JCSM | Journal of Clinical Sleep Medicine

SCIENTIFIC INVESTIGATIONS

Associations among sleep-disordered breathing, arousal response, and risk of mild cognitive impairment in a northern Taiwan population

Cheng-Yu Tsai, MSc[1]; Wen-Hua Hsu, BSc[2,*]; Yin-Tzu Lin, MD[3,*]; Yi-Shin Liu, BSc[2]; Kang Lo, MSc[4]; Shang-Yang Lin, PhD[2]; Arnab Majumdar, PhD[1]; Wun-Hao Cheng, BSc[5]; Kang-Yun Lee, MD, PhD[6,7]; Dean Wu, MD, PhD[4,8,9,10,11]; Hsin-Chien Lee, MD, PhD[12]; Shin-Mei Hsu, BSc[4]; Shu-Chuan Ho, PhD[2]; Feng-Ching Lin, MSc[13]; Wen-Te Liu, MD, PhD[2,4,6]; Yi-Chun Kuan, MD[4,8,9,10,11,14]

[1]Department of Civil and Environmental Engineering, Imperial College London, London, United Kingdom; [2]School of Respiratory Therapy, College of Medicine, Taipei Medical University, Taipei, Taiwan; [3]Department of General Medicine, Shuang Ho Hospital, Taipei Medical University, New Taipei City, Taiwan; [4]Sleep Center, Shuang Ho Hospital, Taipei Medical University, New Taipei City, Taiwan; [5]Graduate Institute of Medical Sciences, College of Medicine, Taipei Medical University, Taipei, Taiwan; [6]Division of Pulmonary Medicine, Department of Internal Medicine, Shuang Ho Hospital, Taipei Medical University, New Taipei City, Taiwan; [7]Division of Pulmonary Medicine, Department of Internal Medicine, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan; [8]Department of Neurology, Shuang Ho Hospital, Taipei Medical University, New Taipei City, Taiwan; [9]Department of Neurology, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan; [10]Taipei Neuroscience Institute, Taipei Medical University, Taipei, Taiwan; [11]Dementia Center, Shuang Ho Hospital, Taipei Medical University, New Taipei City, Taiwan; [12]Department of Psychiatry, Taipei Medical University Hospital, Taipei, Taiwan; [13]Division of Integrated Diagnostic and Therapeutics, National Taiwan University Hospital, Taipei, Taiwan; [14]Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan; *Contributed equally

Study Objectives: Dementia is associated with sleep disorders. However, the relationship between dementia and sleep arousal remains unclear. This study explored the associations among sleep parameters, arousal responses, and risk of mild cognitive impairment (MCI).

Methods: Participants with the chief complaints of memory problems and sleep disorders, from the sleep center database of Taipei Medical University Shuang-Ho Hospital, were screened, and the parameters related to the Cognitive Abilities Screening Instrument, Clinical Dementia Rating, and polysomnography were determined. All examinations were conducted within 6 months and without a particular order. The participants were divided into those without cognitive impairment (Clinical Dementia Rating = 0) and those with MCI (Clinical Dementia Rating = 0.5). Mean comparison, linear regression models, and logistic regression models were employed to investigate the associations among obtained variables.

Results: This study included 31 participants without MCI and 37 with MCI (17 with amnestic MCI, 20 with multidomain MCI). Patients with MCI had significantly higher mean values of the spontaneous arousal index and spontaneous arousal index in the non–rapid eye movement stage than those without MCI. An increased risk of MCI was significantly associated with increased spontaneous arousal index and spontaneous arousal index in the non–rapid eye movement stage with various adjustments. Significant associations between the Cognitive Abilities Screening Instrument scores and the oximetry parameters and sleep disorder indexes were observed.

Conclusions: Repetitive respiratory events with hypoxia were associated with cognitive dysfunction. Spontaneous arousal, especially in non–rapid eye movement sleep, was related to the risk of MCI. However, additional longitudinal studies are required to confirm their causality.

Keywords: mild cognitive impairment, cognitive abilities screening instrument, clinical dementia rating, arousal index, spontaneous arousal index, apnea

Citation: Tsai C-Y, Hsu W-H, Lin Y-T, et al. Associations among sleep-disordered breathing, arousal response, and risk of mild cognitive impairment in a northern Taiwan population. *J Clin Sleep Med.* 2022;18(4): 1003–1012.

BRIEF SUMMARY

Current Knowledge/Study Rationale: The associations between dementia and sleep arousal remain unclear. Therefore, this study examined the associations among polysomnography parameters, the outcomes of Cognitive Abilities Screening Instrument and Clinical Dementia Rating in mild cognitive impairment (MCI) and non-MCI participants.

Study Impact: The results indicated that the MCI patients demonstrated significantly higher mean values of the spontaneous arousal index and spontaneous arousal index in the non–rapid eye movement stage than the non-MCI patients. The apnea-hypopnea index and oxygenation-related parameters were significantly associated with the Cognitive Abilities Screening Instrument score. The spontaneous arousal index and spontaneous arousal index in the non–rapid eye movement stage were associated with the risk of MCI. These findings indicate that recurrent sleep-disordered breathing is related to poor cognitive function and that spontaneous arousal is associated with the risk of MCI.

INTRODUCTION

Mild cognitive impairment (MCI) is a cognitive disorder characterized by a decline in cognitive function; the extent of cognitive impairment in MCI is somewhere between that seen in age-associated cognitive decline and dementia, with no or minimal decline in the activities of daily living. In 2019, approximately 17.3% of the general population aged ≥ 60 years were estimated to have MCI.[1] Possible modifiable risk factors for MCI include depression,[2] diabetes mellitus,[3] hypertension,[4]

and sleep disorders.[5] Obstructive sleep apnea syndrome (OSAS), characterized by a repetitive and complete or partial obstruction of the upper airway and respiratory airflow cessation during sleep, is a common sleep-disordered breathing condition. OSAS can result in intermittent hypoxia related to apnea or hypopnea, recurrent arousal response, and fragmented sleep; it has also been associated with a higher risk of neuropsychological and memory dysfunction.[6,7]

Several mechanisms have been proposed to explain the relationship between cognitive decline and OSAS.[7–9] Patients with OSAS with intermittent hypoxia have worse cognitive function than patients without hypoxia.[10] A 2011 prospective study analyzed the sleep disorder characteristics of 298 older women (age ≥ 65 years) without dementia and indicated that an increased oxygen desaturation index (≥ 15 events/h) was associated with the risk of MCI or dementia after adjustment for age, body mass index (BMI), and ethnicity.[11] Moreover, intermittent hypoxia may increase reactive oxygen species formation, leading to oxidative stress, which may activate inflammatory cytokines and cause brain neuronal injury.[12]

