et al., 2012). There may be a physiological mechanism by which lack of sleep increases the accumulation of Aβ in the brain; conversely, proper sleep reduces the generation of Aβ and enhances its clearance (Xie et al., 2013). Sleep disruption and circadian rhythm disorders often occur in patients with cognitive impairments. Circadian dysfunction and sleep disturbances are the most common features in patients with Alzheimer's disease (AD) (Musiek et al., 2015). The existence of disturbed sleep during preclinical and clinical disease development emphasizes the central role of sleep in the pathogenesis and development of dementia (Uddin et al., 2020).

Furthermore, the prevalence of sleep disorders in patients with dementia is high, and the common ones are REM sleep behavior disorder, increased daytime sleepiness, and sleep breathing syndrome (Wennberg et al., 2017). Approximately 45% of patients with AD have sleep difficulties. These symptoms may persist for several years prior to the medical diagnosis of AD (Urrestarazu and Iriarte, 2016). According to the above evidence, it has strong relationship between age, sleep disorders, and cognitive decline. But the association of sleep disorders with clinical symptoms and age in Chinese older adult patients with and without cognitive decline was unclear.

In this study, we aimed to investigate the correlation between age, sleep quality and cognitive function. Three groups of patients were selected. One consisted of patients with sleep disorders accompanied by cognitive decline (SD-CD) and the other of patients with sleep disorders alone (sleep disorder with no cognitive decline, SD-nCD). The latter were further divided into two groups of old and young according to age. In the SD-CD group and SD-nCD old group, there was no significant difference in the mean age of the subjects. It was used to find indicators of differences other than the age factor. We also compared the SD-nCD old and younger groups to see the effect of the age factor. The clinical characteristics, sleep parameters, and blood indicators of the three groups were analyzed. The differences between the groups, especially those parameters that correlated more with cognitive decline, could be used as biomarkers to assess future cognitive decline. The potential benefits of sleep treatments on cognitive function can also be used as sleep intervention targets for the prevention of cognitive decline.

2. Materials and methods

2.1. Clinical participants

The 78 patients with sleep disorders with or without cognitive decline were diagnosed using the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-V) criteria (Battle, 2013). All of the patients had to meet the following inclusion criteria: (1) they met the sleep disorder diagnosis made by two research psychiatrists according to the DSM-V; (2) they were able to provide informed consent; (3) their disease course was >3 months; (4) if they had severe cognitive decline they used the same cholinesterase inhibitor, donepezil. The exclusion criteria for patient participants were (1) they had other severe mental illnesses or history, including schizophrenia, bipolar disorder, delirium and (2) severe physical diseases such as cancer. Anxiety and depression were not in the exclusion criteria. The group of SD-CD consisted of age- and gender- matched patients reporting sleep disorders and was confirmed by Pittsburgh sleep quality index (PSQI) > 7. The neuropsychological evaluation of cognitive decline was confirmed by mini-mental state examination (MMSE) score <17, 20, and 24 in person with education levels of illiteracy, primary school, and junior high school, respectively.

2.2. Participants recruitment

We recruited inpatients and outpatients at Sleep Medicine Center of Ningbo Kangning Hospital between April 2022 and March 2023. Two screening rounds were conducted as shown

in Figure 1. In the first round, geriatric outpatient psychiatrists conducted a preliminary screening. In the second round, patients who may meet the inclusion criteria were recommended to experienced research psychiatrists. This study was approved by the ethics committee of Ningbo Kangning Hospital. All participants or their legal guardians signed informed consent forms. Demographic characteristics include age, gender, body mass index, and educational level.

2.3. Cognitive assessment

The mini-mental state examination (MMSE) consists of 11 cognitive questions in the areas of orientation, immediate recall, attention, short-term memory, and language. The MMSE has a maximum score of 30, with higher scores indicating better cognitive performance.

2.4. Polysomnography recording

According to standard procedures, polysomnography (PSG) of the participants was recorded from 22:30 pm to 06:30 am in a sleep-monitoring ward. The participants were required to arrive at least 2 h before sleep monitoring to become familiar with the environment. The PSG records were maintained in accordance with the guidelines of the American Academy of Sleep Medicine (Kushida et al., 2005). All recordings included electroencephalograph leads, bilateral electrooculogram leads, submentalis electromyogram leads, and electrocardiograms.

A professional technician evaluated the PSG data according to standard criteria (Malhotra et al., 2018). We collected data on sleep continuity and sleep architecture, including total sleep time (TST), percentage of sleep efficiency (SE), sleep onset latency (SOL), rapid eye movement (REM) latency, percentages of stage 1 sleep (N1), percentages of stage 2 sleep (N2), percentages of slow wave sleep (SWS/N3), and percentages of REM sleep. We also collected data on the apnea hypopnea index (AHI) and oxygen saturation (OS).

