Journal of Psychiatric Research 117 (2019) 24–30

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

Factors associated with fatigue in patients with insomnia

Seog Ju Kim[a,*], Somin Kim[a], Sehyun Jeon[a], Eileen B. Leary[b], Fiona Barwick[b], Emmanuel Mignot[b]

[a] Department of Psychiatry, Sungkyunkwan University School of Medicine, Samsung Medical Center, Seoul, Republic of Korea
[b] Department of Psychiatry and Behavioral Medicine, Stanford University Center for Sleep Sciences and Medicine, Stanford University, CA, USA

ARTICLE INFO

Keywords:
Sleep
Fatigue
Insomnia
Depression
Sleepiness

ABSTRACT

Although fatigue is common in insomnia, the clinical associates of fatigue in patients with insomnia are largely unknown. We aimed to investigate the clinical associates of fatigue in patients with insomnia. Patients visiting the Stanford Sleep Medicine Center completed the Insomnia Severity Index (ISI), Insomnia Symptom Questionnaire (ISQ), the Fatigue Severity Scale (FSS), the Epworth Sleepiness Scale (ESS), and the Patient Health Questionnaire (PHQ-9). Among 6367 patients, 2024 were diagnosed with insomnia (age 43.06 ± 15.19 years; 1110 women and 914 men) according to the ISI and the ISQ. Insomnia patients with severe fatigue (n = 1306) showed higher insomnia symptoms, daytime sleepiness, depression and longer habitual sleep duration than those without severe fatigue (n = 718). Higher insomnia symptoms, daytime sleepiness and depressive symptoms, and longer habitual sleep duration, independently predicted higher fatigue scores. Among insomnia patients with daytime sleepiness (ESS ≥ 10), only habitual sleep duration and depression predicted fatigue scores. The interaction between insomnia severity and daytime sleepiness significantly predicted the severity of fatigue. Depression was a significant mediator between insomnia and fatigue. For 598 insomnia patients undergoing overnight polysomnography (PSG), no significant correlations were found between fatigue and any PSG parameters. The current study suggests that managing insomnia or depression may reduce the fatigue of insomnia patients, whereas arbitrary efforts to prolong sleep duration may worsen their fatigue.

1. Introduction

Insomnia is characterized by persistent complaints of difficulty initiating and/or maintaining sleep despite adequate opportunity to sleep (Schutte-Rodin et al., 2008). Insomnia is usually accompanied by daytime distress and impairment (Lee et al., 2019a,b; American Academy of Sleep Medicine, 2014). Fatigue is a core daytime symptom of insomnia (Theorell-Haglöw et al., 2006).

Fatigue is defined as an overwhelming sense of tiredness, lack of energy, and feeling of exhaustion accompanied by impaired physical or mental functioning (Mariman et al., 2012). Fatigue is the most common and most persistent daytime symptom of insomnia (Riedel and Lichstein, 2000). Patients with insomnia disorder complain of fatigue more than those with any other sleep disorder (Lichstein et al., 1997).

Why insomnia patients are so frequently fatigued is unclear, however, as both insomnia and fatigue are influenced by various confounding factors. For example, insomnia and fatigue often co-occur in a number of medical or psychiatric disorders, particularly major depressive disorder (MDD)(Park et al., 2019; Lee et al., 2019a,b; Seok et al., 2019). As insomnia and fatigue are key features in MDD, both are included in the diagnostic criteria for MDD in the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5)(American Psychiatric Association, 2013). Therefore, the relationship between insomnia and fatigue may be mediated by comorbid depression.

Similarly, sleepiness can also confound the relationship between insomnia and fatigue (Theorell-Haglöw et al., 2006). The term “fatigue” is often viewed as synonymous with sleepiness despite their distinct implications in terms of diagnosis and treatment (Shahid et al., 2010). Excessive daytime sleepiness (EDS) can be manifested in patients with insomnia, particularly those with secondary insomnia caused by primary sleep disorders, such as sleep apnea and restless legs syndrome (RLS)(Lavie, 1983; Chesson et al., 1999). It remains controversial whether insomnia can be divided into alert insomnia with full-day hyperarousal and sleepy insomnia with daytime sleepiness (Chambers and Keller, 1993). Further confusing the clinical picture, EDS can also be a symptom of depression, notably the atypical form and in bipolar disorder.

In theory, insufficient sleep – or curtailed sleep time – in patients with insomnia could also result in fatigue, although this is not likely to be a common occurrence. Insufficient sleep is also associated with

* Corresponding author. Department of Psychiatry, Sungkyunkwan University School of Medicine, Samsung Medical Center 81 Ilwon-ro, Kangnam-gu, Seoul, 06351, Republic of Korea.
E-mail address: ksj7126@skku.edu (S.J. Kim).

https://doi.org/10.1016/j.jpsychires.2019.06.021
Received 5 February 2019; Received in revised form 28 May 2019; Accepted 28 June 2019

cognitive and emotional dysfunction, including depression, even after controlling for EDS (Lee et al., 2012, 2015). A potentially sleep-deprived state of insomnia patients may therefore directly or indirectly cause their fatigue. Unfortunately, although nearly all insomnia patients report "being unable to sleep enough to be rested", insufficient sleep is not synonymous with insomnia. Rather, many patients spend excess time in bed, which leads to shallow sleep. Objective insufficient nocturnal sleep is rare in insomnia and patients are often considered hyper-vigilant. Recently, a separate subtype of truly sleep deprived insomnia patient has been suggested.

Although strong associations have been found between insomnia and fatigue, only few studies have explored the determinants of fatigue in patients with insomnia. One study of 160 patients with insomnia (Fortier-Brochu et al., 2010) reported that subjective sleep disturbances and depressive symptoms were correlated with fatigue. However, these authors did not consider the effects of EDS or insufficient sleep on fatigue. To the best of our knowledge, no study has investigated the effects of various factors, including sleepiness or sleep duration, on fatigue in a large clinical sample with insomnia.