Recurrent arousal from sleep and sleep fragmentation are risk factors for cognitive deficit. Sleep duration, continuity, and intensity play major roles in hippocampal neurogenesis, synaptic plasticity, and memory formation and consolidation.[7,13] Additionally, stable sleep is crucial for neurotoxic metabolite clearance in the brain.[14] Sleep arousal represents abrupt awakening and is significantly associated with sleep deprivation, which may causally affect neurodegeneration.[15] A 2014 United States cross-age study analyzed the sleep behaviors of 59 young adults (mean age = 23.05 years) and 53 older adults (mean age = 62.05 years)[16] and found that sleep continuity was associated with better cognitive performance and executive function in both cohorts. Conversely, chronic fragmented sleep and sleep arousal due to intermittent hypoxia may contribute to the development of neurodegenerative disease.[17] A recent review suggested that sleep arousal was associated with higher β-amyloid 42 levels in the cerebrospinal fluid of patients with MCI.[18] In a rodent study, sleep disruption contributed to cognitive impairment and neurodegeneration.[19] Together, these studies indicate that frequent arousal resulting from reflex responses of central and peripheral chemoreceptors stimulated by airway obstruction or intermittent hypoxia may increase the risk of cognitive impairment. However, the relationship between cognitive decline and the subtypes of sleep arousal remains unclear.

To explore the mechanisms underlying various sleep arousal responses on cognitive impairment, investigating the effect of various arousal responses caused by different stimuli is noteworthy. For example, sleep-disordered breathing causes respiratory arousal, which affects the duration of the rapid eye movement (REM) sleep stage in patients with Alzheimer's disease.[20] Similarly, respiratory arousal was associated with sleep fragmentation and was considered a risk factor for neurodegeneration.[21] An increase in the periodic limb movement–related arousal index was observed in patients with various neurodegenerative diseases.[22] Although patients with cognitive impairment have elevated scores in various subtypes of arousal index, how these indices affect the risk of MCI remains unclear.

This explorative study not only compared sleep parameters between non-MCI and MCI participants but also investigated the associations between sleep disorder indices, including various subtypes of sleep arousal, in different sleep stages and the scores of cognitive assessments. We hope that the study results further the understanding of the association among various subtypes of sleep arousal, sleep hypoxia, and risk of cognitive impairment.

METHODS

Ethics
The protocol of this retrospective study was approved by the Taipei Medical University–Joint Institutional Review Board (TMU–JIRB: N201911007). The procedures of data collection, steps of data deidentification, and statistical examination were in accordance with the approved guidelines.

Study population
For this retrospective study, the target patients were those with the chief complaints of memory problems and sleep disorders from the sleep center of Taipei Medical University Shuang-Ho Hospital (New Taipei City, Taiwan) between March 2015 and October 2019. Their polysomnography (PSG) data and cognitive assessment outcomes were obtained. The inclusion criteria were as follows: (1) 18–85 years of age, (2) a total PSG recording time of > 6 hours, (3) completion of the Cognitive Abilities Screening Instrument (CASI) and the Clinical Dementia Rating (CDR), with a CDR score of 0 (no cognitive impairment) or 0.5 (MCI), (4) receipt of the PSG and cognitive assessment tests within a 6-month interval (in no particular examination order), (5) no current surgery or noninvasive treatment, such as continuous positive airway pressure or oral appliance devices, for OSAS, and (6) no central nervous system disorders such as tumor, stroke, or major head trauma. All the eligible data were analyzed.

PSG results
In-laboratory PSG was conducted using the Embla N7000 (ResMed, San Diego, CA) or Embletta MPR system (Natus Medical, Pleasanton, CA) at the sleep center of Taipei Medical University–Shuang-Ho Hospital. RemLogic software (version 3.41; Embla Systems, Thornton, CO) was employed as the scoring interface. The scoring process involved scoring all the PSG physiological signals by a licensed PSG technologist, and the scores were reviewed by another technologist. Inconsistent scoring outcomes were identified and further discussed to achieve a consensus. All the scoring rules were in accordance with the 2017 American Academy of Sleep Medicine criteria.[23] For the respiratory event, apnea (≥ 90% drop in oronasal thermal sensor signals) and hypopnea (≥ 30% drop in nasal pressure sensor signals with ≥ 3% desaturation or combined with arousal occurrence) were determined. For arousal scoring, the abrupt shift in brainwave signals with alpha (8–12 Hz), theta (4–8 Hz), or high frequency (> 16 Hz, but not spindle) that occurred and lasted at least 3 seconds with at least 10 seconds of steady sleep preceding the alteration was considered. OSAS severity was classified as none (apnea-hypopnea index [AHI] < 5 events/h), mild (AHI: 5–15 events/h), moderate

(AHI: 15–30 events/h), and severe (AHI $\geq$ 30 events/h).[24] The arousal index (ArI) score was calculated as the index sum of spontaneous arousal (SpArI), respiratory arousal (RArI, apnea or hypopnea-induced), limb movement arousal (single, periodic, or respiratory-related), and snore arousal. All the scoring technicians were blinded to the cognitive assessment results of the patients. To compare sleep parameters between patients with and without MCI, data on PSG parameters, including sleep stages and architecture, oximetry summary, and duration of respiratory events, were obtained. Moreover, various arousal and sleep disorder indices were measured to obtain data during total sleep time, REM sleep, and non-REM (NREM) sleep.

Cognitive assessment
The CDR has been commonly used to determine a patient's cognitive impairment level, cognitive performance, and effects of cognitive impairment and performance on daily activities.[25] The CDR contains several subdomains, including memory, orientation, judgment and problem-solving, community affairs, home and hobbies, and personal care. Participants with a CDR score of > 0 are suspected to have cognitive impairment.[25]

The CASI has been widely employed for screening individuals' cognitive abilities and tracing the potential of dementia development.[26] It evaluates attention, concentration, orientation, short-term and long-term memory, abstraction, judgment, and language abilities; visual construction; and list-generating fluency.

This study collected CDR and CASI (CASI-2.0) data from all eligible participants' medical records. In addition, because cognitive performance can be considerably affected by educational level, the statistical models used in this study were adjusted for the participants' educational background (years).

