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ORIGINAL RESEARCH

Association Between Pre-Stroke Subjective Sleep Status and Post-Stroke Cognitive Impairment: A Nationwide Multi-Center Prospective Registry

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Background: Although sleep disorders significantly increase the risk of cognitive impairment, literature is relatively scarce regarding the impact of sleep status on cognitive function in patients with acute ischemic stroke (AIS). We seek to study the association between pre-stroke subjective sleep status and cognitive function at 3 months after stroke.

Patients and methods: Data were analyzed for 1,759 AIS patients from the Impairment of Cognition and Sleep after Acute Ischemic Stroke or Transient Ischemic Attack in Chinese Patients Study (ICONS). Pre-stroke subjective sleep status was assessed by the Pittsburgh Sleep Quality Index (PSQI) and Epworth Sleepiness Scale (ESS). Greater sleep fragmentation was defined as waking up in the middle of the night or early morning ≥3 times a week. Cognitive function was evaluated using the Montreal Cognitive Assessment (MoCA) at 3 months after stroke. Primary endpoint was the incidence of post-stroke cognitive impairment (PSCI) at 3 months after stroke. The association between subjective sleep status and PSCI was evaluated using multivariable logistic regression.

Results: PSCI occurred in 52.1% at 3 months after stroke. Patients with very bad sleep quality before stroke were at increased risk of PSCI (OR, 2.11; 95% CI, 1.11–4.03; P=0.03). Subgroup analysis found that the association between very bad sleep quality and PSCI was more evident among patients with high school education or above (OR, 5.73; 95% CI, 1.92–17.10; P for interaction=0.02). In addition, patients with greater sleep fragmentation before stroke were also at higher risk of PSCI (OR, 1.55; 95% CI, 1.20–2.01; P<0.01). Similarly, subgroup analysis showed that the risk of PSCI was more pronounced among patients without employment (OR, 2.45; 95% CI, 1.59–3.77; P for interaction=0.01).

Conclusion: Very bad sleep quality and greater sleep fragmentation before stroke were identified as independent risk factors for PSCI at 3 months after stroke.

Keywords: subjective sleep status, cognitive impairment, ischemic stroke

Introduction

Vascular cognitive impairment (VCI) has become the second common cause of dementia after Alzheimer's disease.[1] An important subtype of VCI, post-stroke cognitive impairment (PSCI) refers to the decline of cognitive function after stroke, which seriously affects patient's ability of daily living and social function,[2] and increases the risk of stroke recurrence.[3] A cross-sectional study in the Chinese population showed that the prevalence of PSCI was as high as 81%.[3]

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Research shows that the risk of cognitive impairment in patients with sleep disorders is about two to four times higher than the general population.[4] Poor sleep quality may further impair the cognitive function of patients with stroke,[5] whereas good sleep quality is associated with better cognitive performance either in the acute or convalescent stage of ischemic stroke.[6] However, most currently available studies on the relationship between sleep status and PSCI are focused on those with obstructive sleep apnea.[7–9] On the other hand, due to the first night effect, individualized difference and effectiveness of a single assessment, sleep assessment by polysomnography or actigraphy may not fully reflect the actual sleep status of patients, while the self-assessed sleep status may work better in this respect.[10–12]

In light of this, we seek to explore the association between pre-stroke subjective sleep status (including the quality and duration of sleep, sleep fragmentation, daytime sleepiness and sleep medication use) and PSCI at 3 months after stroke.

Methods

Study Design and Participants

The present study uses the data of patients with acute ischemic stroke (AIS) from the Impairment of Cognition and Sleep after acute ischemic stroke or transient ischemic attack in Chinese patients (ICONS) study,[13] which is a subgroup of the China National Stroke Registry-III (CNSR-III). CNSR-III is a nationwide multi-center prospective registry that recruited 15,166 consecutive patients with AIS and transient ischemic attack (TIA) from 201 study sites between August 2015 and March 2018 in China.[14]

A patient would be included in this study if s/he met all the following criteria: 1) age older than 18 years; 2) admission within 7 days after onset of AIS; and 3) ability to complete the baseline and follow-up tests.

Individuals with one of the following conditions were excluded: 1) silent cerebral infarction without symptoms or signs; 2) illiterate; 3) prior diagnosis of cognitive impairment, schizophrenia or psychosis disease; 4) concomitant neurological disorders affecting cognitive or sleep evaluation; 5) did not finish Pittsburgh Sleep Quality Index (PSQI) or Epworth Sleepiness Scale (ESS) at baseline; 6) did not finish Montreal Cognitive Assessment (MoCA) at 3 months after stroke; or 7) without specific education information.

