Title

Sleep disorders, daytime symptoms, and quality of life in veterans with multiple sclerosis: preliminary findings.

Journal

Sleep Advances, 3(1)

Authors

Aljundi, Nawar
Kelly, Monica
Zeineddine, Salam
et al.

Publication Date

2022

DOI

10.1093/sleepadvances/zpac012

Peer reviewed

Sleep Advances, 2022, 1–8

https://doi.org/10.1093/sleepadvances/zpac012
Advance Access Publication Date: 6 May 2022
Original Article

ORIGINAL ARTICLE

Sleep disorders, daytime symptoms, and quality of life in veterans with multiple sclerosis: preliminary findings

Nawar A. Aljundi[1,2], Monica Kelly[3,4], Salam Zeineddine[1,2], Anan Salloum[1,2], Nishtha Pandya[1,2], Q. Afifa Shamim-Uzzaman[5,6,7], Amira N. Badr[8], Michael N. Mitchell[3,4], Abdulghani Sankari[1,2], M. Safwan Badr[1,2] and Jennifer L. Martin[3,4,*,†]

[1]Department of Internal Medicine, Wayne State University School of Medicine, Detroit, MI, USA, [2]John D. Dingell Veterans Affairs Medical Center, Detroit, MI, USA, [3]Geriatric Research Education and Clinical Center, VA Greater Los Angeles Healthcare System, Los Angeles, CA, USA, [4]Department of Medicine, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA, USA, [5]Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, MI, USA, [6]Department of Neurology, University of Michigan Medical School, Ann Arbor, MI, USA, [7]Sleep Disorders Center, VA Ann Arbor Healthcare System, Ann Arbor, MI, USA and [8]Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University, Detroit, MI, USA

[†]Work was performed at Wayne State University and the John D Dingell VA Medical Center in Detroit, MI, USA.
*Corresponding author. Jennifer L. Martin, VA Sepulveda GRECC (11E), 16111 Plummer St., North Hills, CA 91343, USA. Email: Jennifer.martin@va.gov.

Abstract

Study Objectives: Multiple sclerosis (MS) is an autoimmune disease impacting the central nervous system. A hallmark symptom of MS is fatigue, which impairs daytime function and quality of life (QOL). Sleep disorders and disturbances are common in persons with MS and exacerbate fatigue. We evaluated relationships between sleep-disordered breathing (SDB), insomnia symptoms, sleep quality, and daytime functioning in veterans with MS participating in a larger study.

Methods: Twenty-five veterans with clinically diagnosed MS were included (average age = 57 ± 11, 80% male). One had a co-occurring thoracic spinal cord injury. Twenty-four participants completed in-laboratory polysomnography (PSG) to measure apnea-hypopnea index (AHI) and sleep efficiency (PSG-SE). Insomnia Severity Index (ISI) and Pittsburg Sleep Quality Index (PSQI) were used to measure sleep subjectively. The Flinders Fatigue Scale (FFS), Epworth Sleepiness Scale (ESS), PHQ-9 depression scale, and GAD-7 anxiety scale assessed daytime symptoms. The World Health Organization Quality of Life (WHOQOL) was used to assess quality of life. Relationships between sleep (AHI, PSG-SE, ISI, PSQI), daytime symptoms (ESS, FFS, PHQ-9, and GAD-7), and quality of life (WHOQOL) were evaluated with bivariate correlations.

Results: Higher ISI (r = 0.78, 95% CI = [0.54, 0.90], p < .001), higher PSQI (r = 0.51, 95% CI = [0.10, 0.77], p = .017), and lower PSG-SE (r = –0.45, 95% CI = [–0.74, –0.02], p = .041) were associated with worse fatigue (FFS). Higher ISI was also associated with worse WHOQOL (Physical Domain; r = –0.64, 95% CI = [–0.82, –0.32], p = .001). There were no other significant relationships.

Conclusion: In veterans with MS, more severe insomnia and worse sleep quality may be associated with more fatigue and lower quality of life. Recognition and management of insomnia should be considered in future studies of sleep in MS.

Statement of Significance

Multiple sclerosis (MS) is a chronic inflammatory disease that affects many aspects of quality of life. Sleep disorders are prevalent in patients with MS and may contribute to daytime symptom severity and reduced quality of life (QOL). Patients with MS frequently complain of fatigue that is often difficult to treat. The objective of this study was to provide preliminary evidence on the impact of sleep disordered breathing (SDB) and insomnia symptoms on fatigue and QOL among veterans with MS, with the goal of informing future research on sleep-focused treatments in MS. Our findings suggest that the severity of insomnia was associated with greater severity of fatigue. Although findings should be replicated in larger studies, targeted management of insomnia in MS patients may serve as a modifiable factor in reducing fatigue, improving QOL and decreasing disease burden.

Key words: sleep apnea; sleep disordered breathing; insomnia; fatigue; multiple sclerosis; sleep quality

Submitted: 6 January, 2022; **Revised:** 21 April, 2022

Introduction

Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disease of the central nervous system (CNS) involving both the brain and spinal cord. MS primarily affects young adults, resulting in significant neurologic impairment in a substantial proportion of affected individuals [1]. The impact of this condition is far reaching, with Spinal Cord Injury (SCI) and Spinal Cord Disease (SCD), such as MS, being a primary cause for paralysis, second only to stroke [2].

Comorbidities in MS are common and are associated with negative health-related physical and cognitive outcomes [3], including fatigue, sleepiness and impaired quality of life (QOL). Comorbidity may explain the phenotypic diversity of MS presentation as well as the heterogeneity of outcomes in MS [4]. For example, the severity of fatigue, the most burdensome symptom affecting MS patients, had been linked to comorbid depression [5], cognitive deficits [6], disability [7], and sleep disorders [4,8]. Kaminska et al. referred to fatigue as "primary" if it is a direct consequence of MS itself (immune and neurotransmitter dysregulation, CNS mechanisms, endocrine factors, among others) and "secondary" if it is related to a wide array of nondisease associated clinical factors including comorbidities. Understanding the relative contribution of primary and secondary factors can be clinically challenging.

