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A multidimensional approach to sleep health in multiple sclerosis

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Abstract

Background—Although sleep disturbances are common among people with Multiple Sclerosis (PwMS), understanding of their impact has been stymied by limitations in approaches to sleep measurement within this population. The aim of this study was to comprehensively phenotype sleep patterns in PwMS through application of an emerging seven-domain framework that includes sleep duration, continuity, timing, quality, rhythmicity, regularity, and sleepiness.

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Methods—Sleep domains were estimated from wrist-worn accelerometry, Epworth Sleepiness Scale and Pittsburgh Sleep Quality Index responses. Extreme sleep values within each domain were constructed using previously published guidelines. A composite score of extreme values was calculated for each participant. Associations between sleep domains and severity of MS symptoms were explored (pain, fatigue, depressive symptoms, and cognitive dysfunction).

Results—Among n=49 participants, median total sleep time was 456.3 minutes. Median time spent awake after sleep onset was 37 minutes. Sleepiness, abnormal sleep timing, and poor sleep quality affected 33%, 35%, and 45% of participants, respectively. Seventy-six percent had ≥2 sleep domains in extreme ranges. PwMS had longer sleep duration and decreased sleep regularity compared to a non-MS historical cohort of older men. Greater daytime sleepiness, poorer sleep quality, and higher composite sleep health score were associated with more depressive symptoms, and lower sleep rhythmicity was associated with higher fatigue. Associations were observed between measures of cognitive function and sleep fragmentation, duration, quality, rhythmicity, and composite score.

Conclusion—Application of a seven-domain sleep health framework that captures the dynamic and multifaceted aspects of sleep is feasible in PwMS, and offers potential for an improved understanding of the scope and impact of sleep disturbances in PwMS.

Keywords

Multiple Sclerosis; Sleep; Actigraphy; Cognitive Function; Pain; Fatigue

Introduction

Sleep disturbances affect up to 60% of persons with Multiple Sclerosis (PwMS)[1,2] and are linked to several debilitating MS symptoms, including pain, fatigue, depressive symptoms, and cognitive dysfunction.[3–6] Most research on sleep and MS to date has focused on associations between MS symptoms and only one or a few sleep measures in isolation (e.g. duration, quality), often relying on single-point assessments, such as polysomnography, or average sleep metrics captured by actigraphy or surveys. Such approaches do not fully account for sleep rhythmicity, timing, and regularity. Consequently, effects of variability, or the possibility of a combined effect of multiple dimensions of sleep on symptoms, remain underexplored in PwMS.

Building on a call for sleep to be recognized as multidimensional[7], Wallace et al. developed a seven-domain „sleep health" framework to more comprehensively capture and phenotype sleep, including dynamic changes.[8] Domains include: 1) duration (total amount of sleep), 2) continuity (the extent to which sleep is continuous or fragmented), 3) timing (the time that sleep occurs within the 24-hour day), 4) regularity (consistency of the timing of sleep), 5) rhythmicity (strength of the sleep-wake pattern), 6) daytime sleepiness (ability to maintain attentive wakefulness), and 7) quality (subjective appraisal of sleep).[7,8] Persons with Multiple Sclerosis – a population disproportionately affected by sleep disturbances – have yet to be evaluated under this framework.

A unified multidimensional sleep metric could offer new opportunities for consistent and in-depth evaluation of sleep in PwMS. The primary objectives of this study were to provide comprehensive characterization of sleep health among a sample of PwMS, and to quantify the frequency of extreme values of each sleep domain. We also explored associations between sleep characteristics (in isolation and through a composite score of extreme values) using this framework and severity of MS symptoms (pain, fatigue, depressive symptoms, and cognitive dysfunction).

Methods

Procedures were approved by the University of Michigan Institutional Review Board and informed consent was obtained from all participants. Data were extracted from a 2014 study that examined associations between polysomnography-based measures of sleep and cognitive function in PwMS.[6] Inclusion criteria have been described previously.[6] Briefly, patients who raised questions about their sleep or cognition during routine neurology visits were invited to participate. Severe cognitive impairment, severe visual/hearing loss, severe immobility, or severe depression (≥19 on the Patient Health Questionnaire-9) [9] that might negatively impact study participation were exclusionary conditions. The parent study evaluated the relationship between sleep disordered breathing and cognitive impairment, therefore participants who endorsed adherent use of positive airway pressure therapy (≥4 hours/night, most nights/ week) were excluded.