2.5. Blood collection and plasma processing

Blood samples were collected before breakfast by phlebotomists who had experience with older patients. Using a winged blood collection set, 5 ml of whole blood was collected in a procoagulant tube. To allow the measurement of plasma peptides, blood was immediately centrifuged (1400 rpm using a BY-600A type medical centrifuge, Beijing Baiyang Medical Devices Co., China) for 10 min. All blood samples were processed within 30 min of collection and immediately frozen at −80°C.

Blood samples were thawed immediately before analysis. Serum amyloid-β (Aβ), $Aβ_{40}$, $Aβ_{42}$, total tau, phosphorylated tau (ptau), $ptau_{181}$, $ptau_{217}$, IL-1β, vitamin B 12 (VB_{12}), melatonin levels were estimated using ELISA kits (Shanghai Yuanye Bio-Technology Co., China). All procedures were performed according to the manufacturer's instructions. Absorbance was measured at 450 nm using a Sunrise-basic enzyme labeling instrument (Tecan Co., Switzerland) with a reference wavelength of 690 nm. These measurements were transformed into concentrations by comparing the optical densities of the samples with the standard curve values.

2.6. Statistical analysis

For statistical analysis, data are presented as mean ± standard deviation (SDs). Comparisons of the demographic and clinical variables between the different groups were analyzed using analysis of variance (ANOVA) for continuous variables and a chi-squared test for categorical variables. Pearson's correlation was used to analyze the correlation between sleep quality and the cognitive assessment scale. Statistical significance was set at $p < 0.05$. Statistical Package for the Social Sciences (SPSS version 19.0, IBM) was used for all analyses.

The mediation models were made separately for sleep efficiency and N1 stage sleep. This included the following steps: (a) Prediction of the dependent variable (cognitive decline) by the independent variable (aging). (b) Prediction of the mediators (sleep efficiency and N1 stage sleep) by the independent variable (aging). (c) Prediction of the dependent variable (cognitive decline) by both the independent variable (aging) and the mediators (sleep efficiency and N1 stage sleep; for partial mediation it is required that the direct relation between the independent variable and the dependent variable is reduced by inclusion of the mediator to the model) (Preacher and Hayes, 2008). To also formally test the significance of the indirect effects we then additionally employed the SPSS procedure Indirect by Preacher and Hayes (2008), assessing the models with both mediators simultaneously via bootstrapping. Number of bootstrap samples for bias corrected bootstrap confidence intervals was 10,000.

3. Results

3.1. Clinical assessment

The characteristics of the patients included in this study are summarized in Table 1. There were 24 patients with SD-CD, including 9 men and 15 women. The older group of patients with sleep disorder but without cognitive decline (SD-nCD) consisted of 24 patients (9 men and 15 women) with a mean age of 74.0 years, while the younger group was made up 30 patients (13 men and 17 women) with a mean age of 63.5 years. Eight patients with SD-CD were taking sleep-related medications and twenty-one were taking cognitive improvement medications. Fifteen in the older group and twenty in the younger group of patients with SD-nCD were taking sleep medications.

3.2. PSG analysis

As shown in Figure 2 and Table 2, we found significant differences in SE ($F = 7.191$, $p = 0.001$), N1 ($F = 3.757$, $p = 0.028$), AHI ($F = 7.014$, $p = 0.002$), AHI (REM, R) ($F = 3.473$, $p = 0.036$), AHI (No REM, NR) ($F = 6.968$, $p = 0.002$), lowest OS ($F = 5.049$, $p = 0.009$), lowest OS (R) ($F = 6.553$, $p = 0.002$), and lowest OS (NR) ($F = 5.858$, $p = 0.004$) among the three groups. In terms of sleep continuity, the younger SD-nCD group had significantly higher

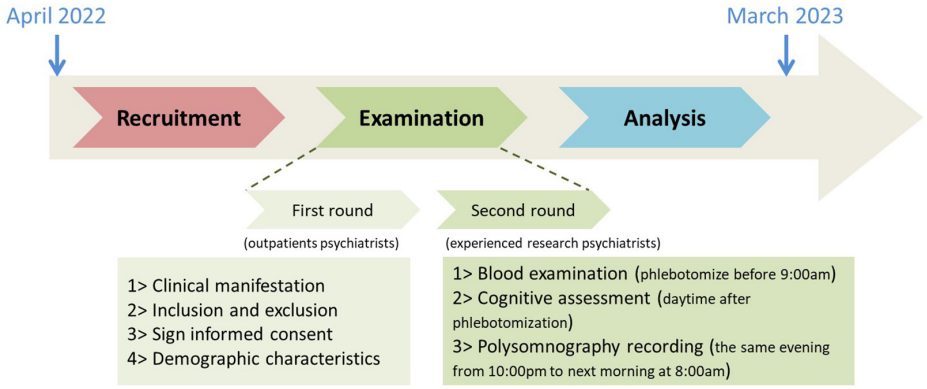

FIGURE 1
Schematic diagram of the study.

