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Original Research Article

Increased Risk of Myofascial Pain Syndrome Among Patients with Insomnia

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Abstract

Objective. The aim of this study is to evaluate the risk of developing myofascial pain syndrome among patients diagnosed with insomnia.

Methods. We conducted a population-based longitudinal study of a matched cohort with 7,895 participants (1,579 patients with insomnia and 6,316 controls) who were selected from the Taiwan National Health Insurance Research Database. The patients were observed for a maximum of 10 years to determine the incidence of newly diagnosed myofascial pain syndrome. A Cox regression analysis was performed to identify the risk factors associated with myofascial pain syndrome in patients with insomnia.

Results. During the 10-year follow-up period, 182 insomnia patients (14.9 per 1,000 person-years) and 379 controls (7.5 per 1,000 person-years) were diagnosed with myofascial pain syndrome. The incidence risk ratio of myofascial pain syndrome between the insomnia and control patients was 2.00 (95% confidence interval [CI] = 1.67–2.38, $P < 0.001$). After adjusting for age, sex, monthly income, urbanization, and comorbidities, the insomnia patients were 1.93 times more likely to develop myofascial pain syndrome (95% CI = 1.62–2.31, $P < .001$) than the control patients. Malignant neoplasm (hazard ratio = 3.08) and living in urban areas (hazard ratio = 3.05) were identified as independent risk factors for myofascial pain syndrome in patients with insomnia.

Conclusions. Patients with insomnia had a higher risk of developing myofascial pain syndrome than controls. This study adds to the understanding of the complex relationship between sleep disturbance and pain.

Key Words. Myofascial Pain; Fibromyalgia; Epidemiology; Insomnia; Risk Factor

Introduction

Myofascial pain syndrome (MPS), including myalgia, myositis, fibromyalgia, and polymyalgia rheumatica, is a debilitating condition characterized by diffuse pain, fatigue, and poor sleep [1,2]. The prevalence of MPS is 6.4% in the general population [3]. Among them, fibromyalgia is associated with high unemployment rate and increased days of absence from work [4]. The pain in patients with MPS may cause sleep disturbances, such as nonrestorative sleep or difficulty in initiating or maintaining sleep [1,5,6]. It is estimated that 70–80% patients with MPS suffer from sleep disturbances [7]. Polysomnography studies of patients with fibromyalgia show a decrease in slow wave sleep [8] and an increase in stage 1 sleep [9]. Insomnia in MPS seems to have the same characteristics as primary insomnia [10].

It has been suggested that poor sleep could exacerbate pain and discomfort [6,11]. The reciprocal relationship

between sleep and pain has been discussed, and the treatment for each disorder is beneficial to the other [12–14]. A recent 11-year follow-up study with a large sample size demonstrated that sleep disturbance is one of the psychosocial factors that predicts chronic widespread pain [15]. It is noteworthy that evidence of pain-induced sleep disturbance is relatively abundant but less is seen in discussing sleep-induced pain [11,16,17]. To our knowledge, only one report conducted in Norway [18] investigated the increased risk of fibromyalgia, a component of MPS, in patients with sleep problems. However, the Norway report enrolled only women with sleep problems, which were assessed by a single question, and the diagnosis or the outcome of fibromyalgia is based on self-reported data but not a specialist's diagnosis. The aim of this study is to investigate the risk of MPS in patients with insomnia. We hypothesized that through sleep disturbance at night for a period of time, people would subsequently suffer from pain problems. A population-based longitudinal cohort study based on the Taiwan National Health Insurance Research Database (NHIRD) was performed to see if patients with insomnia are more likely to get a diagnosis of MPS during a follow-up period of up to nine years. We also determined other clinical and demographic factors, such as medical comorbidities, age, gender, urbanization, and monthly income, which could influence the associations between insomnia and MPS to identify possible risk factors that predict subsequent MPS among patients with insomnia.