Measures

Demographics and information regarding disease duration, disease modifying therapy, and MS subtype were collected at a baseline interview (corroborated by medical chart review). Sleep and symptom questionnaires were also completed at this time and physical disability was assessed by an MS specialist (TJB) using the Expanded Disability Status Scale (EDSS). At the end of the baseline interview, participants were provided with an accelerometer to wear on their wrist for at least seven consecutive nights. Cognitive testing was performed on the same day as the baseline interview. For participants who could not complete cognitive testing at this time, testing was completed as soon as possible (generally within 7–10 days).

Sleep

Self-reported measures: Subjective sleepiness was assessed with the Epworth Sleepiness Scale (ESS).[10] This instrument asks respondents to rate their likelihood of falling asleep in eight situations, with each response scored on a 4-point scale (0–3). A total score was derived by summing item scores (total range 0–24, higher scores indicating greater daytime sleepiness and >10 indicating excessive daytime sleepiness).[10] Sleep quality was evaluated with an item from the 19-item Pittsburgh Sleep Quality Index (PSQI)[11]. This item asks respondents to rate their sleep quality overall during the past month (four response options: very good, fairly good, fairly bad, or very bad).

Actigraphy: Actigraphy, with use of US Food and Drug administration cleared accelerometer devices and associated software, is an accepted method to track sleep over days to weeks for research and clinical purposes.[12,13] Actigraphy is based on the premise

that individuals move more during wakefulness than sleep. Actigraphy output has been verified against gold-standard polysomnography.[12] Participants were asked to continuously wear a wrist-worn accelerometer (Actiwatch 2.0 Philips Respironics, Murrysville, PA) on their non-dominant wrist for a minimum of seven days, except during activities that involved water submersion. Activity data was collected in 30-second epochs. To identify rest intervals, participants were instructed to press an event button at lights out and again when they woke in the morning. Rest intervals were checked against a sleep diary completed by participants. In the case of discordant values (e.g., >30-minute discrepancy in start/end times), intervals were adjusted to reflect sleep diary times. Data downloaded from accelerometers was analyzed with Actiware software (v6.0.9). The following summary statistics were exported per 24-hour period: rest interval duration (minutes), total sleep time (TST) (minutes), sleep onset latency (minutes), time awake after initial sleep onset (WASO) (minutes), and sleep efficiency ([total sleep duration/rest interval duration]*100) (%). Mean values for each parameter were calculated over actigraphic recording days for each participant.

Sleep Domains: Seven sleep domains were defined as: 1) duration (actigraphy-derived mean TST in minutes); 2) continuity (actigraphy-derived mean WASO in minutes); 3) timing (actigraphy-derived mean sleep midpoint clock time); 4) regularity (standard deviation of actigraphy-derived time of waking in hours); 5) rhythmicity (probability of an individual being in the same state at any two time-points 24-hours apart); 6) sleepiness/alertness, (ESS score); 7) quality (PSQI sleep quality item). These followed procedures described by Wallace et al.[8], with the exception of rhythmicity, which was calculated using the approach from Phillips et al.[14]

'Extreme' sleep characteristics also followed Wallace et al. *A priori* cut-points were used for daytime sleepiness (ESS>10), sleep quality (fairly or very bad), and timing (sleep midpoint outside of 2:01–04:00AM). Distributions of values within the current sample were used to identify extremes of sleep duration (lowest and highest sixth, informed by U-shaped associations between sleep and various health outcomes[15]), continuity (highest third of WASO values), rhythmicity (lowest third), and regularity (highest third). For each individual, the number of sleep domains in extreme categories were summed for a composite sleep score.

