

# The association between pain and sleep in fibromyalgia

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## ABSTRACT

**الأهداف:** شائع هو عدم انتظام النوم بين مرضى الألم الليفي العضلي الذين يعانون من الألم الشديد. إن الهدف من هذه الدراسة توضيح العلاقة بين الألم واضطراب النوم أو عدم انتظامه لمرضى الألم الليفي العضلي.

**الطريقة:** البحث في قواعد المعلومات الالكترونية ومنها سايك انفو، كوكراين، بايميد، إمبراسيه و أوفيد بهدف التعرف على مقالات مؤهلة. قام الباحثون باستعراض قواعد البيانات كل على حدى كما قام هؤلاء الباحثون برفع قيمة الأدلة باستخدام مقاييس جودة معتمدة ومؤهلة.

**النتائج:** ستة عشر دراسة نوعية طبقت المعايير الشمولية. ثبت بالبرهان والدليل على أن الألم الليفي العضلي مرتبط بشكل طفيف مع نوعية النوم، الحاجة إلى النوم، مدة النوم. ومرتبطة بشكل كبير باضطرابات النوم، تأخر النوم العميق، والأرق. والنقطة الأهم اكتشاف أعراض اكتئاب ترافقت مع الألم واضطرابات النوم على حد سواء عند مرضى الألم الليفي العضلي.

**الخاتمة:** يجب تطوير استراتيجية للتحكم بالتخفيف من الآلام مع تحسين مستوى النوم وانتظامه. يجدر بالدراسات المستقبلية الأخذ بعين الاعتبار المزاجية واضطراب المشاعر حيث يمكن أن تطرأ حالات مختلطة مع الألم واضطراب النوم في مرضى الألم الليفي العضلي.

**Objective:** To clarify the association between pain and sleep in fibromyalgia.

**Methods:** Electronic databases, including PsycINFO, the Cochrane database for systematic reviews, PubMed, EMBASE, and Ovid were searched to identify eligible articles. Databases independently screened and the quality of evidence using a reliable and valid quality assessment tool was assessed.

**Results:** In total, 16 quantitative studies fulfilled the inclusion criteria. According to the results, increased pain in fibromyalgia was associated with reduced sleep

quality, efficiency, and duration and increased sleep disturbance and onset latency and total wake time. Remarkably, depressive symptoms were also related to both pain and sleep in patients with fibromyalgia.

**Conclusion:** Management strategies should be developed to decrease pain while increasing sleep quality in patients with fibromyalgia. Future studies should also consider mood disorders and emotional dysfunction, as comorbid conditions could occur with both pain and sleep disorder in fibromyalgia.

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Fibromyalgia (FM) is a complicated musculoskeletal syndrome that affects between 0.7% and 4.8% of the global population.<sup>1</sup> Most (90%) individuals with FM are women.<sup>2</sup> According to the American College of Rheumatology (ACR), the criteria for FM diagnosis include pain for at least 3 months, but FM patients also experience poor sleep, fatigue, depression, stress, and anxiety.<sup>3</sup> Most (90%) FM patients experience sleep disorder,<sup>2,4,5,7</sup> which exerts a negative effect on health-related quality of life, leading to issues such as unrefreshing sleep and daytime tiredness, causing difficulties with wakefulness.<sup>8</sup> Observational evidence indicates that FM patients' pain is directly related to poor sleep.<sup>9,10</sup> Several aspects of sleep, including duration, disturbance, and efficiency, could be related to pain.<sup>11</sup> In addition, poor sleep has been shown to decrease both pain thresholds<sup>12</sup> and cognitive skills in pain management.<sup>13</sup> Moreover, a longitudinal analysis showed that interactivity between pain and sleep disturbance was associated with depression in patients with rheumatoid arthritis,<sup>14</sup> and patients with FM have

also been found to experience comorbid conditions such as depression, anxiety, and stress.<sup>3,15</sup>

Although sleep and pain have been evaluated frequently in patients with chronic pain, the nature of the relationship between these variables remains unclear in FM. Identifying the relationship between pain and sleep in FM could provide insight for the development of efficient interventions. Therefore, the goal of this systematic review was to 1) determine whether pain is related to sleep, 2) identify the sleep dimensions related to pain in FM, and 3) provide information regarding future research directions, to facilitate the achievement of better health outcomes in FM.