Data Collection and Data Management

Collected from medical records and clinical interviews by trained neurologists were patient demographics (age, gender, education, occupation), past medical history (hypertension, diabetes, dyslipidemia, stroke, heart failure, atrial fibrillation, coronary heart disease, sleep disorder), lifestyle variables (body mass index, BMI), current smoker, heavy drinker (>60 g/d), physical activity, laboratory results (triglyceride, TG; total cholesterol, TC; high-density lipoprotein, HDL; low-density lipoprotein, LDL; serum uric acid, SUA; high sensitive C-reactive protein, hs-CRP; homocysteine, Hcy; hemoglobin, Hb; and hemoglobin A1c, HbA1C), clinical characteristics (stroke subtype for the Trial of Org 10,172 in Acute Stroke Treatment, TOAST; modified Rankin Scale, mRS; National Institutes of Health Stroke Scale, NIHSS), strategic infarcts determined by MRI imaging (defined as infarcts in the frontal, temporal, or parietal lobes, thalamus or basal ganglia) and scale measurements (the PSQI, ESS, GAD-7 and PHQ-9 at baseline, MoCA at 3 months).

Sleep Status Evaluation

The 19-item self-reported retrospective questionnaire PSQI was used to measure the subjective sleep status before stroke. Subjective sleep quality was assessed by the PSQI global score. According to the scoring principle of PSQI, patients were categorized into four groups: 0–5, 6–10, 11–15, and 16–21 points.[15]

Subjective sleep quality was also assessed with the question "During the past month, how would you rate your sleep quality overall" in PSQI, and patients were divided into four groups based on their answer to this question on sleep quality: very good, good, bad and very bad.

Sleep fragmentation was assessed using the question "During the past month, how often have you had trouble sleeping because you wake up in the middle of the night or early morning" in PSQI. According to the answer, patients

were categorized into two groups: <3 and ≥3 times within a week. The latter condition was defined as greater sleep fragmentation.

The question "During the past month, how many hours of actual sleep did you get at night?" in PSQI was used to assess the actual sleep duration at night, and patients were categorized into two groups: >7 and ≤7 hours. The latter condition was defined as short sleep duration.

We used Epworth Sleepiness Scale (ESS), a self-administered questionnaire, to classify subjective daytime sleepiness before stroke.[16] Patients were categorized into two groups according to their total ESS score: >10 and ≤10. An ESS score >10 was defined as daytime sleepiness.

The use of sleep medication was assessed with the question "During the past month, how often have you taken medicine to help you sleep?" in PSQI and subjects were categorized into two groups: none during the past month and ≥3 times a week. Taking hypnotic drugs 3 times or more per night was defined as frequent use of drugs.

Study Endpoints

The primary endpoint was the incidence of PSCI at 3 months after stroke. MoCA was used to evaluate the cognition function by face-to-face interview at 3 months. If the patient's education level was less than 12 years, a MoCA score of less than 25 was regarded as cognitive impairment. Otherwise, cognitive impairment was defined as a MoCA score of less than 26.[17]

Statistical Analysis

Continuous variables were presented as mean ± standard deviation or median (interquartile range, IQR), and analyzed using the *Kruskal–Wallis* test or *Wilcoxon* rank sum test. Categorical variables were presented as numbers (percentages) and analyzed using chi-square test or Fisher's exact probability test.

Multivariate logistic regression was performed to evaluate the association between different aspects of subjective sleep status before stroke and PSCI at 3 months. Results were presented with odds ratios (ORs) and their 95% confidence intervals (95% CI).

Three models were built to adjust potential covariates. Model 1 was adjusted for age, gender, education level, and occupation. Model 2 was additionally adjusted for medical history variables and blood biochemical parameters. In Model 3, PHQ-9 score at baseline, GAD-7 score at baseline, NIHSS score on admission, mRS score on admission, and strategic infarcts were adjusted in addition to Model 2 adjustments.

Potential interaction was examined with stratification by selected covariates (age, gender, education, employment, prior stroke, prior sleep disorder, PHQ-9 score, GAD-7 score and actual sleep duration at night at baseline).

All analyses were conducted with SAS 9.4 (SAS Institute, Cary, NC). All tests were two-sided, and a P value of <0.05 was considered statistically significant.

Results

Baseline Characteristics

The ICONS study enrolled 2,625 patients from 40 participating sites. After excluding 193 patients with TIA, 306 without PSQI data at baseline, 7 without ESS data at baseline, 280 without 3-month MoCA data, 80 without specific education information, a total of 1,759 patients were included in this analysis (Figure 1).

The socio-demographics and clinical characteristics of the enrolled patients as stratified by outcomes at baseline are shown in Tables 1–2 and.Supplementary Tables 1–4.

