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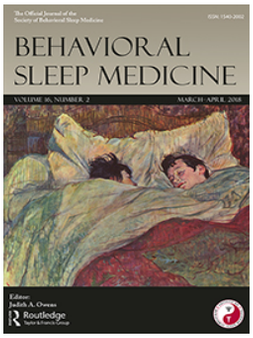
Published in:
Behavioral sleep medicine

DOI:
10.1080/15402002.2016.1173555

Publication date:
2018



Behavioral Sleep Medicine

ISSN: 1540-2002 (Print) 1540-2010 (Online) Journal homepage: http://www.tandfonline.com/loi/hbsm20

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To cite this article: Marianna Vitkova, Zuzana Gdovinova, Jaroslav Rosenberger, Jarmila Szilasiova, Pavol Mikula, Roy E. Stewart, Johan W. Groothoff & Jitse P. van Dijk (2018) Is Poor Sleep Quality Associated With Greater Disability in Patients With Multiple Sclerosis?, Behavioral Sleep Medicine, 16:2, 106-116, DOI: 10.1080/15402002.2016.1173555

To link to this article: https://doi.org/10.1080/15402002.2016.1173555

Published online: 18 May 2016.

Behavioral Sleep Medicine, 16:106–116, 2018

ISSN: 1540-2002 print/1540-2010 online
DOI: 10.1080/15402002.2016.1173555

Routledge
Taylor & Francis Group

Is Poor Sleep Quality Associated With Greater Disability in Patients With Multiple Sclerosis?

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Poor sleep is a serious burden for patients with multiple sclerosis (MS). The aim of this study is to assess whether the association between sleep quality and disability in MS patients is direct or mediated by depression, pain, and fatigue. We collected data from 152 patients with MS who filled out the Pittsburgh Sleep Quality Index, the Hospital Anxiety and Depression Scale, the Multidimensional Fatigue Inventory and one item of the Short Form-36 regarding pain. The

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relationship between poor sleep and disability was found to be indirect, mediated by depression ($p < 0.05$), pain ($p < 0.001$) and physical fatigue ($p < 0.01$). Treatment of sleep disturbances may have beneficial effects beyond improving sleep. It may reduce depression, pain, and physical fatigue, which in turn may lessen disability.

Poor sleep quality is a serious burden for patients with multiple sclerosis (MS) and could have an adverse impact on patients' health and quality of life (Merlino, 2009; Trojan et al., 2012). Research has shown that patients suffering from sleep disturbances have daytime impairment of cognition, mood, or performance that impacts on the patient and potentially on family, friends, coworkers, and caretakers (Schutte-Rodin, Broch, Buysse, Dorsey, & Sateia, 2008). Next, sleep disturbances may contribute to the genesis of fatigue, another debilitating symptom associated with MS (Veauthier et al., 2011). A few studies have even shown that poor sleep quality in MS patients was related to greater disability (Merlino, 2009; Neau et al., 2012). However, research on this topic is scarce with inconsistent findings (Bamer, Johnson, Amtmann, & Kraft, 2010; Merlino, 2009; Neau et al., 2012; Stanton, Barnes, & Silber, 2006). The study of Neau et al. (2012) showed that disturbed night sleep was related to greater disability, estimated using the Expanded Disability Status Scale (EDSS), independently from depression and pain. Merlino et al. (2009) reported similar results, showing that a significantly higher EDSS score was found more frequently among poor sleepers than among good sleepers and that the EDSS score was associated directly with the global PSQI score. On the other hand, some studies have found no connection between the presence of poor sleep quality in MS patients and disability as measured by the EDSS score (Bamer et al., 2010; Stanton et al., 2006). Bamer et al. (2010), exploring the role of multiple factors on sleep problems, did not find a relationship between sleep quality and disability, similar to the results of Stanton et al. (2006). The ambiguity of these results underlines the possible role of other factors that may influence this relationship.