**Methods.** This systematic review aimed to examine the relationship between pain and sleep in FM. While the studies included in the review were not based on the assessment of interventions, Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines<sup>16</sup> were considered during the review. The methodology used in the review was similar to strategies used in previous research<sup>11,17</sup> and involved 3 stages. Stage 1 consisted of a systematic examination of the literature using keywords. Stage 2 involved a) scanning related article titles and abstracts according to particular inclusion criteria, and b) examination of full papers and extraction of evidence. Stage 3 involved the use of a valid quality assessment instrument to classify the included studies according to quality.

**Literature search.** The literature search was completed between November 2011 and March 2016. Electronic databases, including PsycINFO (until December 2012), the Cochrane database of systematic reviews, PubMed, EMBASE, and Ovid (from October 2015 to March 2016), were searched. The database search was performed using a combination of several keywords including “fibromyalgia,” “fibromyalgia syndrome,” “chronic pain,” “pain,” “sleep,” “sleep quality,” “problematic sleep,” and “sleep disturbance/s.” Moreover, the reference lists of all related articles were scanned to identify additional relevant articles.

**Inclusion criteria.** Studies were selected according to language (English), year of publication (from 1990 to 2015), research methods (quantitative), and variables (pain and sleep in FM). The inclusion criteria were as follows: FM patients aged 18 years or older and diagnosed with FM according to ACR criteria as participants 3). The results of the included studies were retrieved according to the significance level for the results, which was set at  $p < 0.05$ . The included studies used different measurement tools to assess sleep and pain. The studies could include measurement of other

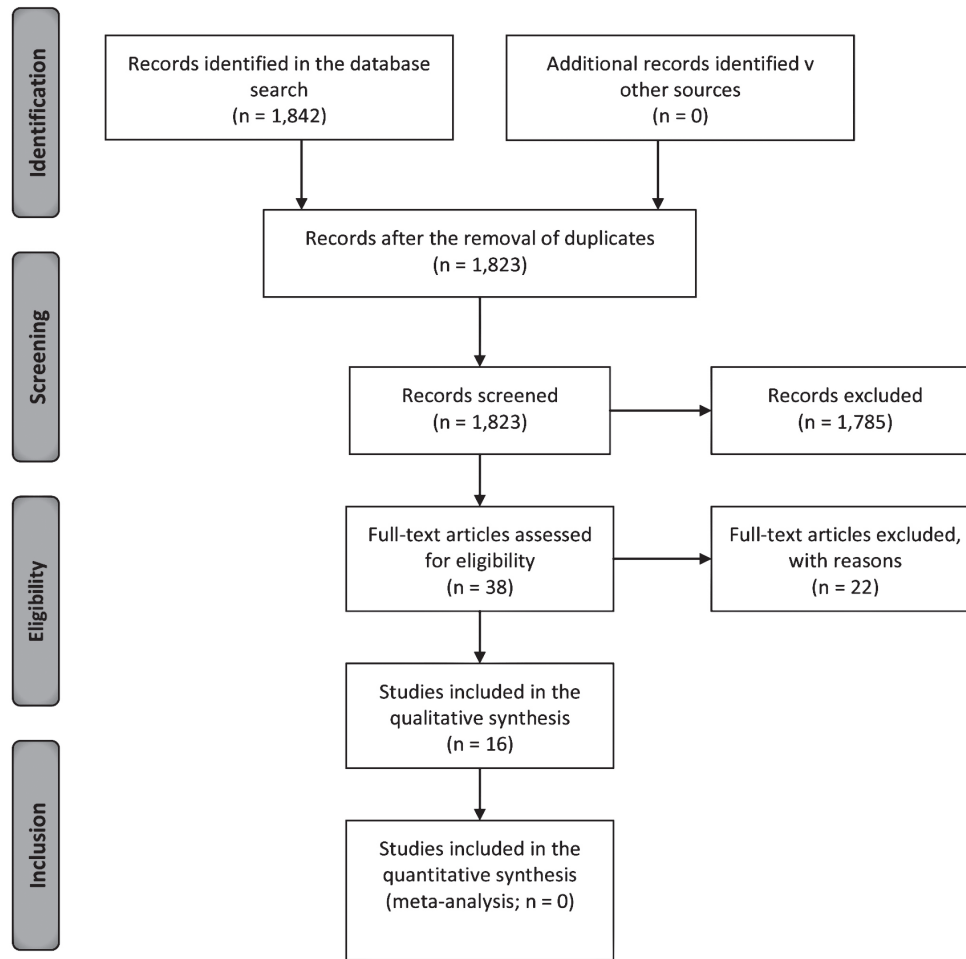
FM symptoms such as depression, stress, physical functioning, fatigue, and anxiety. However, the review focused mainly on remarkable findings regarding pain and sleep, to improve understanding of these variables in FM. Several studies that did not fulfill the inclusion criteria, such as those that did not measure pain and sleep simultaneously, were excluded from the review. In addition, studies examining only facial pain in FM were excluded to avoid misconception.

