

Sleep Quality and Fatigue Are Associated with Pain Exacerbations of Hip Osteoarthritis: An Internet-based Case-crossover Study

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ABSTRACT. Objective. To evaluate the association of sleep quality, sleep duration, and fatigue with hip pain exacerbations in persons with symptomatic hip osteoarthritis (OA).

Methods. Participants (n = 252) were followed for 90 days and asked to complete online questionnaires at 10-day intervals (control periods). A hip pain exacerbation (case periods) was defined as an increase of 2 points in pain intensity compared with baseline on a numeric rating scale (0–10). Subjective sleep quality and sleep duration were assessed using the Pittsburgh Sleep Quality Index, and fatigue was measured by Multidimensional Assessment of Fatigue in both periods. Univariable and multivariable conditional logistic regressions were used to assess the association.

Results. Of the 252 participants, 130 (52%) were included in the final analysis. Univariate association analysis showed that both poor sleep quality and greater fatigue were associated with increased odds of pain exacerbations (OR 1.72, 95% CI 1.04–2.86; OR 1.92, 95% CI 1.21–3.05, respectively). Short sleep duration was not associated with pain exacerbations. Poor sleep quality and greater fatigue remained associated with pain exacerbations after adjustment for physical activity and night pain levels in multivariable analysis. There was no significant interaction between sleep quality and fatigue (p = 0.21).

Conclusion. Poor sleep quality and greater fatigue were related to pain exacerbation in persons with symptomatic hip OA. Sleep disorders and fatigue should be considered when dealing with pain exacerbations. (First Release August 1 2019; J Rheumatol 2019;46:1524–30; doi:10.3899/jrheum.181406)

Key Indexing Terms:

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Osteoarthritis (OA) is common among older adults, and joint pain is the hallmark symptom of this condition¹. The mechanisms of pain in OA are complex and poorly understood. Because pain is the main cause of disability and the major driver of clinical decision making, research to identify the causes and manage the pain in OA is paramount².

Two distinct pain types have been described in individuals with OA³. The first was dull, aching, and became more constant over time. In contrast, the other was intermittent and

varied in intensity and was reported as unpredictable. Intermittent intense pain, especially when unpredictable, had a greater effect on quality of life³. Presence of intermittent pain could predict future poor physical function, while constant pain did not⁴. At present, however, the etiology and/or risk factors for pain exacerbations in persons with OA are largely unknown.

Chronic OA pain, sleep problems, and fatigue are common complaints in medical practice⁵. A study including 2682 individuals found that 71% of the general population and 76.4% of patients with OA had sleep problems, including insomnia and insufficient sleep⁶. Emerging studies found that dysregulated sleep plays an integral role in pain expression either by hyperalgesia or by impaired endogenous pain modulation⁷. Data from healthy adults suggest that subjective sleep quality could also account for fatigue⁸.

Fatigue in patients with OA has not received as much research or clinical attention as that in rheumatoid arthritis (RA), fibromyalgia, and other rheumatic diseases. This might be due to the traditional view of OA as a “noninflammatory” arthritis. However, there is evidence indicating that fatigue levels in individuals with OA were not significantly different compared with those in patients with RA^{9,10}. Persons with lower extremity OA experienced a significant amount of fatigue, which had a substantial effect on their quality of life¹¹. In addition, hyperalgesia following fatigue was considered a factor connecting fatigue and pain in many chronic diseases including OA¹². Although fatigue and sleep quality are related in persons with OA, they are distinct important factors that influence experience of pain.

There is limited understanding of the role of sleep and fatigue in hip OA pain exacerbations. We conducted an Internet-based case-crossover study to evaluate the association of sleep quality, sleep duration, and fatigue with hip pain exacerbations in persons with symptomatic hip OA.

MATERIALS AND METHODS

An Internet-based case-crossover study was designed to assess the association of sleep and fatigue with the risk of hip pain exacerbation, as described in knee OA pain exacerbation studies^{13,14,15,16}. Briefly, the case-crossover design uses each participant as their own control to assess the effects of transient exposures (risk factors) on episodic events (e.g., pain exacerbation) during a certain followup period (e.g., 90 days). The study was approved by the ethics committees of the University of Sydney (HREC 2014/801) and University of Melbourne (HREC 1443509), and all participants provided informed consent.