Global PSQI Score

The global PSQI score were as follows: 0–5 points in 1009 (57.4%); 6–10 points in 541 (30.8%); 11–15 points in 176 (10.0%); and 16–21 points in 33 patients (1.9%), respectively. These four groups differed significantly in gender, age, history of dyslipidemia, coronary heart disease and sleep disorder, TC, HDL, LDL, Hb, strategic infarcts, PHQ-9 score, and GAD-7 score (P<0.05 for all).

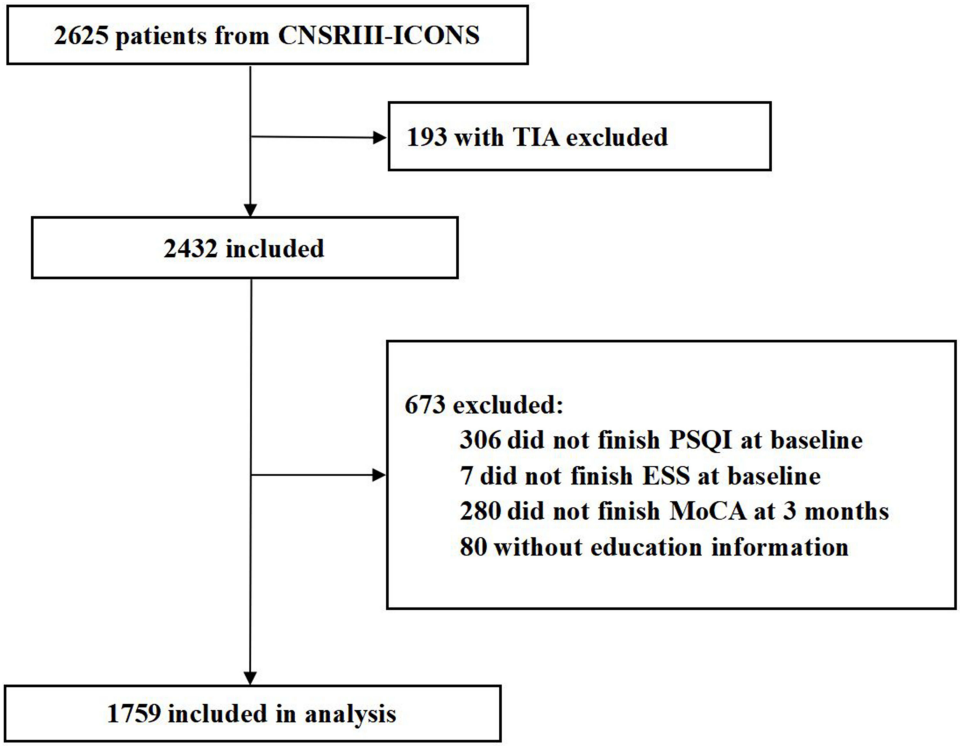

Figure 1 Flowchart of patient enrollment in the study.
Abbreviations: CNSRIII-ICONS, China National Stroke Registry-III-the impairment of cognition and sleep after acute ischemic stroke or transient ischemic attack in Chinese patient study; TIA, transient ischemic attack; PSQI, Pittsburgh Sleep Quality Index; ESS, Epworth Sleepiness Scale; MoCA, Montreal Cognitive Assessment.

Self-Reported Sleep Quality

The self-reported quality of sleep were: very good in 616 (35.0%); good in 793 (45.1%); bad in 273 (15.5%); and very bad in 77 patients (4.4%), respectively (Table 1). These four groups differed significantly with respect to gender, occupation, history of sleep disorder, Hb, PHQ-9 score, and GAD-7 score (P<0.05 for all).

Table 1 Demographic and Clinical Characteristics Stratified by Self-Reported Sleep Quality

Variables	Self-Reported Sleep Quality at 3 Months				P value
	Very Good (n=616)	Good (n=793)	Bad (n=273)	Very Bad (n=77)	
Male gender	482 (78.3)	581 (73.3)	186 (68.1)	43 (55.8)	<0.01
Age (year)	60.1±10.9	61.1±10.6	60.3±10.7	61.3±11.0	0.35
Education					
Elementary or below	181 (29.4)	212 (26.7)	85 (31.1)	23 (29.9)	0.27
Middle school	222 (36.0)	315 (39.7)	109 (39.9)	23 (29.9)	
High school or above	213 (34.6)	266 (33.5)	79 (28.9)	31 (40.3)	
Occupation					
Employed	372 (60.4)	474 (59.8)	162 (59.3)	42 (54.6)	<0.05
Unemployed	67 (10.9)	62 (7.8)	24 (8.8)	14 (18.2)	
Retirement	144 (23.4)	223 (28.1)	79 (28.9)	19 (24.7)	
Unknown	33 (5.4)	34 (4.3)	8 (2.9)	2 (2.6)	
Medical History					
Hypertension	387 (62.8)	501 (63.2)	167 (61.2)	49 (63.6)	0.94
Diabetes	140 (22.7)	165 (20.8)	65 (23.8)	21 (27.3)	0.47

(*Continued*)

Table 1 (Continued).