**Assessment of evidence quality.** Authors used the Effective Public Health Practice Project (EPHPP) quality assessment instrument<sup>18</sup> to categorize the selected studies according to quality. Classifications were then compared to make final decisions regarding the quality of each study. The EPHPP quality assessment instrument was used to analyze the following 6 factors: selection bias, allocation bias, confounders, blinding, data collection methods, and withdrawals and drop-outs.<sup>18</sup> Quality for each factor was rated as “high,” “medium,” or “low.” Overall research quality was considered high, medium, and low if these factors received only high ratings, <4 high ratings and one low rating, and  $\geq 2$  low ratings, respectively. This tool has been identified as a suitable quality assessment instrument for the evaluation of randomized controlled trials and non-randomized controlled trials.<sup>19</sup> In addition, it has been used in >30 systematic reviews.<sup>18</sup>

This systematic review aimed to answer current research questions by systematically specifying, selecting, and critically evaluating related research and analyzing the evidence from the included studies. Systematic reviews may or may not include statistical analysis (meta-analysis) to summarize the findings.<sup>16</sup> As the included studies varied in terms of methodology, participants’ sociodemographic characteristics, and other factors, statistical analysis was not included in the current systematic review, and the evidence was synthesized qualitatively.

**Results. Literature search.** Of 1,842 database citations, 16 studies fulfilled the inclusion criteria for the systematic review (Figure 1). The publication years for the included studies ranged from 1996 to 2015. In addition, the research designs used in the selected studies varied (Table 1). The studies were conducted in the United States,<sup>20-29</sup> Spain,<sup>30-32</sup> the United Kingdom,<sup>33,34</sup> and Turkey.<sup>35</sup>

**Assessment of the quality of included studies.** According to the EPHPP assessment tool, one study demonstrated high,<sup>23</sup> 11 studies demonstrated medium<sup>20,21,24,27-32,34,35</sup> and 4 studies demonstrated as low quality.<sup>25-27,33</sup> (Table 1).



**Figure 1** - Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram illustrating the study inclusion process, adapted from Moher et al.<sup>16</sup>

**Outcome measures. Pain assessment tools.** Most of the studies (n=6) measured pain using the McGill Pain Questionnaire, which has demonstrated very good reliability<sup>36</sup> and validity,<sup>37</sup> and one study used the shorter version of this scale, which has shown good reliability and validity.<sup>38</sup> Three studies used the visual analog scale, which has shown good reliability and validity in various populations.<sup>39-41</sup> Two studies used sensory testing, which evaluates pain threshold on the fingers.<sup>42,43</sup> One study used the pain rating index, which is known to be an effective instrument.<sup>44-46</sup> Two studies used ecological momentary assessment, which involves multiple assessments of individuals in their natural environments.<sup>47,48</sup> In addition, 2 studies used 3 pain subscales from various validated questionnaires,<sup>49,50</sup> and one study used the Health-Related Quality of Life

Questionnaire, which measures several health domains including pain.