Participants and procedures. Eligible participants were required to be ≥ 40 years old; to have hip pain on most days (5–7 days/week or 20–30 days/month) that fluctuated in intensity as described by participants themselves; to have at least 1 hip meeting American College of Rheumatology criteria for hip OA¹⁷; to have Kellgren-Lawrence grade of hip OA ≥ 2 ¹⁸; to have an active e-mail account and access to the Internet and a computer; and to have good understanding of spoken and written English. Persons were excluded if they had a history of total hip replacement in the index hip or a scheduled total hip replacement or consultation with an orthopedic surgeon to have a total hip replacement of the symptomatic hip(s); or history of inflammatory arthritis, osteonecrosis or Paget’s disease affecting the hip.

An online screening survey tool was designed for recruitment of participants in Australia from May 2015 to June 2017. We put the study advertisement with the screening link on different Websites (Facebook, Arthritis Australia, etc.), and in local newspapers or flyers. When a potential study candidate registered interest in participation through the screening survey tool, their contact details were e-mailed to a study coordinator (in Sydney or Melbourne depending on their state). The study coordinators then contacted participants for further assessment and enrollment. Prospective participants were also asked to provide their most recent hip radiograph.

Participants were followed for 90 days and asked to complete online questionnaires at baseline and every succeeding 10-day interval (control periods). The pain level was assessed using a numeric rating scale (NRS; range 0 = “no pain” to 10 = “the worst pain possible”)¹⁹. We asked participants to indicate how bad their hip pain was at its mildest and worst times of their current everyday life at the baseline online visit. Pain exacerbation was then operationally defined as an increase of ≥ 2 points in the participant’s pain level compared with their mildest hip pain level reported at the baseline visit, as in previous studies^{13,14,15,16,20}. When participants experienced a disabling increase in the hip symptoms lasting for more than 8 h without settling, they were also instructed to log on to the Website to determine whether the pain they experienced reached the threshold of a 2-point increase¹⁵. We chose the threshold of 8 h to exclude the frequent short durations of more instantaneous fluctuations to ensure data collection was not overly burdensome, although it was a conservative assessment. We used the mildest pain level at baseline as the comparator to enable identification of the maximum number of meaningful events (pain exacerbation) possible¹⁵. When a participant considered that they were experiencing a pain exacerbation and logged onto the study Website, the online questionnaire automatically determined whether the participant had a pain exacerbation based on the operational definition and guided them to complete the questionnaires (case periods). Participants were not allowed to know what amount constituted a pain exacerbation, to avoid subjectivity or bias. The system sent reminder e-mails during every control period (10-day interval). Any control period would be marked as missing if it could not be finished within 48 h. Risk factor assessment questionnaires for control periods and case periods were the same for all online visits.

Assessment. We used the Pittsburgh Sleep Quality Index (PSQI) and the Multidimensional Assessment of Fatigue (MAF) questionnaires to evaluate sleep quality and fatigue, respectively, in the past week (7 days). PSQI is a self-report instrument used to measure the quality and patterns of sleep in adults for the preceding month²¹. It contains 7 components (sleep duration, sleep disturbance, sleep latency, daytime dysfunction, sleep efficiency, sleep quality, and sleep medication), each scored 0–3, creating 1 global score from 0 to 21, where higher score means worse sleep quality. The PSQI was shown to have strong reliability and validity, and a global score > 5 (poor sleep quality) showed a sensitivity of 98.7 and specificity of 84.4 to differentiate sleep disturbances in insomnia patients from controls^{22,23}. For the purpose of our study, we modified the questionnaires to evaluate the sleep quality for the previous 7 days, which has been used in other studies in a similar way to measure over a shorter time frame^{24,25,26}. Because we had a particular interest in sleep duration compared to the risk of pain exacerbations, we also tested the sleep duration, which is one of the components of the PSQI, and categorized it by the cutoff of 6 h (i.e., short sleep duration defined as < 6 h), as previously used²⁷.