Poor sleep quality in MS has been associated with a spectrum of variables. Mood disorders, pain, and fatigue are the most common symptoms related to poor sleep quality in MS patients (Lunde et al., 2012; Merlino, 2009; Vitkova et al., 2014). Relationship of pain and depression with poor sleep quality have been suggested to be bidirectional, where more severe pain and depression worsen sleep quality and vice versa, while the presence of fatigue is mostly explained as a consequence of poor sleep (Onen, Alloui, Gross, Eschallier, & Dubray, 2001; Paparrigopoulos, Ferentinos, Kouzoupis, Koutsis, & Papadimitriou, 2010). Depression, pain, and fatigue are also known to be associated with greater functional disability in patients with MS (Debouverie, Pittion-Vouyovitch, Brissart, & Guillemin, 2008; Solaro et al., 2004; Mattioli, Bellomi, Stampatori, Parrinelo, & Capra, 2011). A study by Solaro et al. (2004) showed that pain led to greater disability, as measured by the EDSS. Several studies have examined the link between depression and disability with contradictory results (Beiske et al., 2008; Chwastiak et al., 2002; Mattioli et al., 2011). Some of the studies found no association (Beiske et al., 2008; Chwastiak et al., 2002), whereas others found a strong association between these two factors (Mattioli et al., 2011). Other analyses exploring the association between fatigue and disability have shown the presence of fatigue to be related to greater disability (Mills &Young, 2010; Patrick, Christodoulou, Krupp, & New York State MS Consortium, 2009). Moreover, one longitudinal study found that a higher physical dimension of fatigue predicted increased disability after 3 years (Debouverie et al., 2008).

On the basis of the aforementioned studies showing links between sleep quality, depression, pain, fatigue, and disability and previous conflicting results regarding the relationship between poor sleep quality and functional disability, we aim to assess whether this relationship, controlled for age, gender, and disease duration, is direct or indirect, mediated by depression, pain, and physical fatigue. To the best of our knowledge, there is no study investigating the mediating role of depression, pain, and physical fatigue on the relationship between sleep quality and disability in an MS population controlled for age, gender, and disease duration. Understanding of interrelationships between these symptoms may help to find the most effective therapeutic strategies.

METHODS

Sample and Procedure

The participants consisted of a consecutive sample of patients with MS from the eastern part of Slovakia from our clinical MS database. The patients were recruited between September 2011 and January 2014. Exclusion criteria were cognitive dysfunction determined by a Mini Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975) score of < 24 and a history of a psychiatric or medical condition affecting the outcomes of the study. Of the 210 MS patients who were deemed eligible for the study, 58 patients refused to participate (response rate of 72%), and no patients were excluded because of the exclusion criteria. The final sample consisted of 152 patients.

The study was approved by the local Ethics Committee of the Faculty of Medicine, PJ Safarik University in Kosice in 2009. All participants signed an informed consent form prior to the study.

Data for this cross-sectional study were collected by means of mailed self-report questionnaires, a face-to-face interview, and a neurological examination. The invitation letter, the questionnaires, a written informed consent form and a nonresponse sheet were sent to the participant's home by postal mail. After two weeks, patients were contacted by a phone call to arrange an interview, enabling clarification of the patient's responses and completion of missing answers in the questionnaires. After this, a neurological examination was performed; the same neurologist (MV) examined all patients.

Measures

All questionnaires used in this study were translated from the original language into Slovak. A back-translation was then made to ensure that no meaning was lost in the original translation, with final changes in the translated version being made accordingly (Nagyova, 2009).

Sociodemographic and clinical data

Sociodemographic data were obtained from medical records, including information on gender, age, and disease duration.

Disability assessment

The degree of functional disability was measured using the EDSS (Kurtzke, 1983). The final EDSS score was based upon the neurological examination of eight functional systems: pyramidal, cerebellar, brain stem, sensory, bowel and bladder, visual, cerebral (mental), and so forth. Disability is graded on a continuum from 0 (normal neurological examination) to 10 (death caused by MS). EDSS scores from 1.0 to 4.5 refer to people with MS who are fully ambulatory. EDSS scores from 5.0 to 9.5 are defined as impairment to ambulation (Kurtzke, 1983).