Statistical analysis
All statistical examinations were performed using SPSS (version 20.0; IBM, Armonk, NY). The Shapiro-Wilk test was conducted to examine data normality. Continuous variables were compared using Student's *t* test and the Mann-Whitney *U* test, and nominal variables were evaluated using the chi-square test. To investigate the associations between the CASI score and sleep-related parameters, multiple linear regression models, with adjustments for age, sex, BMI, and years of education, were applied. The statistical outcomes are presented as standardized beta coefficients (βs) with 95% confidence intervals (CIs). Next, simple and multivariable logistic regression models (model 1 adjusted for age, sex, and BMI; model 2 adjusted for age, sex, BMI, and oxygen desaturation index $\geq$ 3% [ODI-3%]) were employed to explore the relationship of variables between the non-MCI (CDR = 0) and MCI (CDR = 0.5) groups. The results are reported as crude or adjusted odds ratio (OR) with 95% CIs. The level of significance was set to $P < .05$.

RESULTS

Demographics of study participants
The participants' baseline characteristics stratified by the CDR are presented in **Table 1**. The data of 68 participants were

retrospectively analyzed, including 31 without MCI and 37 with MCI (17 with amnestic MCI and 20 with multidomain MCI). No significant differences were observed in age, sex, or BMI profiles between the groups. The mean CASI score was higher in the non-MCI group (87.58 ± 7.02) than in the MCI group (78.92 ± 12.59; $P < .01$). Additionally, all CASI subdomain scores in the MCI group were lower than those in the non-MCI group, with a significant difference in the short-term memory ($P < .01$), orientation ($P < .05$), and visual construction ($P < .01$) subdomains. OSAS severity was not significantly different between the groups.

Sleep parameters of in-laboratory PSG
Table 2 presents the between-group comparisons of sleep parameters. Sleep efficiency and the percentage of participants in the wake stage in the MCI group were respectively nonsignificantly lower and nonsignificantly higher than those in the non-MCI group. Oximetry parameters and sleep disorder indices were not significantly different between the groups, both overall and for those in different sleep stages.

Table 3 presents a comparison of the arousal indices between the groups. The average values of the SpArI and SpArI in the NREM stage (SpArI$_{NREM}$) were significantly higher in patients with MCI than in those without MCI (SpArI: $P < .05$; SpArI$_{NREM}$: $P < .05$). No significant differences were observed between patients with MCI and patients without MCI in the SpArI in the REM stage, RArI, RArI in the NREM stage, or RArI in the REM stage.

Associations between sleep parameters and CASI score
Table 4 presents a summary of the associations between sleep parameters and CASI total score obtained using multivariable linear regression adjusted for age, sex, BMI, and education years. A 1% decrease in minimum SaO$_2$ was significantly associated with a decreased CASI score (0.30, 95% CI: 0.06–0.55, $P < .05$). The increases of 1 event of ODI-3% and AHI occurring per hour of sleep were significantly associated with a decreased CASI score (ODI-3%: -0.29, 95% CI: -0.53 to -0.05, $P < .05$; AHI: -0.31, 95% CI: -0.55 to -0.06, $P < .05$; respectively). None of the arousal indices in any sleep stage had significant associations with the CASI score.

Increased arousal response associated with the risk of MCI
Table 5 illustrates the associations of arousal indices between patients with and without MCI obtained using logistic regression models. An increase of 1 event of spontaneous arousal per hour of sleep was associated with a 1.12-fold elevated odds ratio (OR; 95% CI: $1.01 - 1.24$, $P < .05$) of presenting with MCI in model 1 adjusted for age, sex, BMI and a 1.16-fold elevated OR (95% CI: $1.03 - 1.30$, $P < .05$) of presenting with MCI in model 2 with additional adjustment for ODI-3%. The result was similar when the analysis was restricted to only the NREM period (model 1: OR: 1.12, 95% CI: 1.02–1.23, $P < .05$; model 2: OR: 1.15, 95% CI: $1.03 - 1.29$, $P < .05$). None of the respiratory-related arousal indices were significantly associated with MCI.

Table 1—Demographic characteristics of the participants stratified by Clinical Dementia Rating score.

Categorical Variable	Non-MCI Group (n = 31)	MCI Group (n = 37)	P
Age (y)a	68.19 ± 7.35	69.65 ± 7.71	.43
Sex (male/female)b	20/11	18/19	.19
BMI (kg/m^2)a	24.16 ± 2.84	23.46 ± 3.98	.41
Neck circumference (cm)a	36.13 ± 3.23	35.14 ± 3.08	.20
Waist circumference (cm)a	86.51 ± 9.63	85.68 ± 10.31	.73
Education (years)c	9.94 ± 4.70	9.51 ± 4.08	.57
CASI scorec	87.58 ± 7.02	78.92 ± 12.59	< .01
Long-term memory	9.77 ± 0.56	9.51 ± 1.35	.86
Short-term memory	10.16 ± 2.31	7.08 ± 3.28	< .01
Attention	6.61 ± 1.28	6.16 ± 1.3	.16
Concentration	7.90 ± 2.01	7.38 ± 2.63	.59
Orientation	17.00 ± 1.77	15.08 ± 4.09	< .05
Abstraction and judgment	9.26 ± 1.69	8.65 ± 1.92	.18
Language abilities	9.58 ± 0.81	9.35 ± 1.25	.45
Visual construction	9.97 ± 0.18	9.27 ± 1.39	< .01
Category fluency	7.00 ± 2.13	6.19 ± 2.44	.41
OSAS severity, n (%)b			.94
Normal	4 (12.90%)	5 (13.52%)	
Mild	6 (19.35%)	9 (24.32%)	
Moderate	9 (29.03%)	11 (29.73%)	
Severe	12 (38.71%)	12 (32.43%)	

Data are expressed as mean ± SD. [a]Differences between groups were assessed using Student's t test. [b]Differences between groups were assessed using the chi-square test. [c]Differences between groups were assessed using the Mann-Whitney U test. BMI = body mass index, CASI = Cognitive Abilities Screening Instrument, MCI = mild cognitive impairment, OSAS = obstructive sleep apnea syndrome.

Subgroup analysis for sex difference

More women than men were enrolled in the MCI group, and because women tend to have more arousals, this study performed a subgroup analysis for sex to identify differences between men and women in sleep parameters and cognitive assessments. **Table S1**, **Table S2**, **Table S3**, and **Table S4** in the supplemental material present the mean values and statistical test results. The minimum peripheral arterial oxygen saturation measured by pulse oximetry (SpO$_2$), ODI-3%, and AHI were significantly associated with CASI score only in men. The SpArI and SpArI$_{NREM}$ were significantly associated with an elevated risk of MCI in men; the ArI and ArI$_{NREM}$ were associated with an increased risk of MCI in model 2 in men only. None of the arousal indices were significantly associated with risk of MCI in women.