The MAF is a 16-item scale that covers 4 dimensions of fatigue: degree and severity, distress, frequency and change over the past week, and effect on daily living. The 4 dimensions were not intended for use as subscales²⁸. The first 15 of the 16 items are used to calculate the global fatigue index (GFI). The score range is 1–50 and higher score indicates more severe fatigue (1 = no fatigue, 50 = severe fatigue)²⁹. A cutoff of 21 was selected based on previous studies to differentiate those with clinically significant fatigue^{30,31}.

We also used the International Physical Activity Questionnaire (IPAQ) short form to evaluate physical activity level during the past 7 days^{32,33}. Three levels of physical activity based on this questionnaire (1 = low,

2 = moderate, 3 = high) were proposed to classify populations. We additionally asked the participants to complete the Hip injury and Osteoarthritis Outcome Score (HOOS) questionnaire in each case and control period. The HOOS is composed of 5 subscales including pain, other symptoms, function in activities of daily living (ADL), function in sport and recreation (Sports/Rec), and hip-related quality of life (QOL). A normalized score (100 indicating no symptoms and 0 indicating extreme symptoms) is calculated for each subscale. Night pain level during the past 7 days in the index hip was derived from the HOOS, because this factor might influence sleep quality and duration by waking the participant during the night or making it difficult to fall asleep, and might also influence the pain experience and fatigue of persons with OA.

Participants were asked to complete these questionnaires related to sleep quality and fatigue at both control and case periods. We also collected demographic details and baseline pain level information. All data were collected on a secure password-protected study Website located on a secure server.

Statistical methods. Baseline characteristics were summarized as mean (SD) for continuous variables and frequency (%) for categorical variables. Independent sample *t* tests, chi-square tests, and nonparametric tests (Wilcoxon rank-sum test) were performed to compare those participants with both case/control periods (*n* = 130) and those without (*n* = 122). Participants who did not provide data on both case and control periods were excluded from the analyses. Characteristics were summarized for all participants enrolled in the study and for the subgroup included in the analysis. The analysis pooled recurrent event (pain exacerbations) data under the assumption that within-subject correlation was accounted for by conditioning on subject-specific variables (observed or unobserved), and observed time-varying factors. Any time overlaps between case and control periods were avoided. Because each participant could contribute multiple case and control periods, a multiple:matched study design was used to assess the association¹³. The univariable association of sleep quality, sleep duration (derived from PSQI), and fatigue to the risk of hip pain exacerbation was assessed separately using conditional logistic regression analysis. Risk factors that showed a univariate association were then included in a multivariable model, adjusting for physical activity level and hip night pain level derived from the HOOS questionnaire. Interactions between risk factors were investigated by including an interaction term alongside the main effects. OR were reported with corresponding 95% CI. All analyses were conducted using Stata version 15 (StataCorp LLC).

RESULTS

Among the 252 participants recruited (mean age $62.2 \pm \text{SD } 8.3$ yrs; body mass index $28.7 \pm 6.1 \text{ kg/m}^2$), 199 (79%) were female and 242 (96%) were white. More than 60% of participants had received higher than high school education and 79.7% performed light physical work (sedentary work or standing occupation; Table 1). Participants completed the questionnaire 9.5 times on average [median 10; interquartile range (IQR) 2]. The average number of control periods was 8.1/person and the average number of case periods was 1.4/person.

One hundred thirty (130/252; 52%) participants provided data for both control (average 6.2 per person ± 2.6 ; range 1–9) and case periods (average 2.3 per person ± 1.7 ; range 1–9) and were included in the analysis. On average, the mildest pain level was 2.5 ± 2.1 (numerical rating scale), and the worst pain level was 8.0 ± 1.8 . The baseline night pain level was 1.9 ± 1.0 (range 0–4). Findings on the subscales of HOOS were as follows: pain 52.0 ± 18.0 ; symptoms 50.5 ± 20.4 ; ADL 54.7 ± 21.9 ; Sports/Rec 32.7 ± 26.6 ; and QOL

38.1 ± 20.7 . The median IPAQ score was 3 (IQR 2; Table 1). There were statistically significant differences in sex, baseline pain level, night pain level, and HOOS subscale scores between participants with both case/control periods (*n* = 130) and those without (*n* = 122). More females with higher baseline pain and night pain level and lower HOOS subscale scores had at least 1 episode of pain exacerbation (with both case and control periods).