Pain

Pain intensity was assessed using the sum of three-items from the Pain Intensity short form 3a of the Patient Reported Outcomes Measurement Information System-29 (PROMIS-29) Health Profile[16]: "How intense was your pain at its worst?"; "How intense was your average pain?"; "What is your level of pain right now?" (response options: 1=no pain; 5=very severe pain, possible range 3–15). Pain interference was assessed using the Pain Interference Short Form of PROMIS-29.[16,17] Participants rated level of pain interference pertaining to four functions over the past seven days (difficulty taking in new information because of pain; pain interfering with the ability to concentrate; pain interfering with the ability to remember things; and pain making it difficult to fall asleep). Item responses ranged from 1: "Not at

all", to 5: "Very much"). This instrument has been validated for PwMS[18] with excellent internal consistency.[19]

Fatigue

Fatigue was assessed with the Fatigue Severity Scale (FSS).[20] This instrument includes nine statements about fatigue during the past week (e.g., My fatigue prevents sustained physical functioning), with seven ordinal response options (1=completely disagree; 7=completely agree). Responses are summed and can be averaged to a mean score that ranges between 1–7. Higher scores reflect greater fatigue.

Depressive symptoms

Depressive symptoms were measured with The Patient Health Questionnaire-9 (PHQ-9).[21] Respondents rate how often they have experienced nine depressive symptoms over a two-week period (0: not at all to 3: nearly every day) with responses summed to derive a total score (total range 0–27). This instrument is valid and reliable for use with PwMS.[22]

Cognitive function

Performance in seven cognitive domains was assessed with the Minimal Assessment of Cognitive Function in MS (MACFIMS) Battery.[23] Tests included the California Verbal Learning Test-II (CVLT-II), Paced Auditory Serial Addition Test (PASAT), Symbol Digit Modalities Test (SDMT), Brief Visuospatial Memory Test – Revised (BVMT-R), Judgement of Line Orientation Test (JLO), Controlled Oral Word Association Test (COWAT), and the Free Sort Test from the Delis-Kaplan Executive Function System (D-KEFS). CVLT-II assesses verbal memory, learning and executive function. Three measures were examined: CVLT-II Total (age-based standard scale score for verbal recall over five trials); CVLT-II First (age-based standard scale score for verbal recall after the first trial); and CVLT-II Discriminability Index (ability to identify target words compared to distractor words). Higher scores indicate better performance. PASAT assesses working memory, attention, processing speed and calculation ability. Participants listen to a series of audiotaped digits (every 2 or 3 seconds) and must add each consecutive digit to the preceding one. Scores reflect correct responses at each rate (PASAT-2 or PASAT-3). SDMT assesses psychomotor speed, attention and working memory. Participants use a reference key to pair numbers to a set of nine associated symbols as quickly as possible in 90 seconds. BVMT-R assesses spatial learning and memory using a drawing task that requires participants to accurately reproduce six geometric figures from memory (after viewing stimuli for 10 seconds) over three learning trials. Delayed free recall of the figures is tested after 25 minutes. Scores include BVMT-Total (age-based standard T score for total recall over three trials); and BVMT-Delayed (age-based standard T score for free recall after delay). JLO is an age- and sex-adjusted test of visuospatial skills and judgement. Participants visually match two angled lines to lines in a semicircle of 11 radii, over 30 trials. COWAT is a test of verbal fluency, requiring participants to produce as many words that begin with F, A, and S as possible over three 60-second trials (total score=total number of words produced across three trials). The Free Sort Test assesses executive functioning through two trials of sorting six cards into two groups of three cards that are similar, and then describing how the sort was completed. An age-based scaled-score reflect total correct sorts across both trials.

Statistical Methods

Summary statistics were calculated for all variables (mean/standard deviation, median/interquartile range, or number/percentage for categorical variables). Linear regression was used to estimate associations between sleep and symptom severities. All symptom variables were treated as continuous in linear regression models. All decisions regarding categorization and reference group selection for sleep variables are described in the „Sleep Domains" section of the Methods and/or in Table 3. The non-extreme group were used as the reference group for all sleep parameters to facilitate consistent interpretation.

Results

Of 57 participants recruited to the parent study[6], those with acceptable actigraphy recordings without technical malfunction or data loss (n=49) were included (mean age 47.6 (SD 10.0), 61% female). MS disease duration ranged from 1–33 years (median 8). Thirty-three participants had relapsing-remitting MS (67%), 11 had secondary progressive MS (23%), and 5 had primary progressive MS (10%). Fifty-five percent were on disease modifying therapy and median EDSS score was 3.0.

Sleep

Descriptive statistics for sleep domains are presented in Table 1. Participants had a median of eight actigraphy recording nights (min-max=7–11). Sleep parameters were averaged over the recording duration for each participant. Aggregate descriptive statistics are reported here.