TABLE 1 Demographics and clinical characteristics of study participants.

Characteristics		SD-D group	SD-nD group		F/χ^2	*P*
		Older	Younger			
Number		24	24	30	0.923	0.630
Sex (Men/Women)		9/15	9/15	13/17	3.282	0.070
Age (years)		73.5 ± 8.7	74.0 ± 3.7	63.5 ± 3.4	30.406	<0.001
BMI		21.5 ± 3.1	22.7 ± 2.5	22.3 ± 2.6	1.272	0.286
Education (years)		6.0 ± 2.1	6.1 ± 1.1	6.4 ± 1.2	0.583	0.560
Sleep disorder type	SSD	15	23	30	12.159	<0.001
	SSD accompanied by OSA	9	1	0	12.159	<0.001
Dementia duration		3.4 ± 1.85	0	0	NA	NA
Hypertension		18	17	12	4.550	0.014
Diabetes mellitus		6	7	4	1.073	0.347
Sleep medicine		19	23	30	4.743	0.011
Dementia medicine		21	0	0	178.273	<0.001
PSQI		13.7 ± 4.27	12.0 ± 5.59	11.67 ± 5.98	0.198	0.820
MMSE		13.0 ± 6.8	25.7 ± 4.2	26.9 ± 3.3	63.994	<0.001
Drug (sleep)		8	15	20	5.997	0.017
Drug (cognition)		21	1	1	91.323	<0.001

Means ± SDs. SD-D, patients with dementia and sleep disorder; SD-nD, patients with no dementia and sleep disorder; BMI, body mass index; MMSE, Mini-Mental State Examination; SSD, sleep structure disorders; OSA, obstructive sleep apnea.

SE than the other two groups. In terms of sleep architecture, the proportion of N1 stage sleep was significantly higher in the SD-CD group than in the other two groups. AHI was significantly higher in the older SD-nCD group than in the younger group. For minimum blood OS, blood oxygen was significantly lower in the SD-CD group than in the SD-nCD group.

3.3. Subgroups analysis of younger SD-nCD patients

The sleep parameters SE and N1 were significantly different between the younger and older SD-nCD groups. As shown in Figure 3, analysis of data from the younger SD-nCD patients revealed that when the group was divided into SE < SE average and SE > SE average groups, there were significant differences in the TST and SWS percentages between the two groups, in addition to significant differences in SE. When the group was divided into N1 < N1 average and N1 > N1 average groups, there were significant differences in the N2 percentages between the two groups. Statistical analysis was performed using the *t*-test.

3.4. Pearson correlation between cognitive and sleep parameters

As shown in Figure 4, MMSE scores were significantly correlated with SWS, average OS, lowest OS, and lowest OS (R)

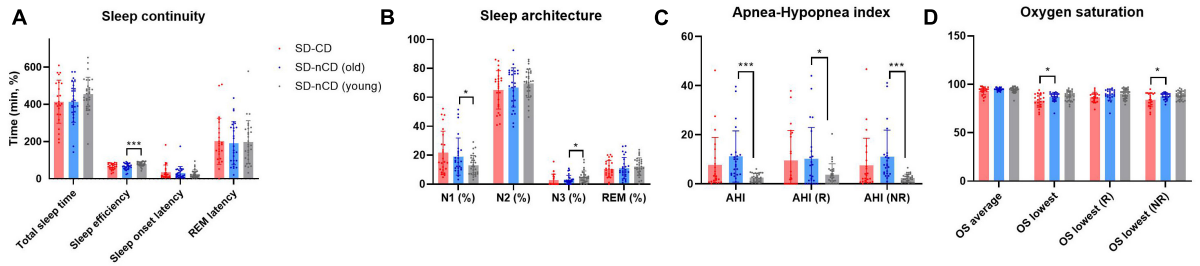

FIGURE 2
Polysomnography (PSG) parameters (**A**, sleep continuity; **B**, sleep architecture; **C**, apnea-hypopnea index; **D**, oxygen saturation) of three groups of patients with SD-CD (red), SD-nCD older group (blue), and SD-nCD younger group (gray). *$p < 0.05$, ***$p < 0.001$.