**Sleep assessment tools. Subjective tools.** Most of the studies (n=10) assessed sleep using the Pittsburgh Sleep Quality Index,<sup>51,52</sup> which has demonstrated reliability and validity. In addition, 2 studies used different reliable, valid questionnaires,<sup>53,54</sup> and 2 studies used sleep diaries via ecological momentary assessment, which has been identified as effective assessment method.<sup>55,56</sup> Another study used a sleep subscale from a different validated questionnaire.<sup>49</sup> However, several studies used multiple measurement tools to evaluate sleep.

**Objective tools.** Two studies used polysomnography (PSG) recording, which allows objective assessment of sleep parameters.<sup>57</sup> Polysomnography is a very reliable means of assessing sleep in patients with chronic conditions.<sup>58,59</sup> In addition, one study used actigraphy,

**Table 1** - Descriptive characteristics of the studies and comparison of the outcomes.

Study	Design	Participants			Sleep assessment method	Findings	Quality of the study
		N	Gender	Mean±SD			
Affleck et al <sup>20</sup> (1996)	Repeated measures	50 with FM	All female	43.96±8.23	Subjective	a) Pain intensity: 39.75 (17.02; max = 84) b) Sleep duration: 6.47 (0.86) h:m c) Waking episodes: 1.76 (0.98; max = 6) d) Refreshing sleep: 2.59 (1.02; max = 6) e) Pain was related to pain attention ( $p<0.01$ ) and sleep quality ( $p<0.05$ ), but pain attention was not significantly associated with sleep quality f) Pain attention was related to pain intensity the following day ( $p<0.001$ ) g) Sleep quality at night was associated with pain intensity during the day ( $p<0.001$ ) h) Greater daytime pain intensity was associated with poorer sleep quality ( $p<0.05$ )	Medium
Ağargün et al <sup>35</sup> (1999)	Cross-sectional	16 with FM	13 female, 3 male	30.3±8.6	Subjective	a) Sleep quality: 1.3 (1.1; max = 3 for each component) b) Sleep disturbance: 1.9 (0.9) c) Habitual sleep efficiency: 0.6 (1.0) d) Pain threshold was negatively associated with subjective sleep quality ( $p=0.018$ ), habitual sleep efficiency ( $p=0.021$ ), and sleep disturbance ( $p=0.019$ ) scores e) Pain threshold was not significantly related to sleep duration ( $p=0.055$ ), sleep latency ( $p=0.06$ ), or daytime dysfunction ( $p=0.35$ )	Medium
Nicassio et al <sup>21</sup> (2002)	Cross-sectional & repeated measures	105 with FM	96 female, 6 male	51.63±11.82	Subjective	a) Pain was positively related to depression ( $p<0.001$ ), but sleep quality was negatively related to pain ( $p<0.01$ ) and depression ( $p<0.01$ ) b) Daytime pain intensity was associated with poorer sleep quality ( $p<0.001$ ) c) Poorer sleep quality was related to stronger pain intensity during the day or evening ( $p<0.001$ )	Medium
Theadom et al <sup>33</sup> (2007)	Cross-sectional	101 with FM	94 female, 7 male	55±11.76	Subjective	a) Poor sleep (99%) b) Pain: 30.77 (18.56; max health = 100) c) Sleep duration: 6.37 (1.82) h:m d) Unrefreshing sleep: 7.97 (1.89; 10 = very unrefreshing) e) Low levels of enjoyment of sleep: 6.88 (2.33; 10 = very unenjoyable) f) Significant relationship between poor sleep and pain and negative affect ( $p<0.01$ ) g) Sleep quality predicted pain ( $p<0.05$ )	Low
Hamilton et al <sup>22</sup> (2007)	Ecological momentary assessment	27 with RA  22 with FM	19 female, 8 male;  19 female, 3 male	51.22±9.89	Subjective	a) Pain: 3.05 (0.93; max = 6) b) Sleep duration: 7.20 (1.01) h:m c) Sleep quality: 3.36 (1.25) (max = 7) d) Sleep quality was significantly associated with pain ( $p<0.01$ ) e) Participants with FM reported greater pain intensity ( $p<0.05$ ) and lower sleep quality ( $p<0.05$ ) relative to those with RA f) Sleep disturbance mediated the relationship between pain and stress ( $p<0.01$ ) e) Sleep quality was associated with pain ( $p<0.005$ ) f) Sleep disturbance was significantly related to sleep quality ( $p<0.001$ )	Low
Bigatti et al <sup>23</sup> (2008)	Randomized controlled trial	600 with FM	571 female, 29 male	53.92±11.45	Subjective	a) Pain: 1.68 (0.68; max = 6) b) Poor sleep quality: 11.22 (3.96) (max = 21) c) Significant relationship between sleep quality and pain ( $p<0.01$ ) d) Poor sleep was associated with greater pain intensity ( $p<0.05$ ) e) Pain was associated with depression ( $p<0.01$ ) and poor physical functioning f) Sleep was associated with depression ( $p<0.01$ )	High