Methods

Data Sources

Taiwan instituted the National Health Insurance program, a mandatory single-payer program that offers comprehensive medical care coverage, including outpatient, inpatient, emergency, and traditional Chinese medicine services, to almost 99% of residents on March 1, 1995. As of 2014, 99.9% of Taiwan's population was enrolled [19]. Since 1996, the National Health Insurance reimbursement data have been transferred to the National Health Research Institute in Taiwan for further management and establishment of a medical claims database, the National Health Insurance Research Database (NHIRD). The NHIRD contains comprehensive data on clinical visits, including patients' demographic characteristics, medical expenditure, prescription claims data, surgery code (each code represents a surgery), treatment code (each code represents a different treatment, such as general or local anesthesia), and diagnostic codes based on the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM). Patient confidentiality is maintained in accordance with the directives of the National Health Insurance (NHI) Bureau in Taiwan, and all investigators must sign an agreement that guarantees patient confidentiality before using the database. The NHIRD has been used extensively in epidemiologic research in Taiwan. Covering the years 1996 to 2009, 1 million people, approximately 4.3% of the population in Taiwan, were systematically and randomly selected from the Longitudinal Health Insurance Database 2005 (LHID 2005), which is a data set of the NHIRD in this study. The LHID 2005 contains all the original claim data of 1,000,000 beneficiaries enrolled in 2005 and randomly sampled from the year 2005 Registry for Beneficiaries of the NHIRD, where the registration data of everyone who was a beneficiary of the National Health Insurance program during the period of January 1, 2005, to January 1, 2006, were drawn for random sampling. There are approximately 25.68 million individuals in this registry. All the registration and claims data of these 1,000,000 individuals collected by the National Health Insurance program constitute the LHID 2005. There was no significant difference in the sex distribution ($\chi 2 = 0.008$, degree of freedom $= 1$, $P = 0.931$) between the patients in the LHID 2005 and the original NHIRD [20]. The Institutional Review Board of the Taipei Veterans General Hospital approved this study (2013-03-035AC).

Study Population

We conducted a cohort case control study by defining patients age 20 years and older who were newly diagnosed with insomnia by psychiatrists between January 1, 2000, and December 31, 2002, from the LHID 2005 data. Insomnia was defined based on ICD-9-CM codes 780.52, 307.40, 307.41, 307.42, 307.43, and 307.44. In order to ensure the diagnostic validity and homogeneity of patients, we selected only patients who had at least two consensual diagnoses of insomnia for the study group. We excluded patients who were ever diagnosed with myofascial pain syndrome (MPS, ICD-9-CM codes 729.1 myofascial pain/myofascial pain syndrome) before enrollment. For each patient with insomnia included in the final cohort, we randomly selected four age-, sex-, and enrollment date–matched control patients from the LHID 2005 who were not diagnosed with insomnia or MPS. All insomnia patients and controls were observed until 1) diagnosed with MPS twice by either a rheumatologist, physiatrist, neurologist, orthopedist, or anesthetist; 2) death; 3) withdrawal from the NHI system; or 4) December 31, 2009. The primary clinical outcome assessed was specialist-diagnosed MPS twice. We estimated the monthly income of patients based on their insurance premium, which is calculated based on the total income of beneficiaries. Monthly income was grouped into low (monthly income $<$ NT$20,000), medium (monthly income $>$ NT$20,000 but $<$ NT$40,000), and high (monthly income $\geq$ NT$40,000) income levels. Urbanization was divided into three groups: urban, suburban, and rural. Urbanization and monthly income levels were used to represent socioeconomic status.

Statistical Analyses

After stratifying the data according to sex and age (younger than age 65 years or equal to or older than 65 years), we calculated the incidence of newly diagnosed MPS in the patient groups. We performed chi-square and independent *t* tests to examine the differences of

the demographic characteristics between the patients with insomnia and controls.

A Cox proportional-hazards regression model was used to identify variables predicting MPS in the whole sample, as well as among the subsample of patients with insomnia. Control variables, such as age, sex, common comorbidities, urbanization, and monthly income, were included as covariates in the univariate model. The ICD-9-CM classification system was used again for defining the existence of comorbidities, including hypertension (ICD-9 codes: 401–405), diabetes mellitus (ICD-9 code: 250), dyslipidemia (ICD-9 code: 272), coronary artery disease (ICD-9 codes: 410–414), congestive heart failure (ICD-9 code: 428), cirrhosis (ICD-9 codes: 571.2, 571.5, and 571.6), cerebrovascular disease (ICD-9 codes: 430–438), and malignancy (ICD-9 codes: 140–239). In univariate analyses, variables that were possibly associated with the development of MPS with a P value of less than 0.1 were entered into the multivariate Cox proportional hazards regression model by using the forward selection technique for adjusting the possibility of confounding effects. In addition, we used the Cox regression model twice. First, the method was used to identify variables predicting MPS in the whole sample. Second, we applied the method again among the subsample of insomnia cohort to identify possible risk factors for MPS among patients with insomnia.