TABLE 2 Polysomnographic parameters of study participants.

Characteristics	SD-D group	SD-nD group		F/?[2]	*P*
		Older	Younger		
Sleep continuity					
TST, min	414.1 ± 115.8	417.6 ± 92.8	425.0 ± 138.9	0.059	0.943
SE,%	66.7 ± 16.7	66.3 ± 15.0	79.4 ± 12.4	7.191	**0.001**
SOL, min	34.0 ± 40.1	26.4 ± 18.4	26.9 ± 21.7	0.750	0.476
REM latency, min	201.7 ± 123.8	193.2 ± 115.5	197.1 ± 114.9	0.031	0.969
Sleep architecture, %total sleep time					
N1, %	21.6 ± 15.0	19.1 ± 13.2	13.1 ± 6.7	3.757	**0.028**
N2, %	65.1 ± 13.2	67.1 ± 13.4	69.7 ± 9.8	0.998	0.374
SWS, %	2.7 ± 4.2	3.0 ± 3.1	5.0 ± 4.1	2.891	0.062
REM, %	10.5 ± 5.9	10.7 ± 7.3	12.2 ± 6.0	0.539	0.586
Apnea-hypopnea index (AHI)					
AHI	7.7 ± 11.2	11.2 ± 10.4	2.6 ± 1.7	7.014	**0.002**
AHI (R)	9.6 ± 12.1	10.3 ± 12.7	3.7 ± 4.4	3.473	**0.036**
AHI (NR)	7.5 ± 11.1	11.1 ± 10.8	2.3 ± 1.6	6.968	**0.002**
Oxygen saturation (OS)					
OS average	93.3 ± 4.1	94.8 ± 1.5	94.2 ± 2.9	1.402	0.253
OS lowest	83.3 ± 6.9	87.0 ± 4.8	88.1 ± 4.9	5.049	**0.009**
OS lowest (R)	73.9 ± 31.3	89.4 ± 5.7	90.3 ± 5.0	6.553	**0.002**
OS lowest (NR)	84.1 ± 7.3	87.6 ± 3.4	88.9 ± 4.2	5.858	**0.004**

Means ± SDs. D-SD, patients with dementia and sleep disorder; nD-SD, patients with no dementia and sleep disorder; TST, total sleep time; SE, sleep efficiency; SOL, sleep onset latency; REM, rapid eye movement; AHI, apnea-hypopnea index; OS, oxygen saturation. The bold values represent statistical significance ($p < 0.05$).

($r = 0.256$, $p = 0.024$, $r = 0.330$, $p = 0.004$, $r = 0.414$, $p < 0.001$, $r = 0.280$, $p = 0.016$, respectively).

3.5. Receiver operating characteristic curve

For the SD-CD and older SD-nCD groups, the mean ages of the patients in both groups were matched. The sleep parameters of the two groups could be used to enhance the accuracy of dementia diagnosis. In Figure 5, as seen by the receiver operating characteristic (ROC) curve, the area under the curve (AUC) was significantly higher after combining multiple sleep indicators than with a single cognitive indicator.

3.6. Blood parameters

We tested cognitive-related indicators in blood, including Aβ, $Aβ_{40}$, $Aβ_{42}$, total tau, phosphorylated tau protein (ptau), $ptau_{181}$, $ptau_{217}$, inflammatory factor IL-1β, vitamin B_{12} (VB_{12}), and melatonin (Table 3). In the SD-CD group, aside from $ptau_{217}$, the values of other parameters were significantly higher than those of the SD-nCD group. In the SD-nCD group, $ptau_{181}$ expression was higher in the older subgroup than in the younger subgroup (Figure 6).

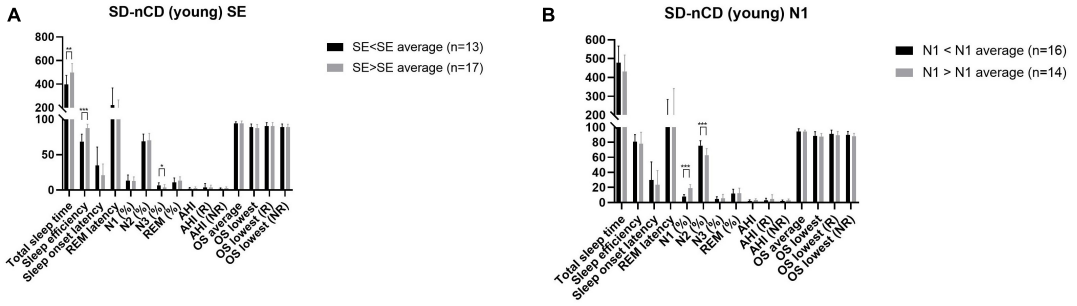

FIGURE 3
Polysomnography parameters (**A**, SE subgroup; **B**, N1 subgroup) of the younger group of patients with SD-nCD. Gray bar represent the values larger than average. Black bar represent the values less than average. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