Sensitivity analysis for the dataset that excluded participants without REM sleep during PSG

Because this study compared sleep parameters in the REM and NREM stages, values were missing for REM stage variables in participants without a REM stage. Consequently, this could have caused underestimation of the event index of the NREM period because the participants who did not have REM sleep may have exhibited longer NREM sleep duration. Therefore, we performed sensitivity analyses for the dataset that excluded participants without REM sleep during PSG.

Table S5, **Table S6**, **Table S7**, **Table S8**, and **Table S9** in the supplemental material list the statistical results. Two female participants with MCI were excluded due to lack of REM sleep. Most sleep parameters demonstrated similar outcomes compared with the results of including non-REM participants. The mean ArI in the NREM stage (ArI$_{NREM}$) was significantly higher in patients with MCI than in those without MCI (P < .05). In addition, significant associations between decreased CASI score, hypopnea index, and especially hypopnea index in the non–rapid eye movement stage were observed.

DISCUSSION

Sleep-disordered breathing and related clinical symptoms, such as intermittent hypoxia, arousal response, and fragmented sleep, have a strong relationship with the pathophysiology of MCI. However, how they affect cognitive decline has remained uncertain. Therefore, we compared various sleep indices between participants with and without MCI and determined their relationships with the CASI score. Furthermore, the associations between sleep disorder indices and various arousal indices were explored and compared between participants with and without MCI.

Table 2—Comparison of sleep parameters between the participants with and without MCI.

Categorical Variable	Non-MCI Group (n = 31)	MCI Group (n = 37)	P
Sleep architecture			
Sleep efficiency (%)	72.20 ± 12.19	67.92 ± 20.18	.67
Wake (% of SPT)	22.63 ± 11.77	26.98 ± 18.51	.61
NREM (% of SPT)	69.30 ± 10.98	63.88 ± 16.28	.30
REM (% of SPT)[a]	8.09 ± 6.15	9.67 ± 5.08	.26
WASO (min)	76.24 ± 38.55	87.84 ± 56.42	.74
TST (min)	261.69 ± 45.37	247.29 ± 72.69	.76
Oximetry parameter			
Mean SpO_2 (%)	95.41 ± 1.69	95.76 ± 1.42	.59
Minimum SpO_2 (%)	83.55 ± 7.72	85.32 ± 7.75	.13
ODI-3% (events/h)	23.55 ± 16.76	22.41 ± 16.42	.83
Sleep disorder index (events/h)			
AHI	24.61 ± 17.53	22.81 ± 16.43	.73
AI	3.25 ± 3.88	6.05 ± 10.66	.80
AI_{NREM}	2.84 ± 3.46	6.02 ± 11.11	.71
AI_{REM}[a]	6.40 ± 11.99	6.27 ± 11.62	.33
HI	21.35 ± 16.87	16.76 ± 13.08	.35
HI_{NREM}	21.13 ± 17.65	16.22 ± 13.44	.38
HI_{REM}[a]	22.97 ± 20.96	22.04 ± 19.19	.45

Data are expressed as mean ± SD. Differences between groups were assessed using the Mann-Whitney *U* test. [a]Two participants with MCI did not have a REM stage during the polysomnography. AHI = apnea-hypopnea index, AI = apnea index, AI_{NREM} = apnea index in the non–rapid eye movement stage, AI_{REM} = apnea index in the rapid eye movement stage, HI = hypopnea index, HI_{NREM} = hypopnea index in the non–rapid eye movement stage, HI_{REM} = hypopnea index in the rapid eye movement stage, MCI = mild cognitive impairment, NREM = non–rapid eye movement, ODI-3% = oxygen desaturation index ≥ 3%, REM = rapid eye movement, SpO_2 = peripheral arterial oxygen saturation measured by pulse oximetry, SPT = sleep period of time, TST = total sleep time, WASO = wake time after sleep onset.

The mean values of the SpArI significantly differed between patients with and without MCI; moreover, patients with MCI had lower sleep efficiency and higher wake percentage. Sleep arousal refers to the abrupt alteration from a sleep period to partial wakefulness and the subsequent return to sleep.[27] Accordingly, frequent sleep arousals fragment the sleep cycle, affect the sleep architecture, and interrupt the metabolism of neurodegenerative biomarkers. A 2014 longitudinal study indicated that decreased sleep efficiency and frequent awakenings of > 5 minutes during sleep were associated with subsequent cognitive decline among 2822 cognitively healthy community-dwelling older men.[28] Another study suggested associations between poor self-reported sleep efficiency and higher neurodegenerative biomarker levels in the cerebral spinal fluid of 101 healthy adults.[29] Furthermore, sleep arousals may disrupt continuous sleep, indirectly interrupting neurotoxic protein removal from the brain,[30] which may increase the risk of MCI. However, no difference was noted in the RArI values in NREM or REM stages in the present study; this may be because OSAS severity and oximetry parameters were not significantly different between the groups. The SpArI in the NREM stage was significantly higher in the MCI group than in the non-MCI group. NREM sleep consolidates long-term memories and strengthens memories by promoting interactions between the hippocampus

and neocortex.[31–33] Spontaneous arousal from NREM sleep may disrupt this mechanism and cause cognitive decline. Collectively, our findings agreed with that of other studies that patients with cognitive impairment have higher sleep arousal indices and wake percentages.

Regarding the respiratory event and RArI values in this study, the approximate values of the AHI and ODI-3% were determined. The mean value of respiratory arousal induced by apnea or hypopnea was lower than the AHI. These outcomes may be explained by the observation that the majority of respiratory events were accompanied with oxygen desaturation, and a few respiratory events were accompanied with arousal termination. Previous related studies have indicated that 20%–30% of respiratory events were not terminated with a arousal response.[34,35] Another recent study recruited continuous positive airway pressure–treated patients and lowered the support level to simulate hypoxia and obstructive airflow.[36] Those outcomes indicated that the average 6.4 ± 1.1 respiratory events terminated without arousal, whereas the mean of respiratory events terminated with arousal was 9.6 ± 1.4. Collectively, the lower RArI in this current study is in accordance with previous findings.

Next, our findings indicated that the overall SpArI values and those during NREM sleep were associated with an

Table 3—Comparison of arousal indices between the participants with and without MCI.