Objective sleep variables on polysomnography (PSG) and subjective reports on sleep can be largely different (Kay et al., 2015). Insomnia patients, especially those with paradoxical insomnia, tend to underestimate their sleep duration (Rezaie et al., 2018). Recent studies on insomnia have reported that objective short sleep time could predict prognosis and medical complication, while subjective reports of sleep time could not (Vgontzas et al., 2012; Bathgate et al., 2016; Johann et al., 2017). Although insomnia itself do not require PSG according to the clinical guideline (Kushida et al., 2005), objective variables on PSG may have clinical meanings different from self-report in insomnia research.

The objective of this study was to explore the independent determinants of fatigue in insomnia patients using a large sample of adults who had visited a sleep clinic. Our first hypothesis was that insomnia patients complaining of severe fatigue would show more severe insomnia symptoms. Our second hypothesis was that insomnia severity itself would predict fatigue above and beyond other insomnia-related factors, including habitual sleep duration, daytime sleepiness, and depression. Our last hypothesis was that the relationship between insomnia severity and fatigue would differ depending on the existence of daytime sleepiness. We also explored the association between fatigue and objective sleep variables on PSG, and the potential mediating factors between insomnia severity and fatigue, although these analyses are exploratory without a priori hypotheses.

2. Methods

2.1. Participants

Medical charts and polysomnographic findings of 6367 patients who visited the Stanford Sleep Medicine Center and comudex (ISI)(Bastien et al., 2001), and (2) presence of insomnia based on the criteria of the Insomnia Severity Questionnaire (ISQ)(Okun et al., 2009).

Two-step screening was used to determine the presence or absence of insomnia and to ensure that insomnia symptoms were rigorously and clearly identified. First, individuals who scored > 7 on the on the ISI (n = 5313) were selected and administered the ISQ. Among them, 3944 patients was diagnosed with insomnia by the ISQ criteria (Fig. 1). Severe medical conditions or other sleep disorders that commonly cause secondary insomnia were excluded. Mild or benign medical conditions were not excluded considering the recent concept of comorbid insomnia.

We intended to exclude patients whose insomnia was better explained by medical condition or other sleep disorders as the diagnostic criteria of insomnia disorder (American Academy of Sleep Medicine, 2014). However, as it is too difficult to decide these conditions without comprehensive clinical evaluations, we set following operational

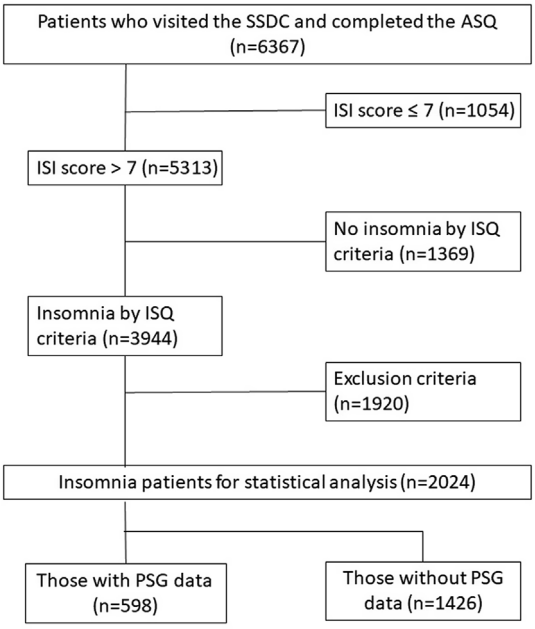

Fig. 1. Inclusion and exclusion of study subjects.

exclusion criteria: (1) severe medical conditions (malignancy under active treatment, severe organ failure, recent cerebrovascular accidents, repeated and refractory seizure, neurocognitive disorder, psychosis, or severe brain damage), (2) age < 18 years, (3) pregnancy, (4) regular participation in shiftwork, (5) narcolepsy; (6) moderate to severe sleep apnea [apnea hypopnea index (AHI) > 15] in patients with PSG data or previous history of the diagnosis of sleep apnea in patients without PSG data; (7) severe periodic limb movements during sleep [periodic limb movements index (PLMI) > 50)](Natarajan, 2010); (8) moderate to severe RLS defined by the ASQ (Leary et al., 2015). Among 3944 patients who met inclusion criteria, 1920 patients were excluded according to these criteria. Finally, data from 2024 patients with insomnia were chosen for the analysis (Fig. 1). The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human subjects/patients were approved by the Institutional Review Board of Stanford University (protocol #41283).

2.2. Measures

The ASQ is a comprehensive electronic sleep disorders questionnaire consisting of novel questions and validated measures (Leary et al., 2013). The purpose of the ASQ is to collect standardized subjective sleep data on diverse communities (including sleep clinics, clinical trials, large cohort studies, and the general population) while building a research repository of anonymized ASQ data. It uses complex branching logic to lead users through a comprehensive set of questions covering topics relevant to sleep, including current sleep symptoms, sleep habits and schedule, daytime fatigue, medical history, and current medications. It also asks about symptoms of, and previous treatments, for other sleep disorders, including insomnia, obstructive sleep apnea (OSA), RLS, narcolepsy and other disorders. It is set up in a modular fashion and takes approximately 20 min to complete for a healthy user and 35 min for a sleep clinic patient. ASQ data on habitual sleep latency, habitual sleep duration, and weekday sleep efficiency (the ratio of total time asleep to total time in bed) were used in these analyses.

Among sleep habit variables in ASQ, habitual sleep duration has been chosen for main analysis. Short habitual sleep duration can

represent insufficient sleep or long-term partial sleep deprived state, while it is not included in the criteria or the definition of insomnia. On the contrary, sleep efficiency, sleep latency, or wake time after sleep onset directly represent the initial, middle or terminal sleeping difficulties, which are core criteria of insomnia. As we used ISI for assessing severity of insomnia, these sleep habit variables were not included in the main analysis. The habitual sleep duration has been defined by the question "On average, how much sleep do you get on week nights?". The participants were requested to answer by minutes. Other demographic and clinical data, including comorbid medical conditions, were collected by reviewing the electronic medical records.

The ISI (Bastien et al., 2001) was used to screen for insomnia. The ISI is a seven-item questionnaire with a five-point scale. Three items are on the severity of initial, maintenance or terminal insomnia. Other four items are on the satisfaction, interference, noticeability, and distress of sleep problems. Higher ISI scores indicate more insomnia symptoms. ISI is suitable for measuring severity of insomnia among patients with definite insomnia, as it is more focused on the interference or disability of sleep problem. However, sole reliance on ISI for the diagnosis of insomnia may be insufficient, especially in clinic visiting patients who may have diverse sleep problems.