Sleep quality

The Pittsburgh Sleep Quality Index (PSQI) is a self-administered questionnaire that assesses sleep quality and disturbances over the previous 4-week period (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). It consists of 19 questions, resulting in seven domain scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. Each domain has a possible score of 0–3, where a higher score indicates poorer sleep. The global PSQI score is the sum of all the domains scores (range 21); a higher score means lower quality of sleep, and a score higher than 5 indicates poor sleep (Buysse et al., 1989). Cronbach's alpha was 0.87 in our sample.

Depression

The depression subscale of the self-administered Hospital Anxiety and Depression Scale (HADS) questionnaire was used to measure the level of depression (Zigmond & Snaith, 1991). This questionnaire comprises 14 items. Seven of those assess the severity of depressive symptoms. Each item is rated on a 4-point scale ranging from 0 (no problem) to 3 (extreme problem), yielding the summary score of depression subscale (HADS-D), which ranges from 0 to 21, with a higher score meaning worse depression. A score of 7 or lower identifies noncases, 8–10 possible cases, and $\geq$ 11 definite cases (Zigmond, & Snaith, 1991). In the present study, Cronbach's alpha for the depression subscale was 0.85.

Pain

To assess pain we asked participants the pain question from the SF-36 (Ware & Sherbourne, 1992): "in the past months, how intense was your pain?" The score ranges from 1 (no pain) to 6 (very severe pain), with a higher score indicating more severe pain (Ware & Sherbourne, 1992).

Fatigue

The Multidimensional Fatigue Inventory (MFI-20) comprises 20 items that are designed to measure fatigue in five dimensions: general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue (Smets, Grassen, Bonke, & De Haes, 1995). There are 4 items in each dimension that are rated on a 5-point Likert scale; patients mark how much they agree with the given statements: 1 ("Yes, that is true") and 5 ("No, that is not true"). The total score in each dimension ranges from 4 (no fatigue) to 20 (highest possible fatigue; Smets et al., 1995). Only the physical fatigue dimension was used in our study. Cronbach's alpha for physical fatigue was 0.85.

Statistical Analyses

Firstly, the characteristics of the sample (age, gender, disease duration, quality of sleep, pain, depression, and physical fatigue) were described. Next, hierarchical regression analyses were performed using the enter method to explore the association between sleep quality and disability. In the first step, the relationship between sleep quality and disability was analyzed, and in the second step it was controlled for age, gender, and disease duration. In the third step, depression, pain, and physical fatigue were added to the model. Finally, bivariate correlations and multiple linear regression analyses were performed in order to calculate data for mediations. Tests of mediation (specific indirect effects for each mediator) were conducted to test our hypothesis that the effect of sleep quality on disability is mediated by the selected variables (depression, pain, and physical fatigue). Statistical analyses were performed using IBM SPSS 20.0 for Windows and Mplus version 7.1 (Muthén, & Muthén, 1988–2012).

RESULTS

The main clinical and demographic data for the sample are given in Table 1. The MS sample consisted of 152 patients (75% women) with an average age of 40 ± 10 years and mean disease duration of 7.5 ± 5.4 years. The mean EDSS score was 3.1 ± 1.31. The mean PSQI score was 6.1 ± 3.8.

TABLE 1
Demographic and Clinical Characteristics of the Sample

	All
	N (%) or Mean ± SD (range)
No. of patients, *n*	152
Gender	
Female	115 (75.2)
Disease duration	7.5 ± 5.4 (1–28)
Age (years)	40.0 ± 10.0 (18–61)
Clinical course	
Relapse-remitting	122 (79.7)
Secondary -progressive	31 (20.3)
EDSS	3.1 ± 1.3 (1.0–8.0)
PSQI	6.1 ± 3.8 (0–16)
HADS-depression	5.7 ± 4.2 (0–19)
Pain (SF-36)	2.8 ± 1.4 (1–6)
Physical fatigue (MFI-20)	13.5 ± 4.9 (4–20)

Note. EDSS: Expanded Disability Status Scale; *PSQI*: Pittsburgh Sleep Quality Index; *HADS*: Hospital Anxiety and Depression Scale; *SF-36*: Short-Form Health Survey; *MFI-20*: Multidimensional Fatigue Inventory-20.