Variables	Self-Reported Sleep Quality at 3 Months				P value
	Very Good (n=616)	Good (n=793)	Bad (n=273)	Very Bad (n=77)	
Dyslipidemia	53 (8.6)	69 (8.7)	29 (10.6)	5 (6.5)	0.65
Stroke	137 (22.2)	160 (20.2)	58 (21.3)	14 (18.2)	0.74
Heart failure	4 (0.7)	2 (0.3)	0 (0.0)	1 (1.3)	0.18
Atrial fibrillation	31 (5.0)	33 (4.2)	15 (5.5)	6 (7.8)	0.47
Coronary heart disease	65 (10.6)	83 (10.5)	29 (10.6)	14 (18.2)	0.22
Sleep disorder	14 (2.3)	43 (5.4)	59 (21.6)	28 (36.4)	<0.01
Laboratory results					
Triglyceride (mmol/L)	1.4 (1.0–2.0)	1.4 (1.0–2.0)	1.4 (1.0–1.9)	1.4 (1.1–1.9)	0.80
Total cholesterol (mmol/L)	4.1 (3.4–4.8)	4.1 (3.4–4.9)	4.1 (3.4–4.8)	4.3 (3.7–4.9)	0.62
High-density lipoprotein (mmol/L)	1.1 (0.9–1.3)	1.1 (0.9–1.3)	1.1 (0.9–1.3)	1.2 (0.9–1.4)	0.30
Low-density lipoprotein (mmol/L)	2.4 (1.8–3.1)	2.4 (1.8–3.1)	2.3 (1.8–3.0)	2.6 (1.8–3.1)	0.79
Serum uric acid (μmol/L)	297.2 (245.5–355.5)	293.9 (242.0–351.0)	295.5 (244.0–352.0)	283.0 (247.0–359.0)	0.63
hs-CRP (mg/L)	1.5 (0.8–3.3)	1.7 (0.8–4.4)	1.7 (0.7–3.7)	1.3 (0.6–4.1)	0.64
Homocysteine (μmol/L)	17.4 (13.5–22.9)	16.6 (13.0–22.4)	16.5 (13.0–23.3)	14.9 (12.7–18.1)	0.17
Hemoglobin (g/L)	143.0 (133.0–153.0)	144.0 (134.1–154.0)	140.0 (131.0–151.0)	142.0 (130.0–151.0)	0.03
Hemoglobin A1C (%)	6.0 (5.5–7.0)	5.9 (5.5–6.8)	6.0 (5.5–7.5)	6.0 (5.5–8.0)	0.56
Body mass index (kg/m^2)	25.1 (23.2–27.1)	24.8 (23.0–26.9)	24.7(22.7–26.7)	25.0 (23.2–27.6)	0.23
Current smoker	229 (37.2)	290 (36.6)	94 (34.4)	27 (35.1)	0.88
Heavy drinker	50 (8.1)	42 (5.3)	20 (7.3)	3 (3.9)	0.13
Physical activity	406 (65.9)	520 (65.6)	175 (64.1)	59 (76.6)	0.22
NIHSS score on admission	3.0 (1.0–5.0)	3.0 (1.0–5.0)	3.0 (1.0–4.0)	3.0 (2.0–5.0)	0.66
mRS score on admission	1.0 (1.0–2.0)	1.0 (1.0–2.0)	1.0 (1.0–3.0)	2.0 (1.0–2.0)	0.75
Stroke subtype for TOAST					0.59
Large artery atherosclerosis	156 (25.3)	182 (23.0)	68 (24.9)	17 (22.1)	
Cardiogenic embolism	36 (5.8)	33 (4.2)	15 (5.5)	2 (2.6)	
Small artery occlusion	153 (24.8)	232 (29.3)	79 (28.9)	22 (28.6)	
Other/Unknown	271 (44.0)	346 (43.6)	111 (40.7)	36 (46.8)	
Strategic infarcts	324 (52.6)	401 (50.6)	141 (51.7)	42 (54.6)	0.84
PHQ-9 score	0.0 (0.0–3.0)	2.0 (0.0–4.0)	4.0 (3.0–8.0)	9.0 (6.0–14.0)	<0.01
GAD-7 score	0.0 (0.0–2.0)	1.0 (0.0–3.0)	3.0 (0.0–6.0)	5.0 (2.0–12.0)	<0.01

Notes: Values are mean ± standard deviation or median (interquartile range, IQR), or n (%).
Abbreviations: hs-CRP, high sensitive C-reactive protein; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; TOAST, the Trial of Org 10,172 in Acute Stroke Treatment; PSQI, Pittsburgh Sleep Quality Index scale; PHQ-9, Patient Health Questionnaire-9; GAD-7, General Anxiety Disorder-7.