The SAS statistical software for Windows, version 9.3 (SAS Institute, Cary, NC, USA), was used for data extraction, computation, linkage, processing, and sampling. All other statistical analyses were performed using SPSS statistical software for Windows, version 20 (IBM, Armonk, NY, USA). Relationships were considered statistically significant when P values were less than 0.05.

Results

Participant Selection

There were 2,023 patients with insomnia enrolled from 2000 to 2002. After exclusion of previous history of MPS and age under 20 years, the final sample was comprised of 1,579 patients with new-onset insomnia and 6,316 controls (Figure 1). Among them, 52.6% were women. The median age at enrollment was 46.3 years (interquartile range [IQR] = 34.2–56.9 years), and the median follow-up periods for the insomnia patients and controls were 7.7 years (IQR = 7.3–9.0 years) and 8 years (IQR = 7.4–9.0 years), respectively. Comorbidities, including hypertension, diabetes mellitus, dyslipidemia, congestive heart failure, cirrhosis, and cerebrovascular disease, were reported more frequently in the insomnia patients than in the controls. Table 1 shows the demographic and clinical variables of the insomnia patients and controls.

Incidence Rate of Myofascial Pain Syndrome

During the study period, 182 (11.5%) insomnia patients (14.9 per 1,000 person-years) and 379 (6%) controls

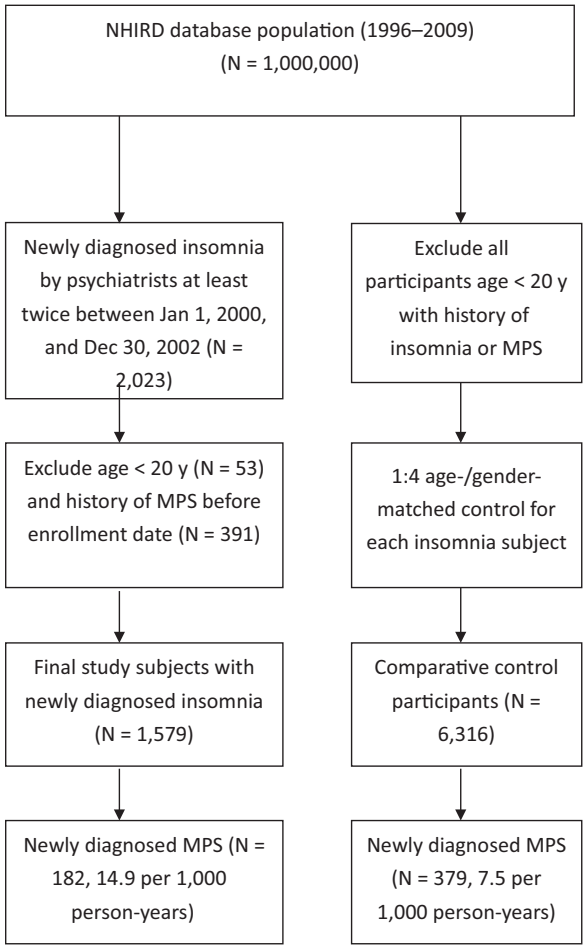

Figure 1 Flowchart of participants selection. NHIRD = National Health Insurance Research Database; MPS = myofascial pain syndrome.

(7.5 per 1,000 person-years) were diagnosed with MPS. The incidence risk ratio (IRR) of MPS between the insomnia patients and controls was 2.00 (95% CI = 1.67–2.38, $P < 0.0001$). When the patients were stratified according to sex and age, the IRR of MPS remained higher among the insomnia patients than among the controls. For patients age 65 years or older, the IRR was 1.81 (95% CI = 1.16–2.77, $P = 0.0045$); for patients younger than age 65 years, the IRR was 2.05 (95% CI = 1.67–2.5, $P < 0.0001$); for male patients, the IRR was 2.27 (95% CI = 1.72–2.97, $P < 0.0001$); for female patients, the IRR was 1.54 (95% CI = 1.20–1.96, $P = 0.0003$) (Table 2).