TABLE 2
Hierarchical Regression Model: Factors Associated With Disability (EDSS)

	B	*β (p-value)*	R^2	*Adjusted* R^2	Δ R^2	*F/sig F change*
1. Model			.13	.12***	.13	21.70***
Sleep quality (PSQI)	.12	.35***				
2. Model			.35	.33***	.23	20.07***
Sleep quality (PSQI)	.10	.31***				
Age	.03	.22**				
Gender	–.54	–.20**				
Disease duration	.07	.31***				
3. Model			.45	.43***	.02	17.02*
Sleep quality (PSQI)	.03	.09				
Age	.02	.12				
Gender	–.50	–.18*				
Disease duration	.06	.29***				
Depression (HADS-D)	.11	.19**				
Pain (SF-36)	.23	.27***				
Physical fatigue (MFI-20)	.05	.20*				

Note. Adjusted R^2: explained variance by the predictors; Gender: male gender was set as the reference category; *PSQI*: Pittsburgh Sleep Quality Index; *HADS-D*: Hospital Anxiety and Depression Scale–Depression Subscale; *SF*-3: Short-Form Health Survey; *MFI-20*: Multidimensional Fatigue Inventory. ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$.

Factors Associated With Disability

Hierarchical regression analyses were carried out to find the relationship between sleep quality and disability, controlled for the other study variables. Firstly, the relationship between sleep quality and disability was controlled for age, gender, and disease duration. This model explained 33% of the variance in the EDSS score and confirmed that poor sleep quality is significantly associated with greater disability ($\beta = .31$, $p \leq .001$) after adjustment for age, gender, and disease duration. In the following step, depression, pain, and physical fatigue were entered to explore whether this relationship remains significant after controlling for these variables. The final model explained 43% of the variance in the EDSS score, but the quality of sleep was no longer found to be significantly associated with disability ($\beta = 0.09$, $p > 0.05$). The predictors of EDSS were disease duration ($\beta = .29$, $p \leq .001$), depression ($\beta = .19$, $p \leq .01$), pain ($\beta = .27$, $p \leq .001$), physical fatigue ($\beta = .17$, $p \leq .05$) and male gender ($\beta = –.18$, $p \leq .05$).

Mediation

Because the results of the regression analysis did not show a direct relationship between sleep quality and disability, multiple mediations were used to test the hypothesis that the effect of sleep quality on disability might be mediated by depression, pain and physical fatigue.

Following the Mplus version 7.1 guidelines for mediation analyses, bivariate correlations among the study variables were completed. The results showed a significant regression coefficient between sleep quality and all potential mediators: depression ($\beta = .23$, $p < 0.01$), pain ($\beta = .48$, $p < 0.01$), and physical fatigue ($\beta = .28$, $p < .01$), as well as significant relationships between disability and depression ($\beta = .19$, $p < .01$), pain ($\beta = .27$, $p < .01$) and

	Effects of sleep quality to disability	Est./S.E	Significance
Total direct	0.08	1.01	0.311
Total indirect	0.26	5.08	<0.001
Specific indirect			
depression	0.04	2.0	0.036
pain	0.13	3.2	0.001
physical fatigue	0.06	2.2	0.027
physical fatigue/pain	0.03	2.1	0.030