Median average daily TST was 456.31 minutes (7 hours 36 minutes) and median average WASO was 37 minutes. The average nightly sleep midpoint fell between 2:01am and 4:00am for 65% of the group. Thirty-three percent had pathological daytime sleepiness (ESS>10), and 45% had poor sleep quality (fairly or very bad self-reported sleep quality over the past month). Regarding rhythmicity, median probability of being in same state at any two time points 24 hours apart was 0.72. For sleep regularity, median standard deviation of actigraphy-based wake time was 1.02 hours. Overall, 76% had at least two sleep domains that fell in extreme ranges.

MS symptoms and sleep

Descriptive statistics for pain, fatigue, and depressive symptoms are presented in Table 2; associations with sleep domains are presented in Table 3. Daytime sleepiness was associated with depressive symptom severity. Having an ESS score >10 was associated with a 3.2-point higher score on PHQ-9 compared to ESS score ≤10 (p=0.04). Depressive symptoms were also associated with sleep quality. Those who reported poor quality sleep scored on average, 2.84 points higher on PHQ-9 compared to those with good quality sleep (p=0.05). Although no actigraphy-measured sleep variables in isolation were associated with PHQ-9, an association with the composite score was noted. Each additional „extreme" sleep characteristic was associated with a 1.20 higher PHQ-9 score (p=0.01). This association was not significant if subjective measures (ESS and sleep quality) were excluded from the composite sleep score (B=0.83, p=0.14).

The most extreme category for sleep rhythmicity was associated with higher FSS score (B=1.17, p=0.01). The association between composite sleep score and fatigue was not significant. No significant associations were observed between sleep domains (in isolation or composite) and pain variables.

Cognitive function and sleep

Descriptive statistics for cognitive function are presented in Table 2, and their association with sleep domains in Supplementary Tables S1-S3. No significant associations were identified between CVLT-II or PASAT scores and sleep domains (in isolation or composite). For JLO, the most extreme third for sleep continuity (greater sleep fragmentation) was associated with a 2.58 lower score (p=0.02). Higher composite sleep score was also associated with a lower JLO score (B=−0.82, p=0.02). There were no statistically significant associations between sleep variables and SDMT or BVMT total scores. However, contrary to expectations, short or long sleep duration (compared to medium) was associated with a higher BVMT-delayed score, and poor sleep quality was associated with higher COWAT score (p=0.04). There was a positive association between Free Sort Test performance and sleep rhythmicity; being in the lowest third associated with a 1.66 lower score (p=0.02). A higher composite sleep score was also associated with a lower Free Sort Test score (B=−0.42, p=0.048).

Discussion

This study is the first to apply an emerging seven-domain sleep framework to comprehensively phenotype sleep in PwMS. Through more in-depth assessment of the distribution of sleep duration, continuity, timing, quality, rhythmicity, regularity and sleepiness, we found that excessive daytime sleepiness (33%), abnormal sleep timing (35%), and poor sleep quality (45%) were common. Additionally, our sample had longer sleep duration and decreased sleep regularity in comparison to a cohort of older adult males without MS (median sleep duration 456.31min versus 391.00min; standard deviation of wake time 1.02hours versus 0.57 hours).[8] A composite sleep score allowed us to quantify the frequency of sleep disturbance across multiple domains and explore new relationships with MS symptoms.

These findings lay the foundation for a more complete understanding of the manifestations and impact of sleep disturbances in PwMS. Sleep duration, typically assessed cross-sectionally by self-report, has arguably been the most frequently relied upon measure of sleep, while the presence/absence of a clinical disorder (chronic insomnia or restless legs syndrome) has typically served as a marker of disturbed sleep.[7] Although relevant, use of isolated sleep parameters is unlikely to reveal the true impact or consequences of suboptimal sleep in a given population. Indeed, early work has already linked poor sleep health, defined by a multi-domain composite score, to mortality[8], obesity[24], and psychological distress[24,25] in non-MS populations. Conversely, better sleep health has been associated with greater physical activity.[26] Despite these intriguing findings, adoption of more systematic sleep evaluations in PwMS has yet to gain traction. Consequently, sufficient understanding of

the role of sleep health in chronic disease remains incomplete; particularly in MS, where cognitive issues, pain, and fatigue - symptoms closely linked to sleep - are common.