Insomnia as a Risk Factor for Myofascial Pain Syndrome

After we adjusted for age, sex, comorbidities, urbanization, and monthly income, the hazard ratio (HR) for developing MPS during the follow-up period was 1.93 times (95% CI = 1.62–2.31, $P < 0.001$) higher for the

Table 1 Baseline characteristics of patients with and without insomnia

	Patients with insomnia N = 1,579		Patients without insomnia N= 6,316		
Demographic data	N	%	N	%	*P*
Age (IQR), y	46.3 (34.2–56.9)		46.3 (34.3–57.1)		0.998
≥65	240	15.2	970	15.3	0.907
<65	1,339	84.8	5,346	84.7	
Sex					
Male	748	47.4	2,992	47.4	0.999
Female	831	52.6	3,324	52.6	
Comorbidities					
Hypertension	368	23.3	1,048	16.6	<0.001
Diabetes mellitus	196	12.4	533	8.4	<0.001
Dyslipidemia	221	13.3	580	9.2	<0.001
Coronary artery disease	14	0.9	43	0.7	0.405
Congestive heart failure	50	3.2	99	1.6	<0.001
Cirrhosis	29	1.8	51	0.7	0.001
Cerebrovascular disease	93	5.9	223	3.5	<0.001
Malignant neoplasms	23	1.5	87	1.4	0.810
Degree of urbanization					
Urban	920	58.3	3,844	60.9	0.162
Suburban	512	32.4	1,908	30.2	
Rural	147	9.3	564	8.9	
Income group					
Low income	861	54.5	2,962	46.9	<0.001
Median income	548	34.7	2,454	38.9	
High income	170	10.8	900	14.2	
Follow-up (median), y	7.7 (7.3–9.0)		8.0 (7.4–9.0)		<0.001

IQR = interquartile range.

Table 2 Incidence of myofascial pain syndrome in patients with and without insomnia

	Patients with insomnia		Patients without insomnia			
	No. of MPS	Per 1,000 person-years	No. of MPS	Per 1,000 person-years	RR (95% CI)	*P*
Total	182	14.9	379	7.5	2.00 (1.67–2.38)	<.0001
Follow-up, mean (SD), y	3.84 (2.44)		4.03 (2.47)			.378
Age, y						
≥65	32	64.4	75	37.8	1.81 (1.16–2.77)	.0045
<65	150	56.1	304	28.9	2.05 (1.67–2.50)	<.0001
Sex						
Male	84	14.6	155	6.4	2.27 (1.72–2.97)	<.0001
Female	98	15.2	224	9.9	1.54 (1.20–1.96)	.0003

CI = confidence interval; MPS = myofascial pain syndrome; RR = risk ratio.

insomnia patients than for controls (Table 3). There was a trend that the HR of patients age 65 years and older was 1.17 times (95% CI = 0.91–1.5, $P = 0.058$) higher than patients younger than age 65 years. Female patients have a higher risk of getting MPS (HR = 1.22, 95% CI = 1.03–1.45, $P = 0.014$) than male ones.

Risks Factors for Myofascial Pain Syndrome in Patients with Insomnia

We applied a univariate analysis to predict the development of MPS in the subsample of insomnia patients. The results indicated that having hypertension (HR = 1.46,

Table 3 Risk factors for myofascial pain syndrome in patients with and without insomnia

	Univariate analysis		Multivariate analysis	
Predictive variables	HR (95% CI)	*P*	HR (95% CI)	*P*
Insomnia	2.00 (1.67–2.38)	<0.001	1.93 (1.62–2.31)	<0.001
Age (≥65 y = 1, <65 y = 0)	1.37 (1.11–1.69)	0.003	1.17 (0.91–1.50)	0.058
Sex (female = 1, male = 0)	1.22 (1.03–1.44)	0.022	1.22 (1.03–1.45)	0.020
Comorbidities				
Hypertension	1.65 (1.36–1.99)	<0.001	1.37 (1.09–1.73)	0.008
Diabetes mellitus	1.67 (1.31–2.12)	<0.001	1.31 (0.99–1.71)	0.054
Dyslipidemia	1.52 (1.20–1.93)	0.001	1.12 (0.85–1.46)	0.423
Coronary artery disease	1.30 (0.54–3.14)	0.555		
Congestive heart failure	1.59 (0.95–2.66)	0.075	1.07 (0.63–1.83)	0.793
Cirrhosis	1.15 (0.51–2.57)	0.736		
Cerebrovascular disease	1.58 (1.11–2.26)	0.012	1.12 (0.77–1.63)	0.565
Malignant neoplasms	1.96 (1.16–3.34)	0.013	1.80 (1.06–3.08)	0.030
Degree of urbanization				
Urban	1.62 (1.15–2.29)	0.006	1.71 (1.21–2.43)	0.002
Suburban	1.26 (0.87–1.82)	0.220	1.31 (0.90–1.89)	0.156
Rural	Reference			
Income group				
Low income	0.96 (0.75–1.23)	0.760		
Median income	0.84 (0.65–1.08)	0.176		
High income	Reference			

CI = confidence interval; HR = hazard ratio.