Two case periods in the PSQI questionnaires and 1 control period in the MAF questionnaires were lost during followup. Participants' mean global PSQI score was 8.3 ± 4.7 , with median 8 (IQR 7), and of the 1104 case and control periods, 67% (737/1104) had poor sleep quality, and 23% (256/1104) had a sleep duration < 6 h (average sleep duration 6.5 ± 1.6 h; Table 2 and Table 3). Of the subscales, sleep disturbance was reported as the most severe. The mean GFI score was 18.6 ± 12.7 (median 19, IQR 21.2). Among the 1105 case and control periods, 48% (534/1105) had greater fatigue (GFI score > 21), and 22.9% (253/1105) had no fatigue at all.

Chi-square test showed there was an association between sleep quality and fatigue (*p* < 0.001), indicating that participants who had poor sleep quality were more likely to have fatigue. Similarly, short sleep duration was also associated with greater fatigue (*p* < 0.001).

In univariable conditional logistic regression analysis, poor sleep quality during the last 7 days was significantly associated with increased odds of pain exacerbations (global PSQI score > 5 vs ≤ 5 : OR 1.72, 95% CI 1.04–2.86). Greater fatigue (GFI > 21) during the last 7 days was also associated with an increased risk of hip pain exacerbation (unadjusted OR 1.92, 95% CI 1.21 to 3.05). We found no association between sleep duration and pain exacerbations (≥ 6 h vs < 6 h: OR 1.40, 95% CI 0.78–2.51).

In multivariable analysis, poor sleep quality and greater fatigue remained significantly associated with pain exacerbations after adjustment for physical activity and night pain levels (Table 4). There was no statistically significant interaction between sleep quality and fatigue (*p* = 0.21).

DISCUSSION

To our knowledge, this is the first study to examine risk factors for pain exacerbations in persons with hip OA. Our findings demonstrate that poor sleep quality and fatigue were associated with pain exacerbation independent from physical activity level and hip night pain level in persons with symptomatic hip OA. Short sleep duration (< 6 h) was not associated with pain exacerbations. These findings should promote further investigation into interventions targeting sleep and fatigue for pain in persons with hip OA.

To date, effective and safe treatments for OA and its related pain are limited. Despite the importance of pain in persons with OA, the quality and characteristics of OA pain are less well studied³. While pain from OA has long been considered a chronic condition, the symptoms experienced

Table 1. Baseline characteristics of the participants.

Characteristic	All Participants, n = 252	Participants*, n = 130	p**
Age, yrs	62.2 ± 8.3	62.5 ± 8.1	0.54
Female, n (%)	199 (79)	111 (85.4)	0.01
Body mass index, kg/m ²	28.7 ± 6.1	29.0 ± 6.3	0.34
Index hip right, n (%)	143 (56.7)	72 (55.4)	0.65
Race, n (%)			
White	242 (96)	123 (95)	0.53
Others	10 (4)	7 (5)	
Education, n (%)			
Less than high school	37 (14.7)	21 (16.2)	0.61
Completed high school	58 (23)	27 (20.7)	
Higher than high school	157 (62.3)	82 (63.1)	
Occupational physical workload level, n (%)			
Sedentary (mostly sitting)	111 (44)	52 (40)	0.12
Standing occupation, physically light	90 (35.7)	51 (39.2)	
Manual work	47 (18.7)	24 (18.5)	
Heavy manual work	4 (1.6)	3 (2.3)	
Baseline pain level (0–10)			
Mildest	2.3 ± 1.9	2.5 ± 2.1	0.02
Worst	7.6 ± 1.9	8.0 ± 1.8	0.02
Night pain level (0–4)	1.8 ± 1.0	1.9 ± 1.0	0.03
Hip injury and Osteoarthritis Outcome Score			
Pain	55.5 ± 17.3	52.0 ± 18.0	0.001
Symptoms	53.0 ± 19.4	50.5 ± 20.4	0.03
Activities of daily living	59.4 ± 21.7	54.7 ± 21.9	< 0.001
Sports/recreation	36.5 ± 27.1	32.7 ± 26.6	0.02
Quality of life	41.5 ± 19.6	38.1 ± 20.7	0.004
International Physical Activity Questionnaire score (range 1–3); median (IQR)	3 (2)	3 (2)	0.53

Data are mean ± SD unless otherwise indicated. *With both case and control periods. **Independent sample t test, chi-square test, and nonparametric test were performed between participants with both case/control periods (n = 130) and those without (n = 122). IQR: interquartile range.