More systematic sleep assessments under this framework hold the potential to inform interventional research for MS symptoms under a more unified framework, building on important MS-sleep discoveries from the past decade. For example, studies of polysomnography in PwMS have identified compelling associations between poor sleep efficiency, sleep fragmentation, and higher sleep apnea severity.[27–29] Higher sleep efficiency is associated with better performance on tests of processing speed and executive function[5], while reduced sleep efficiency is associated with fatigue in PwMS.[29] Obstructive sleep apnea (OSA) severity and nocturnal arousals have been linked to worse visual memory, verbal memory, and executive functioning.[6] These findings have laid important groundwork regarding the link between sleep and MS symptoms that warrant further study with use of consistent and comprehensive approaches.

Although polysomnography is considered the gold-standard for objective sleep measurement, the associated cost and burden limits longitudinal data collection in the natural environment and is impractical for >1–2 nights use. Application of a seven-domain framework highlights the value of “in the wild” sleep assessments using actigraphy as feasible and cost-effective. Although actigraphy-measured night-to-night variability in sleep duration (in combination with self-reported sleep quality), has been associated with greater fatigue and anxiety[30], assessment of sleep regularity and rhythmicity using this tool have yet to receive due attention in MS.

The exploratory study of sleep domains and MS symptoms in our sample deserve comment as significant associations between self-reported sleep disturbance and pain intensity[31], pain interference, and depressive symptoms have been reported previously.[32–34] Due to the small sample size, our ability to identify associations between sleep and symptom variables could have been underpowered. This would explain why previously reported associations (e.g., between sleep and pain) were not replicated in our cohort. However, due to power issues, observed statistically significant effects may also be spurious or over-estimates of a true effect (e.g., the unexpected direction of associations between sleep variables and measures of cognitive function). To avoid selective reporting, we have presented all analyses for comparison with future studies. Although the present study was not designed or powered to detect significant relationships between cognitive function and sleep domains, the association between visual-spatial function and sleep continuity and duration is noteworthy and warrants future attention. The association between being in the extreme category for sleep rhythmicity and higher levels of fatigue also merits further study, as sleep rhythmicity could serve as a potential sleep-based target to treat fatigue in MS.

Our findings suggest that the qualitative value of each individual sleep domain holds more clinical relevance than the summed composite score. For example, being in an extreme category for one/two sleep domains may drive associations between composite score and symptom severity. We observed such a scenario in which two subjective sleep measures (quality and daytime sleepiness) but no actigraphic measures of sleep were associated with depressive symptom severity. In this case, the subjective measures were

sufficient to drive an association between composite sleep health score and depressive symptom severity. This finding may be attributable to subjective sleep variables (poor sleep quality and daytime sleepiness) impacting on depressive symptom severity. However, it is also possible that the association reflects the subjective nature of the dependent and independent variables. Although Wallace et al. have argued that if appreciated as "a single multidimensional construct, rather than a series of separate characteristics, [it] could provide a more comprehensive understanding of its predictive ability"[35], we believe the framework may be best used as a tool to encourage multidimensional sleep assessment that extends beyond familiar measures of duration and quality.

Study strengths include rich sleep phenotyping using a pre-specified framework and extensive assessment of cognitive function. Limitations include a relatively small sample size which could have prevented identification of significant associations and precluded our ability to adjust for covariates. Specifically, we did not adjust for presence of OSA, which was present in 27 participants. Adjustment for concomitant sleep disorders, comorbidities, and use of medications for sleep, pain or depression are recommended in future studies. We applied domains included in an existing sleep health framework and have generated preliminary values for future study populations. However, it is possible that the framework may omit important sleep-related variables that may help to better define an individual's overall sleep phenotype or signature. Specifically, frequency and duration of daytime napping is not included in the current framework. Chronotype is also not incorporated, which may be of particular importance given the inclusion of sleep timing within the framework. Furthermore, the broad categories included in the measure of sleep quality (PSQI sleep quality item, categorizing poor sleep quality as "fairly bad" or "very bad" compared to "fairly good" or "very good") may introduce misclassification; examination of the inclusion and impact of a more sensitive tool would be valuable. Exploration of the clinical utility of an expanded and/or refined sleep health framework may therefore be warranted. Our application of the sleep health framework to assess associations with chronic symptoms may also be limited by different time frames included in subjective measures (e.g., sleep quality over the past month; depressive symptoms over the past two weeks).

