

The relationship between fatigability and sleep quality in people with multiple sclerosis

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Abstract

Background: Perceived fatigue and fatigability are constructs of multiple sclerosis (MS)-related fatigue. Sleep disturbances lead to poor sleep quality, which has been found to be associated with perceived fatigue in people with MS (PwMS). However, the relationship between fatigability and sleep quality is unknown.

Objective: To explore the relationship between physical and cognitive fatigability with self-reported and objective measures of sleep quality in PwMS.

Methods: Fifty-one ambulatory PwMS participated in the study. Physical fatigability was measured by percent-change in meters walked on the six-minute walk test (6MWT) and in force exerted on a repeated maximal hand grip test. Cognitive fatigability was measured using response speed variability on the continuous performance test. Self-report sleep quality was measured using the Pittsburgh Sleep Quality Index, and objective sleep quality was measured using 1 week of actigraphy.

Results: Components of the Pittsburgh Sleep Quality Index and several actigraph parameters were significantly associated with physical fatigability and cognitive fatigability. However, controlling for depression eliminated the association between the sleep outcomes and cognitive fatigability and attenuated the association between the sleep outcomes and physical fatigability.

Conclusion: Poor sleep quality is related to fatigability in MS but depression appears to mediate these relationships.

Keywords: Multiple sclerosis, sleep quality, physical fatigability, cognitive fatigability

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Introduction

Multiple sclerosis (MS)-related fatigue is one of the most debilitating symptoms affecting people with MS (PwMS).¹ It interferes with daily function and is a major cause of unemployment.² MS-related fatigue is an umbrella term consisting of two different constructs: perceived fatigue and fatigability.³ Perceived fatigue is reported by the individual as tiredness in performing physical and cognitive tasks that interfere with daily function.⁴ Fatigability can be objectively quantified by a clinician or researcher and is the measure of change in the performance of physical or cognitive tasks over a period of time.³ Physical fatigability is the reduced ability to complete sustained physical tasks such as walking constantly for several minutes.³ Cognitive fatigability is described as the inability to sustain concentration and attention during demanding cognitive tasks such as following conversations.³

Approximately 60% of PwMS report experiencing sleep disturbances that eventually result in overall poor sleep quality.⁵ It has been suggested that sleep disturbances might exacerbate MS-related fatigue through excessive activation of the central nervous system (CNS).⁶ The exact mechanisms remain unclear, but excessive activation of the CNS may result from recurrent sleep arousals, central mechanisms such as lesions on the suprachiasmatic nucleus in the hypothalamus that regulates circadian rhythms, or elevation of certain inflammatory cytokines which may contribute to both sleep disturbances and increased MS-related fatigue.⁶ Poor sleep quality has been associated with a reduction in several quality of life indices including physical function, psychological well-being, and work ability.⁷ Furthermore, reduced sleep quality is associated with increased perceived fatigue in PwMS.^{8–11}



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However, it is unknown if poor sleep quality is associated with fatigability in PwMS. Understanding the relationship between fatigability and sleep quality will emphasize the need to consider sleep quality as an important clinical characteristic during the management of MS-related fatigue; sleep disturbances are often overlooked by clinicians in PwMS.¹² If poor sleep quality is found to be associated with fatigability in PwMS, then management of sleep disturbances could lead to improvements in fatigability and associated improvement in daily function for PwMS. Therefore, the purpose of this study was to investigate the relationship between fatigability and sleep quality in PwMS using both self-report and objective sleep measures.

Due to the involvement of the aforementioned central mechanisms in sleep disturbances and MS-related fatigue as well as the previous evidence that shows an association between poor sleep quality and perceived fatigue in PwMS, we hypothesized that poor sleep quality would be associated with physical and cognitive fatigability in PwMS.