There is abundant literature on the prevalence of sleep disturbances and fatigue in MS, and a growing body of evidence suggests that SDB is more prevalent in patients with MS than in the general population [9,10]. Moreover, in recent studies of MS patients, the prevalence of insomnia was disproportionately high, with estimated rates ranging from 22% to 50% [11–13]. One large cross-sectional survey study of sleep disorders [10] found that while 38% of individuals living with MS screened positive for symptoms of sleep disordered breathing (SDB), 32% for moderate-to-severe insomnia, and 37% for restless legs syndrome, only a small fraction of respondents had spoken to a healthcare provider about any of their sleep complaints, even though 60% reported high levels of fatigue and 30% reported excessive daytime sleepiness. Routinely, the impairment in daytime function and QOL in patients with MS is attributed directly to the MS without consideration of the role that sleep disruption may play in daytime symptom severity. Therefore, although patients with MS have been shown to suffer from the negative consequences of SDB and insomnia, they seem to be underdiagnosed as well as undertreated for these conditions [10,14].

The prevalence of psychiatric disorders, such a depression and anxiety is higher in patients with MS, compared to the general population. A recent meta-analysis estimated that the prevalence of clinically significant depressive or anxiety symptoms was high in patients with MS, at 35% and 34%, respectively [15]. Potential explanations for such a high prevalence of psychiatric symptoms include MS-related immunological or inflammatory processes, or challenges related to the condition, such as inadequate coping or insufficient social support. Additionally, insomnia is associated with increased depression and anxiety in patients with MS. In one study, 78% of MS patients with insomnia experienced depression and anxiety symptoms at baseline which improved to 43% of patients with psychotherapy intervention [16]. Clearly, depression and anxiety may adversely affect daily function and impair quality of life.

Veterans also represent a unique subpopulation of patients with MS. Over a period of 10 years, sleep apnea and insomnia were the most commonly diagnosed sleep disorders in veterans who use VA healthcare. Also, diagnosed posttraumatic stress disorder was associated with the highest rates of diagnosed sleep disorders [17].

As part of a larger study on sleep disorders in spinal cord injury and diseases, the current analysis sought to provide preliminary evidence on the relationship between measures of sleep disorders and sleep quality and daytime symptoms including fatigue, daytime sleepiness, depression, anxiety, and quality of life. We hypothesized that worse SDB, worse insomnia and poorer objective (polysomnography sleep efficiency, PSG-SE) and subjective (patient-reported) sleep quality would be related to worse fatigue, worse sleepiness, more depression and anxiety, and lower quality of life among MS patients.

Methods

We analyzed data from a subset of participants diagnosed with MS who were participating in a larger clinical trial (NCT02830074) for participants with either SCD or SCI. Recruitment was from a sample of all veterans receiving care for either SCD or SCI at the participating medical center. Baseline assessments consisted of in-laboratory polysomnography (PSG) as well as questionnaires assessing both daytime and nighttime function. For the current analyses, we utilized the baseline assessment data from the subset of 25 participants diagnosed with MS who were enrolled in the trial. The Institutional Review Boards of Wayne State University School of Medicine and the Detroit Veterans Affairs Medical Center approved the study protocol. Written informed consent was obtained from all participants (with an option for participants unable to use their upper extremities to provide witnessed verbal consent).

Inclusion criteria for the parent study were: veterans with a spinal cord injury or disease who were at least 3 months post injury or post-diagnosis, and received care at the participating medical center. Potential participants were excluded if they were receiving mechanical ventilation, were using positive airway pressure (PAP) therapy for SDB at optimal compliance (since the parent trial related to treatment of SDB), had a clinical contraindication that prevented PAP use, a recent health event that impacted sleep (e.g. recent stroke, recent surgery, or hospitalization), current/recent alcohol or substance abuse (<90 days sobriety), were self-described as too ill to engage in study procedures, or were unable to provide self-consent for participation (e.g., due to dementia).

Baseline assessments included one night of laboratory PSG and study questionnaires (described below), which were conducted over 1 or 2 visits to the research laboratory based on the participant's preferences. To reduce burden of completing questionnaires and as a result of physical limitations of many study participants, questionnaire items were read aloud using standard scripts, and response options were shown to each participant visually. A research assistant recorded each participant's answers after they verbally confirmed their responses as listed on the response option list. Data from the questionnaires were then entered into a Research Electronic Data Capture (REDCap) secure, web-based database hosted at the study site and exported for analysis [18].

Study measures

Demographics. Participants completed a questionnaire assessing demographic information including age, gender, race/ethnicity, marital status, employment status, living situation, and income.

Sleep measures. *Polysomnography (PSG)* was conducted to ascertain the presence and severity of SDB. Each PSG was scored according to the current AASM scoring manual by trained technicians who met the scoring accuracy standards set by the AASM Interscorer reliability program [19]. All PSG scoring was further reviewed by a board-certified sleep specialist. Scorers and physicians were blinded to questionnaire scores. Each record was scored for standard polysomnographic parameters including, total sleep time, sleep efficiency (PSG-SE, time spent asleep divided by time in bed and multiplied by 100 for a percentage) [20], sleep onset latency (minutes from lights out to first epoch of any sleep stage), percentage of time spent in each of the four sleep stages (N1, N2, N3 and Rapid Eye Movement sleep), waketime after sleep onset (time spent awake after sleep onset, and before final awakening time), arousal index (average number of electroencephalographic arousals per hour of sleep), periodic leg movement index (number of periodic leg movements per hour of sleep), as well as blood oxygen desaturation. Scoring of respiratory events followed the following criteria: apneas were defined as the cessation of airflow for 10 s or longer with continued respiratory effort (obstructive apneas) or lack of respiratory effort (central apneas). Hypopneas were defined as a reduction in airflow (≥30%) lasting 10 s or longer, accompanied by either a ≥3% oxygen desaturation or an arousal. The severity of SDB was expressed by the apnea–hypopnea index (AHI), defined as the number of apneas and hypopneas per hour of sleep. Objective sleep efficiency was defined as the number of minutes scored as sleep divided by the number of minutes in bed, converted to a percent.