In conclusion, we have characterized and provided initial reference values for seven domains of sleep and quantified the composite sleep health burden in PwMS. Our finding that extremes in multiple sleep domains is common demonstrates a need for a more comprehensive approach to sleep assessment in PwMS, and incorporation of such an approach into MS research. Uptake of this standardized multidimensional assessment would support harmonization of future research that could inform development of targeted sleep treatments to reduce MS morbidity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- A seven-domain framework was used to evaluate the sleep health of people with MS.
- Objective sleep domains: duration, continuity, timing, regularity, rhythmicity.
- Subjective sleep domains: daytime sleepiness and perception of sleep quality.
- Seventy-six percent of the sample had extreme values for ≥2 sleep domains.

Table 1.

Sleep descriptive statistics

Sleep Framework Domain	Participant assessment method	Median (IQR) for the sample	Categorical variables	Categories % (N)
Duration	Actigraphy-based mean total sleep time (mins)	456.31 (429.90, 485.50)	Short *: <=419.57 Medium: 419.57–515.5 Long *: >515.5	18.37% (9) 65.31% (32) 16.33% (8)
Continuity	Actigraphy-based mean time awake after sleep onset (mins)	37 (24.81, 52.57)	<44.94 >=44.94 **	67.35% (33) 32.65% (16)
Timing	Actigraphy-based mean sleep midpoint (midpoint of bed and wake time)	03:21 (02:64, 04:03)	Early: ≤ 02:00 Middle: 02:01–04:00 Late: >04:00	8.16% (4) 65.31% (32) 26.53% (13)
Sleepiness/ alertness	Epworth Sleepiness Scale score	8 (4, 11)	<= 10 >10	67.35% (33) 32.65% (16)
Quality	PSQI sleep quality item	1 (1, 2)	<=1 >1	55.10% (27) 44.90% (22)
Rhythmicity	Probability of being in same state at any 2 time points 24 hours apart	0.72 (0.68, 0.76)	<0.69 *** >=0.69	34.69% (17) 65.31% (32)
Regularity	Standard deviation of actigraphy wake time (hours)	1.02 (0.86, 1.30)	<1.17 >=1.17 **	67.35% (33) 32.65% (16)
Composite sleep variable	Total number of extreme sleep domain measures	2 (2,4)	0 1 2 3 4 5 6 7	10.20% (5) 14.29% (7) 30.61% (15) 16.33% (8) 18.37% (9) 6.12% (3) 4.08% (2) 0% (0)

* Short duration category=lowest sixth of the distribution; Long duration category=highest sixth of the distribution

** Most extreme (highest) third of the distribution

*** Most extreme (lowest) third of the distribution

Domain definitions from Wallace et al.[8], except rhythmicity, which used an approach from Phillips et al.[14]

Table 2.

MS symptom scores

	Median (IQR)	Mean (SD)
Depression		
Patient Health Questionnaire-9 score	6 (3, 9)	7.0 (5.1)
Pain		
Intensity (short form sum score)	7 (3,9)	6.5 (2.7)
Interference (short form sum score)	6 (4, 10)	7.4 (3.8)
Fatigue		
Fatigue Severity Scale	5.1 (3.9, 6.3)	4.8 (1.5)
Cognitive function		
California Verbal Learning Test-II Total	49 (43, 57)	49.5 (9.6)
California Verbal Learning Test-II First	−1 (−1.5, 0)	−0.58 (0.89)
California Verbal Learning Test-II Discriminability	0 (0, 0.5)	0.23 (0.7)
Paced Auditory Serial Addition Test-3	44 (37, 54)	43.5 (11.5)
Paced Auditory Serial Addition Test-2	33 (24, 42)	33.0 (11.0)
Judgement of Line Orientation Test	27 (25, 29)	26.7 (3.7)
Symbol Digit Modalities Test (correct)	48 (39, 56)	48.4 (12.1)
Brief Visuospatial Memory Test (Revised) - Total	44 (36, 58)	46.1 (14.0)
Brief Visuospatial Memory Test (Revised) - Delayed	51 (41, 58)	47.3 (14.5)
Controlled Oral Word Association Test (total score)	36 (26, 43)	35.0 (11.5)
Free Sort Test from the Delis-Kaplan Executive Function System (no. of correct sorts)	11 (10, 13)	11.1 (2.3)

Table 3.