Materials and methods

Participants

Participants were recruited in a consecutive manner from the MS clinic at the University of Kansas Medical Centre (KUMC) and through personal referral from consented participants over a 9 month period. The inclusion criteria were (1) 18–60 years of age, (2) relapsing–remitting or secondary progressive MS,¹³ (3) ability to ambulate with/without an assistive device, and (4) a score >24 on the Mini Mental Status Exam (MMSE).¹⁴ Exclusion criteria were (1) a history of alcohol/drug abuse or nervous system disorder other than MS, (2) severe physical, neurological, or sensory impairments that would interfere significantly with testing, (3) developmental history of learning disability or attention-deficit/hyperactivity disorder, (4) relapse and/or corticosteroid use within four weeks of assessment, (5) self-report of known untreated sleep disorder (such as sleep apnea, insomnia, or restless leg syndrome), (6) uncorrected vision loss that would interfere significantly with testing, (7) acute ischemic cardiovascular event or coronary artery bypass surgery less than 3 months ago, and (8) uncontrolled blood pressure with medication (BP > 190/110 mmHg). The study protocol was approved by the KUMC institutional review board.

Procedure

Participants were instructed to refrain from exercise for at least 24 hours prior to testing day, consuming caffeine beyond typical daily consumption so individuals were stimulated at their usual amount, and taking medications other than the ones they typically use. Participants first underwent a battery of questionnaires to assess their mood and sleep quality then performed the fatigability measures in random order. After the assessment, each participant was given an actigraph device and instructed to wear it for a week. Demographic characteristics were obtained from all the participants.

Sleep measures

The Pittsburgh Sleep Quality Index (PSQI) was utilized to measure self-report sleep quality over the past month.¹⁵ The PSQI is comprised of seven different components scores as well as a single global score ranging from 0–21 with a higher score indicating worse sleep quality.

An actigraph was used to objectively quantify sleep quality. Actigraphy is a cost effective method to measure sleep/wake cycles and has been used in PwMS.¹⁶ Each participant was given an actigraph device (Model wGT3X-BT[®], ActiGraph Corp, Pensacola, FL) with a stamped envelope to return it via USPS. Instructions were to wear the actigraph on their dominant wrist for seven consecutive days and remove it only during showering or swimming. The parameters of interest from the actigraph include: sleep efficiency, total sleep time, total time in bed, wake after sleep onset, and number of awakenings. Participants completed a sleep log to report napping time, time in bed, time in bed with lights out to sleep, time between light out to being asleep (latency), time woke in morning, and time got out from.

Fatigability measures

Physical fatigability was measured using change in performance on the six-minute walk test (6MWT) and hand held dynamometer grip strength test. The 6MWT has been previously modified in administration and scoring to assess physical fatigability in PwMS.¹⁷ In addition, time-remaining prompts were eliminated and participants were not informed of the test length. Physical fatigability was calculated as a percent change in the distance walked between the first and sixth minute.

The second measure to assess physical fatigability was change in performance on a grip strength test previously used in PwMS.¹⁸ Participants performed

15 trials of maximal hand grip contractions using a JAMAR hydraulic hand-held dynamometer,¹⁸ holding each contraction for five seconds, with a five-second rest between repetitions. The examiner informed the participants when to squeeze the handle by saying “Squeeze now” and then continue squeeze maximally until the examiner said “Stop.” A metronome heard only by the examiner using a headset was used to maintain the five-second intervals. Physical fatigability was calculated by measuring the percent change in kilograms (kg) between the first and last trial. The test was first administered using the dominant hand and then repeated using the non-dominant hand.

The continuous performance test (Connors 3TM) was utilized to assess cognitive fatigability using the response speed variability (RSV) score.¹⁹ RSV was previously found to be effective in detecting cognitive fatigability in PwMS.²⁰ The mean RSV T-score, the primary outcome measure of the RSV of the participant was used as the main outcome variable.

Other measures

To demonstrate that the fatigability tests were fatiguing the participants, current perceptions of fatigue were assessed immediately preceding and following each measure using the 1 item visual analog fatigue scale.²¹ The participants placed a mark (X sign) on a 100 mm line between “not at all fatigued” to “extremely fatigued” to indicate their current level of fatigue. The outcome measure was the value of the length in mm along the line the participants placed the mark at. Participants also completed the Beck Depression Inventory-Fast Screen,²² to assess depression, and the Patient Determined Disease Steps,²³ which measures disease status in PwMS.