The presence or absence of significant insomnia was finally defined by ISQ, while ISI were used for first screening and severity measuring. The ISQ (Okun et al., 2009) was administered through the ASQ to individuals who scored > 7 on the ISI. The ISQ was a 13-item self-report questionnaire to differentiate the presence or absence of insomnia. ISQ was designed to provide clinically relevant definition of insomnia which is consistent with diagnostic classification criteria. The ISQ is based on the DSM-IV criteria for primary insomnia (American Psychiatric Association, 2000), which are in accordance with the American Academy of Sleep Medicine's (AASM) Research Diagnostic Criteria (RDC)(Edinger et al., 2004). High reliability (Cronbach alpha = 0.89) and high specificity (> 90%) were established in ISQ in a previous study (Okun et al., 2009).

The Fatigue Severity Scale (FSS)(Krupp et al., 1989) was used to assess fatigue. The FSS is a nine-item questionnaire that addresses the effects of fatigue on everyday functioning, including motivation, physical activity and work, family, and social behavior. The cut-off score for severe fatigue of > 36 was used to divide patients with insomnia into groups with and without severe fatigue.

The Epworth Sleepiness Scale (ESS)(Johns, 1991) was used to measure daytime sleepiness. The ESS uses a four-point scale to assess the likelihood that the subject will doze off or fall asleep in eight different situations. An ESS score > 10 indicates the presence of EDS and was used as a threshold when subjects were split by presence of daytime sleepiness.

The Patient Health Questionnaire (PHQ-9)(Kroenke and Spitzer, 2002), a nine-item self-report module, was used to assess depressive symptoms. The PHQ-9 uses a four-point scale to ask about DSM-IV criteria for depression.

PSG were conducted by the decision of sleep physicians after clinical evaluation of medical features. Usually, PSG were performed to evaluate sleep-related breathing disorders, parasomnia, narcolepsy or seizure. The insomnia without symptoms/signs suggesting above sleep disorders does not typically necessitates PSG. Of the 2024 insomnia patients, 598 underwent overnight polysomnography (PSG). Level 1 nocturnal PSG were performed in a sleep lab. The sleep stage and events were scored according to the criteria of the AASM Manual for the Scoring of Sleep and Associated Events (American Academy of Sleep Medicine, 2007). The PSG parameters used for the current study were the AHI, the PLMI, total sleep time (TST), sleep efficiency (SE), wakefulness after sleep onset (WASO), REM latency, sleep latency, and the sleep stages N1, N2, N3, and REM.

2.3. Statistical analyses

Patients with insomnia per ISQ cut-off were divided into two groups: those with and without severe fatigue per FSS cut-off. Group differences in demographic and clinical characteristics involving continuous variables were evaluated using independent *t*-tests. Group differences involving categorical variables were assessed using the chi-square test. Pearson's correlation analysis was used to investigate associations between fatigue and those factors that differed between insomnia patients with and without fatigue. For those factors significantly associated with fatigue, a multiple regression analysis was performed to determine the independent effects of each factor on fatigue.

As there are many association between independent variables, two additional analyses were conducted to examine the effects of daytime sleepiness, depression, and habitual sleep duration on the relationship between insomnia severity and fatigue severity. To examine possible interaction effects, 3 different interaction terms (ISI x ESS, ISI x PHQ-9, and ISI x habitual sleep duration) were included in the regression model. To examine possible mediating effects of daytime sleepiness, depression or habitual sleep duration in the relationship between insomnia severity (independent variable) and fatigue severity (dependent variable), mediation analyses were also conducted (Sobel, 1982). A two-tailed p-value < .05 was considered significant. All statistical analyses were conducted using SPSS software version 20.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Demographic and clinical characteristics

Among 2024 patients with insomnia (age = 43.06 ± 15.19; range 18–90 years), 1110 were women (59.03%) and 914 were men (40.97%). The demographic and clinical characteristics of the patients are displayed in Table 1.

Table 1
Comparison of demographic data or insomnia-related variables between insomnia patients with and without severe fatigue.

	Total (*N* = 2024)	Insomnia patients with severe fatigue (*N* = 1306)	Insomnia patients without severe fatigue (*N* = 718)		
	mean ± SD	mean ± SD	mean ± SD	t	p
Age	43.06 ± 15.19	41.70 ± 14.85	45.54 ± 15.49	5.49	< 0.01
Gender	Female = 1110 (54.84%)	Female = 750 (57.43%)	Female = 360 (50.14%)	chi = 9.93	< 0.01
ESS	7.66 ± 5.18	8.10 ± 5.24	6.86 ± 4.97	5.18	< 0.01
ISI	17.74 ± 4.74	18.29 ± 4.80	16.73 ± 4.45	7.15	< 0.01
PHQ-9	9.14 ± 5.43	10.81 ± 5.41	6.10 ± 3.94	20.52	< 0.01
Habitual sleep duration	363.17 ± 133.29	368.77 ± 137.86	352.97 ± 123.99	2.56	0.01

Abbreviation: ESS = Epworth Sleepiness Scale; ISI = Insomnia Severity Index; MWT = Mean Wake Time at night; PHQ-9 = Patient Health Questionnaire; FSS = Fatigue Severity Scale.

3.2. Comparison between insomnia patients with and without severe fatigue

Insomnia patients with and without severe fatigue differed significantly by age, gender, and all self-report symptoms (see Table 1). Insomnia patients with severe fatigue were 4 years younger, were more likely to be female (odds ratio = 1.34), and reported 16 min longer habitual sleep duration (all $p < .01$). They also reported more insomnia symptoms (ISI = 18.29 ± 4.80 versus 16.73 ± 4.45, $p < 0.01$), more daytime sleepiness (ESS = 8.10 ± 5.24 versus 6.86 ± 4.97, $p < 0.01$) and more depression symptoms (PHQ-9 = 10.81 ± 5.41 versus 6.10 ± 3.94, $p < 0,01$)(Table 1).