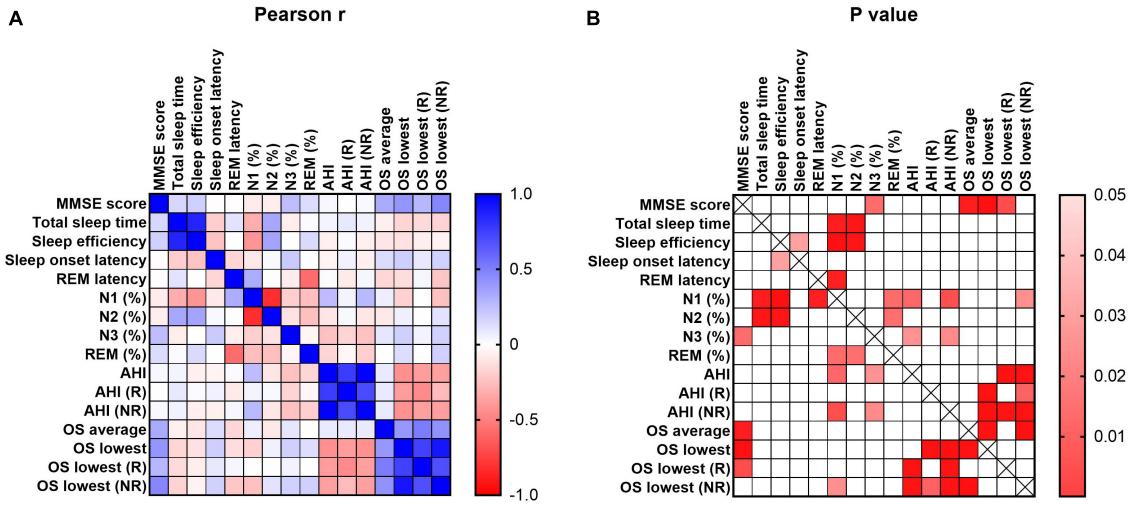

FIGURE 4
Pearson correlation of cognitive and sleep parameters. MMSE represents the cognitive level of participants. The sleep parameters included total sleep time, sleep efficiency, sleep onset latency, REM latency, percent of N1, N2, N3 and REM, AHI in REM stage and NREM stage, OS average and lowest value of REM and NREM stage. The scale bar represents the Pearson coefficient r and *P*-values.

3.7. Mediation effect analysis

Figure 7 represents the regression models testing the relations between aging (independent variable) and sleep efficiency, N1 stage sleep (mediator), and cognitive decline (dependent variable). The regression models revealed that aging was related to higher levels of cognitive decline before ($\beta = -0.43$, $P < 0.001$) and after ($\beta = -0.38$, $P < 0.001$) adjustment of gender, body mass index (BMI), and education level. Moreover, regression models revealed that aging were also related to sleep efficiency ($\beta = -0.81$, $P < 0.001$) control for gender, BMI, and education level.

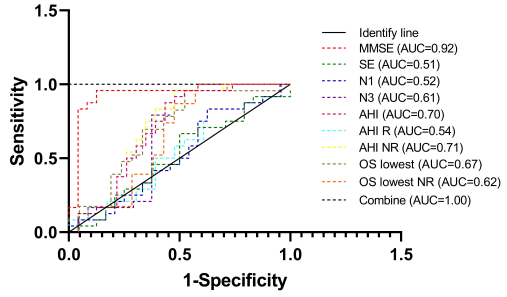

FIGURE 5
Receiver operating characteristic curves of different parameters of diagnosis. Combination of cognitive parameter and sleep parameters can improve the sensitivity and specificity.

4. Discussion

Age affects both sleep and cognition. The present study showed significant differences in SE and the proportion of N1 stage sleep among people of different ages. Regardless of dementia, SE was higher in the younger group and lower in the older age group. The proportion of N1 stage sleep was lower in the younger group and higher in the older group, regardless of dementia. This indicates that sleep structure changes significantly with age. The minimum OS index was significantly lower in the dementia group than in the cognitively normal group, at both higher and lower ages. In

TABLE 3 Blood parameters of study participants.