Actigraph data analysis

ActiLife software (version 6.11.8) was used to perform wear time validation and to analyze the sleep data using the Cole–Kripke algorithm which has been validated for use in adult populations.²⁴ To be included in the data analysis, participants had to have at least four valid days of wear time (a valid day was defined as at least 10 hours of wear time per day which is equivalent to 600 minutes).²⁵ No individuals were excluded based on these criteria. The average wear time was 84%. One trained researcher reviewed each actigraph report and used the sleep log was used to verify the actigraph data. If the sleep log and actigraph data were within ≤ 30 minute agreement for time in bed, time out of bed, and total sleep time, the

actigraph data was used in analysis.²⁶ If there was a >30 minute difference between the sleep log data and actigraph data, the sleep graphs generated by the ActiLife software were visually examined and sleep periods were manually entered using the sleep log.²⁶

Statistical analysis

Data were entered into SPSS version 23 (IBM SPSS Statistics 23, ©IBM) for statistical analysis. Descriptive statistics were calculated for the demographics and all other variables and assumptions of normality were tested using the Shapiro-Wilk test. If assumptions of normality were met for continuous variables, Pearson’s product correlations were utilized to explore the association between the fatigability measures and sleep quality measures. Spearman’s product correlations were utilized when the assumptions of normality were not met and in variables of ordinal level. Differences in pre- and post-testing acute perceptions of fatigue measured using the one-item visual analog fatigue scale were analyzed using Wilcoxon signed-rank tests. Alpha level was set at 0.05.

Results

Fifty-one individuals participated in this study with a mean age of 47 ± 10.1 years old, mild disease severity 1.8 ± 1.6 , and minimal to mild depression 3.7 ± 3.1 (Table 1). The average number of medications was 7.19 ± 5 with a range 0–20 (Table 1). Actigraph details are listed in Table 2.

Fatigability and current perceived fatigue

There was a decrease in meters walked on the 6MWT by 12.7% ($p < .001$), the force exerted in the grip strength test decreased by 35.9% on the dominant hand ($p < .001$) and 33.2% on the non-dominant hand ($p < .001$), and current perceived fatigue was significantly higher following performance of each fatigability measure ($p > .001$ on all tests).

Association between physical fatigability and self-reported sleep quality

There were no significant associations between the PSQI global score and any of the physical fatigability measures (Table 3). There was a significant association between the sleep duration component of the PSQI and grip test percent change in the dominant hand ($\rho = -.397$, $p = .004$) and non-dominant hand ($\rho = -.366$, $p = .008$). There was also a significant association between the sleep quality component (a single self-rating question of the overall sleep quality) and the grip test percent change of

Table 1. Demographic and clinical characteristics of the study sample.

Gender (<i>n</i>)	43 F 8 M
Age	47 (10.1)
MS type (<i>n</i>)	46 RR 5 SP
Disease duration	12.6 (7.6)
Patient Determined Disease Steps	1.8 (1.6)
Mini Mental Status Exam	28.7 (1.6)
Beck Depression Inventory	3.7 (3.1)
Medications (<i>n</i> = 46)	7.19 (5.0) Range 0–20
Classification (<i>n</i>)*:	
Disease-modifying	25
Antiviral	4
Spasticity	14
Pain	15
Depression	18
Anxiety	2
Vitamin	32
Stimulant	9
Bladder activity	7
Sleep aid	5
Other	30
None	1
Caffeinated drinks/day (<i>n</i> = 45)	1.92 (1.34) Range 0–6
Data are reported as mean (standard deviation) expect when indicated number (<i>n</i>). RR: relapsing–remitting MS, SP: secondary progressive MS. *Number of individuals taking a medication within the listed classification. Individuals may be taking more than one medication within the classification.	

the non-dominant hand ($\rho = -.284, p = .043$). The 6MWT percent change score was not significantly associated with any of the PSQI components (Table 3). Post-hoc controlling for depression attenuated the significant correlations (Table 4). The sleep quality component and the grip test percent change of the dominant hand was also significant after controlling for depression ($\rho = -.358, p = .011$; Table 4).

Association between cognitive fatigability and self-reported sleep quality

There was no significant association between the PSQI global score and the cognitive fatigability measure (Table 3). The RSV score was significantly associated with the daytime dysfunction component of the PSQI ($\rho = .303, p = .030$). However, this association was no longer significant after controlling for depression ($\rho = .234, p = .102$; Table 4). There was no significant association between cognitive fatigability and the remaining PSQI components (Table 3).