Insomnia patients who underwent PSG were also younger ($t = 4.37$, $p < .01$) and more likely to be female (59.03% vs. 53.09%, $\chi^2 = 6.01$, $p = .01$) than were insomnia patients who did not undergo PSG. They had lower ISI scores ($t = 2.81$, $p = .01$), shorter sleep latencies ($t = 4.12$, $p < .01$), and longer habitual sleep durations reported on the ASQ ($t = 2.30$, $p = .02$) than patients who did not undergo PSG. However, there were no differences on any PSG sleep parameters between insomnia patients with and without severe fatigue. Both groups showed normal sleep architecture (N1 = 8.8%, N2 = 59.7%, N3/N4 = 15.8%, REM = 19.1%), with total sleep time > 6.5 h and sleep efficiency > 80% despite wakefulness after sleep onset of 70 min (see Table 2). No differences in the ESS, PHQ, FSS, or average time awake at night were detected between insomnia patients with and without PSG data.

3.3. Correlation between insomnia, sleepiness, depression, sleep duration and fatigue

Correlational analyses showed that FSS scores were significantly and positively correlated with levels of self-reported depressive symptoms (PHQ, $r = .54$, $p < .001$), insomnia symptoms (ISI, $r = 0.22$, $p < .001$), daytime sleepiness (ESS, $r = 0.15$, $p < .001$), and habitual sleep duration ($r = 0.08$, $p < .001$)(Fig. 2). ISI scores were positively correlated with PHQ scores ($r = 0.40$, $p < .001$), and negatively with ESS scores ($r = -.10$, $p < .00$) and sleep duration ($r = -.34$, $p < .001$). The ESS scores were positively associated with PHQ scores ($r = 0.08$, $p < .001$) and sleep duration ($r = 0.15$, $p < .001$). PHQ scores were negatively correlated with sleep duration ($r = -.15$, $p < .001$). No significant correlations were found between FSS scores and any of the PSG parameters.

3.4. Independent predictors of fatigue

A multiple regression analysis was performed with FSS score as the dependent variable and variables significantly correlated with fatigue as criterion variables (age, gender, PHQ-9, ISI, ESS, and habitual sleep duration)(Table 3). The multiple regression model showed that fatigue was significantly predicted by younger age (standardized ß = −.09, < .001), female gender (ß = 0.05, $p < .01$), longer habitual sleep duration (ß = 0.12, $p < .001$), and higher levels of daytime sleepiness (ESS, ß = 0.11, $p < .001$), insomnia symptoms (ISI, ß = 0.07, $p < .01$), and depressive symptoms (PHQ-9, ß = 0.50, $p < .001$). When interaction terms for insomnia severity and daytime sleepiness, depression or sleep duration (ISI x ESS, ISI x PHQ-9, and ISI

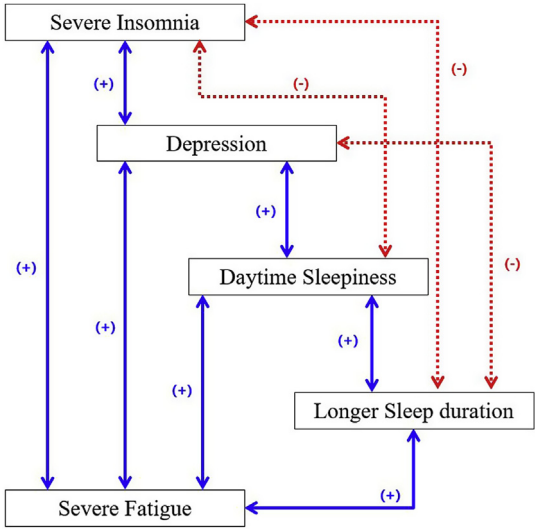

Fig. 2. Correlation between Insomnia severity, Daytime sleepiness, Depression, Habitual sleep duration, and Fatigue severity. Note: Solid lines indicate positive correlation, while dashed lines indicate negative correlation.

Table 3
Predictors of fatigue in all patients with insomnia.

Variable	*B*	*t*	R^2
(constant)		11.21***	.33***
Age	−.09	−4.91***	
Gender	.05	2.68**	
ESS	.11	5.91***	
PHQ-9	.50	24.78***	
ISI	.07	3.20**	
Habitual sleep duration	.12	6.00***	

Note. Multiple regression model (independent variables = age, gender, ESS, PHQ-9, ISI, and sleep duration; dependent variable = FSS).
Abbreviations: ISI = Insomnia Severity Index; ESS = Epworth Sleepiness Scale; PHQ-9 = Patient Health Questionnaire; FSS = Fatigue Severity Scale.
**p < .01, ***p < .001.

Table 2
Nocturnal Polysomnographic data of insomnia patients with and without severe fatigue.

		Total (N = 598)	Insomnia patients with severe fatigue (N = 185)	Insomnia patients without severe fatigue (N = 413)		
		mean ± SD	mean ± SD	mean ± SD	t	p
PSG	AHI	8.31 ± 3.53	8.28 ± 3.47	8.36 ± 3.66	0.24	0.81
	PLMI	4.06 ± 8.37	3.86 ± 8.06	4.50 ± 9.03	0.86	0.39
	TST (min)	398.19 ± 82.13	401.15 ± 83.87	391.56 ± 77.91	1.32	0.19
	SE (%)	81.52 ± 12.76	81.34 ± 12.89	81.91 ± 12.49	0.51	0.61
	WASO (min)	69.55 ± 58.10	69.44 ± 57.95	69.80 ± 58.60	0.07	0.94
	STAGE 1 (%)	8.77 ± 5.66	8.69 ± 5.79	8.97 ± 5.35	0.57	0.57
	STAGE 2 (%)	59.66 ± 11.20	59.42 ± 11.71	60.20 ± 9.99	0.79	0.43
	STAGE 3 (%)	12.49 ± 10.85	12.71 ± 11.01	12.01 ± 10.48	0.73	0.47
	STAGE 4 (%)	3.26 ± 6.53	3.33 ± 6.77	3.12 ± 5.98	0.36	0.72
	STAGE R (%)	19.06 ± 6.88	19.18 ± 7.17	18.80 ± 6.20	0.62	0.54
	REM latency (min)	128.26 ± 82.53	131.82 ± 85.39	120.32 ± 75.37	1.58	0.12
	Sleep latency (min)	17.97 ± 26.50	18.51 ± 24.93	16.76 ± 29.75	0.75	0.46

Abbreviation: SL = sleep latency; TST = total sleep time; WASO = waking after sleep onset.

x habitual sleep duration) were included in the regression model, only the interaction between insomnia severity and daytime sleepiness (ISI x ESS, ß = −.27, p < 0.001) significantly predicted the severity of fatigue.