The *Insomnia Severity Index (ISI)* [21] is a commonly used measure of insomnia symptom severity. The ISI evaluates severity of sleep onset and sleep maintenance difficulties, issues with early morning awakening, sleep dissatisfaction, interference of sleep difficulties with daytime function, noticeability of sleep problems by others, and distress caused by sleep difficulties. The ISI uses a five-point Likert scale from 0 to 4, where 0 is no problem and 4 is a very severe problem. The total scores fall into the following categories: 0–7 is defined as the absence of insomnia, 8–14 is defined as subthreshold insomnia, 15–21 is defined as moderate insomnia, and 22–28 is defined as severe insomnia [21]. The ISI is therefore a tool to describe how insomnia affects a person's day-to-day life with scores and clinical implications that are sensitive to treatment [22].

The *Pittsburgh Sleep Quality* Index (PSQI) is an 18-item questionnaire that broadly measures sleep quality over the span of one month, using both open-ended and Likert scale items. In this study, a three-subscale scoring system that has superior psychometric properties to the original seven-subscale version was used [23]. Total PSQI scores above 5 are considered to represent poor sleep quality. The PSQI has been shown to differentiate between good and poor sleepers with high validity and reliability [24,25].

Measures of daytime symptoms. The *Flinder's Fatigue Scale (FFS)* is a clinically sensitive tool developed to assess daily fatigue particularly in association with insomnia [26]. The FFS is a seven-item scale that measures various characteristics of fatigue (frequency, severity, how problematic fatigue is, consequences of fatigue, and how insomnia patients perceive their fatigue in association with sleep) experienced over the past 2 weeks. Six items are presented in Likert format with scores ranging from 0 (not at all) to 4 (extremely). One item measures the time of day when fatigue is experienced and uses a multiple-items checklist. It is scored as the sum of all times of the day options chosen by the patient. FFS scores range from 0 to 31 with higher scores indicating more severe fatigue. Scores can be divided into borderline (13–15), moderate (16–20), and severe (≥21) fatigue.

The *Epworth Sleepiness Scale (ESS)* is an 8-item questionnaire rating the likelihood of falling asleep during everyday activities [27]. Scores are presented in the Likert format 0–3 and total ESS scores range from 0 to 24 with higher scores indicating more severe daytime sleepiness. ESS scores of 10 and above indicate clinically significant sleepiness and scores over 15 indicate clinically severe excessive daytime sleepiness symptoms.

The *Patient Health Questionnaire-9 (PHQ-9)* is a standard clinical questionnaire to assess clinical depression and has widespread use in outpatient settings as a screening measure for depression [28]. Scores are presented in the Likert format 0–3 and total PHQ-9 scores range from 0 to 27 with higher scores indicating more severe symptoms of depression. PHQ-9 scores over 20 indicate clinically significant depressive symptoms. For Pearson correlations between the PHQ-9 scores and sleep measures, we removed the sleep item from the PHQ-9 total score.

The *Generalized Anxiety Disorder-7 (GAD-7)* is a tool frequently used in outpatient psychiatric or primary care facilities to gather information on the severity of anxiety [29]. Scores follow the Likert format 0–3 and total GAD-7 scores range from 0 to 21 with higher scores indicating more severe anxiety symptoms, and scores over 14 indicate clinically significant anxiety symptoms.

The Primary Care PTSD Screening (PC-PTSD) was used to assess risk for PTSD. (6) This tool uses four questions based on Diagnostic and Statistical Manual-IV PTSD symptoms to assess whether the participant has experienced any PTSD symptoms related to exposures to traumatic events. Participants responding positively by answering "yes" to any 3 of the 4 questions were classified as high risk for PTSD. A cut-off score of > 2 is optimally sensitive for identifying veterans who would meet diagnostic criteria for PTSD.(7)

Quality of life. *World Health Organization Quality of Life: Brief Version (WHOQOL-BREF)* is a 26-item self-rated questionnaire that assesses overall quality of life in four domains: physical health, psychological, social, and environment [30]. All questions follow a Likert score format from 1 to 5, scaled in a positive direction with higher scores denoting better QOL. The mean score of items within each domain is used to calculate the domain scores. Mean scores are then multiplied by 4 to make domain scores comparable with the scores used in WHOQOL-100.

Data analysis

Descriptive statistics were computed for all study variables (*mean/SD* or *n/%*). Bivariate Pearson correlations were used to test relationships between sleep variables and measures of daytime symptoms and quality of life. To evaluate for the potential impact of outliers, scatterplots for all bivariate relationships were generated and inspected (see Supplementary Fig. S1). Although the study sample size is too small for hypothesis-driven multivariable analyses, we conducted supplementary multiple regression analyses with FSS, ESS, PHQ-9 (without sleep item), and GAD-7 as outcomes, with each sleep-related variable as the predictor, adding age and sex as covariates (to account for the possible impact of demographic factors) to provide additional clarity of our findings. For each test, $p < .05$ was considered statistically significant. Analyses were conducted using Stata 17.0 [31].