Association between physical fatigability and actigraphy sleep quality

The 6MWT percent change score was significantly associated with the average awakenings time ($\rho = -.393, p = .004$; Table 5). However, this association was no longer significant after controlling for depression ($\rho = -.202, p = .159$; Table 6). The grip test percent change score of the non-dominant hand showed a significant association with sleep efficiency ($r = .364, p = .009$), total sleep time ($r = .357, p = .010$), and wake after sleep onset ($r = -.311, p = .026$) and these associations remained significant after controlling for depression (Table 6). The remaining actigraph parameters were not significantly associated with the fatigability measures (Table 5).

Association between cognitive fatigability and actigraphy

The RSV score was significantly associated with sleep efficiency ($r = -.342, p = .015$). The variability score was also significantly associated with wake after sleep onset ($r = .294, p = .039$; Table 5). However, these associations were no longer significant after controlling for depression (Table 6). Cognitive fatigability was not associated with the remaining actigraph parameters (Table 5).

Discussion

This is the first study that explored the relationship between physical and cognitive fatigability and sleep quality in PwMS. The findings demonstrate that less reported time spent sleeping is associated with higher physical fatigability assessed using grip test percent change but not 6MWT percent change and this relationship was attenuated after controlling for depression. Higher cognitive fatigability is associated with self-report higher daytime dysfunction, but not after controlling for depression. The findings using actigraphy indicate that higher physical fatigability is associated with a longer duration of

Table 2. Descriptive statistics of the self-reported (PSQI global score) and objective (actigraph) sleep measures.

PSQI (global score)	Total time in bed (min)	Total sleep time (min)	Sleep efficiency (%)	Wake after sleep onset (min)	Number of awakenings	Average awakening time (min)
8.1 (3.8)	489.3 (85.4)	439.1 (86)	89.5 (4.7)	48.2 (21)	12.3 (4.7)	4.1 (1.6)

Data are reported as mean (standard deviation).
PSQI: Pittsburgh Sleep Quality Index.

Table 3. Bivariate correlation analysis between the fatigability measures and the PSQI components.

PSQI	Fatigability measures			
	6MWT % change	Grip test % change, dominant	Grip test % change, non-dominant	RSV
Global	-.040 (.781)	-.216 (.128)	-.125 (.382)	.045 (.755)
Sleep quality	.100 (.487)	-.212 (.136)	-.284* (.043)	.064 (.656)
Sleep latency	-.175 (.221)	-.120 (.401)	-.034 (.812)	-.068 (.635)
Sleep duration	.074 (.604)	-.397* (.004)	-.366* (.008)	.112 (.434)
Sleep efficiency	.036 (.801)	-.265 (.061)	-.106 (.459)	-.070 (.624)
Sleep disturbances	.027 (.852)	.029 (.841)	-.133 (.353)	-.031 (.832)
Sleep medication	-.046 (.748)	.082 (.568)	.082 (.569)	-.049 (.733)
Daytime dysfunction	-.015 (.917)	-.103 (.472)	-.034 (.811)	.303* (.030)

Data are reported as correlation coefficient r (p -value).
*Statistically significant, $p < .05$.
PSQI: Pittsburgh Sleep Quality Index, 6MWT: six-minute walk test, RSV: response speed variability.

Table 4. Partial correlation analysis between the fatigability measures and the PSQI components with controlling for depression.

PSQI	Fatigability measures			
	6MWT % change	Grip test % change, dominant	Grip test % change, non-dominant	RSV
Global	-.035 (.811)	-.229 (.109)	-.228 (.111)	-.053 (.717)
Sleep quality	.164 (.256)	-.358* (.011)	-.349* (.013)	-.100 (.490)
Sleep latency	-.182 (.205)	-.112 (.438)	-.053 (.714)	-.146 (.313)
Sleep duration	.035 (.812)	-.402* (.004)	-.321* (.023)	.037 (.800)
Sleep efficiency	.045 (.758)	-.107 (.461)	-.130 (.368)	-.115 (.426)
Sleep disturbances	.059 (.685)	-.088 (.544)	-.174 (.227)	-.025 (.862)
Sleep medication	-.156 (.279)	.104 (.470)	.055 (.706)	-.031 (.833)
Daytime dysfunction	-.013 (.930)	-.071 (.623)	-.070 (.631)	.234 (.102)

Data are reported as correlation coefficient r (p -value).
*Statistically significant, $p < .05$.
PSQI: Pittsburgh Sleep Quality Index, 6MWT: six-minute walk test, RSV: response speed variability.

awakenings during the night assessed using 6MWT percent change score, but not after controlling for depression; higher physical fatigability is associated with lower sleep efficiency, lower total sleep time,

and longer wake time after the initiation of sleep assessed grip test percent change score of the non-dominant hand even after controlling for depression. Higher cognitive fatigability is associated with lower

Table 5. Bivariate correlation analysis between the fatigability measures and the actigraph sleep parameters.