Mediation effects of daytime sleepiness, depression, and habitual sleep duration (all mediating variables) between insomnia severity (independent variable) and fatigue severity (dependent variable) were also examined. In the mediation analyses, depression was a significant partial mediator between insomnia severity and fatigue severity (Sobel test statistic = 16.28, p < 0.01). The insomnia severity significantly predicted depression and fatigue severity in simple regression. Both insomnia and depression significantly predicted the fatigue severity in multiple regression model using insomnia severity and depression as independent variables. Daytime sleepiness and habitual sleep duration did not mediate the effects of insomnia on fatigue.

3.5. Predictors of fatigue in insomnia patients with and without excessive daytime sleepiness

As the interaction between insomnia severity (ISI) and daytime sleepiness (ESS) predicted the severity of fatigue (FSS), the insomnia group was divided into those with and without daytime sleepiness. The results of the multiple regression analyses – in which FSS was the dependent variable and age, gender, ISI, PHQ and habitual sleep duration were the independent variables) differed depending on level of daytime sleepiness (Table 4). Age (ß = −.12, p < .001), PHQ (ß = 0.49, p < .001), ISI (ß = 0.10, p < .01) and habitual sleep duration (ß = 0.10, p < 0.001) significantly predicted FSS scores in insomnia patients without EDS. However, only gender (ß = 0.07, p < .05), PHQ scores (ß = 0.55, p < .001), and habitual sleep duration (ß = 0.16, p < .001) – but not ISI scores – were predictive of FSS scores of insomnia patients with EDS.

4. Discussion

Consistent with our first hypothesis, insomnia patients with severe fatigue had more severe insomnia symptoms. They also showed more daytime sleepiness, depressed mood, and longer habitual sleep duration. Our findings suggest that significant fatigue in insomnia could be a proxy for insomnia severity. The severity of insomnia predicted fatigue independently from daytime sleepiness, depression, and habitual sleep duration.

Table 4
Predictors of fatigue in insomnia patients with and without excessive daytime sleepiness.

	Variable	*B*	*t*	R^2
Insomnia patients without EDS (ESS score < 10)	(constant)		1.98**	.30***
	Age	−.12	−4.91***	
	Gender	.04	1.61	
	PHQ-9	.49	19.36***	
	ISI	.10	3.58***	
	Habitual sleep duration	.10	3.91***	
Insomnia patients with EDS (ESS score ≥ 10)	(constant)		2.34**	.34***
	Age	−.04	−1.09	
	Gender	.07	2.09*	
	PHQ-9	.55	16.01***	
	ISI	−.004	−0.12	
	Habitual sleep duration	.16	4.98***	

Note. Multiple regression model (independent variables = age, gender, ESS, PHQ-9, ISI, and sleep duration; dependent variable = FSS).
Abbreviations: EDS = excessive daytime sleepiness; ISI = Insomnia Severity Index; ESS = Epworth Sleepiness Scale; PHQ-9 = Patient Health Questionnaire; FSS = Fatigue Severity Scale.
**p < .01, ***p < .001.

Our second hypothesis was also supported, as the severity of insomnia predicted the severity of fatigue even after controlling for age, gender, daytime sleepiness, depression, habitual sleep duration, and the interaction between insomnia and other variables. This finding suggests that fatigue in insomnia is caused by unknown characteristics of insomnia (i.e., characteristics other than depressed mood, daytime sleepiness, or insufficient habitual sleep duration). One possibility may be that fatigue reflects dysfunctional cognition or beliefs about sleep, which are commonly reported by patients with chronic insomnia (Woodley and Smith, 2006; Morin et al., 2007). One study found that fatigue in depressed patients with insomnia was more strongly associated with dysfunctional beliefs about sleep than with the overall severity of insomnia or depression (Carney et al., 2014). Specifically, ruminating about fatigue or avoiding activities after poor nocturnal sleep was associated with fatigue (Morin et al., 2007). Dysfunctional beliefs about sleep and fatigue might increase the severity of insomnia by leading to nighttime hyperarousal in bed and daytime hypervigilance to fatigue. Cognitive Behavioral Therapy for Insomnia (CBT-I), which addresses the fear of wakefulness at night or fatigue during daytime activities, could be useful for these patients.

Another finding, which corresponded to our last hypothesis, was that insomnia severity was associated with fatigue only in insomnia patients without daytime sleepiness. To our knowledge, this is the first report to identify the determinants of fatigue in relation to daytime sleepiness in a large clinical sample of insomnia patients. This finding suggests that fatigued patients who report daytimes sleepiness have a different phenotype (Chambers and Keller, 1993; Pillai et al., 2015). The fatigue of patients with both insomnia and daytime sleepiness was mainly associated with depressed mood. It has been proposed that insomnia with daytime sleepiness is a very common feature of major depression (Fava, 2004). Our findings suggest that the determinants of fatigue differ between “alert” insomnia without daytime sleepiness and “sleepy” insomnia with daytime sleepiness. Fatigue combined with daytime sleepiness and insomnia might be caused by depression rather than by sleepiness or insomnia itself.

A complex interrelationship was found between insomnia severity, daytime sleepiness, depressive symptoms, habitual sleep duration, and fatigue. Fatigue was positively correlated with insomnia severity, daytime sleepiness, depressive symptoms, and habitual sleep duration. All these factors independently and significantly predicted fatigue in the regression model, even after controlling for each other. However, insomnia severity was positively correlated only with depression, whereas it was negatively correlated with daytime sleepiness and habitual sleep duration. The less daytime sleepiness despite short sleep duration in severer insomnia may represent hyper-arousal state of severe insomnia. This is in line with a recent reports that patients with subthreshold insomnia showed higher daytime sleepiness than those with severer insomnia (Pillai et al., 2015). Depression was positively correlated with daytime sleepiness but negatively correlated with habitual sleep duration, which are in line with previous reports on the association between depression and sleep in adolescents (Lee et al., 2012) or nurse (Chen et al., 2019).