Arousal Variable (Events/h)	Non-MCI Group (n = 31)	MCI Group (n = 37)	P
ArI	20.26 ± 9.66	23.19 ± 9.89	.11
ArI$_{NREM}$	20.30 ± 10.40	23.91 ± 10.52	.08
ArI$_{REM}$[a]	23.23 ± 25.48	19.97 ± 16.88	.45
SpArI	8.43 ± 4.48	11.94 ± 7.30	< .05
SpArI$_{NREM}$	8.56 ± 4.70	12.46 ± 8.03	< .05
SpArI$_{REM}$[a]	6.35 ± 7.13	10.18 ± 10.89	.07
RArI	10.14 ± 9.57	9.51 ± 8.99	.78
RArI$_{NREM}$	10.10 ± 9.99	9.61 ± 9.27	.84
RArI$_{REM}$[a]	10.92 ± 14.13	11.31 ± 14.63	.36
SnArI	0.30 ± 0.9	0.09 ± 0.31	.65
SnArI$_{NREM}$	0.23 ± 0.78	0.09 ± 0.34	.73
SnArI$_{REM}$[a]	1.06 ± 3.67	0.08 ± 0.34	.41
LArI	1.32 ± 1.29	1.52 ± 1.42	.66
LArI$_{NREM}$	1.35 ± 1.40	1.62 ± 1.60	.57
LArI$_{REM}$[a]	4.69 ± 21.46	0.58 ± 1.31	.22

Data are expressed as mean ± SD. Differences between groups were all assessed using the Mann-Whitney *U* test. [a]Two participants with MCI did not have a REM stage during the polysomnography. ArI = arousal index, ArI$_{NREM}$ = arousal index in the non–rapid eye movement stage, ArI$_{REM}$ = arousal index in the rapid eye movement stage, LArI = limb movement arousal index, LArI$_{NREM}$ = limb movement arousal index in the non–rapid eye movement stage, LArI$_{REM}$ = limb movement arousal index in the rapid eye movement stage, MCI = mild cognitive impairment, RArI = respiratory arousal index, RArI$_{NREM}$ = respiratory arousal index in the non–rapid eye movement stage, RArI$_{REM}$ = respiratory arousal index in the rapid eye movement stage, REM = rapid eye movement, SnArI = snore arousal index, SnArI$_{NREM}$ = snore arousal index in the non–rapid eye movement stage, SnArI$_{REM}$ = snore arousal index in the rapid eye movement stage, SpArI = spontaneous arousal index, SpArI$_{NREM}$ = spontaneous arousal index in the non–rapid eye movement stage, SpArI$_{REM}$ = spontaneous arousal index in the rapid eye movement stage.

increased risk of MCI. After adjustment for the desaturated oxygen desaturation effect (ODI-3%), the significant associations remained. This may be due to the sleep fragmentation caused by repetitive spontaneous arousals from sleep. As mentioned earlier, after the initial arousal phase, individuals often experience a lighter sleep stage or even wakefulness; this may impair memory consolidation and neurodegenerative protein metabolism. Similar observations were documented in previous studies. Lower mean sleep efficiency was significantly associated with the risk of MCI in 473 older American women.[37] A 2012 study explored the effect of sleep fragmentation on memory function decline in 24 participants and reported changes in the sleep architecture and brainwave density in the participants with MCI, which appeared to negatively affect memory consolidation.[38] Another Australian study in 2010 reported that the elevated total arousal index was related to poor nonverbal learning and problem-solving in 15 patients with MCI.[39] Regarding NREM sleep, a 2008 study concluded that after arousal from NREM sleep, the cerebral blood flow velocity declined by 15%.[40] A 2012 report noted an elevated number of arousal events in NREM and reduced sleep efficiency in 25 amnestic patients with MCI with apolipoprotein E genotyping-4 expression (ApoE-4).[41] Similarly, the arousal index was also increased in NREM sleep in 25 Italian older adults with MCI.[42] The present study also observed that an increased risk of MCI was associated with the SpArI$_{NREM}$. Furthermore, regarding the arousal effect between respiratory events and spontaneous

occurrence, the aforementioned nonsignificant difference in the RArI and its values in NREM or REM stages between the non-MCI and MCI groups may prevent us from drawing a conclusion. In other words, the similar OSAS severity and sleep disorder indices in these 2 groups may reflect similar responses of respiratory arousal. Additional studies controlling for the OSAS factor are required to compare the effects of spontaneous and respiratory arousals. Taken together, the findings imply that spontaneous sleep arousal, especially in the NREM stage, may reduce cerebral blood flow, affect memory consolidation, and increase MCI risk.

The relationships between sleep parameters and cognitive function decline were explored in this study. The CASI score was negatively associated with AHI and ODI-3% but positively associated with the minimum SpO$_2$. These observations may partially be explained by the fact that intermittent hypoxic episodes altered the structure of the hippocampus, which is involved in learning and memory. Oxidative stress may be another risk factor. A review article concluded that OSAS-induced intermittent hypoxia can elevate hypoxia-inducible factor-1α protein expression and the reactive oxygen species level in the hippocampal neurons of a rodent model. Thus, hippocampal disruption can impair both long-term potentiation and spatial memory, eventually leading to cognitive impairment in the intermittent hypoxia animal model.[43] Consistent with our findings on the interaction between chronic hypoxemia and cognitive decline, a Canadian study reported that patients with

Table 4—Associations between sleep parameters and CASI score.

Categorical Variable	Beta Coefficient (95% CI)	P
Oximetry parameter		
Mean SpO$_2$ (%)	0.08 (−0.17 to 0.33)	.52
Minimum SpO$_2$ (%)	0.30 (0.06 to 0.55)	< .05
ODI-3% (events/h)	−0.29 (−0.53 to −0.05)	< .05
Sleep disorder index (events/h)		
AHI	−0.31 (−0.55 to −0.06)	< .05
AI	−0.17 (−0.41 to 0.06)	.15
AI$_{NREM}$	−0.19 (−0.43 to 0.04)	.11
AI$_{REM}$[a]	−0.03 (−0.27 to 0.21)	.79
HI	−0.23 (−0.48 to 0.01)	.06
HI$_{NREM}$	−0.24 (−0.49 to 0.01)	.06
HI$_{REM}$[a]	−0.15 (−0.4 to 0.1)	.23
Arousal variable (events/h)		
ArI	−0.15 (−0.40 to 0.11)	.25
ArI$_{NREM}$	−0.16 (−0.41 to 0.09)	.20
ArI$_{REM}$[a]	−0.0 (−0.25 to 0.24)	.99
SpArI	−0.01 (−0.23 to 0.25)	.94
SpArI$_{NREM}$	−0.0 (−0.24 to 0.23)	.98
SpArI$_{REM}$[a]	−0.0 (−0.25 to 0.24)	.97
RArI	−0.15 (−0.40 to 0.09)	.22
RArI$_{NREM}$	−0.16 (−0.41 to 0.09)	.20
RArI$_{REM}$[a]	−0.14 (−0.39 to 0.11)	.28