Table 1. Characteristics of study participants ($N = 25$)

Variable	*Mean* (*SD*; range) or *n* (%)
Age	56.9 (11.2; 35–79)
Gender, male	20 (80%)
Race/Ethnicity*	
White	14 (56.0%)
African-American/Black	11 (44.0%)
Hispanic	1 (4.0%)
Hawaiian/Pacific Islander	0 (0.0%)
American Indian/Alaska Native	0 (0.0%)
Asian	0 (0.0%)
Other	0 (0.0%)
Multi-race	1 (4.0%)
Employment status	
Employed for wages	1 (4.0%)
Retired	15 (60.0%)
Unable to work/Unemployed	14 (56.0%)
Household income	
<$20,000	3 (12.0%)
$20,001–$50,000	9 (36.0%)
>$50,001	13 (52.0%)
Education, years	14.4 (2.1; 12–20)
Marital status	
Married/living as married	12 (48.0%)
Divorced/separated	11 (44.0%)
Widowed	1 (4.0%)
Single, never married	1 (4.0%)
Living location	
Own home/apartment	22 (88.0%)
Home of a relative or friend	3 (12.0%)
Residential facility	0 (0.0%)

Results

Characteristics of study participants are shown in Table 1. Mean age was 57 years. Eighty percent of the participants were men, and only 4% were employed for wages. On the PC-PTSD, 44% of participants scored as high risk for PTSD.

Table 2 provides summary information on sleep measures. Of the 24 participants with PSG data, 23 (95.8%) had SDB, with 33.3% having mild SDB (AHI 5–14.9 events per hour), 29.2% having moderate SDB (AHI 15–29.9 events per hour) and 33.3% having severe SDB (AHI greater than or equal to 30 events per hour). On average, participants experienced significant sleep disturbance reflected on the ISI and PSQI. Nineteen (76%) participants scored in the abnormal range on the PSQI, and 8 (32%) scored above the cut-off for moderate insomnia on the ISI.

Daytime symptom and quality of life measures are summarized in Table 2. Thirteen participants (52%) had moderate fatigue (FFS score ≥ 16) and 10 (40%) had severe fatigue (FFS score ≥ 21). Nine participants (36%) had clinically significant sleepiness (ESS score ≥ 10). Three (12%) participants had moderate depression (PHQ-9 score ≥ 15) and 2 (8%) had severe depression (PHQ-9 score ≥ 20). Seven participants (28%) had moderate anxiety (GAD-7 score ≥ 10) and 3 (12%) severe anxiety (GAD-7 score ≥ 15).

Relationship between sleep and daytime symptoms

Table 3 summarizes correlations between sleep measures and daytime symptom measures. SDB severity (measured as the

Table 2. Descriptive information on sleep, daytime symptoms and quality of life ($N = 25$)

Sleep variables	*Mean*	Standard deviation
Apnea Hypopnea Index (AHI)*	27.1	19.8
Sleep Efficiency from PSG (PSG-SE)*	71.7	17.3
Insomnia Severity Index (ISI)	11.5	6.7
Pittsburgh Sleep Quality Index (PSQI) Total Score	9.3	4.4
PSQI Subscale 1: Sleep Efficiency	2.8	2.3
PSQISubscale2: Perceived Sleep Quality	4.2	2.1
PSQI Subscale 3: Daily Disturbances	2.7	1.4
Daytime symptom measures		
Flinder's Fatigue Scale (FFS)	17.3	8.7
Epworth Sleep Scale (ESS)	8.0	5.6
Patient Health Questionnaire-9(PHQ-9)	8.6	6.3
Patient Health Questionnaire-9 (PHQ-9), excluding sleep item	7.3	5.8
Generalized Anxiety Disorder-7 (GAD-7)	6.7	5.6
Primary Care PTSD Screening Questionnaire (PC-PTSD) items endorsed	2.1	2.1
Quality of Life (World Health Organization Quality of Life – Brief Version; WHOQOL-BREF)		
WHOQOL-BREF Physical Domain	52.3	19.2
WHOQOL-BREF Psychological Domain	60.0	16.4
WHOQOL-BREF Social Domain	59.0	23.3
WHOQOL-BREF Environmental Domain	70.9	15.3

*$n = 24$; Higher scores on ISI, PSQI, FFS and ESS are indicative of worse symptoms. Higher scores on WHOQOL-BREF indicate better quality of life.

Table 3. Relationships between sleep measures and daytime functioning (*r* [95% confidence interval]).

	Flinder's fatigue scale (FFS)	Epworth sleepiness scale (ESS)	Patient health questionnaire-9 (PHQ-9)ǂ	Generalized anxiety disorder-7 (GAD-7)
Apnea hypopnea index (AHI)	−0.19 [−0.57, 0.25]	0.09 [−0.32, 0.48]	0.07 [−0.35, 0.46]	0.04 [−0.37, 0.44]
PSG-sleep efficiency (SE)	−0.45* [−0.74, −0.02]	−0.03 [−0.44, 0.39]	−0.44* [−0.72, −0.03]	−0.60** [−0.81, −0.24]
Insomnia severity index (ISI)	0.78*** [0.54, 0.90]	0.18 [−0.23, 0.54]	0.51** [0.15, 0.76]	0.52* [0.16, 0.76]
Pittsburgh sleep quality index (PSQI)	0.51* [0.10, 0.77]	0.23 [−0.21, 0.58]	0.36 [−0.06, 0.67]	0.42* [0.004, 0.71]

*$p < .05$,
**$p < .01$,
***$p < .001$; ǂ PHQ-9 excluding the sleep item; Of note, correlations of the PHQ-9 including the sleep item were comparable to the results reported above: AHI $r = 0.004$, $p = .98$; PSG-SE $r = -0.42$, $p = .04$; ISI $r = 0.56$, $p = .003$; and PSQI $r = 0.41$, $p = .051$.

apnea-hypopnea index—AHI) was not significantly correlated with fatigue, sleepiness, depression, or anxiety. Lower PSG-SE was associated with higher fatigue and depression. Greater insomnia severity was associated with higher levels of fatigue, depression, and anxiety. Worse overall sleep quality (PSQI total score) was correlated with elevated fatigue and anxiety. Of the three PSQI subscales, there was a correlation between PSQI Daily Disturbances and fatigue ($r = 0.68$, 95% CI = [0.36, 0.86], $p < .001$), depression [excluding sleep item] ($r = 0.55$, 95% CI = [0.19, 0.78], $p = .006$), and anxiety ($r = 0.43$, 95% CI = [0.03, 0.71], $p = .036$). There were no significant associations between the PSQI Sleep Efficiency or PSQI Perceived Sleep Quality subscales and daytime symptom measures. There were also no significant associations between any of the nighttime sleep measures and daytime sleepiness (ESS total score). Figure 1 shows the relationship between ISI (Panel A) and AHI (Panel B) and FSS scores. Supplementary Tables S1–S16 provide models including age and sex as covariates.