On the exploration over the mediating factors between insomnia and fatigue, we found that depression partially mediated the effect of insomnia on fatigue. This result showed that depressive symptoms due to insomnia may aggravate fatigue, although insomnia itself also had direct effects on the fatigue. Previous studies reported that people with chronic insomnia are vulnerable to major depression, and that depression may produce fatigue (Baglioni and Riemann, 2012; Lee et al., 2019a,b). Our finding of mediation analysis suggests that preventing or treating depression may be beneficial for relieving fatigue in insomnia patients.

However, daytime sleepiness or habitual sleep duration did not mediate the association between insomnia and fatigue. These findings may be due to the opposite direction of association as shown in the correlation analysis. Insomnia severity was negatively correlated with

sleepiness and sleep duration. On the contrary, fatigue severity was positively correlated with sleepiness and sleep duration.

Another interesting finding was that insomnia patients with severe fatigue reported sleeping longer than those without severe fatigue. Although insomnia severity was associated with short habitual sleep duration, fatigue severity was associated with long habitual sleep duration. Insomnia patients tend to believe that their fatigue is caused by insufficient habitual sleep duration and that it can be eliminated only by restoring sleep time (Woodley and Smith, 2006; Morin et al., 2007). Our current finding is opposite to this commonly presumed notion. It is indeed unclear why we found an association between long habitual sleep duration and fatigue in insomnia patients. One could hypothesize that patients with fatigue might be sleepier and sleep longer. Alternatively and more probably, insomnia patients with fatigue may make compensatory efforts to prolong habitual sleep duration, reflecting the dysfunctional belief that spending more time in bed will reduce their daytime fatigue. Our results suggest that increasing habitual sleep duration may not eliminate fatigue; rather, it may aggravate fatigue in patients with insomnia. If this hypothesis is correct, CBT-I, which restricts time in bed to help insomnia patients consolidate their sleep, should also help to alleviate fatigue in these patients.

We found that fatigue was associated with female gender and younger age. These associations were independent from insomnia severity, daytime sleepiness, depression, and habitual sleep duration. Previous studies in general population have reported the association between female gender and fatigue (Watt et al., 2000; Schwarz et al., 2003; Engberg et al., 2017). However, the previous reports on the association between age and fatigue have been inconsistent. Earlier papers reported the association between older age and fatigue in Danish and German population (Watt et al., 2000; Schwarz et al., 2003). A recent study has reported that younger age was correlated with higher fatigue in Swedish population (Engberg et al., 2017). The current study reports that younger age was more related to fatigue at least within patients visiting sleep clinic with insomnia.

Although many subjective variables from the sleep questionnaires were associated with fatigue in insomnia, no PSG abnormalities showed this association. This finding is in line with a previous study reporting no association between PSG-defined sleep disturbances and fatigue in patients with insomnia (Fortier-Brochu et al., 2010). Our study suggests that, among those with insomnia, a subjective evaluation of habitual sleep disturbance is a stronger predictor of fatigue than objective sleep disturbance defined by one-night PSG. In addition, there were no differences in AHI or PLMI in subjects with and without fatigue, which indicates that a diagnosis of mild OSA or PLMS on PSG may not affect fatigue complaints in insomnia patients. These findings may seem opposite to the previous studies reporting the association between AHI and fatigue in patients with sleep apnea (Moore et al., 2001), or the association between PLMI and fatigue in patients with PLMS (Haba-Rubio et al., 2004). Of note, it is unclear whether moderate/severe OSA or severe PLMI is associated with fatigue in insomnia patients, as these patients were excluded from the study.

In the current study, insomnia patients who underwent PSG were younger and female predominant than those without PSG data. They also had milder insomnia symptoms and longer sleep duration. It may be due to various factors associated with the clinical decision whether PSG would be performed or not. PSG is usually performed for the patients with medical features suggesting sleep-related breathing disorders, parasomnia, narcolepsy or seizure. Patients who visit sleep clinics with mild insomnia might have other sleep problems requiring PSG. However, obstructive sleep apnea, most common indication for PSG, is common in middle-aged or male gender (Resta et al., 2003; Basoglu and Tasbakan, 2018). Younger or female insomnia patients may have undergone PSG for unknown other social or psychological reasons.

The current study has several clinical implications. In line with previous studies (Vitiello et al., 2014; Kallestad et al., 2015), our study suggests that improvements in insomnia may reduce associated fatigue. Our results also suggest that managing daytime sleepiness or depression in insomnia patients may diminish fatigue. Notably, according to our current study, efforts to prolong habitual sleep duration appear to aggravate fatigue in insomnia patients. Instead, limiting time in bed and correcting maladaptive beliefs about nighttime sleep and daytime fatigue, as occurs in CBT-I, are more likely improve symptom. Future studies examining the effects of CBT-I on fatigue in patients with insomnia could help to confirm this hypothesis.

Several limitations of this study should be mentioned. First, although our sample size was large, subjects with insomnia were those who visited a sleep clinic and thus findings cannot be generalized to a community sample. Second, the present study relied primarily on self-report measures rather than objective assessments, as one-night PSG findings were examined in only a portion of subjects. Third, insomnia in the current study was defined based on self-questionnaires and medical records, although a diagnosis of insomnia disorder should be based on a clinical evaluation by clinicians. Diagnosis of insomnia disorder with diagnostic interview would be needed for future studies. Fourth, medication effects were not carefully evaluated as possible confounders, as medications for insomnia can impact daytime sleepiness, sleep duration, depression and fatigue. Lastly, the cross-sectional design of the current study cannot disentangle causal relationships but only report associations between fatigue, insomnia, and other insomnia-related factors.