Multivariable linear regression models were adjusted for age, sex, body mass index, and education years. [a]Two participants with MCI did not have a REM stage during the polysomnography. AHI = apnea-hypopnea index, AI = apnea index, AI$_{NREM}$ = apnea index in the non–rapid eye movement stage, AI$_{REM}$ = apnea index in the rapid eye movement stage, ArI = arousal index, ArI$_{NREM}$ = arousal index in the non–rapid eye movement stage, ArI$_{REM}$ = arousal index in the rapid eye movement stage, CASI = Cognitive Abilities Screening Instrument, CI = confidence interval, HI = hypopnea index, HI$_{NREM}$ = hypopnea index in the non–rapid eye movement stage, HI$_{REM}$ = hypopnea index in the rapid eye movement stage, MCI = mild cognitive impairment, ODI-3% = oxygen desaturation index ≥ 3%, RArI = respiratory arousal index, RArI$_{NREM}$ = respiratory arousal index in the non–rapid eye movement stage, RArI$_{REM}$ = respiratory arousal index in the rapid eye movement stage, REM = rapid eye movement, SpArI = spontaneous arousal index, SpArI$_{NREM}$ = spontaneous arousal index in the non–rapid eye movement stage, SpArI$_{REM}$ = spontaneous arousal index in the rapid eye movement stage, SpO$_2$ = peripheral arterial oxygen saturation measured by pulse oximetry.

MCI with a higher AHI and those with nocturnal hypoxemia had significantly lower memory and information processing speed.[44] Another study documented that functional connectivity, which was positively correlated with CASI scores, was negatively associated with the AHI in a south Taiwan population.[45] Overall, elevated AHI and hypoxemia-related parameters were considered the risk factors for MCI in patients with sleep-disordered breathing.

This study had some limitations. First, amyloid or tau positron emission tomography images and cerebrospinal fluid samples were not available for our participants, precluding a comprehensive assessment of neurodegenerative biomarkers. We were unable to investigate the bidirectional effect between hyperphosphorylation in the ascending arousal system and tau or amyloid pathology. These data may provide robust evidence for associations among sleep-disordered breathing, arousal responses, and cognitive impairment. Second, the brain images of recruited participants were not collected for analysis,

although we excluded participants with central nervous system lesions. Detailed brain magnetic resonance imaging data may provide insights into alterations in columns of the targeted brain region, which may have implications for the associations among MCI, hypoxia, and sleep arousal response. Third, genetic factors, especially ApoE-4, enhance the risk of cognitive decline.[46] However, we did not collect blood samples to determine gene expression data. Furthermore, this was a single-center study with all participants being Han Taiwanese; therefore, our results may not be generalizable to other ethnicities. Additional multicenter studies that include multiple ethnicities are required. Moreover, sleep parameters from in-laboratory PSG may be affected by several other factors not measured in the present study, including environmental factors, the complexity of the examination equipment, and the first-night effect. To mitigate these effects and comprehensively understand sleep conditions, repetitive in-laboratory PSG or consecutive home sleep testing should be considered. Moreover, sleep arousal has

Table 5—Associations (ORs) of arousal indices between the participants with and without MCI.

Arousal Variable (Arousals/h)	Crude OR (95% CI)[a]	Model 1 (95% CI)[b]	Model 2 (95% CI)[c]
ArI	1.03 (0.98–1.09)	1.06 (1.00–1.13)	1.08 (1.00–1.16)
ArI$_{NREM}$	1.04 (0.99–1.09)	1.06 (1.00–1.12)	1.08 (1.01–1.15)
ArI$_{REM}$[d]	0.99 (0.97–1.02)	0.99 (0.97–1.02)	0.99 (0.97–1.02)
SpArI	1.12 (1.01–1.23)†	1.12 (1.01–1.24)†	1.16 (1.03–1.30)†
SpArI$_{NREM}$	1.11 (1.01–1.23)†	1.12 (1.02–1.23)†	1.15 (1.03–1.29)†
SpArI$_{REM}$[d]	1.05 (0.99–1.11)	1.06 (0.99–1.12)	1.06 (0.99–1.13)
RarI	0.99 (0.94 to 1.05)	1.01 (0.95 to 1.06)	0.99 (0.90 to 1.10)
RArI$_{NREM}$	1.00 (0.95 to 1.05)	1.01 (0.95 to 1.06)	1.00 (0.90 to 1.10)
RArI$_{REM}$[d]	0.99 (0.95 to 1.03)	1.00 (0.96 to 1.04)	0.99 (0.95 to 1.04)

†$P < .05$. [a]Simple logistic regression models. [b]Model 1: adjusted for age, sex, body mass index. [c]Model 2: adjusted for age, sex, body mass index, and ODI-3%. [d]Two participants with MCI did not have a REM stage during the polysomnography. ArI = arousal index, ArI$_{NREM}$ = arousal index in the non–rapid eye movement stage, ArI$_{REM}$ = arousal index in the rapid eye movement stage, CI = confidence interval, MCI = mild cognitive impairment, ODI-3% = oxygen desaturation index ≥ 3%, OR = odds ratio, RArI = respiratory arousal index, RArI$_{NREM}$ = respiratory arousal index in the non–rapid eye movement stage, RArI$_{REM}$ = respiratory arousal index in the rapid eye movement stage, REM = rapid eye movement, SpArI = spontaneous arousal index, SpArI$_{NREM}$ = spontaneous arousal index in the non–rapid eye movement stage, SpArI$_{REM}$ = spontaneous arousal index in the rapid eye movement stage.

been associated with the variability of the heart rate and blood pressure.[47] Investigating the relationships between these hemodynamic parameters and different arousal types may provide further understanding of the effect of arousal-induced heart-brain interaction on MCI development. Therefore, future work should conduct such an investigation. Furthermore, various factors may alter the sleep architecture of PSG, such as long-term sleep deprivation; daytime naps; daytime physical activity; usage of alcohol, caffeine, or tobacco; and medications (eg, hypnotics or antidepressants). The lack of this background information limits the exploration of relationships between PSG parameters and cognitive assessment outcomes. The number of short awakening events without arousal scoring, because of the insufficient arousal duration (< 3 seconds) or the lack of steady sleep preceding the event (< 10 seconds), was not calculated; however, other parameters were considered for evaluating the awakening time (eg, wake time after sleep onset, total sleep time, and sleep efficiency). This factor may also affect cognitive function and should be considered in future work. Finally, this study analyzed random one-night PSG outcomes. Because neurodegeneration is a long-term process,[48] a longitudinal study with continuous follow-up (eg, annually) for PSG and cognitive assessment is essential for investigating the causal relationships among sleep arousal, hypoxemia, and cognitive function. Therefore, further studies that include multiday sleep parameters, regular follow-ups, biomarkers of neurodegenerative disorder and detailed brain images, and participants from various ethnicities are required to provide robust evidence of the effect of sleep parameters on cognitive function.