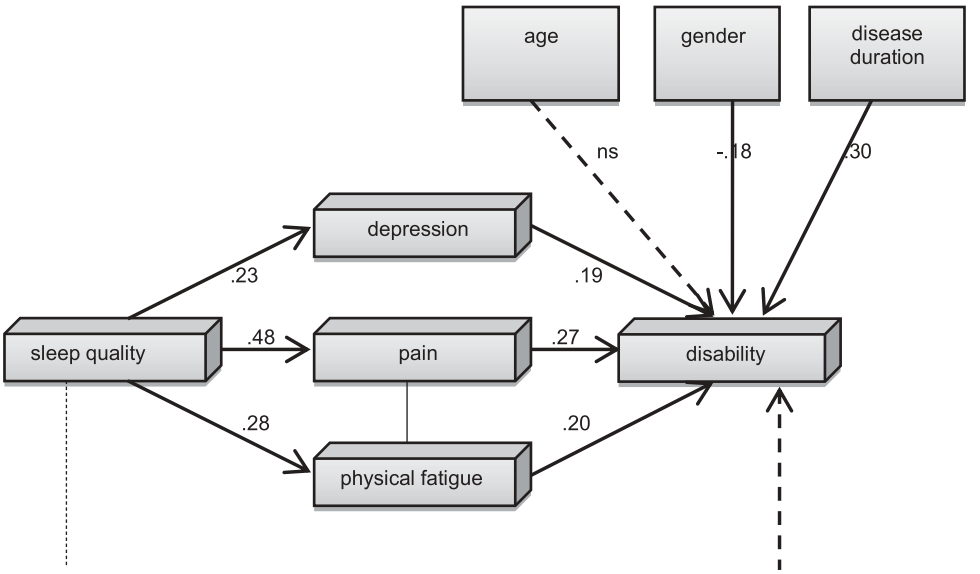

FIGURE 1 Final model showing depression, pain, and physical fatigue as significant mediators in the association between sleep quality and disability controlled for age, gender, and disease duration.

physical fatigue (β = .20, $p < .01$). The initial relationship between sleep quality and disability was also significant (β = .35, $p < .01$).

Finally, the standardized indirect effects for each mediator were calculated. The results confirmed that all variables—depression ($p < .05$), pain ($p < .001$), and physical fatigue ($p < .01$)—carried an influence of sleep quality on disability (Figure 1).

DISCUSSION

The aim of this study was to assess whether the association between sleep quality and functional disability in MS patients, controlled for age, gender, and disease duration, was direct or mediated by depression, pain, and physical fatigue. Our results showed that poorer sleep quality was

associated with greater disability after controlling for age, gender, and disease duration; however, after controlling for depression, pain, and physical fatigue, the significant relationship between sleep quality and disability disappeared. The mediation model in this study indicated that poorer sleep quality is related to greater disability, but this relationship was indirect and was fully mediated by depression, pain, and physical fatigue.

Research exploring the association between sleep quality and disability has thus far been scarce and has not presented any conclusive findings (Bamer et al., 2010; Merlino, 2009; Neau et al., 2012; Stanton et al., 2006). Our results indicating that poorer sleep quality was not associated with greater disability after controlling for age, gender, disease duration, depression, pain and physical fatigue are in line with the analyses of Bamer et al. (2010) and Stanton et al. (2006). These studies also provided evidence that the EDSS score was not significantly associated with sleep problems after controlling for several sociodemographic and clinical variables. On the other hand, a few studies have presented contrasting results (Merlino, 2009; Neau et al., 2012). Specifically, a study by Merlino et al. (2009) showed that a significantly higher EDSS score was found more frequently among poor sleepers than among good sleepers, and that the EDSS score was correlated directly with the global PSQI score, although the relationship was not controlled for other variables. Contradictory findings of previous research (Merlino, 2009; Neau et al., 2012) indicate that other factors may play a role in this relationship, but none of these studies analyzed the possible mediating effect of other variables on the relationship between sleep quality and disability.

Depression is a frequent disabling neuropsychiatric symptom in MS. Our mediation model showed that poor sleep quality in MS patients may worsen depressive symptoms, which in turn may be associated with greater disability. Several studies have clearly shown that poor sleep quality and depression are closely linked (Bamer et al., 2010; Vitkova et al., 2014) and appear to have a bidirectional relationship, where unrestful sleep worsens depression and vice versa (Paparrigopoulos et al., 2010). On the other hand, research investigating whether more depressive MS patients also have higher disability did not find such consistent results. Some studies found no significant association (Beiske et al., 2008; Chwastiak et al., 2002), whereas others found a strong association between depression and disability (Mattioli et al., 2011; Tsivgoulis, 2007).