Sleep Fragmentation

The times of sleep fragmentation within a week were <3 in 1325 (75.3%) and ≥3 in 434 patients (24.7%), respectively (Table 2). The two groups differed significantly in gender, age, education, occupation, history of diabetes, coronary heart disease, and sleep disorder, TC, HDL, LDL, Hcy, Hb, HbA1C, PHQ-9 score, and GAD-7 score (P<0.05 for all).

Sleep Duration

The sleep duration were >7 hours in 906 (51.5%) and ≤7 hours in 853 (48.5%). The two groups differed significantly in education, history of sleep disorder, TC, HDL, LDL, strategic infarcts, PHQ-9 score, and GAD-7 score (P<0.05 for all).

Table 2 Demographic and Clinical Characteristics Stratified by Sleep Fragmentation

Variables	Times of Sleep Fragmentation within a Week		P value
	<3 (n=1325)	≥3 (n=434)	
Male gender	1001 (75.6)	291 (67.1)	<0.01
Age (year)	59.9±11.0	62.8±9.5	<0.01
Education			
Elementary or below	353 (26.6)	148 (34.1)	0.01
Middle school	517 (39.0)	152 (35.0)	
High school or above	455 (34.3)	134 (30.9)	
Occupation			
Employed	818 (61.7)	232 (53.5)	<0.01
Unemployed	107 (8.1)	60 (13.8)	
Retirement	336 (25.4)	129 (29.7)	
Unknown	64 (4.8)	13 (3.0)	
Medical History			
Hypertension	817 (61.7)	287 (66.1)	0.09
Diabetes	279 (21.1)	112 (25.8)	0.04
Dyslipidemia	115 (8.7)	41 (9.5)	0.63
Stroke	282 (21.3)	87 (20.1)	0.58
Heart failure	6 (0.5)	1 (0.2)	1.00
Atrial fibrillation	59 (4.5)	26 (6.0)	0.19
Coronary heart disease	125 (9.4)	66 (15.2)	<0.01
Sleep disorder	73 (5.5)	71 (16.4)	<0.01
Laboratory results			
Triglyceride (mmol/L)	1.4 (1.0–1.9)	1.4 (1.0–1.9)	0.49
Total cholesterol (mmol/L)	4.1 (3.4–4.8)	4.3 (3.4–5.1)	<0.01
High-density lipoprotein (mmol/L)	1.1 (0.9–1.3)	1.1 (0.9–1.4)	0.01
Low-density lipoprotein (mmol/L)	2.4 (1.8–3.0)	2.6 (1.8–3.2)	<0.01
Serum uric acid (μmol/L)	297.0 (244.0–353.0)	289.0 (236.0–353.0)	0.28
hs-CRP (mg/L)	1.6 (0.8–3.8)	1.7 (0.7–4.0)	0.98
Homocysteine (μmol/L)	17.1 (13.4–23.5)	15.3 (12.6–20.4)	<0.01
Hemoglobin (g/L)	143.0 (134.0–154.0)	142.0 (131.0–151.0)	0.01
Hemoglobin A1C (%)	5.9 (5.5–6.9)	6.1 (5.6–7.4)	0.04
Body mass index (kg/m^2)	24.9 (23.1–27.0)	24.8 (22.9–27.0)	0.72
Current smoker	493 (37.2)	147 (33.9)	0.21
Heavy drinker	83 (6.3)	32 (7.4)	0.42
Physical activity	865 (65.3)	295 (68.0)	0.30
NIHSS score on admission	3.0 (1.0–5.0)	3.0 (2.0–5.0)	0.75
mRS score on admission	1.0 (1.0–2.0)	1.0 (1.0–3.0)	0.28
Stroke subtype for TOAST			
Large artery atherosclerosis	321 (24.2)	102 (23.5)	0.97
Cardiogenic embolism	64 (4.8)	22 (5.1)	
Small artery occlusion	368 (27.8)	118 (27.2)	
Other/Unknown	572 (43.2)	192 (44.2)	
Strategic infarcts	694 (52.4)	214 (49.3)	0.27
PHQ-9 score	1.0 (0.0–4.0)	4.0 (1.0–8.0)	<0.01
GAD-7 score	1.0 (0.0–3.0)	1.5 (0.0–5.0)	<0.01

Notes: Values are mean ± standard deviation or median (interquartile range), or n (%).