SDB severity (measured as the apnea-hypopnea index—AHI) was not significantly correlated with fatigue, sleepiness, depression, or anxiety. Lower PSG-SE was associated with higher fatigue and depression. Greater insomnia severity was associated with higher levels of fatigue, depression, and anxiety. Worse overall sleep quality (PSQI total score) was correlated with elevated fatigue and anxiety.

Relationship between sleep measures and quality of life

Greater insomnia symptoms (ISI total score) were associated with worse quality of life on the WHOQOL-BREF Physical Domain ($r = -0.64$, 95% CI = [−0.82, −0.32], $p = .001$), and higher PSG-SE was associated with better quality of life on the WHOQOL-BREF Environmental Domain ($r = 0.43$, 95% CI = [0.02, 0.71], $p = 0.042$). There were no other significant relationships between sleep measures and quality of life.

Discussion

Sleep disorders are common in patients with MS and may contribute to the severity of fatigue, a common manifestation of MS [32]. Disrupted sleep could also lead to MS disease symptom progression [33]. Therefore, targeting comorbid conditions is key to improving fatigue in MS.

Our study suggests the following novel findings that should be evaluated in future research: (1) insomnia severity (as measured by ISI) was associated with worse daytime fatigue and quality of life (as measured on the FFS and WHOQOL-BREF, respectively); (2) subjective sleep disturbance (as measured by PSQI scores) was associated with worse daytime fatigue (as measured by the FFS); and (3) fatigue may be unrelated to the severity of SDB in a predominantly male sample of veterans with MS who use VA healthcare.

Fatigue affects more than 80% of MS patients, is present at every disease stage, and is the most challenging disease symptom to manage [32]. Along with cognitive impairment, fatigue in MS represents a leading cause of physical disability and early retirement [34]. Fatigue needs to be differentiated from daytime sleepiness. The MS Council [35] defines fatigue as a "subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities" whereas sleepiness is defined as the propensity to fall asleep." A recent study highlighted that MS patients with sleep problems reported fatigue as a main complaint rather than overt sleepiness [9], contrary to the traditional portrayal of sleepiness as a primary symptom of SDB [36].

The absence of a significant correlation between SDB severity and fatigue has been seen in non-MS population studies but was unexpected in our sample of MS patients. One study in Korea found that sleepiness and insomnia symptoms were related to fatigue, but AHI was not [37]. One clinical trial found that PAP therapy reduced sleepiness but not fatigue in MS patients, although hours of PAP use was not considered as a variable in this study [38]. This may also be the case in MS patients, even though fatigue is a common symptom of both SDB and MS.

The high prevalence of insomnia among our participants (32%) is also consistent with other studies [10,11]. We considered several possibilities to explain the relationship between insomnia and MS. First, insomnia may be a direct consequence of MS and MS-related symptoms such as pain, muscle spasms, and nocturia; or it may emerge as a result of medication side effects, notably systemic corticosteroids, used in the management of MS [39]. Likewise, comorbid depression and/or anxiety are often associated with insomnia symptoms, and these mental health conditions are common in those living with MS [5]. One study showed that treating depression with psychotherapy improved insomnia symptoms in MS patients [16] suggesting that addressing mental health symptoms that are common in MS