**Table 1** - Descriptive characteristics of the studies and comparison of the outcomes (Continuation)

Theadom et al <sup>34</sup> (2008)	Cross-sectional	83 with FM 83 HC	91.6% female for both groups	52.59±11.42	Subjective	a) Pain: 29.58 (18.10; max health = 100) b) DBAS: 65.21 (16.42) (max = 100) c) Sleep quality: 2.06 (0.76) (max = 3 for each sleep component) d) Sleep latency: 3.25 (1.57) e) Sleep duration: 1.27 (1.17) f) Sleep efficiency: 1.86 (1.22) g) Sleep disturbance: 2.39 (0.62) h) Overall sleep quality: 14.71 (4.29) i) Participants with FM had significantly higher levels of DBAS, pain, and poor sleep (c, d, e, f, g, h) relative to healthy controls ( $p<0.01$ ) j) Higher levels of DBAS were significantly related to greater pain intensity ( $p<0.05$ ) and poorer sleep quality ( $p<0.05$ ) in participants with FM k) Higher levels of perceived stress were significantly related to greater pain intensity ( $p<0.01$ ) and sleep disturbance ( $p<0.05$ ) in participants with FM	Medium
O'Brien et al <sup>24</sup> (2010)	Cross-sectional	116 with FP 55 with BP 121 with FM	241 female, 51 male	46.67±12.05	Subjective	a) Overall sleep quality: 13.83 (4.19; max = 21) b) Sleep onset latency: 53.18 (51.71) min c) Total sleep time: 5.68 (1.59) hours d) Patients with FM reported significantly longer sleep onset latency relative to those with FP ( $p<0.05$ ) and BP e) Participants with FM and BP showed poorer sleep quality relative to those with FP ( $p<0.001$ ) f) Participants with FM reported greater sleep disturbance relative to those with BP ( $p<0.05$ ) and FP ( $p<0.001$ ) g) Participants with FM and BP reported shorter total sleep time relative to those with FP ( $p<0.01$ and $p<0.001$ , respectively) h) 61.6% of participants with chronic pain reported poor sleep i) Pain was significantly related to poor sleep ( $p<0.01$ ) j) Poorer sleep exerted a significant effect on pain ( $p<0.01$ )	Medium
Miro et al <sup>30</sup> (2011)	Cross-sectional	104 with FM 86 HC	All female	46.39±7.60	Subjective	a) Pain intensity: 7.41 (1.67; max = 10) b) Sleep quality: 2.10 (0.79; max = 3 for each sleep component) c) Sleep latency: 2.06 (0.94) d) Sleep duration: 2.11 (1.01) e) Sleep efficiency: 2.08 (1.16) f) Sleep disturbance: 2.15 (0.61) g) Daily dysfunction: 2.42 (0.81) h) Overall sleep quality: 15.15 (3.99; max = 21) i) 98% of participants with FM reported poor sleep j) Participants with FM showed significantly higher pain intensity and poorer sleep quality relative to healthy controls ( $p<0.001$ ). k) Poorer sleep quality was significantly associated with greater pain intensity ( $p<0.01$ ) and depression ( $p<0.01$ ) in participants with FM l) Pain exerted a significant effect on sleep quality ( $p<0.001$ )	Medium
Schaefer et al <sup>25</sup> (2011)	Cross-sectional	203 with FM	192 female, 11 male	47.9±10.9	Subjective	a) 91% of participants reported pain b) 85.7% of participants who were severely affected by FM reported sleep disturbance c) Increased sleep-related problems were associated with greater FM intensity ( $p<0.001$ ). d) 58% reported depressive symptoms	Low