Abbreviations: hs-CRP, high sensitive C-reactive protein; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; TOAST, the Trial of Org 10,172 in Acute Stroke Treatment; PSQI, Pittsburgh Sleep Quality Index scale; PHQ-9, Patient Health Questionnaire-9; GAD-7, General Anxiety Disorder-7.

Daytime Sleepiness

The Epworth Sleepiness Scale were >10 in 192 (10.9%) and ≤10 in 1567 patients (89.1%), respectively. The two groups differed significantly in history of hypertension and sleep disorder, BMI, PHQ-9 score, and GAD-7 score (P<0.05 for all).

Use of Sleep Medication

1677 patients (98.0%) did not use any sleep medication while 35 patients (2.0%) used three or more times a week. The two groups differed significantly in age, history of coronary heart disease and sleep disorder, current smoker, PHQ-9 score, and GAD-7 score (P<0.05 for all).

Association Between Pre-Stroke Subjective Sleep Status and PSCI at 3 Months

At 3 months after stroke, 916 patients (52.1%) had PSCI as confirmed by MoCA. With all potential confounding factors adjusted in Model 3, the global PSQI score, actual sleep duration at night, daytime sleepiness, and the use of sleep medication before stroke were not found to be significantly associated with PSCI at 3 months (P>0.05 for all).

However, patients with very bad sleep quality before stroke had a 2.11-fold higher risk of PSCI at 3 months compared to those with very good sleep quality (OR, 2.11; 95% CI, 1.11–4.03; P=0.03). In addition, compared to those with episodes of fragmented sleep of <3 times a week, patients with greater sleep fragmentation before stroke had a 1.55-fold higher risk of PSCI at 3 months (OR, 1.55; 95% CI, 1.20–2.01; P<0.01) (Table 3).

Table 3 Impact of Subjective Sleep Status on Cognitive Function at 3 Months After Stroke

Subjective Sleep Status	Model 1			Model 2			Model 3		
	OR (95% CI)	P value	P for Trend	OR (95% CI)	P value	P for Trend	OR (95% CI)	P value	P for Trend
Global PSQI score		<0.01	<0.01		<0.01	<0.01		0.36	0.28
6–10	1.14 (0.92–1.42)			1.11 (0.89–1.40)			0.98 (0.77–1.24)		
11–15	1.72 (1.22–2.44)			1.65 (1.13–2.41)			1.25 (0.83–1.88)		
16–21	3.35 (1.41–7.92)			3.40 (1.42–8.17)			2.02 (0.79–5.14)		
Self-reported sleep quality		<0.01	0.02		<0.01	0.03		0.03	0.82
Good	0.97 (0.78–1.21)			0.97 (0.78–1.22)			0.93 (0.74–1.17)		
Bad	1.01 (0.75–1.36)			1.03 (0.75–1.42)			0.82 (0.58–1.16)		
Very bad	3.12 (1.76–5.54)			3.18 (1.75–5.81)			2.11 (1.11–4.03)		
Sleep fragmentation		<0.01	<0.01		<0.01	<0.01		<0.01	<0.01
≥3 times a week	1.79 (1.42–2.26)			1.75 (1.37–2.23)			1.55 (1.20–2.01)		
Actual hours of sleep at night		0.03	0.03		0.13	0.13		0.34	0.34
≤7	1.24 (1.02–1.51)			1.18 (0.96–1.44)			1.11 (0.90–1.37)		
Daytime sleepiness		0.14	0.14		0.22	0.22		0.99	0.99
ESS>10	1.27 (0.92–1.74)			1.23 (0.89–1.69)			1.00 (0.71–1.41)		
Use of sleep medication		0.16	0.16		0.21	0.21		0.68	0.68
≥3 times a week	1.72 (0.81–3.62)			1.62 (0.76–3.44)			1.18 (0.54–2.55)		

Notes: Reference groups for these six variables are 0–5, very good, <3 times a week, >7 hours, ESS≤10 and none during past month, respectively. Model 1: Adjusted for age, gender, education and occupation. Model 2: Adjusted for Model 1 + history of hypertension, diabetes, dyslipidemia, stroke, atrial fibrillation and sleep disorder, total cholesterol, triglyceride, high and low-density lipoprotein, serum uric acid and hemoglobin. Model 3: Adjusted for Model 2 + PHQ-9 and GAD-7 scores at baseline, NIHSS and mRS scores on admission, and strategic infarcts.