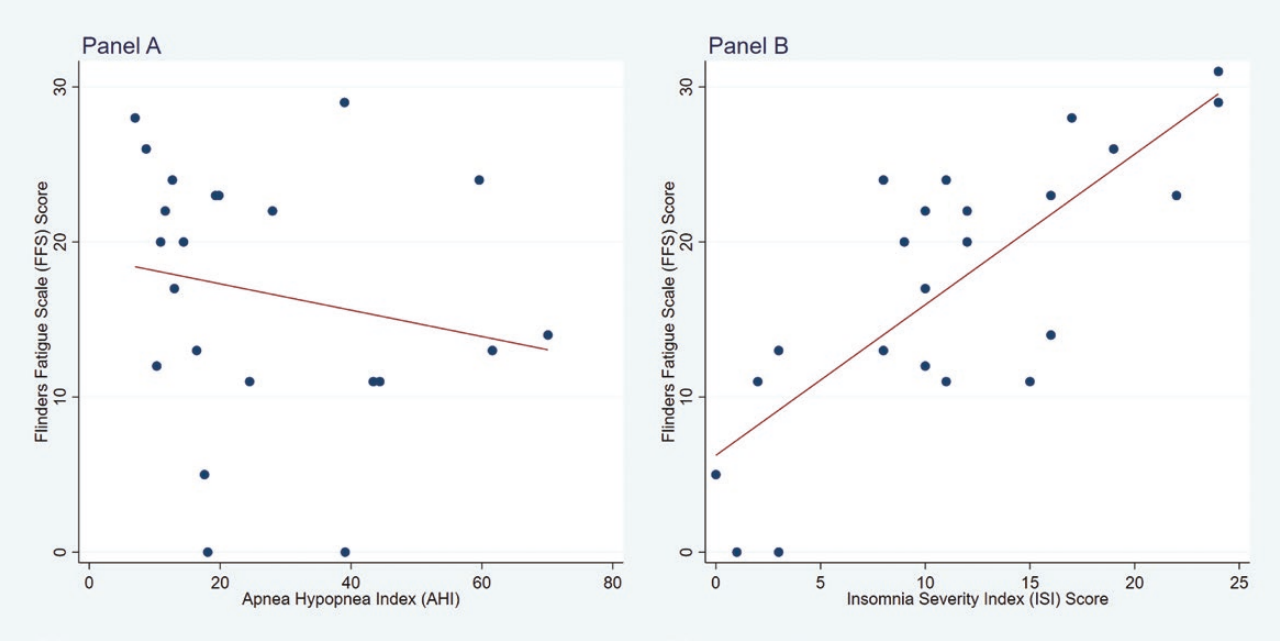

Figure 1. Fatigue, insomnia and sleep disordered breathing: Higher scores on the insomnia severity index (ISI, Panel A) were significantly associated with higher scores on Flinders Fatigue Scale (n = 23; r = 0.78, 95% CI = [0.54, 0.90], p < .001). Higher apnea hypopnea index (AHI; Panel B) were not (n = 22, r = –0.19, 95% CI = [–0.57, 0.25], p = .395).

may improve sleep. Finally, changes in behavior to accommodate MS-related symptoms may reduce overall activity levels and increase time spent in bed, leading to subsequent insomnia problems. The 3 P's model of insomnia suggests that poor sleep habits, such as extended time in bed not spent sleeping, perpetuate insomnia [40].

Longitudinal studies of patients with MS addressing sleep symptoms and comorbid conditions are needed to fully illuminate these complex relationships. The first-line treatment approach for insomnia disorder in adults is cognitive-behavioral therapy for insomnia (CBT-I) [41,42]. Clinically, fatigue is considered both a symptom and consequence of insomnia [43], and adaptations of CBT-I so that it is tailored for patients with MS have shown promising results including improved sleep and reduced fatigue [44].

Finally, our data illustrate that sleep efficiency was associated with the environmental domain of the WHOQOL-BREF (e.g., access to resources, safety, noise pollution, and comfort) and correlated inversely with the severity of fatigue. These findings suggest a lack of resources, and environmental disturbances are significant enough to impact objective sleep quality in individuals with MS.

Several factors should be considered for proper interpretation of our preliminary findings. Our study stems from a VA-funded clinical trial on treatment of SDB in individuals receiving VA healthcare for SCI/D; therefore, recruitment methods sought to be inclusive to enhance generalizability to the population of Veterans. As such, we took multiple steps to recruit from the entire population of potentially eligible veterans; however, this approach introduces limitations in the generalizability to nonveteran populations. First, the study sample is limited to MS with spinal cord involvement, and the findings may not generalize to veterans without spinal cord involvement. Second, most participants were men, which is representative of the VA patient population, but is not representative of the overall non-Veteran population of MS patients. Men with MS do experience unique challenges; for example, men with MS are more likely to experience depression, are less likely to have adequate psychosocial support, and are less likely to believe in their ability to function with MS compared to women with MS [45]. While we did not exclude women from the study, we also do not have enough women to statistically compare men and women within this study. While it appears that women are more susceptible to being diagnosed with MS, recent literature has suggested men actually having worse and faster progression of disease [46]. This may also explain the higher rates of SDB as SDB is more common in men than women. Additionally, it is important to note that the prevalence of MS has been continuously increasing in both men and women over the last several decades [47].

The generalizability of our study is limited to patients with MS with spinal cord involvement and it is not clear whether our findings would differ in patients with MS without spinal cord involvement. We also enrolled participants receiving a variety of pharmacologic MS treatments, some of which may influence sleep, including disease-modifying therapies, analgesics, or medications to treat neuropathic pain (such as gabapentin) [48]. MS pharmacology may represent a potential modifier affecting sleep, and possibly the severity of underlying comorbid SDB [49,50].

The current analyses describe data from a relatively small sample of participants (only individuals with MS) who were enrolled in a larger clinical trial that recruited both individuals with SCI and SCD. Small studies can be impacted by influential data points, and although there were no obvious cases (see Supplementary Figure S1), it is still possible that findings are driven by a small number of individuals. Follow-up analyses shown in supplementary materials reflect that some of the findings were not significant when age and sex were added as covariates; however, it is not clear whether the nonsignificant multivariable models are a result of a very small number of

subjects per variable and the overall pattern of results reflects that insomnia was associated with fatigue, depression and anxiety symptoms, but AHI was not. In future research, additional covariates should be considered in larger studies of insomnia and SDB in MS. Overall, our findings suggest that while SDB is often the most suspected sleep disorder in individuals with significant medical comorbidities such as MS, consideration of insomnia is also critical.

Generalizability may also be limited since most participants (96%) had SDB, which is likely a result of the targeted recruitment for the parent clinical trial. All but one of the participants met the AHI cutoff for SDB, while almost two-thirds met criteria moderate or severe SDB. The high prevalence of SDB could point to gender distribution as a potential cause. To the best of our knowledge, there has not been any literature reported on sex differences as it relates to OSA in patients with MS. Furthermore, the aim of this study was to achieve generalizability as it relates to clinical care, thus we used one night of PSG monitoring to assess sleep parameters. This is a potential limitation in capturing night-to-night variability in SDB.

Despite many strengths, including both objective and subjective evaluation of sleep in a clinical population interested in treatment for sleep disorders, the cross-sectional nature of our study precludes firm causal inferences. The associations identified in this study indicate that if cause-and-effect relationships do exist, insomnia and disturbed sleep could contribute substantially to fatigue, a multidimensional factor that ranks among the most debilitating symptoms of MS. This underscores the importance of timely diagnosis of sleep disorders in patients with MS and improving access to evidence-based treatments for insomnia such as CBT-I. Providers caring for MS patients should be comfortable performing basic screening for common sleep disorders in this patient population and navigating the referral process as needed. It is possible that treatment of sleep disorders such as insomnia may not only improve sleep but alleviate daytime fatigue and improve quality of life, despite the progressive nature of MS, as poor sleep may ultimately impair the ability to rebound from MS relapses.