**Table 1** - Descriptive characteristics of the studies and comparison of the outcomes (Continuation)

Wagner et al <sup>26</sup> (2012)	Cross-sectional	2,196 with FM 2,194 HC	-	57.56 (-)	Subjective	a) 63.05% of participants with FM demonstrated multiple sleep-related problems b) They also indicated significantly greater sleep difficulty relative to healthy controls ( $p<0.001$ ) c) Pain intensity in FM increased with the number of sleep-related problems (19.08%, 30.77%, and 43.26% for those with 0, 1, and 2 sleep-related problems, respectively)	Low
Hamilton et al <sup>27</sup> (2012)	Cross-sectional	35 with FM	All female	47.08±10.47	Subjective	a) Poor sleep: 13.91 (max = 21) b) Sleep quality was significantly associated with sensory ( $p<0.01$ ) and affective ( $p<0.01$ ) pain c) Sleep exerted a significant effect on pain ( $p<0.01$ ) d) The effect of pain helplessness on the association between sleep quality and pain was significant ( $p<0.01$ ) e) Pain affected the relationship between sleep and depression ( $p<0.05$ )	Medium
Anderson et al <sup>28</sup> (2012)	Repeated measures	74 with FM	70 female, 4 male	52.6±9.8	Objective Subjective	a) Pain intensity: 53.0 (20.3; max = 100) b) Total wake time: 120.9 (67.8) min c) Total sleep time: 390.1 (66.8) min d) Objective total wake time: 101 (52) min e) Objective total sleep time: 395.5 (76) min f) Pain was significantly related to objective total wake time ( $p=0.05$ ) g) Pain was significantly related to negative mood ( $p=0.002$ ) h) Negative mood significantly affected pain ( $p=0.04$ ) i) Negative mood was significantly related to objective ( $p=0.006$ ) and subjective ( $p=0.03$ ) total wake time	Medium
Diaz-Piedra et al <sup>31</sup> (2014)	Cross-sectional	55 with FM	All female	47.62±7.64	Objective Subjective	a) Poor sleep quality: 14.63 (3.44; max = 21) b) Objective total sleep time: 425.69 (67.24) min c) Wake percentage: 16.22% (10.69) d) Sleep efficiency: 83.76% (10.72) e) Sleep latency: 28.63 (27.66) min f) Wake time after sleep onset: 57.25 (43.02) min g) Pain: 23.73 (9.53; max = 45) h) Pain was significantly related to objective total sleep time ( $p<0.005$ ), wake percentage ( $p<0.01$ ), objective sleep efficiency ( $p<0.005$ ) and objective sleep latency ( $p<0.01$ ) i) Pain was also significantly related to subjective poor sleep ( $p<0.01$ ) j) Pain was significantly affected subjective sleep quality ( $p<0.02$ ) and depression ( $p<0.05$ )	Medium
Kothari et al <sup>29</sup> (2015)	Repeated measures	220 with FM	195 female, 25 male	51.25±11.02	Subjective	a) Sleep duration: 6: 37 (1.93) h:m b) Moderate sleep quality: 2.432 (1.175; max = 5) c) Pain: 2.439 (1.218; max = 5) d) Sleep quality was significantly related to pain ( $p<0.01$ ) e) Sleep disturbance exerted a significant effect on pain ( $p<0.001$ ) f) Negative affect was significantly related to sleep quality ( $p<0.01$ ) and pain ( $p<0.01$ ) g) Pain exerted a significant effect on the relationship between sleep quality and activity interference ( $p<0.001$ )	Medium
Diaz-Piedra et al <sup>32</sup> (2015)	Cross-sectional	53 with FM 36 HC	All F	45.9±7.2	Objective Subjective	a) Objective total sleep time: 7:09 (1:08) h:m b) Sleep latency stage: 24:10 (20:52) min d) Objective total wake time: 15.3% (9.3) e) Subjective sleep quality: 14.3 (3.4; max = 21) f) Pain intensity: 21.2 (9.4; max = 45) g) Participants with FM reported poor sleep (98.1%) h) Objective total wake time ( $p=0.005$ ) and subjective sleep quality ( $p<0.05$ ) differed significantly between participants with FM and healthy controls i) Objective total wake time ( $p<0.001$ ) and depression ( $p=0.009$ ) exerted significant effects on subjective sleep quality in participants with FM	Medium