Blood parameters	SD-D group	SD-nD group		*F*	*P*
		Older	Younger		
Aβ, ng/mL	426.99 ± 52.72	372.04 ± 74.88	367.47 ± 47.28	8.032	**0.001**
$Aβ_{40}$, pg/mL	375.89 ± 64.75	324.62 ± 86.47	326.50 ± 55.14	4.414	**0.015**
$Aβ_{42}$, pg/mL	695.20 ± 71.90	600.95 ± 107.33	599.55 ± 65.91	11.037	**0.000**
tau, pg/mL	215.75 ± 38.01	181.57 ± 45.98	187.90 ± 29.95	5.615	**0.005**
ptau, pg/mL	299.07 ± 55.97	275.25 ± 65.08	260.17 ± 41.32	3.470	**0.036**
$ptau_{181}$, ng/mL	59.07 ± 6.67	51.64 ± 9.27	46.37 ± 5.96	20.032	**0.000**
$ptau_{217}$, pg/mL	900.81 ± 176.20	859.30 ± 209.88	867.75 ± 152.39	0.367	0.694
IL-1β, pg/mL	87.69 ± 9.74	78.14 ± 9.97	76.01 ± 8.24	11.512	**0.000**
VB_{12}, pg/mL	491.53 ± 118.55	558.41 ± 142.06	617.38 ± 99.93	7.358	**0.001**
melatonin, pg/mL	8.73 ± 2.50	9.34 ± 2.47	10.81 ± 2.02	5.831	**0.004**

Means ± SDs. D-SD, patients with dementia and sleep disorder; nD-SD, patients with no dementia and sleep disorder; Aβ, amyloid β; VB, vitamin B. The bold values represent statistical significance ($p < 0.05$).

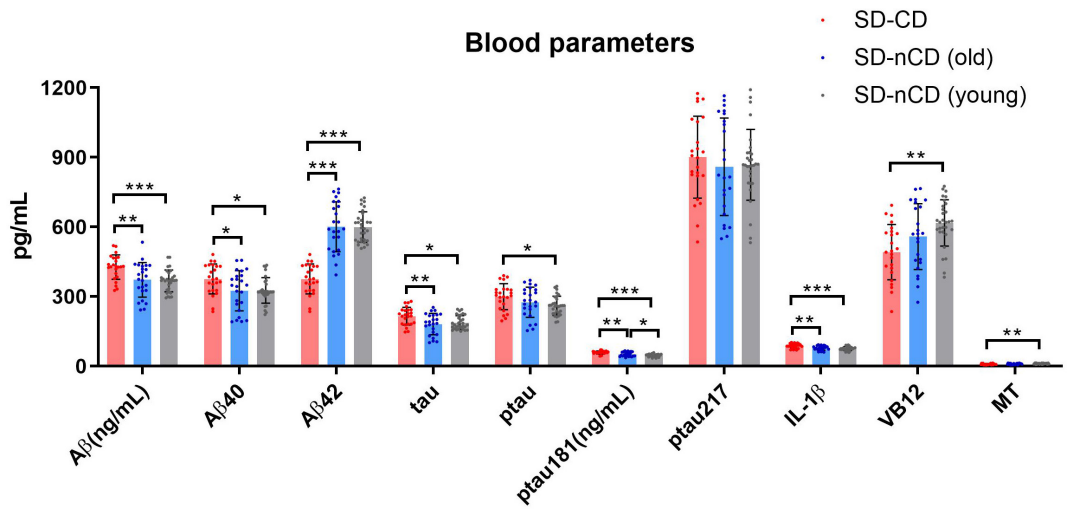

FIGURE 6
Blood parameters in the SD-CD and SD-nCD groups. The parameters include cognitive biomarkers of total Aβ, Aβ40, Aβ42, tau, Phosphorylated tau, Phosphorylated tau181 and 217, the inflammatory factor, Vitamin B12 and melatonin. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

fact, as age increased, SE decreased, whereas the proportion of N1 stage sleep increased. Other studies in healthy individuals have suggested that objectively measured total sleep time, sleep latency, slow wave sleep, wake after sleep onset, and REM sleep decrease through adulthood; however, SE continues to significantly decrease in adults aged 60 years and older (Ohayon et al., 2004).