Conclusion

In veterans with MS, insomnia symptom severity was associated with daytime fatigue and decreased quality of life. Insomnia may represent a modifiable cause of daytime fatigue in patients with MS, and screening for sleep disorders such as insomnia can directly inform intervention decisions. These preliminary findings suggest recognition and management of insomnia may improve outcomes in this population although replication in larger studies including both men and women are needed.

Supplementary Material

Supplementary material is available at *SLEEP Advances* online.

Funding

This research was supported by Veterans Affairs Rehabilitation Research and Development Service, (RX002116; PI Badr). Dr. Martin was supported by a Veterans Affairs Heath Services Research and Development Service, Research Career Scientist Award (#RCS 20-191), and NIH/NHLBI K24 HL143055. This work was also supported by VA Greater Los Angeles Healthcare System (VAGLAHS) Geriatric Research, Education and Clinical Center (GRECC). All authors have agreed to be accountable for all aspects of the work.

Disclosure Statement

The authors have no conflicts of interest to declare. The work performed does not represent the views of the Department of Veterans Affairs or the US Government. Dr. Martin is a member of the Board of Directors of the American Academy of Sleep Medicine (AASM). This work does not represent the views of the AASM and are solely those of the author.

References

1. Ghasemi N, *et al*. Multiple sclerosis: pathogenesis, symptoms, diagnoses and cell-based therapy. *Cell J*. 2017;**19**(1):1–10. doi:10.22074/cellj.2016.4867.
2. Sankari A, *et al*. Sleep disordered breathing and spinal cord injury: challenges and opportunities. *Curr Sleep Med Rep*. 2017;**3**(4):272–278. doi:10.1007/s40675-017-0093-0.
3. Marrie RA. Comorbidity in multiple sclerosis: implications for patient care. *Nat Rev Neurol*. 2017;**13**(6):375–382. doi:10.1038/nrneurol.2017.33.
4. Kaminska M, *et al*. Obstructive sleep apnea is associated with fatigue in multiple sclerosis. *Mult Scler*. 2012;**18**(8):1159–1169. doi:10.1177/1352458511432328.
5. Bakshi R, *et al*. Fatigue in multiple sclerosis and its relationship to depression and neurologic disability. *Mult Scler*. 2000;**6**(3):181–185. doi:10.1177/135245850000600308.
6. Weinges-Evers N, *et al*. Correlation of self-assessed fatigue and alertness in multiple sclerosis. *Mult Scler*. 2010;**16**(9):1134–1140. doi:10.1177/1352458510374202.
7. Merkelbach S, *et al*. Fatigue, sleepiness, and physical activity in patients with multiple sclerosis. *J Neurol*. 2011;**258**(1):74–79. doi:10.1007/s00415-010-5684-3.
8. Veauthier C, *et al*. Fatigue in multiple sclerosis is closely related to sleep disorders: a polysomnographic cross-sectional study. *Mult Scler*. 2011;**17**(5):613–622. doi:10.1177/1352458510393772.
9. Braley TJ, *et al*. Obstructive sleep apnea and fatigue in patients with multiple sclerosis. *J Clin Sleep Med*. 2014;**10**(2):155–162.
10. Brass SD, *et al*. The underdiagnosis of sleep disorders in patients with multiple sclerosis. *J Clin Sleep Med*. 2014;**10**(9):1025–1031. doi:10.5664/jcsm.4044.
11. Alhazzani AA, *et al*. Insomnia among non-depressed multiple sclerosis patients: a cross-sectional study. *Egypt J Neurol Psychiatr Neurosurg*. 2018;**54**(1):17–17. doi:10.1186/s41983-018-0016-0.
12. Bamer AM, *et al*. Prevalence of sleep problems in individuals with multiple sclerosis. *Mult Scler*. 2008;**14**(8):1127–1130. doi:10.1177/1352458508092807.
13. Viana P, *et al*. InMS: chronic insomnia disorder in multiple sclerosis – a Portuguese multicentre study on prevalence, subtypes, associated factors and impact on quality of life. *Multiple Sclerosis Related Disord*. 2015;**4**(5):477–483. doi:10.1016/j.msard.2015.07.010.