CONCLUSIONS

By using a dataset on sleep parameters and cognitive assessments in a northern Taiwan population, we found the CASI score had positive associations with minimum SpO$_2$ and negative associations with the AHI and ODI-3%. Sleep-disordered breathing and intermitted hypoxia were related to cognitive dysfunction. Moreover, this study demonstrated correlations between overall SpArI values and those during NREM sleep and risk of MCI. Patients with MCI had significantly higher values of the SpArI and SpArI$_{NREM}$. These outcomes imply that the spontaneous arousal response, especially when occurring in the NREM stage, was associated with global brain function and the risk of MCI. However, to confirm the causality, a further longitudinal study is required.

ABBREVIATIONS

AHI, apnea-hypopnea index
ArI, arousal index
ArI$_{NREM}$, arousal index in the non–rapid eye movement stage
BMI, body mass index
CASI, Cognitive Abilities Screening Instrument
CDR, Clinical Dementia Rating
CI, confidence interval
MCI, mild cognitive impairment
NREM, non–rapid eye movement
ODI-3%, oxygen desaturation index ≥ 3%
OR, odds ratio
OSAS, obstructive sleep apnea syndrome
PSG, polysomnography
RArI, respiratory arousal index
REM, rapid eye movement
SpArI, spontaneous arousal index
SpArI$_{NREM}$, spontaneous arousal index in the non–rapid eye movement stage
SpO$_2$, peripheral arterial oxygen saturation measured by pulse oximetry

REFERENCES

1. Pessoa RMP, Bomfim AJL, Ferreira BLC, Chagas MHN. Diagnostic criteria and prevalence of mild cognitive impairment in older adults living in the community: a systematic review and meta-analysis. *Arch Clin Psychiatry Sao Paulo.* 2019;46(3): 72–79.

2. Dotson VM, Beydoun MA, Zonderman AB. Recurrent depressive symptoms and the incidence of dementia and mild cognitive impairment. *Neurology.* 2010;75(1):27–34.

3. Luchsinger JA, Reitz C, Patel B, Tang M-X, Manly JJ, Mayeux R. Relation of diabetes to mild cognitive impairment. *Arch Neurol.* 2007;64(4):570–575.

4. Reitz C, Tang M-X, Manly J, Mayeux R, Luchsinger JA. Hypertension and the risk of mild cognitive impairment. *Arch Neurol.* 2007;64(12):1734–1740.

5. Bombois S, Derambure P, Pasquier F, Monaca C. Sleep disorders in aging and dementia. *J Nutr Health Aging.* 2010;14(3):212–217.

6. Leng Y, McEvoy CT, Allen IE, Yaffe K. Association of sleep-disordered breathing with cognitive function and risk of cognitive impairment: a systematic review and meta-analysis. *JAMA Neurol.* 2017;74(10):1237–1245.

7. Gosselin N, Baril A-A, Osorio RS, Kaminska M, Carrier J. Obstructive sleep apnea and the risk of cognitive decline in older adults. *Am J Respir Crit Care Med.* 2019; 199(2):142–148.

8. Engleman H, Joffe D. Neuropsychological function in obstructive sleep apnoea. *Sleep Med Rev.* 1999;3(1):59–78.

9. Kielb SA, Ancoli-Israel S, Rebok GW, Spira AP. Cognition in obstructive sleep apnea-hypopnea syndrome (OSAS): current clinical knowledge and the impact of treatment. *Neuromolecular Med.* 2012;14(3):180–193.

10. Findley LJ, Barth JT, Powers DC, Wilhoit SC, Boyd DG, Suratt PM. Cognitive impairment in patients with obstructive sleep apnea and associated hypoxemia. *Chest.* 1986;90(5):686–690.

11. Yaffe K, Laffan AM, Harrison SL, et al. Sleep-disordered breathing, hypoxia, and risk of mild cognitive impairment and dementia in older women. *JAMA.* 2011; 306(6):613–619.

12. Zhou L, Chen P, Peng Y, Ouyang R. Role of oxidative stress in the neurocognitive dysfunction of obstructive sleep apnea syndrome. *Oxid Med Cell Long.* 2016; 2016:9626831.

13. Djonlagic I, Saboisky J, Carusona A, Stickgold R, Malhotra A. Increased sleep fragmentation leads to impaired off-line consolidation of motor memories in humans. *PLoS One.* 2012;7(3):e34106.

14. Xie L, Kang H, Xu Q, et al. Sleep drives metabolite clearance from the adult brain. *Science.* 2013;342(6156):373–377.

15. Horner RL, Sanford LD, Pack AI, Morrison AR. Activation of a distinct arousal state immediately after spontaneous awakening from sleep. *Brain Res.* 1997; 778(1):127–134.

16. Wilckens KA, Woo SG, Kirk AR, Erickson KI, Wheeler ME. Role of sleep continuity and total sleep time in executive function across the adult lifespan. *Psychol Aging.* 2014;29(3):658–665.

17. Abbott SM, Videnovic A. Chronic sleep disturbance and neural injury: links to neurodegenerative disease. *Nat Sci Sleep.* 2016;8:55–61.

18. Wang C, Holtzman DM. Bidirectional relationship between sleep and Alzheimer's disease: role of amyloid, tau, and other factors. *Neuropsychopharmacology.* 2020; 45(1):104–120.

19. Tartar JL, Ward CP, McKenna JT, et al. Hippocampal synaptic plasticity and spatial learning are impaired in a rat model of sleep fragmentation. *Eur J Neurosci.* 2006; 23(10):2739–2748.

20. Gaeta AM, Benítez ID, Jorge C, et al. Prevalence of obstructive sleep apnea in Alzheimer's disease patients. *J Neurol.* 2020;267(4):1012–1022.