Abbreviations: OR, odds ratio; CI, confidence interval; ESS, Epworth Sleepiness Scale; PSQI, Pittsburgh Sleep Quality Index.

Subgroup Analysis

In subgroup analysis, when stratified by selected covariates (age, gender, education, employment, prior stroke, prior sleep disorder, PHQ-9 score, GAD-7 score, and actual sleep duration at night), the association of PSCI at 3 months with very bad sleep quality before stroke was more evident among patients with high school education or above (OR, 5.73; 95% CI, 1.92–17.10; P for interaction=0.02) (Table 4). Similarly, the risk of PSCI at 3 months with greater sleep fragmentation before stroke was more pronounced among patients without employment (OR, 2.45; 95% CI, 1.59–3.77; P for interaction=0.01) (Table 5).

Discussion

To the best of our knowledge, this analysis may represent the first multi-centered, large sample, prospective study that evaluated the impact of pre-stroke subjective sleep status on cognitive function after AIS. Consistent with previous studies,[18–21] the prevalence of PSCI at 3 months after stroke was 52.1% in this series. The results showed that self-reported very bad sleep quality and greater sleep fragmentation before stroke were associated with 2.11-fold and 1.55-fold higher risk of developing PSCI at 3 months after stroke, respectively. While no association was found between other parameters of pre-stroke subjective sleep status with PSCI, including global PSQI score, daytime sleepiness, and sleep medication use.

Many previous studies have shown that sleep fragmentation significantly increases the risk of cognitive impairment,[4,22–24] which may lead to worse performance on delayed recall, semantic fluency, and digit span.[25] We

Table 4 Subgroup Analysis of Association Between Self-Reported Very Bad Sleep Quality and PSCI

Subgroups	No. of Patients	No. of Events (%)	Odds Ratio (95% Confidence Interval)	P for Interaction
Age (year)				
<65	1111	32 (2.9)	1.58 (0.73–3.41)	0.19
≥65	648	27 (4.2)	4.64 (1.20–17.87)	
Gender				
Male	1292	32 (2.5)	2.24 (0.98–5.15)	0.89
Female	467	27 (5.8)	1.59 (0.52–4.81)	
Education				
≤Middle school	1170	34 (2.9)	1.14 (0.51–2.58)	0.02
≥High school	589	25 (4.2)	5.73 (1.92–17.10)	
Employment status				
Employed	1050	29 (2.8)	1.28 (0.56–2.94)	0.06
No	632	30 (4.7)	9.34 (2.35–37.04)	
Prior stroke				
Yes	369	13 (3.5)	3.42 (0.36–32.36)	0.85
No	1390	46 (3.3)	1.94 (0.97–3.87)	
Prior sleep disorder				
Yes	144	23 (16.0)	3.80 (0.61–23.54)	0.51
No	1615	36 (2.2)	2.06 (0.97–4.39)	
PHQ-9 score				
≤4	1317	6 (0.5)	1.66 (0.40–6.93)	0.74
>4	432	53 (12.3)	1.76 (0.74–4.20)	
GAD-7 score				
≤4	1453	25 (1.7)	2.63 (1.08–6.40)	0.70
>4	303	34 (11.2)	1.42 (0.46–4.38)	
Actual hours of sleep at night				
>7	906	14 (1.5)	6.96 (1.36–35.50)	0.06
≤7	853	45 (5.3)	1.24 (0.58–2.67)	

Notes: Adjusted for the same variables as in Model 3 (Table 3), except for the stratified variables.
Abbreviations: PHQ-9, Patient Health Questionnaire-9; GAD-7, General Anxiety Disorder-7.

Table 5 Subgroup Analysis of Association Between Greater Sleep Fragmentation and PSCI

Subgroups	No. of Patients	No. of Events (%)	Odds Ratio (95% Confidence Interval)	P for Interaction
Age (year)				
<65	1111	150 (13.5)	1.65 (1.19–2.28)	0.94
≥65	648	133 (20.5)	1.65 (1.07–2.52)	
Gender				
Male	1292	184 (14.2)	1.63 (1.20–2.22)	0.67
Female	467	99 (21.2)	1.33 (0.81–2.18)	
Education				
≤middle school	1170	207 (17.7)	1.68 (1.23–2.30)	0.79
≥high school	589	76 (12.9)	1.55 (0.98–2.45)	
Employment status				
Employed	1050	139 (13.2)	1.17 (0.84–1.65)	0.01
No	632	138 (21.8)	2.45 (1.59–3.77)	
Prior stroke				
Yes	369	64 (17.3)	1.63 (0.89–2.99)	0.61
No	1390	219 (15.8)	1.56 (1.17–2.08)	
Prior sleep disorder				
Yes	144	48 (33.3)	1.00 (0.42–2.41)	0.45
No	1615	235 (14.6)	1.63 (1.24–2.14)	
PHQ-9 score				
≤4	1317	150 (11.4)	1.75 (1.28–2.38)	0.32
>4	432	131 (30.3)	1.20 (0.75–1.92)	
GAD-7 score				
≤4	1453	197 (13.6)	1.77 (1.32–2.37)	0.10
>4	303	86 (28.4)	0.87 (0.47–1.62)	
Actual hours of sleep at night				
>7	906	82 (9.1)	1.48 (0.96–2.30)	0.77
≤7	853	201 (23.6)	1.63 (1.16–2.28)	