Actigraph	Fatigability Measures			RSV
	6MWT % change	Grip test % change, dominant	Grip test % change, non-dominant	
Sleep efficiency	.080 (.574)	.128 (.371)	.364* (.009)	−.342* (.015)
Total sleep time	−.220 (.122)	.242 (.088)	.357* (.010)	−.028 (.849)
Wake after sleep onset	−.137 (.337)	−.128 (.371)	−.311* (.026)	.294* (.039)
Total time in bed	−.249 (.079)	.259 (.067)	.254 (.073)	.048 (.740)
Number of awakenings	.181 (.204)	−.050 (.725)	−.066 (.645)	.163 (.257)
Average awakening time	−.393* (.004)	−.044 (.760)	−.240 (.090)	.142 (.326)

Data are reported as correlation coefficient r (p -value).
*Statistically significant, $p < .05$.
6MWT: six-minute walk test, CPT: continuous performance test.

Table 6. Partial correlation analysis between the fatigability measures and the actigraph sleep parameters with controlling for depression.

Actigraph	Fatigability measures			RSV
	6MWT % change	Grip test % change, dominant	Grip test % change, non-dominant	
Sleep efficiency	−.036 (.803)	.227 (.113)	.384* (.006)	−.232 (.105)
Total sleep time	−.095 (.512)	.237 (.098)	.291* (.040)	−.031 (.832)
Wake after sleep onset	.019 (.897)	−.143 (.321)	−.304* (.032)	.185 (.199)
Number of awakenings	.233 (.103)	−.043 (.766)	.003 (.983)	.064 (.660)
Average awakening time	−.202 (.159)	−.076 (.598)	−.387 (.006)	.120 (.406)

Data are reported as correlation coefficient r (p -value).
*Statistically significant, $p < .05$.
6MWT: six-minute walk test, CPT: continuous performance test.

sleep efficiency and longer wake time after the initiation of sleep assessed using actigraphy, but not after controlling for depression. These findings support our hypothesis that poor sleep quality would be associated with physical and cognitive fatigability in PwMS, but indicates depression may mediate some of these relationships. Several of the fatigability and sleep measures were not found to be significantly associated which limits the interpretation of this study, but should spur future studies to continue to investigate the association between physical and cognitive fatigability and sleep quality (both self-report and objectively assessed) in individuals with MS.

The fatigability measures utilized in this study resemble everyday life activities (walking, hand motion, sustained attention, etc.) and these activities did cause fatigue in our participants based on the

significant deterioration in performance and the significant increase in acute perceptions of fatigue. In line with our findings, Goldman et al. showed deterioration in walking performance during the 6MWT in PwMS compared to healthy controls.¹⁷ Functional neuroimaging evidence demonstrates an association between decreased activation of motor and non-motor cortico-subcortico pathways in the brain during the execution of a motor task in PwMS.²⁷ The motor tasks represented in the present study are the 6MWT and hand grip test which both showed deterioration in performance for PwMS and are interpreted as physical fatigability. The correlation between physical fatigability and some of the actigraph measures may be partially explained through central mechanisms that involve decreased activation of non-motor pathways that are involved in regulating sleep quality like the hypothalamus,

and through elevated inflammatory cytokines in the CNS that are associated with increased MS-related fatigue and sleep disturbances in PwMS. It is possible that poor sleep quality may exacerbate physical fatigability in PwMS and future studies are needed to verify this contention.