21. Fewell JE. The effect of short-term sleep fragmentation produced by intense auditory stimuli on the arousal response to upper airway obstruction in lambs. *J Dev Physiol.* 1987;9(5):409–417.

22. Bliwise DL, Trotti LM, Yesavage JA, Rye DB. Periodic leg movements in sleep in elderly patients with Parkinsonism and Alzheimer's disease. *Eur J Neurol.* 2012; 19(6):918–923.

23. Berry RB, Brooks R, Gamaldo C, et al. AASM scoring manual updates for 2017 (version 2.4) *J Clin Sleep Med.* 2017;13(5):665–666.

24. Quan SF, Gillin JC, Littner MR, Shepard JW; Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. *Sleep.* 1999;22(5):667–689.

25. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology.* 1993;43(11):2412–2414.

26. Lin K-N, Liu H-C. Clinical dementia rating (CDR), Chinese version. *Acta Neurol Taiwan.* 2003;12(3):154–165.

27. EEG arousals: scoring rules and examples: a preliminary report from the Sleep Disorders Atlas Task Force of the American Sleep Disorders Association. *Sleep.* 1992;15(2):173–184.

28. Blackwell T, Yaffe K, Laffan A, et al; Osteoporotic Fractures in Men (MrOS) Study Group. Associations of objectively and subjectively measured sleep quality with subsequent cognitive decline in older community-dwelling men: the MrOS sleep study. *Sleep.* 2014;37(4):655–663.

29. Sprecher KE, Koscik RL, Carlsson CM, et al. Poor sleep is associated with CSF biomarkers of amyloid pathology in cognitively normal adults. *Neurology.* 2017; 89(5):445–453.

30. Cedernaes J, Osorio RS, Varga AW, Kam K, Schiöth HB, Benedict C. Candidate mechanisms underlying the association between sleep-wake disruptions and Alzheimer's disease. *Sleep Med Rev.* 2017;31:102–111.

31. Diekelmann S, Born J. The memory function of sleep. *Nat Rev Neurosci.* 2010; 11(2):114–126.

32. Schreiner T, Rasch B. Boosting vocabulary learning by verbal cueing during sleep. *Cereb Cortex.* 2015;25(11):4169–4179.

33. Miyamoto D, Hirai D, Fung CC, et al. Top-down cortical input during NREM sleep consolidates perceptual memory. *Science.* 2016;352(6291): 1315–1318.

34. Dingli K, Fietze I, Assimakopoulos T, Quispe-Bravo S, Witt C, Douglas NJ. Arousability in sleep apnoea/hypopnoea syndrome patients. *Eur Respir J.* 2002; 20(3):733–740.

35. Younes M. Role of arousals in the pathogenesis of obstructive sleep apnea. *Am J Respir Crit Care Med.* 2004;169(5):623–633.

36. Jordan AS, Eckert DJ, Wellman A, Trinder JA, Malhotra A, White DP. Termination of respiratory events with and without cortical arousal in obstructive sleep apnea. *Am J Respir Crit Care Med.* 2011;184(10):1183–1191.

37. Diem SJ, Blackwell TL, Stone KL, et al. Measures of sleep–wake patterns and risk of mild cognitive impairment or dementia in older women. *Am J Geriatr Psychiatry.* 2016;24(3):248–258.

38. Westerberg CE, Mander BA, Florczak SM, et al. Concurrent impairments in sleep and memory in amnestic mild cognitive impairment. *J Int Neuropsychol Soc.* 2012; 18(3):490–500.

39. Naismith SL, Rogers NL, Hickie IB, Mackenzie J, Norrie LM, Lewis SJ. Sleep well, think well: sleep-wake disturbance in mild cognitive impairment. *J Geriatr Psychiatry Neurol.* 2010;23(2):123–130.

40. Bangash MF, Xie A, Skatrud JB, Reichmuth KJ, Barczi SR, Morgan BJ. Cerebrovascular response to arousal from NREM and REM sleep. *Sleep.* 2008; 31(3):321–327.

41. Hita-Yañez E, Atienza M, Gil-Neciga E, Cantero JL. Disturbed sleep patterns in elders with mild cognitive impairment: the role of memory decline and ApoE ε4 genotype. *Curr Alzheimer Res.* 2012;9(3):290–297.

42. Maestri M, Carnicelli L, Tognoni G, et al. Non-rapid eye movement sleep instability in mild cognitive impairment: a pilot study. Sleep Med. 2015;16(9): 1139–1145.

43. Prabhakar NR, Peng YJ, Nanduri J. Hypoxia-inducible factors and obstructive sleep apnea. *J Clin Invest.* 2020;130(10):5042–5051.

44. Beaudin AE, Raneri JK, Ayas NT, et al. Cognitive function in a sleep clinic cohort of patients with obstructive sleep apnea. *Ann Am Thorac Soc.* 2020; 18(5).

45. Chang YT, Chen YC, Chen YL, et al. Functional connectivity in default mode network correlates with severity of hypoxemia in obstructive sleep apnea. *Brain Behav.* 2020;10(12):e01889.

46. Liu DS, Pan XD, Zhang J, et al. APOE4 enhances age-dependent decline in cognitive function by down-regulating an NMDA receptor pathway in EFAD-Tg mice. *Mol Neurodegener.* 2015;10(7).

47. Blasi A, Jo J, Valladares E, Morgan BJ, Skatrud JB, Khoo MC. Cardiovascular variability after arousal from sleep: time-varying spectral analysis. *J Appl Physiol 1985.* 2003;95(4):1394–1404.

48. Sperling R, Mormino E, Johnson K. The evolution of preclinical Alzheimer's disease: implications for prevention trials. *Neuron.* 2014;84(3):608–622.

ACKNOWLEDGMENTS

SUBMISSION & CORRESPONDENCE INFORMATION

Address correspondence to: Wen-Te Liu, MD, PhD, School of Respiratory Therapy, College of Medicine, Taipei Medical University, Taipei, Taiwan, No. 250, Wuxing Street, Taipei City 110, Taiwan; Tel: +886-2-2736-1661, Fax: +886-2-2739-1143; Email: lion5835@gmail.com; and Yi-Chun Kuan, MD, Department of Neurology, School of Medicine, College of Medicine, Taipei Medical University, New Taipei City, Taiwan, No. 291, Zhongzheng Rd., Zhonghe District, New Taipei City, 23561, Taiwan; Tel: +886-2-2249-0088, Fax: +886-2-2249-0088; Email: Yckuang2@gmail.com

DISCLOSURE STATEMENT