We also found that pain is closely related to poor sleep quality and disability. In general, sleep and pain represent two strictly associated clinical conditions, and their relationship is considered to be bidirectional (Lautenbacher, Kundermann, & Krieg, 2006; Onen et al., 2001; Schuh-Hofera et al., 2013). That is, having pain disrupts the initiation and maintenance of sleep, whereas it is also possible that sleep disruption worsens pain (Lautenbacher et al., 2006). Research findings supported this by showing that sleep deprivation may interfere with pain processes that enhance pain sensitivity (Onen et al., 2001). Another study showed that a single night of sleep deprivation is able to induce generalized hyperalgesia (Schuh-Hofera et al., 2013). On the other hand, higher pain levels in MS patients are associated with greater disability. Several studies have confirmed this relationship (Ehde, 2003; Solaro et al., 2004). Solaro et al. (2004) showed a correlation between pain and EDSS. Moreover, this correlation was present for both neuropathic and somatic pain. Cross-sectional results from a study by Ehde et al. (2003) pointed out the contribution of pain to disability measured by EDSS; however, the authors stated that more research with longitudinal data is needed to clarify the causal pathways.

Fatigue is a disabling MS symptom that affects up to 80% of MS patients (Krupp et al., 1995; Mills &Young, 2010). Our results show that MS patients who complain of sleep disturbances have a greater level of fatigue, and those who experience greater levels of fatigue, especially its physical dimension, may then become increasingly disabled. These results are supported by previous research showing a significant relationship between poor sleep quality and an increased level of fatigue (Braley, Segal, & Chervin, 2014; Brass, Li, & Auerbach, 2014; Mills &Young, 2010; Veauthier, 2011). The study of Kaynak et al. (2006) showed that sleep disturbance in MS patients was a significant independent contributor to fatigue. We found that patients with a greater level of physical fatigue also had greater disability. This finding was confirmed in a longitudinal study by Debouverie et al. (2008), which showed that more physical fatigue predicted increased disability after 3 years.

This study is the first one conducted among MS patients that presents a complex model controlled for age, gender, and disease duration showing that the relationship between sleep quality and disability is mediated by depression, pain, and physical fatigue. Some limitations of this study should be mentioned. Most of the variables were evaluated by means of self-reported questionnaires, which may have introduced some bias although these have been used in different cultural settings and properly translated. It would be interesting to include both self-reported and objective measures of sleep disturbances such as polysomnograms to obtain a more comprehensive assessment of sleep problems. In addition, the use of better standardized questionnaires such as The Patient-Reported Outcomes Measurement Information System (PROMIS) could provide us with more comprehensive data regarding sleep quality, but regrettably a Slovak translation did not exist at the moment we performed the study. A second limitation is that the study has a cross-sectional design, which does not allow us to fully explore the causal pathways between the studied variables. It is possible that functional disability may affect depression, pain severity, and fatigue, which in turn may affect sleep quality. It is likely that the relationships are bidirectional to some extent. Longitudinal research is needed to examine the interrelationships between these variables to clarify causal associations.

The presented mediation model implies that the treatment of sleep disturbances may have beneficial effects beyond improving sleep. It may reduce depressive symptoms, levels of pain, and physical fatigue, which in turn may lessen disability. Again, the importance of longitudinal studies of samples of MS patients in predicting disability over time is emphasized by the current findings. Moreover, poor sleep quality can be the result of several specific sleep disorders such as restless leg syndrome, obstructive sleep apnoea, and insomnia, which are all common in patients with multiple sclerosis (Lunde, Bjorvatn, Myhr, & Bø, 2013). Therefore, it would be interesting to study if some differences exist in the relationship of specific sleep disorders with disability and how they contribute to overall quality of life of patients with multiple sclerosis.

FUNDING

This work was supported by the Slovak Research and Development Agency under contract No. APVV-0220-10 (80%). Furthermore, this work was supported by the Agency of the Slovak Ministry of the Education, Science, Research, and Sport of the Slovak Republic for the Structural Funds of the EU under project No. ITMS: 26220120058 (20%).

REFERENCES

Bamer, A. M., Johnson, K. L., Amtmann, D. A., & Kraft, G. H. (2010). Beyond fatigue: Assessing variables associated with sleep problems and use of sleep medication in multiple sclerosis. *Clinical Epidemiology*, *2*, 99–106.