14. Hensen HA, *et al*. Sleep-disordered breathing in people with multiple sclerosis: prevalence, pathophysiological mechanisms, and disease consequences. *Front Neurol*. 2018;**8**:740–740.
15. Boeschoten RE, *et al*. Prevalence of depression and anxiety in multiple sclerosis: a systematic review and meta-analysis. *J Neurol Sci*. 2017;**372**:331–341. doi:10.1016/j.jns.2016.11.067.
16. Baron KG, *et al*. Impact of psychotherapy on insomnia symptoms in patients with depression and multiple sclerosis. *J Behav Med*. 2011;**34**(2):92–101. doi:10.1007/s10865-010-9288-2.
17. Alexander M, *et al*. The national veteran sleep disorder study: descriptive epidemiology and secular trends, 2000–2010. *Sleep* 2016;**39**(7):1399–1410. doi:10.5665/sleep.5972.
18. Harris PA, *et al*. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;**42**(2):377–381. doi:10.1016/j.jbi.2008.08.010.
19. Berry RB, *et al*. AASM scoring manual updates for 2017 (Version 2.4). *J Clin Sleep Med*. 2017;**13**(5):665–666. doi:10.5664/jcsm.6576.
20. Shrivastava D, *et al*. How to interpret the results of a sleep study. *J Community Hosp Intern Med Perspect* 2014;**4**(5):24983–24983. doi:10.3402/jchimp.v4.24983.
21. Bastien CH, *et al*. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Med*. 2001;**2**(4):297–307. doi:10.1016/s1389-9457(00)00065-4.
22. Morin CM, *et al*. The Insomnia Severity Index: psychometric indicators to detect insomnia cases and evaluate treatment response. *Sleep* 2011;**34**(5):601–608. doi:10.1093/sleep/34.5.601.
23. Cole JC, *et al*. Validation of a 3-factor scoring model for the Pittsburgh sleep quality index in older adults. *Sleep* 2006;**29**(1):112–116. doi:10.1093/sleep/29.1.112.
24. Backhaus J, *et al*. Test–retest reliability and validity of the Pittsburgh Sleep Quality Index in primary insomnia. *J Psychosom Res*. 2002;**53**(3):737–740. doi:10.1016/s0022-3999(02)00330-6.
25. CME examination. *J Am Acad Dermatol*. 2015;**72**(6):942.
26. Gradisar M, *et al*. The Flinders Fatigue Scale: preliminary psychometric properties and clinical sensitivity of a new scale for measuring daytime fatigue associated with insomnia. *J Clin Sleep Med*. 2007;**3**(7):722–728.
27. Johns M, *et al*. New method for measuring daytime sleepiness: the Epworth Sleepiness Scale. *Sleep* 1991;**14**(6):540–545.
28. Levis B, *et al*. Accuracy of Patient Health Questionnaire-9 (PHQ-9) for screening to detect major depression: individual participant data meta-analysis. *BMJ* 2019;**365**:l1476–l1476.
29. Jordan P, *et al*. Psychometric analysis of the Generalized Anxiety Disorder scale (GAD-7) in primary care using modern item response theory. *PLoS One*. 2017;**12**(8):e0182162–e0182162. doi:10.1371/journal.pone.0182162.
30. Development of the World Health Organization WHOQOL-BREF quality of life assessment. The WHOQOL Group. *Psychol Med*. 1998;**28**(3):551–558.
31. "StataCorp" *Stata Statistical Software [computer program]*. Version 17. College Station, TX: StataCorp LLC.; 2021.
32. Kos D, *et al*. Origin of fatigue in multiple sclerosis: review of the literature. *Neurorehabil Neural Repair*. 2008;**22**(1):91–100. doi:10.1177/1545968306298934.
33. Merlino G, *et al*. Prevalence of 'poor sleep' among patients with multiple sclerosis: an independent predictor of mental and physical status. *Sleep Med*. 2009;**10**(1):26–34. doi:10.1016/j.sleep.2007.11.004.
34. Simmons RD, *et al*. Living with multiple sclerosis: longitudinal changes in employment and the importance of symptom management. *J Neurol*. 2010;**257**(6):926–936. doi:10.1007/s00415-009-5441-7.
35. Council M. *Fatigue and multiple sclerosis: evidence-based management strategies for fatigue in multiple sclerosis*. Washington, DC: Paralyzed Veterans of America; 1998.
36. Bixler EO, *et al*. Excessive daytime sleepiness in a general population sample: the role of sleep apnea, age, obesity, diabetes, and depression. *J Clin Endocrinol Metab*. 2005;**90**:4510–4515.
37. Kim SA, *et al*. Factors affecting fatigue severity in patients with obstructive sleep apnea. *Clin Respir J* 2017;**11**(6):1045–1051. doi:10.1111/crj.12682.
38. Khadadah S, *et al*. Effect of continuous positive airway pressure treatment of obstructive sleep apnea-hypopnea in multiple sclerosis: a randomized, double-blind, placebo-controlled trial (SAMS-PAP study). *Mult Scler*. 2022;**28**(1):82–92.
39. Stanton BR, *et al*. Sleep and fatigue in multiple sclerosis. *Multiple Sclerosis Journal*.4 2006;**12**:481–486.
40. Spielman AGP. The varied nature of insomnia. In: PJ H, ed. *Case Studies in Insomnia*. New York, NY: Springer; 1991.
41. Qaseem A, Kansagara D, Forciea MA, Cooke M, Denberg T, Physicians CGCotACo. Management of chronic insomnia disorder in adults: a clinical practice guideline from the American College of Physicians. *Ann Internal Med*. 2016;**165**(12):892.
42. Edinger JD, *et al*. Behavioral and psychological treatments for chronic insomnia disorder in adults: an American Academy of Sleep Medicine clinical practice guideline. *J Clin Sleep Med* 2021;**17**(2):255–262.
43. Medicine AAoS. *International Classification of Sleep Disorders:* 3rd ed. Darien, IL: American Academy of Sleep Medicine; 2014.
44. Clancy M, *et al*. Outcomes of cognitive-behavioral treatment for insomnia on insomnia, depression, and fatigue for individuals with multiple sclerosis: a case series. *Int J MS Care* 2015;**17**(6):261–267. doi:10.7224/1537-2073.2014-071.
45. Upton D, *et al*. What are the support needs of men with multiple sclerosis, and are they being met? *Int J MS Care* 2015;**17**(1):9–12. doi:10.7224/1537-2073.2013-044.
46. Voskuhl RR, *et al*. Sex differences in brain atrophy in multiple sclerosis. *Biol Sex Diff*. 2020;**11**(1):49. doi:10.1186/s13293-020-00326-3.
47. Walton C, *et al*. Rising prevalence of multiple sclerosis worldwide: insights from the Atlas of MS, third edition. *Mult Scler*. 2020;**26**(14):1816–1821. doi:10.1177/1352458520970841.
48. Rocchi C, *et al*. Sleep in multiple sclerosis patients treated with interferon beta: an actigraphic study. *Neurol Res*. 2020;**42**(9):744–748. doi:10.1080/01616412.2020.1773629.
49. Good P, *et al*. Impact of opioid therapy on sleep and respiratory patterns in adults with advanced cancer receiving palliative care. *J Pain Symptom Manage*. 2018;**55**(3):962–967. doi:10.1016/j.jpainsymman.2017.11.026.
50. Braley TJ, *et al*. Sleep and cognitive function in multiple sclerosis. *Sleep* 2016;**39**(8):1525–1533. doi:10.5665/sleep.6012.