A very interesting finding is that the relationship between self-report daytime dysfunction, sleep efficiency, and WASO measured using actigraphy and cognitive fatigability was negated after controlling for depression. Evidence suggests that fatigue and depression are likely interrelated,²⁸ and depression has been associated with impaired cognitive function in PwMS,^{29,30} however, little is known about the impact of depression on physical or cognitive fatigability. This study suggests that depression mediates the relationship between sleep measures and cognitive fatigability, but perhaps not physical fatigability or at least has less impact on physical fatigability. Future studies are needed to examine the impact of depression on the relationship between sleep measures and fatigability in PwMS.

In the present study, actigraph sleep parameters were significantly correlated with grip physical fatigability differently based on hand dominance. Severijns *et al.*,¹⁸ who used a similar hand grip test protocol to measure fatigability in PwMS, showed that despite a deterioration in performance during the test of both hands, there was no significant difference in physical fatigability based on hand dominance or affected side in PwMS. The authors argued that the involvement of central factors rather than peripheral muscle weakness influenced the findings.¹⁸ A recent functional neuroimaging study showed that PwMS demonstrated a decline in the activation of cortical motor and non-motor regions during a sustained motor task compared to healthy controls, suggesting the involvement of central factors with fatigability.²⁷ Therefore, it is likely that the significant association between the actigraph and physical fatigability of the non-dominant hand but not with the dominant hand in the current study is not due to hand dominance. Instead, it is possible that failure of the motor central regions to excite hand muscles was further exacerbated during the grip test on the non-dominant hand as it always followed the dominant side test. Further studies are needed to verify these conclusions and perhaps explore if a resting period between the two tests might change the findings.

The current study found that actigraph sleep parameters showed more relationships with physical fatigability measures than self-report sleep parameters.

One possible explanation is the previously reported lack of agreement between self-report sleep quality on the PSQI and objective sleep measures using actigraphy.³¹ (1) PwMS have been shown to underestimate their sleep quality on the PSQI;³² (2) the length and time period of reporting the two sleep quality measurements is different; one month for the PSQI reported before the assessment vs. 1-week for actigraphy measured after the assessment. Furthermore, actigraphy has also been shown to overestimate sleep efficiency and total sleep time.³³ Future studies are necessary to explore if having the actigraph measurement overlap with the PSQI reports would yield more agreement between the sleep quality measures.

The current study has some limitations. First, a control group of individuals without MS was not included, which limits the interpretation of the results. Also, generalizability is limited as the sample had mild disease severity and mostly relapsing-remitting MS. However, our findings are clinically important as they suggest an association between poor sleep quality and fatigability in a sample of individuals with mild disease impairments. Another limitation is that participants were instructed to continue taking their usual medications on the day of the assessment. This might affect the results by improving or inhibiting performance and responses on the tests depending on the medication, but our results clearly show there are still detriments in performance as well as poor sleep quality even with the usage of fatigue or sleep related medications. In addition, keeping the participants on their usual medication provides clinically relevant information as it reflects their normal daily habits.

Around 50% of PwMS have a diagnosable sleep disorder, but a much higher percentage of sleep disorders remain undiagnosed.³⁴ Although individuals with a self-report of a known untreated sleep disorder were excluded from participating in the current study, it is possible that there were participants with an undiagnosed sleep disorder which may have influenced our findings. There is evidence suggesting a significant association between obstructive sleep apnea and higher perceived fatigue in PwMS,³⁵ and based on the findings of the current study we expect that the presence of sleep disorders would affect the performance of physical and cognitive tasks. Future studies should consider actively screening for sleep disorders and then explore the relationship between sleep disorders and fatigability in PwMS. In addition, future studies may explore if treatment of sleep disorders or sleep disturbances improves fatigability, as

evidence suggests that treating sleep disorders significantly decreases perceived fatigue in PwMS.³⁶

Fatigability is an important construct of MS-related fatigue that is a common debilitating symptom in the MS population. What makes the current study findings significant is this is the first study to suggest that poor sleep quality (self-reported and objective) may be related to decreased task performance in both physical and cognitive aspects, but the relationship between sleep measures and cognitive fatigability is mediated by depression. As fatigability is related to the ability to efficiently perform tasks that require effortful activity such as walking or engaging in a conversation,³ poor sleep quality may further aggravate fatigability and may worsen the performance of everyday life tasks. Additional studies are needed to further investigate the relationship between physical and cognitive fatigability and sleep quality, how depression impacts this relationship, and determine if interventions to address sleep quality or depression would impact fatigability in individuals with MS.

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