Beiske, A. G., Svensson, E., Sandanger, I., Czujko, B., Pedersen, E. D., Aarseth, J. H., …Myhr, K. M. (2008). Depression and anxiety amongst multiple sclerosis. *European Journal of Neurology*, *15*, 239–245.

Braley, T. J., Segal, B. M., & Chervin, R. D. (2014). Obstructive sleep apnea and fatigue in patients with multiple sclerosis. *Journal of Clinical Sleep Medicine*, *10*, 155–162.

Brass, D. S., Li, C. S., & Auerbach, S. (2014). The underdiagnosis of sleep disorders in patients with multiple sclerosis. *Journal of Clinical Sleep Medicine*, *10*, 1025–1031.

Buysse, D. J., Reynolds, C. F., 3rd, Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh Sleep Quality Index: A new instrument for psychiatric practise and research. *Psychiatry Research*, *28*,193–213.

Chwastiak, L., Ehde, D. M., Gibbons, L. E., Sullivan, M., Bowen, J. D., & Kraft, G. H. (2002). Depressive symptoms and severity of illness in multiple sclerosis: Epidemiologic study of a large community sample. *The American Journal of Psychiatry*, *159*, 1862–1868.

Debouverie, M., Pittion-Vouyovitch, S., Brissart, H., & Guillemin, F. (2008). Physical dimension of fatigue correlated with disability change over time in patients with multiple sclerosis. *Journal of Neurology*, *255*, 633–636.

Ehde, D. M., Gibbons, L. E., Chwastiak, L., Bombardier, C. H., Sullivan, M. D., & Kraft, G. H. (2003). Chronic pain in a large community sample of persons with multiple sclerosis. *Multiple Sclerosis*, *9*, 605–611.

Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, *12*, 189–198.

Kaynak, H., Altintas, A., Kaynak, D., Uyanik, O., Saip, S., Ağaoğlu, J., …Siva, A. (2006). Fatigue and sleep disturbance in multiple sclerosis. *European Journal of Neurology*, *13*, 1333–1339.

Krupp, L. B., Coyle, P. K., Doscher, C., Miller, A., Cross, A. H., Jandorf, L., …Grimson, R. (1995). Fatigue therapy in multiple sclerosis: Results of a double-blind, randomized, parallel trial of amantadine, pemoline and placebo. *Neurology*, *45*, 1956–1961.

Kurtzke, J. F. (1983). Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS). *Neurology*, *33*, 1444–1452.

Lautenbacher, S., Kundermann, B., & Krieg, J. C. (2006). Sleep deprivation and pain perception. *Sleep Medicine Reviews*, *10*, 357–369.

Lunde, H. M., Aae, T. F., Indrevag, W., Aarseth, J., Bjorvatn, B., Myhr, K. M., …Bo, L. (2012). Poor sleep in patients with multiple Sclerosis. *PLoS ONE*, *7*, e49996.

Lunde, H. M., Bjorvatn, B., Myhr, K. M., & Bø, L (2013). Clinical assessment and management of sleep disorders in multiple sclerosis: A literature review. *Acta Neurologica Scandinavica,127*, 24–30.

Mattioli, F., Bellomi, F., Stampatori, C., Parrinello, G., & Capra, R. (2011). Depression, disability and cognitive impairment in multiple sclerosis: a cross sectional Italian study. *Neurological Sciences*, *32*, 825–832.

Merlino, G., Fratticci, L., Lenchig, C., Valente, M., Cargnelutti, D., Picello, M., …Gigli, G. L. (2009). Prevalence of "poor sleep" among patients with multiple sclerosis: an independent predictor of mental and physical status. *Sleep Medicine*, *10*, 26–34.

Mills, R. J., & Young, C. A. (2010). The relationship between fatigue and other clinical features of multiple sclerosis. *Multiple Sclerosis*, *17*, 604–612.

Muthén, L. K., & Muthén, B. O. (1998–2012). *Mplus user's guide* (7th ed.). Los Angeles, CA: Muthén & Muthén.

Nagyova, I. (Ed.). (2009). *Measuring health and quality of life in the chronically ill*. Kosice, Slovakia: Equilibria.