RA - rheumatoid arthritis, HC - healthy controls, FP - facial pain, BP - back pain, FM - fibromyalgia, max - maximum score, h:m - hours and minutes, DBAS - dysfunctional beliefs and attitudes about sleep, all scores are presented as means (standard deviations),  
<sup>a</sup>Scores presented as median values (interquartile ranges)

which is strongly associated with PSG with respect to sleep duration.<sup>60,61</sup>

**Dimension of sleep.** Sleep duration was subjectively assessed in 8 studies<sup>20,22,24,29,30,33-35</sup> and objectively assessed in 2 studies.<sup>31,32</sup> One study<sup>28</sup> assessed sleep duration both objectively and subjectively. In addition, 4 studies<sup>24,28,31,32</sup> indicated reductions in total sleep time in FM patients. One study<sup>31</sup> reported that objective total sleep time was significantly associated with pain, while another study<sup>35</sup> found that this relationship was non-significant. In total, 9 studies of medium quality and 2 studies of low quality consistently demonstrated reduced sleep duration in FM patients.

Sleep quality was subjectively evaluated by 13 studies<sup>20-24,27,29-35</sup>. Studies of high (n=1), medium (n=9), and low quality (n=2) reported poor sleep quality in FM. Most studies found a significant relationship between pain and poor sleep quality in individuals with FM. Sleep disturbance was assessed subjectively in 8 studies<sup>22,24-26,29,30,34,35</sup>. In total, medium (n=5) and low quality (n=3), consistently reported that FM patients experienced pain and sleep disturbance. In addition, 4 studies reported subjective<sup>24,30,34,35</sup> and 2 studies reported objective<sup>31,32</sup> sleep onset latency. In total, 6 studies of medium quality reported that sleep onset latency ranged between approximately 24 and 58 min. Three studies of medium quality examined objective total wake time;<sup>28,31,32</sup> of these, 2 studies reported that total wake time was significantly associated with pain in individuals with FM.<sup>28,31</sup>

Moreover, 3 and 2 studies of medium quality reported reduced subjective<sup>30,34,35</sup> and objective<sup>31,32</sup> sleep efficiency, respectively. In addition, 2 of these studies<sup>31,35</sup> found that sleep efficiency was significantly associated with pain in FM patients. One medium quality study<sup>34</sup> showed relationships between dysfunctional beliefs and attitudes about sleep and poor sleep quality and pain in FM (Table 1).

**Overall sleep.** Nine studies (one high, 5 medium, and 3 low quality) found that sleep exerted a significant effect on pain in FM;<sup>20-24,26,27,29,33</sup> however, one study of medium quality<sup>28</sup> failed to demonstrate this effect. In contrast, 4 studies of medium quality<sup>21,30,31,35</sup> showed that pain significantly influenced sleep. However, in 2 studies of medium quality,<sup>23,32</sup> this effect was nonsignificant (Table 1).

**Pain, sleep, and mood.** A few studies (2 medium and one low quality) demonstrated that negative affect and stress were associated with sleep quality<sup>29,33</sup> and pain.<sup>29,34</sup> Similarly, one study of medium quality showed that negative mood was significantly related to pain and objective and subjective total wake time.<sup>28</sup>

In addition, one study of medium quality showed that negative mood mediated the relationship between pain and sleep in FM.<sup>24</sup> In contrast, 7 studies (one high, 5 medium, and one low quality) reported that FM patients experienced depression.<sup>21,23,25,27,30-32</sup> Moreover, depression was independently associated with pain and sleep in FM.<sup>21,23,27</sup> Two studies of moderate quality indicated that pain and sleep quality influenced depression independently;<sup>31,32</sup> however, only one of these studies demonstrated that depression influenced sleep directly<sup>32</sup> (Table 1).