Associations between sleep domains and symptoms of depression, pain intensity, pain interference, and fatigue*

Sleep domain	Description	Depressive symptoms (PHQ-9 score)	Pain intensity (SF sum score)	Pain interference (SF sum score)	Fatigue (Fatigue Severity Scale)
		B (95% confidence interval), p value			
Duration	Medium duration	Reference group			
	Short or long duration	0.57 (−2.51, 3.66), p=0.71	0.42 (−1.21, 2.05), p=0.61	1.47 (−0.79, 3.74), p=0.20	0.10 (−0.84, 1.04), p=0.83
Continuity	Average mean wake time after sleep onset**	0.03 (−0.03, 0.09), p=0.31	0.0002 (−0.03, 0.03), p=0.99	−0.001 (−0.05, 0.04), p=0.96	0.001 (−0.02, 0.02), p=0.89
	Least extreme two-thirds	Reference group			
	Most extreme third	1.61 (−1.49, 4.71), p=0.30	−0.17 (−1.83, 1.49), p=0.84	−0.48 (−2.82, 1.86), p=0.68	−0.22 (−1.17, 0.73), p=0.65
Timing	Middle (02:01–04:00)	Reference group			
	Early or late	1.20 (−1.87, 4.27), p=0.44	0.51 (−1.12, 2.14), p=0.53	0.66 (−1.64, 2.96), p=0.56	0.14 (−0.80, 1.07), p=0.77
Sleepiness	Epworth Sleepiness Scale score, continuous	0.45 (0.19, 0.71), **p=0.001**	0.12 (−0.03, 0.27), p=0.13	0.13 (−0.09, 0.35), p=0.23	0.07 (−0.01, 0.16), p=0.09
	Epworth Sleepiness Scale ≤10	Reference group			
	Epworth Sleepiness Scale >10	3.19 (0.19, 6.18), **p=0.04**	0.48 (−1.17, 2.13), p=0.56	−0.11 (−2.45, 2.23), p=0.93	0.58 (−0.36, 1.52), p=0.22
Quality	PSQI Sleep Quality item=very or fairly good	Reference group			
	PSQI Sleep Quality item=fairly or very bad	2.84 (0.005, 5.68), **p=0.05**	0.60 (−0.96, 2.15), p=0.44	1.91 (−0.23, 4.04), p=0.08	0.59 (−0.30, 1.47), p=0.19
Rhythmicity	Continuous	−6.97 (−29.31, 15.37), p=0.53	−8.16 (−19.78, 3.46), p=0.16	−8.36 (−24.93, 8.20), p=0.32	−3.44 (−10.17, 3.29), p=0.31
	Least extreme two-thirds	Reference group			
	Most extreme (lowest) third	1.29 (−1.77, 4.36), p=0.40	0.51 (−1.12, 2.14), p=0.53	0.30 (−2.00, 2.61), p=0.79	1.17 (0.30, 2.04), **p=0.01**
Regularity	Continuous	1.11 (−1.64, 3.86), p=0.42	0.97 (−0.47, 2.41), p=0.18	0.89 (−1.16, 2.95), p=0.39	−0.18 (−1.02, 0.66), p=0.67
	Least extreme two-thirds	Reference group			
	Most extreme third	1.61 (−1.49, 4.71), p=0.30	0.39 (−1.27, 2.04), p=0.64	1.10 (−1.22, 3.42), p=0.35	0.16 (−0.79, 1.11), p=0.73

Sleep domain	Description	Depressive symptoms (PHQ-9 score)	Pain intensity (SF sum score)	Pain interference (SF sum score)	Fatigue (Fatigue Severity Scale)
Composite score (continuous)		1.20 (0.31, 2.10), **p=0.01**	0.27 (−0.23, 0.77), p=0.29	0.49 (−0.22, 1.19) p=0.17	0.25 (−0.03, 0.53), p=0.08

*Unadjusted analysis

**Continuous variable

Bold: p≤0.05

PSQI: Pittsburgh Sleep Quality Index