Notes: Adjusted for the same variables as in Model 3 (Table 3), except for the stratified variables.
Abbreviations: PHQ-9, Patient Health Questionnaire-9; GAD-7, General Anxiety Disorder-7.

speculate that this may be ascribed to the nocturnal sleep duration, in other words, frequent arousal may lead to insufficient sleep and damage cognitive function. This was echoed in the subgroup analysis showing that the damaging effect of greater sleep fragmentation is more evident in patients with short sleep duration, although no interaction was observed.

Previous studies have shown a U-shaped relationship between sleep duration and the risk of cognitive impairment, which is very likely to occur with either too short or too long a sleep duration.[22,26–28] The impairment of those who slept 4 hours or less per night was equivalent to the effect of aging 8 years to their age.[29] The optimal sleep duration for about 5.6–6.0 hours per night is associated with lower risk of cognitive impairment.[22] However, this study did not show a significant association between nocturnal sleep duration and PSCI. This may be related to the grouping of patients in the study, because neither >7 hours nor ≤7 hours of sleep may fully reflect extreme sleep conditions.

Falck and associates found that sleep quality of older adults with stroke was poorer than non-stroke counterparts, and older adults with stroke and poor sleep quality may experience larger deficits in cognitive performance.[5] Animal experiments confirmed that ischemic stroke can lead to increased slow-wave sleep and decreased rapid eye movement sleep, promoting the rehabilitation of neurological function.[30,31] Injury to central nervous system caused by stroke may increase the sleep needs of the elderly to promote the repair of the damaged brain tissue. Poor sleep quality may have an adverse effect on the recovery of neural function after stroke,[32] including cognitive function.[33]

Notably, our subgroup analysis showed that the association of PSCI with very bad sleep quality before stroke was more evident among patients with high school education or above. It is inconsistent with previous view that people with

higher cognitive reserves are better able to cope with cognitive disruption caused by sleep problems.[4] We think that one possible mechanism could be a floor effect, whereby the less educated patients are already close to the floor while the more educated individuals are way above the floor and as such have more pronounced cognitive impairment after stroke. Subsequently, we used the rate of MoCA score change from baseline to 3 months after stroke to test this hypothesis, while no significant difference was shown between the two groups (Supplementary Table 5). Relevant mechanisms need to be further studied. In addition, we found among patients without employment, the association of PSCI with greater sleep fragmentation was more pronounced. Extensive social engagement may reduce the risk of cognitive decline through mental stimulation and brain function activation.[34]

Previous study has confirmed that subjective sleep disturbances are related with increased risk of stroke in Chinese adults.[35] We should notice that vascular risk factors and comorbidities may also disturb sleep, and controlling these adverse factors may help to reduce the occurrence of sleep disorders. Improvement of sleep status may contribute the secondary prevention of stroke, reduce the recurrence, and improve the quality of life of stroke patients.[36,37]

Study Limitations

This study has several inherent limitations. First, while objective measurement like polysomnography was neither feasible nor available in a multi-center trial, cognitive impairment may affect the validity of self-reported sleep status, therefore the sleep status assessed in this study may not reflect what it was in reality. Second, sleep duration was taken as a categorical variable rather than a continuous one in PSQI, which precludes the possibility of performing a more accurate and quantitative assessment. Finally, despite the adjustment of multiple covariates, some other unmeasured confounders may be missed in this analysis that potentially affect the results.

Conclusions

This study shows that both very bad sleep quality and greater sleep fragmentation before stroke significantly increase the risk of PSCI at 3 months after stroke. These results highlight the importance of sleep in AIS patient, which implies that early diagnosis and treatment of sleep disorders may help reduce the incidence of PSCI.

Ethics Approval

The study protocol was reviewed and approved by the ethics committee of Beijing Tiantan Hospital. All the study participants provided informed consent to take part in this study, in accordance with the Declaration of Helsinki.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this study.

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