95% CI = 1.06–2.01, $P = 0.020$), diabetes mellitus (HR = 1.64, 95% CI = 1.12–2.41, $P = 0.011$), or malignant neoplasm (HR = 2.99, 95% CI = 1.41–6.37, $P = 0.004$), and residing in an urban area (HR = 2.92, 95% CI = 1.36–6.25, $P = 0.006$) are significant predictive factors (Table 4). The multivariate analysis results confirmed that having malignant neoplasm (HR = 3.08, 95% CI = 1.45–6.58, $P = 0.004$) and living in an urban region (HR = 3.05, 95% CI = 1.42–6.55, $P = 0.004$) were independent risk factors for MPS in the patients with insomnia.

Discussion

The incidence rate of MPS in insomnia patients was 14.9 per 1,000 person-year. The risk of developing MPS was higher among the insomnia patients (HR = 1.93) than the controls, which confirmed our hypothesis that sleep disturbance increases the risk of subsequent pain problems. Malignant neoplasm (HR = 3.08) and residing in an urban area (HR = 3.05) were found to be independent risk factors for MPS in patients with insomnia. The strengths of this study are the large sample size, long follow-up period, and diagnosis of clinical MPS and insomnia by specialists. In addition, our study applied an unbiased and randomized sampling process, which enabled every subject in the database to have the same opportunity to be enrolled once their condition fitted the enrollment criteria. Because participation in the NHI program is mandatory and all residents of Taiwan can access low-cost health care services, referral bias is low and follow-up compliance is high.

The pathogenesis of MPS is unknown, but current evidence suggests that cytokines such as increased interleukin 6 (IL-6) may play a role in it [21–23]. Sleep is hypothesized to be a restorative process, which is important for the proper functioning of the immune system [24]. Sleep loss and disordered sleep are thought to impair immune responses, and several studies have demonstrated that insomnia is associated with elevated levels of cytokines, especially IL-6 [25–27]. The elevation of cytokines in both insomnia and MPS might explain our finding that patients with insomnia were at risk of developing MPS. In addition, we found a trend that patients with and without insomnia who were age 65 years or older had a higher risk of MPS, which is also consistent with the Norway Brief Report [18]. Older adults may be particularly vulnerable to the effects of sleep disturbance due to significant age-related changes in both sleep and inflammatory regulation such as elevation of IL-6 [28]. Finally, female patients are more likely to get MPS than male ones. A previous report showed that female patients with fibromyalgia had increased release of inflammatory cytokines in response to stress [29]. A gender difference was found in sleep loss–induced functional alteration of cytokine responses, with females expressing greater cellular immune activation as compared with males [30,31].

Table 4 Risk factors for myofascial pain syndrome in patients with insomnia

	Univariate analysis		Multivariate analysis	
Predictive variables	HR (95% CI)	*P*	HR (95% CI)	*P*
Age (≥65 = 1, <65 = 0)	1.26 (0.86–1.84)	0.239		
Sex (Female = 1, Male = 0)	1.04 (0.78–1.40)	0.777		
Comorbidities				
Hypertension	1.46 (1.06–2.01)	0.020	1.35 (0.96–1.89)	0.082
Diabetes mellitus	1.64 (1.12–2.41)	0.011	1.48 (0.99–2.21)	0.055
Dyslipidemia	1.05 (0.69–1.59)	0.820		
Coronary artery disease	1.25 (0.31–5.02)	0.758		
Congestive heart failure	1.34 (0.63–2.86)	0.445		
Cirrhosis	0.62 (0.15–2.51)	0.504		
Cerebrovascular disease	1.60 (0.94–2.71)	0.083	1.35 (0.78–2.35)	0.283
Malignant neoplasms	2.99 (1.41–6.37)	0.004	3.08 (1.45–6.58)	0.004
Degree of urbanization				
Urban	2.92 (1.36–6.25)	0.006	3.05 (1.42–6.55)	0.004
Suburban	2.09 (0.95–4.61)	0.067	2.16 (0.98–4.76)	0.057
Rural	Reference		Reference	
Income group				
Low income	0.82 (0.52–1.27)	0.368		
Median income	0.77 (0.48–1.23)	0.272		
High income	Reference			

CI = confidence interval; HR = hazard ratio.