5. Conclusions

The present study revealed that fatigue in insomnia was associated with the severity of insomnia and that this association was independent of daytime sleepiness, depression, or habitual sleep duration. However, this association was more pronounced in insomnia patients without daytime sleepiness. Depression, daytime sleepiness, and prolonged habitual sleep duration were also related to fatigue in insomnia patients. The current study suggests that treating insomnia symptoms may relieve the fatigue of insomnia patients, whereas prolongation of habitual sleep duration may worsen their fatigue.

FINANCIAL SUPPORT

This study was supported by the Brain Research Program through the National Research Foundation of Korea, funded by the Ministry of Science, ICT & Future Planning (No.2016M3C7A1904336) and National Research Foundation of Korea grant funded by the Korean government (MEST) (No. 2016R1A2B4011561).

Conflicts of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2019.06.021.

References

American Academy of Sleep Medicine, 2014. International Classification of Sleep Disorders. 3rd Ed. Diagnostic and Coding Manual. American Academy of Sleep Medicine, Chicago.
American Academy of Sleep Medicine, 2007. The AASM Manual for the Scoring of Sleep and Associated Events. American Academy of Sleep Medicine, Westchester, IL.
American Psychiatric Association, 2000. Diagnostic and Statistical Manual of Mental Disorders-4. American Psychiatric Press, Washington DC.
American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders-5. American Psychiatric Press, Washington DC.
Baglioni, C., Riemann, D., 2012. Is chronic insomnia a precursor to major depression? Epidemiological and biological findings. Curr. Psychiatr. Rep. 14 (5), 511–518.