Among patients with dementia, sleep disorders are associated with poor cognitive function, even in those with mild dementia (Moran et al., 2005). Moreover, disturbed sleep parameters have been linked to an increased risk of the subsequent development of dementia. The deterioration of circadian rhythms begins early in dementia and progresses throughout the disease course (Hatfield et al., 2004). In this study, N1 and SE changed with age and cognitive level of the participants. This suggests that there may be some potential sleep parameters in the younger SD-nCD group that reflect cognitive function. Further analysis of the data from the younger group revealed that patients with greater than average SE had a significantly higher total sleep duration and a significantly lower SWS stage sleep percentage. Patients with N1 stage sleep percentages lower than the mean had a significantly higher N2 stage sleep percentage. According to previous studies, SE is equal to the total sleep time divided by bedtime (Didikoglu and Maharani, 2020). In the SE < SE average condition, N3 sleep duration was significantly prolonged. N3 sleep may be a better indicator of clinical sleep quality than SE sleep. A shorter total sleep time may be related to a longer N3 sleep. There was no feeling of fatigue after sleeping.

AHI and OS were not affected by age but differed significantly in the different cognitive level groups. Sleep parameters can be used as indicators to determine cognitive levels. Regarding the correlation between cognition and sleep, we found that cognitive assessment scores were significantly correlated with the percentage of sleep during SWS and with the minimum OS of sleep. Improvements in sleep quality can also be used to prevent cognitive

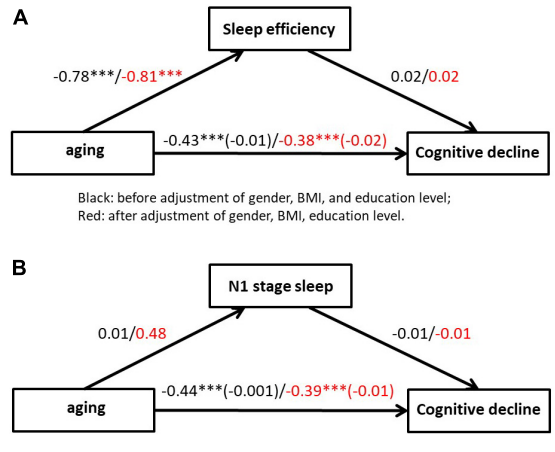

FIGURE 7
Mediation of the relationship between aging and cognitive decline by mediation effect of sleep efficiency **(A)** and N1 stage sleep **(B)**. Coefficients are standardized regression coefficients that are controlled for gender, BMI and education level. The coefficient in brackets represents the standardized regression coefficient when the mediator is also in the model. ***$p < 0.001$.

decline, especially interventions for OSA (Malhotra and White, 2002; Calik, 2016). Targeting modifiable risk factors is critical to reduce the onset and progression of dementia. Depression-related cognitive decline, treated with antidepressant methods, can alleviate sleep disturbances (Gebara et al., 2018). Sleep-disordered breathing is associated with a higher incidence of all-cause dementia, AD, and vascular dementia (Shi et al., 2018).

There is a growing body of literature on sleep and cognitive function in older adults. SD-CD represents neurodegenerative-associated cognitive changes, whereas SD-nCD represents normal- or age-related cognitive changes. Age-related cognitive changes result from developmental maturation. Both SWS and REM sleep decreased with age. In future, the clinical characteristics of patients in the SD-nCD group with sleep structures similar to those in the SD-CD group will be investigated after expanding the sample size. These characteristics could be used as indicators for the early diagnosis of diseases. Moreover, the cognition domain, including memory, attention, and executive functioning, can be considered to explain changes in sleep architecture, fragmentation, quality, and neurological conditions.

Plasma Aβ levels have emerged as a possible predictor of cognitive decline and dementia. This may be modified by health-related factors associated with the risk of dementia. These include insulin resistance and diabetes (Li et al., 2015; Peters et al., 2017), acute cerebral accidents (Kalaria et al., 2016) and impaired sleep (Sanchez-Espinosa et al., 2014; Spira et al., 2014). Epidemiological studies on sleep and cognition have suggested that sleep disorders are a risk factor for cognitive decline and may also be a concomitant disorder of cognitive impairment (Wennberg et al., 2017). Therefore, identifying patients with cognitive decline due to sleep disorders may greatly improve prevention strategies and treatment decisions for cognitive impairment.

Because of the insidious onset of dementia, some early-stage patients do not show cognitive decline but rather sleep disturbances or depressed mood. As the disease progresses, mild cognitive impairment (MCI) gradually appears (Jack et al., 2018). MCI is characterized by cognitive decline with some probability of developing dementia; however, it may also be maintained in MCI. Two-thirds of individuals with either dementia or MCI have sleep disorders (A ncoli-Israel et al., 1991). In addition, there is a physiological decline in sleep quality with age, especially in the length and quality of non-rapid eye-movement sleep. A previous study showed that the risk of AD was 1.68 times higher in patients with sleep disorders than in healthy controls, and more than 60% of patients with MCI and AD had at least one type of sleep disorder (Guarnieri et al., 2012). Previous studies also have shown that elderly patients with sleep disorders not accompanied with dementia have poor executive function due to their poor sleep quality including low sleep efficiency, REM sleep behavior disorder, et al. (Lerche et al., 2018; Boeve et al., 2022). In the future study, exploring the association between sleep disorders and executive functioning is worth investigating. Moreover, although in this study we did not obtain the exact disease course of patients in SD-CD group, we found that previous studies showed sleep abnormalities prior to dementia, usually in the period of mild cognitive decline, which early than dementia many years. The impaired sleep represents one of the earliest symptoms of dementia (Casagrande and Forte, 2022).