Poor sleep and pain were assumed to have a close interaction, and investigating their relationship became important out of clinical interest. The reciprocal relationship of insomnia and pain has been discussed in the past years. The painful symptoms may induce a hyperarousal state, which can interfere with sleep stability and cause poor sleep at night in patients with fibromyalgia [6,32]. A recent study demonstrated that noxious stimuli in the sciatic nerve of mice can cause glutamate release with subsequent astrocyte activation and γ-aminobutyric acid (GABA) reduction at the anterior cingulate cortex (ACC) [33]. Using the optogenetic technique [34], this study demonstrated that these in vivo activated astrocytes triggered sleep disturbances probably by reduction of GABA at the ACC. Clinically, insomnia patients with comorbid MPS commonly complain about painful symptoms that worsen at daytime after a disturbed nighttime sleep [35]. Patients with chronic pain would engage in more daytime physical activity after a better nighttime sleep compared with those with poor sleep the previous night [36]. This implies that poor nighttime sleep might worsen pain symptoms at daytime, which prevents patients from engaging in physical activities. In addition, short-term improvement of insomnia predicted long-term relief of pain and fatigue in those with comorbid osteoarthritis and insomnia [12]. The results of our study depicted a temporal relationship from insomnia to MPS, which further supported the finding from a recent study that sleep quality is a consistent predictor of pain the next day [37]. Currently, the most acceptable hypothesis is that sleep deprivation can induce hyperalgesic change and interfere with analgesic treatment mechanisms of action [16,38]. Our results further suggest that people with pain problems should avoid sleep deprivation in order to prevent pain exacerbation or even to improve pain symptoms.

Malignant neoplasm was an independent predictive factor of developing MPS in both the whole sample and the subsample of insomnia patients. MPS might be an initial presentation of cancer or a chronic pain syndrome affecting postsurgery pain problems and quality of life [39–43]. A study demonstrated that the incidence of MPS in postsurgery breast cancer patients was 44.8% (N = 52/116, 95% CI = 35.6–54.3) [42]. Patients with malignant neoplasm have different cytokine patterns, especially with elevated IL-6 and IL-10 [44]. Whether these elevated cytokines were the cause of MPS in patients with malignancy deserves further investigations. In addition, the relationship between insomnia and cancer is prominent [45] and might explain the higher hazard ratio in the subgroup of insomnia than in the whole sample of our study. We suggest patients with comorbid insomnia and cancer should be careful about pain symptoms and treat insomnia aggressively.

It is important to highlight the increased risk of developing MPS in insomnia patients who live in urban settings compared with those who live in rural areas, independent of monthly income level. The prevalence of MPS in urban vs rural populations has been reported with inconsistent results. Some studies report a higher prevalence in rural

areas [1,46] but other epidemiological surveys demonstrate a higher prevalence in urban areas [47,48]. Several studies report that air pollution is related to the elevated levels of inflammatory cytokines such as IL-6 [49–51]. In urban areas, people often lead a stressful lifestyle and the air pollution–induced immune change might be the combined reason for the high risk of MPS in insomnia patients.

There are some limitations in this study that need to be addressed. First, because ICD-9-CM codes 729.1 and 725 represent several different chronic pain disorders including myalgia, myositis, fibromyalgia, and polymyalgia rheumatic, we used MPS to cover all the diagnoses above. We were unable to delineate the association between insomnia and specific disorders under this category. However, we only enrolled patients with the above diagnoses twice that were confirmed by board-certified specialists, which increased the validity of diagnosis of MPS. Second, the nature of the claimed database limited the precise evaluation of the time of onset and symptom severity of MPS patients, personal lifestyle, family history, and environmental factors. Third, we were unable to assess the severity of insomnia based on the claimed database or to further evaluate the impact of the severity of insomnia on the association of subsequent MPS. Fourth, our target population was patients with insomnia and we enrolled relatively young subjects, thus all medical comorbidities were rare and difficult to assess as independent risk factors for MPS. Further studies aimed on these medical comorbidities are encouraged.

Conclusion

Our results support the hypothesis that sleep disturbance may induce pain symptoms, especially in chronic pain disorders such as MPS. Patients with insomnia, especially those who reside in urban affluent areas, are at risk of developing MPS in later life. Future investigations about the mechanisms of sleep disturbance contributing to exacerbated pain, such as hyperalgesic change or interrupted analgesia, are warranted.

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