Neau, J. P., Paquereau, J., Auche, V., Mathis, S., Godeneche, G., Ciron, J., & Bouche, G. (2012). Sleep disorders and multiple sclerosis. A clinical and polysomnography study. *European Neurology*, *68*, 8–15.

Onen, S. H., Alloui, A., Gross, A., Eschallier, A., & Dubray, C. (2001). The effects of total sleep deprivation, selective sleep interruption and sleep recovery on pain tolerance thresholds in healthy subjects. *Journal of Sleep Research*, *10*, 35–42.

Paparrigopoulos, T., Ferentinos, P., Kouzoupis, A., Koutsis, G., & Papadimitriou, G. N. (2010). The neuropsychiatry of multiple sclerosis: Focus on disorders of mood, affect and behavior. *International Review of Psychiatry*, *22*, 14–21.

Patrick, E., Christodoulou, C., Krupp, L. B., & New York State MS Consortium. (2009). Longitudinal correlates of fatigue in multiple sclerosis. *Multiple Sclerosis, 15*, 258–261.

Schuh-Hofera, S., Wodarskic, R., Pfaua, D. B., Caspani, O., Magerl, W., Kennedy, J. D., …Treede, R. D. (2013). One night of total sleep deprivation promotes a state of generalized hyperalgesia: A surrogate pain model to study the relationship of insomnia and pain. *Pain*, *154*, 1613–1621.

Schutte-Rodin, S., Broch, L., Buysse, D., Dorsey, C., & Sateia, M. (2008). Clinical guideline for the evaluation and management of chronic insomnia in adults. *Journal of Clinical Sleep Medicine*, *4*, 487–504.

Smets, E. M. A., Grassen, B., Bonke, B., & De Haes, J. C. (1995). The multidimensional fatigue inventory (MFI) psychometric qualities of an instrument to assess fatigue. *Journal of Psychosomatic Research*, *39*, 315–332.

Solaro, C., Brichetto, G., Amato, M. P., Cocco, E., Colombo, B., D'Aleo, G., …Mancardi, G. L. (2004). The prevalence of pain in multiple sclerosis: A multicentric cross- sectional study. *Neurology*, *63*, 919–921.

Stanton, B. R., Barnes, F., & Silber, E. (2006). Sleep and fatigue in multiple sclerosis. *Multiple Sclerosis*, *12*, 481–486.

Trojan, D. A., Kaminska, M., Bar.Or, A., Benedetti, A., Lapierre, Y., Da Costa, D., …Kimoff, R. J. (2012). Polysomnographic measures of disturbed sleep are associated with reduced quality of life in multiple sclerosis. *Journal of Neurological Sciences, 316*, 158–163.

Tsivgoulis, G., Triantafyllou, N., Papageorgiou, C., Evangelopoulos, M. E., Kararizou, E., Sfagos, C., …Vassilopoulus, D. (2007). Associations of the Expanded Disability Status Scale with anxiety and depression in multiple sclerosis outpatients. *Acta Neurologica Scandinavica*, *115*, 67–72.

Veauthier, C., Radbruch, H., Gaede, G., Pfueller, C. F., Dörr, J., Bellmann-Strobl, J., ...Sieb, J. P. (2011). Fatigue in multiple sclerosis is closely related to sleep disorders: A polysomnographic cross-sectional study. *Multiple Sclerosis*, *17*, 613–622.

Vitkova, M., Gdovinova, Z., Rosenberger, J., Szilasiova, J., Nagyová, I., Mikula, P., …van Dijk, J. P. (2014). Factors associated with poor sleep quality in patients with multiple sclerosis differ by disease duration. *Disability and Health Journal*, *14*, 466–471.

Ware, J. E., Jr., & Sherbourne, C. D. (1992). The MOS 36-item short form health survey (SF-36). I. Conceptual framework and item selection. *Medical Care*, *30*, 473–483.

Zigmond, A. S., & Snaith, R. P. (1991). The hospital anxiety and depression scale. *Acta Psychiatrica Scandinavica*, *67*, 361–370.