Bastien, C.H., Vallières, A., Morin, C.M., 2001. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. Sleep Med. 2 (4), 297–307.
Basoglu, O.K., Tasbakan, M.S., 2018. Gender differences in clinical and polysomnographic features of obstructive sleep apnea: a clinical study of 2827 patients. Sleep Breath. 22 (1), 241–249.
Bathgate, C.J., Edinger, J.D., Wyatt, J.K., Krystal, A.D., 2016. Objective but not subjective short sleep duration associated with increased risk for hypertension in individuals with insomnia. Sleep 39 (5), 1037–1045.
Carney, C.E., Moss, T.G., Lachowski, A.M., Atwood, M.E., 2014. Understanding mental and physical fatigue complaints in those with depression and insomnia. Behav. Sleep Med. 12 (4), 272–289.
Chambers, M.J., Keller, B., 1993. Alert insomniacs: are they really sleep deprived? Clin. Psychol. Rev. 13 (7), 649–666.
Chen, L., Luo, C., Liu, S., Chen, W., Liu, Y., Li, Y., Du, Y., Zou, H., Pan, J., 2019. Excessive daytime sleepiness in general hospital nurses: prevalence, correlates, and its association with adverse events. Sleep Breath. 23 (1), 209–216.
Chesson, A.L., Wise, M., Davila, D., Johnson, S., Littner, M., Anderson, W.M., Hartse, K., Rafecas, J., 1999. Practice parameters for the treatment of restless legs syndrome and periodic limb movement disorder. Sleep 22 (7), 961–968.
Edinger, J.D., Bonnet, M.H., Bootzin, R.R., Doghramji, K., Dorsey, C.M., Espie, C.A., Jamieson, A.O., McCall, W.V., Morin, C.M., Stepanski, E.J., 2004. Derivation of research diagnostic criteria for insomnia: report of an American Academy of sleep medicine work group. Sleep 27 (8), 1567–1596.
Engberg, I., Segerstedt, J., Waller, G., Wennberg, P., Eliasson, M., 2017. Fatigue in the general population- associations to age, sex, socioeconomic status, physical activity, sitting time and self-rated health: the northern Sweden MONICA study 2014. BMC Public Health 17 (1), 654.
Fava, M., 2004. Daytime sleepiness and insomnia as correlates of depression. J. Clin. Psychiatry 65 (Suppl. 16), 27–32.
Fortier-Brochu, É., Beaulieu-Bonneau, S., Ivers, H., Morin, C.M., 2010. Relations between sleep, fatigue, and health-related quality of life in individuals with insomnia. J. Psychosom. Res. 69 (5), 475–483.
Haba-Rubio, J., Staner, L., Krieger, J., Macher, J.P., 2004. What is the clinical significance of periodic limb movements during sleep? Neurophysiol. Clin. 34 (6), 293–300.
Johann, A.F., Hertenstein, E., Kyle, S.D., Baglioni, C., Feige, B., Nissen, C., McGinness, A.J., Riemann, D., Spiegelhalder, K., 2017. Insomnia with objective short sleep duration is associated with longer duration of insomnia in the Freiburg Insomnia Cohort compared to insomnia with normal sleep duration, but not with hypertension. PLoS One 12 (7), e0180339.
Johns, M.W., 1991. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 14 (6), 540–545.
Kallestad, H., Jacobsen, H.B., Landrø, N.I., Borchgrevink, P.C., Stiles, T.C., 2015. The role of insomnia in the treatment of chronic fatigue. J. Psychosom. Res. 78 (5), 427–432.
Kay, D.B., Buysse, D.J., Germain, A., Hall, M., Monk, T.H., 2015. Subjective-objective sleep discrepancy among older adults: associations with insomnia diagnosis and insomnia treatment. J. Sleep Res. 24 (1), 32–39.
Kroenke, K., Spitzer, R.L., 2002. The PHQ-9: a new depression diagnostic and severity measure. Psychiatr. Ann. 32 (9), 509–515.
Krupp, L.B., LaRocca, N.G., Muir-Nash, J., Steinberg, A.D., 1989. The Fatigue Severity Scale: application to patients with multiple sclerosis and systemic lupus erythematosus. Arch. Neurol. 46 (10), 1121–1123.
Kushida, C.A., Littner, M.R., Morgenthaler, T., Alessi, C.A., Bailey, D., Coleman Jr., J., Friedman, L., Hirshkowitz, M., Kapen, S., Kramer, M., Lee-Chiong, T., Loube, D.L., Owens, J., Pancer, J.P., Wise, M., 2005. Practice parameters for the indications for polysomnography and related procedures: an update for 2005. Sleep 28 (4), 499–521.
Lavie, P., 1983. Incidence of sleep apnea in a presumably healthy working population: a significant relationship with excessive daytime sleepiness. Sleep 6 (4), 312–318.
Leary, E.B., Malunjkar, S., Ruoff, C.M., Walsh, J.K., Mignot, E., 2015. Validation of the alliance sleep questionnaire (ASQ) restless legs syndrome module in sleep disordered patients. Sleep 38 (Suppl. l), A432.
Leary, E.B., Malunjkar, S., Qadri, S., Ruoff, C.M., Sullivan, S.S., Walsh, J.K., Mignot, E., 2013. Deployment of the alliance sleep questionnaire (ASQ) at the Stanford sleep disorders clinic (SSDC) as standard of care. Sleep 36 (Suppl. l), A413.
Lee, J., Choo, H., 2019a. Serotonin receptors for treatment of insomnia. Chronobiol. Med. 1 (1), 14–20.
Lee, S.H., Shin, H.S., Park, H.Y., Kim, J.L., Lee, J.J., Lee, H., Won, S.D., Han, W., 2019b. Depression as a mediator of chronic fatigue and post-traumatic stress symptoms in middle east respiratory syndrome survivors. Psychiatry. Investig. 16 (1), 59–64.
Lee, Y.J., Cho, S.J., Cho, I.H., Kim, S.J., 2012. Insufficient sleep and suicidality in adolescents. Sleep 35 (4), 455–460.
Lee, Y.J., Park, J., Kim, S., Cho, S.J., Kim, S.J., 2015. Academic performance among adolescents with behaviorally induced insufficient sleep syndrome. J. Clin. Sleep. Med. 11 (1), 61–68.
Lichstein, K.L., Means, M.K., Noe, S.L., Aguillard, R.N., 1997. Fatigue and sleep disorders. Behav. Res. Ther. 35 (8), 733–740.
Mariman, A., Vogelaers, D., Hanoulle, I., Delesie, L., Tobback, E., Pevernagie, D., 2012. Validation of the three-factor model of the PSQI in a large sample of chronic fatigue syndrome (CFS) patients. J. Psychosom. Res. 72 (2), 111–113.
Moore, P., Bardwell, W.A., Ancoli-Israel, S., Dimsdale, J.E., 2001. Association between polysomnographic sleep measures and health-related quality of life in obstructive sleep apnea. J. Sleep Res. 10 (4), 303–308.
Morin, C.M., Vallieres, A., Ivers, H., 2007. Dysfunctional beliefs and attitudes about sleep (DBAS): validation of a brief version (DBAS-16). Sleep 30 (11), 1547–1554.
Natarajan, R., 2010. Review of periodic limb movement and restless leg syndrome. J. Postgrad. Med. 56 (2), 157–162.
Okun, M.L., Kravitz, H.M., Sowers, M.F., Moul, D.E., Buysse, D.J., Hall, M., 2009. Psychometric evaluation of the Insomnia Symptom Questionnaire: a self-report measure to identify chronic insomnia. J. Clin. Sleep. Med. 5 (1), 41–51.
Park, H.Y., Jeon, H.J., Bang, Y.R., Yoon, I.Y., 2019. Multidimensional comparison of cancer-related fatigue and chronic fatigue syndrome: the role of psychophysiological markers. Psychiatry. Investig. 16 (1), 71–79.
Pillai, V., Roth, T., Drake, C.L., 2015. The nature of stable insomnia phenotypes. Sleep 38 (1), 127–138.
Riedel, B.W., Lichstein, K.L., 2000. Insomnia and daytime functioning. Sleep Med. Rev. 4 (3), 277–298.
Resta, O., Caratozzolo, G., Pannacciulli, N., Stefàno, A., Giliberti, T., Carpagnano, G.E., De Pergola, G., 2003. Gender, age and menopause effects on the prevalence and the characteristics of obstructive sleep apnea in obesity. Eur. J. Clin. Investig. 33 (12), 1084–1089.
Rezaie, L., Fobian, A.D., McCall, W.V., Khazaie, H., 2018. Paradoxical insomnia and subjective-objective sleep discrepancy: a review. Sleep Med. Rev. 40, 196–202.
Schwarz, R., Krauss, O., Hinz, A., 2003. Fatigue in the general population. Onkologie 26 (2), 140–144.
Seok, B.J., Jeon, S., Cho, S.J., Kim, S.J., 2019. The effects of medical or psychiatric diseases on the association between morningness-eveningness and somatization. Chronobiol. Med. 1 (1), 26–31.
Shahid, A., Shen, J., Shapiro, C.M., 2010. Measurements of sleepiness and fatigue. J. Psychosom. Res. 69 (1), 81–89.
Schutte-Rodin, S., Broch, L., Buysse, D., Dorsey, C., Sateia, M., 2008. Clinical guideline for the evaluation and management of chronic insomnia in adults. J. Clin. Sleep. Med. 4 (5), 487.
Sobel, M.E., 1982. Asymptotic confidence intervals for indirect effects in structural equation models. Socio. Methodol. 13, 290–312.
Theorell-Haglöw, J., Lindberg, E., Janson, C., 2006. What are the important risk factors for daytime sleepiness and fatigue in women? Sleep 29 (6), 751–757.
Vgontzas, A.N., Fernandez-Mendoza, J., Bixler, E.O., Singareddy, R., Shaffer, M.L., Calhoun, S.L., Liao, D., Basta, M., Chrousos, G.P., 2012. Persistent insomnia: the role of objective short sleep duration and mental health. Sleep 35 (1), 61–68.
Vitiello, M.V., McCurry, S.M., Shortreed, S.M., Baker, L.D., Rybarczyk, B.D., Keefe, F.J., Von Korff, M., 2014. Short-term imp rovement in insomnia symptoms predicts long-term improvements in sleep, pain, and fatigue in older adults with comorbid osteoarthritis and insomnia. Pain 155 (8), 1547–1554.
Watt, T., Groenvold, M., Bjorner, J.B., Noerholm, V., Rasmussen, N.A., Bech, P., 2000. Fatigue in the Danish general population. Influence of sociodemographic factors and disease. J. Epidemiol. Community Health 54 (11), 827–833.
Woodley, J., Smith, S., 2006. Safety behaviors and dysfunctional beliefs about sleep: testing a cognitive model of the maintenance of insomnia. J. Psychosom. Res. 60 (6), 551–557.