Aging can alter both sleep timing and quality, which can be disruptive in AD. Increased production of Aβ and reduced Aβ clearance are caused by the close interplay of Aβ, sleep disturbance, and increased wakefulness. In addition to Aβ, the impact of tau pathology is possibly noteworthy for the sleep deprivation observed in AD. Core AD cerebrospinal fluid biomarkers, including $A\beta_{42}$, total tau, and ptau, can reflect the key elements of AD pathophysiology before the emergence of symptoms (Cui et al., 2022). In future, blood abnormalities in patients with sleep disorders should be investigated in depth to assist in the early diagnosis of dementia. Although the relationship between cause and effect is still ambiguous, there is a strong correlation between aging, sleep disturbance, and cognitive decline, and there may be some indicators in the sleep structure parameters that can help us identify patients with a tendency for cognitive decline at a younger age. Although blood markers have been studied more in cognitive disorders, they have been less in studies of sleep disorders with cognitive decline, and we tried to find some significant differences in blood of three groups in order to find biomarkers suitable for mass screening using sleep indicators combined with blood biomarkers. This minimally invasive approach may significantly improve the sensitivity of early diagnosis which can be used as an effective tool for mass screening.

The limitations of this study are as follows: (1) Comprehensive neuropsychological evaluations were not conducted due to the complexity of clinical process. In this study we adopted MMSE to conduct cognitive assessment. Although MMSE was widely used in screening cognitive impairment, it has low performance in detecting minor neurocognitive disorder or dementia in early stages due to its limited capacity to detect complex cognitive domain disorders. In addition, MMSE has some false-negative results in people with high educational levels. (2) It is unclear whether sleep-related medications have direct effect on cognition. Short-acting sleep medications usually do not lead to next-day drowsiness and have no effect on cognitive assessment; long-acting sleep medications have the potential to cause patients to experience

poor daytime functioning in the following day, and may have some effect on cognitive assessment. In this study, many patients used drugs to improve sleep, while the effects of sleep drugs on PSG or cognition were not investigated. We try to recruited patients with consistent medications to improve the confounding factor control. This also led to a relatively small sample size. (3) Although there was association between sleep and cognition disease, the study cannot explain the causality due to it was a retrospective study.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by the Ethics Committee of Ningbo Kangning Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

XM and ZZ contributed to the original draft of the manuscript. JW and ZQ conducted the experiments. HY and CZ proofread the manuscript. All authors have read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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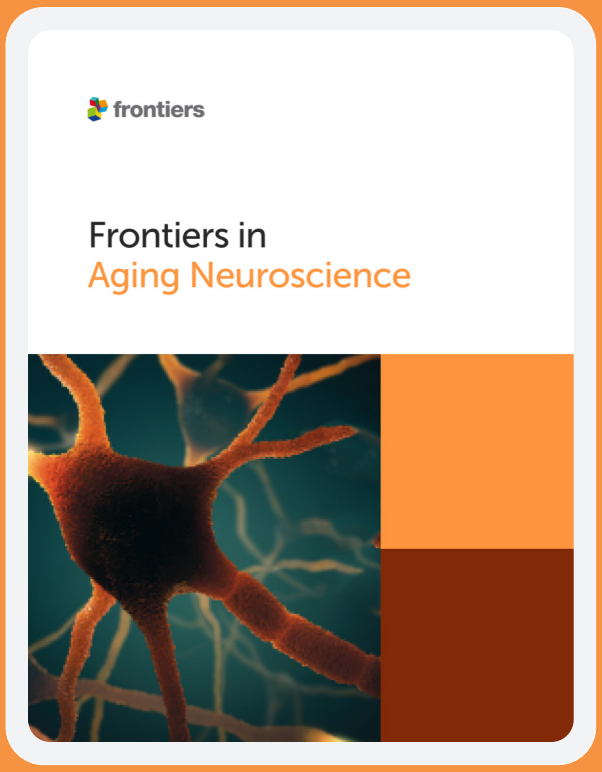

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