Table 2. Pittsburgh Sleep Quality Index (PSQI) and global fatigue index (GFI) scores and subscales, and sleep disturbance components from the PSQI (130 participants).

Scoring (range)*	Median (IQR)
Global PSQI score (0–21)	8 (7); mean 8.3 ± 4.7
Sleep duration (0–3)	0 (1)
Sleep disturbance (0–3)	2 (1)
Sleep latency (0–3)	1 (1)
Daytime dysfunction (0–3)	1 (2)
Sleep efficiency (0–3)	1 (3)
Sleep quality (0–3)	1 (1)
Sleep medication (0–3)	0 (1)
GFI score (1–51)	19 (21.2); mean 18.6 ± 12.7
Fatigue degree (1–10)	6 (3)
Fatigue severity (1–10)	5 (4)
Distress (1–10)	3 (4)
Impact on daily living (0–10)	1.7 (2.3)
Frequency (1–4)	3 (2)

*For a range of 0–3 in PSQI subscales, 0 = better, 3 = worse; for GFI score, higher score represents greater fatigue severity. Fatigue degree and effect on daily living have anchors of “Not at all” (1 or 0) to “A great deal” (10); fatigue severity has anchors of “Mild” (1) to “Severe” (10); and distress has anchors of “No distress” (1) to “A great deal of distress” (10). Frequency ranged from “Hardly any days” (1) to “Every day” (4). IQR: interquartile range.

by patients are neither constant nor stable³⁴. Studies found that most persons with OA experienced intermittent pain or pain exacerbations in their daily life³⁵. If the risk factors for these pain exacerbations could be identified, many such episodes could be prevented.

Both poor sleep and fatigue can significantly reduce overall quality of life³⁶. The mechanism of the relationship between sleep/fatigue and pain in OA remains unclear. This relationship is complex and likely bidirectional because pain can influence sleep/fatigue and poor sleep/greater fatigue increases pain perception. In a study with healthy persons, sleepy individuals experienced hyperalgesia in response to a painful stimulus compared with non-sleepy individuals³⁷. Researchers found that disturbance of sleep could produce a local and generalized hyperalgesic state in OA, while selective deprivation of slow-wave (deep) sleep or rapid eye movement sleep could reduce the pain thresholds^{5,38,39}. There are studies suggesting that decline in physical functioning is linked with systemic inflammation and pain⁷. However, we found that poor sleep quality was associated with pain exacerbations independent of physical activity level. Although reduced sleep time was associated with an increase in pain reports, the total amount of sleep time was less important than

Table 3. Univariate association of sleep quality, sleep duration, and fatigue and hip pain exacerbation (130 participants). Three separate models were used to test the association using conditional logistic regression (univariable and multivariable).

Independent Variables	Case Periods (%)	Control Periods (%)	OR (95% CI)	p
Sleep quality*				
Good	91 (31)	276 (34)	1.0 (reference)	
Poor	205 (69)	532 (66)	1.72 (1.04–2.86)	0.036
Sleep duration**, hrs				
≥ 6	195 (66)	653 (81)	1.0 (reference)	
< 6	101 (34)	155 (19)	1.40 (0.78–2.51)	0.254
Fatigue***				
No	125 (42)	446 (55)	1.0 (reference)	
Yes	173 (58)	361 (45)	1.92 (1.21–3.05)	0.006

*Association of sleep quality and pain exacerbation. A global Pittsburgh Sleep Quality Index score ≤ 5 indicates good sleep quality, and > 5 indicates poor sleep quality. Two case periods were lost during followup. **Association of sleep duration and pain exacerbation. ***Association of fatigue and pain exacerbation. A cutoff score of 21 on the global fatigue index was used to detect significant fatigue. One control period was lost during followup.

Table 4. Multivariable association of sleep quality and fatigue and hip pain exacerbations in 1 model.

Independent Variables	OR (95% CI)*	p
Sleep quality		
Good	1.0 (reference)	
Poor	2.71 (1.42–5.16)	0.003
Fatigue		
No	1.0 (reference)	
Yes	2.55 (1.41–4.63)	0.002

*Adjusted for physical activity level and night pain level and the interaction term included.

the continuity of sleep in affecting chronic pain^{27,40}. We also found that self-reported short sleep duration (< 6 h) was not associated with pain exacerbations in hip OA.

Fatigue has been linked with pain and poor sleep in OA, although the mechanism of fatigue in OA remains unclear²². We found that sleep quality and fatigue were associated, but they still play independent roles in the risk of hip pain exacerbations, as the result of interaction analysis was not significant. Most studies investigating the role of fatigue in OA are cross-sectional and thus cannot establish the direction of causality between fatigue and pain. Fatigue and pain often co-occur, and more fatigue was found to be strongly associated with more pain⁴¹. Zautra, *et al* reported that daily pain fluctuation in OA was related to fatigue levels³². The change of physical fatigue was also related to pain and physical function³³. In a preclinical study, researchers found that widespread hyperalgesia was enhanced by fatigue in mice, which could lead to worse pain^{42,43}. Central nervous proinflammatory cytokine production related to fatigue has been reported, which suggests that fatigue might influence central nervous activity leading to pain by sensitization of central neurons^{12,44}. Other studies found that mean GFI scores were 10.0 ± SD 1.8 (17.0 ± 11.3⁴⁵) in healthy people, 24.6 ± SD 11.1 in people with RA, and 27.7 ± SD 10.8 in people with OA^{22,45}. However, in our study the mean GFI

was 18.6 ± SD 12.7 (median 19, IQR 21.2), which is much lower than that reported by Stebbings, *et al*, 27.7 ± SD 10.8⁴⁶. This could be explained by the higher severity of OA in their cohort, because participants were recruited from the waiting list for joint replacement surgery⁴⁶.

The risk factors that contribute to OA pain exacerbations have rarely been studied. A similar study on knee OA found that knee injury and buckling during the past 7 days was associated with knee pain exacerbation¹⁴. Moreover, negative affect and passive pain coping strategies were also risk factors for pain exacerbations¹⁶. Weather factors (such as high humidity or high temperature) did not influence pain exacerbations in persons with knee OA¹⁵. We are not aware of research related to risk factors for pain exacerbations in persons with hip OA.

Our findings were derived from the use of novel Internet-based methods that can facilitate real-time data recording. The use of the Internet has become an integral part of daily life; active Internet users as a percentage of the total population in Australia in 2015 and 2016 were 89% and 88%, respectively, according to the Australian Bureau of Statistics. Many studies show that Web-based investigations and data collected by Internet methods (e.g., online questionnaires) reveal quality as good as those collected using traditional methods, and are potentially more efficient^{47,48}.

Our study has limitations: all participants were required to have access to the Internet and a good understanding of English, thus findings from this convenience sample may not be generalizable to all persons with hip OA. Some other potential confounding factors or mediators such as medication use, injury, and psychological factors may also play a role. Although we adjusted for physical activity level, the potential mechanism is complex because there may be multiple pathways linking these factors, in which they may play more than one role, and this needs to be confirmed by further specific studies. The sleep disturbance assessment was subjective and future studies could use objective methods for assessment of sleep duration and quality (e.g.,

actigraphy). There is potential for recall bias because the data were collected based on retrospective self-report questionnaires. Participants were required to complete a number of questionnaires at regular intervals over 90 days, which could impose a participant burden leading to underreporting of pain exacerbations and incomplete questionnaires. However, such a potential bias, if it exists, would be likely to dilute any association. Whether a causal relationship exists between sleep quality and fatigue and pain exacerbations should be further validated using additional longitudinal cohort studies to confirm our findings.

We found that poor sleep quality and fatigue were both related to pain exacerbations in persons with symptomatic hip OA independent of physical activity level and nocturnal pain level. However, the relationship between these factors with pain exacerbations is likely to be complex, and this needs to be elaborated by future research. There is a need for assessment of sleep quality and fatigue among persons with hip OA, which may reduce pain and improve overall quality of life. Interventions to reduce OA pain may be enhanced by giving more attention to sleep and fatigue in persons with hip OA.

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