**Summary.** The findings demonstrated a significant association between pain and poor sleep in FM patients. In addition, pain exerted a significant effect on sleep, and sleep exerted a significant effect on pain. However, although only half of the studies included in the review analyzed psychological variables, the finding that depression was associated with both pain and sleep in FM patients was remarkable (Table 1).

**Discussion.** The objective of this systematic review was to enhance understanding regarding the relationship between pain and sleep in FM. The findings showed that FM patients who experienced intense pain also experienced poor sleep. More specifically, several sleep dimensions, including total wake time and sleep quality, disturbance, efficiency, onset latency, and duration, were associated with pain in FM patients.

The results of the review indicated that FM patients experienced greater pain intensity and poorer sleep (manifested as sleep disturbance, daytime sleepiness, and daytime dysfunction) relative to healthy individuals.<sup>26,30,32,34</sup> In addition, overall sleep was negatively associated with pain in FM patients. Disorders in the dimensions of sleep could affect overall sleep, which could interact with pain.<sup>11</sup>

The findings identified sleep disturbance, which was associated with pain,<sup>35</sup> as a sleep dimension that FM patients experienced frequently.<sup>22,24-26,29,30,34,35</sup> Sleep disturbance could be regarded as failure of the reparative function of sleep,<sup>62-64</sup> which could cause hyperalgesia.<sup>13,65-68</sup> Patients with chronic pain, including FM, rheumatoid arthritis, osteoarthritis, cancer pain, headaches, and chronic fatigue syndrome, reported different types of sleep disturbance.<sup>11,69,70</sup> Moreover, sleep disturbance has been identified as a principal symptom of FM<sup>5,71</sup> and associated with both sleep quality and pain intensity.<sup>72-74</sup> Sleep disturbance in FM has been defined as difficulty falling asleep and maintaining sleep, reductions in sleep time, multiple interruptions to sleep during the night, and unrefreshing sleep.<sup>72,75-77</sup> These problems could result in poor sleep quality,

reduced sleep efficiency, and increased sleep onset latency.<sup>64,78</sup> The results of this review are consistent with those of previous studies that reported increased sleep onset latency, reduced sleep duration, and poor sleep efficiency in FM patients. Sleep efficiency was associated with both subjective and objective pain,<sup>31,35</sup> while total wake time was associated solely with objective pain, in FM patients.<sup>28,31</sup> The review also included one study<sup>31</sup> indicating that pain was objectively related to sleep duration and sleep onset latency. However, another study<sup>35</sup> did not observe subjective relationships between these sleep dimensions and pain. Although both studies<sup>31,35</sup> were of medium quality, various findings in the review could have resulted from differences between objective and subjective sleep measurements.

The association between pain and sleep is complicated.<sup>79</sup> Clinical and experimental evidence has indicated that chronic pain is associated with increased levels of irritability during sleep,<sup>80,81-83</sup> resulting in awakening.<sup>84</sup> Several longitudinal studies involving patients with chronic pain have established that pain and poor sleep could affect one another.<sup>67,80</sup> The findings of this review support the results of previous research suggesting that pain and sleep share a bidirectional relationship, which is difficult to understand in FM. The number of studies indicating that sleep influenced pain was higher relative to that of studies suggesting that pain influenced sleep.

However, pain and sleep might not share a direct relationship in FM.<sup>82,85</sup> This relationship could be affected by various factors, including mood disorders, in patients with chronic pain.<sup>86-92</sup> The current findings<sup>21,23,25,27,30-32</sup> indicated that FM patients experienced depression in parallel with pain and poor sleep. In addition, few studies in the review considered the significant role of pain-related cognition, such as pain attention<sup>20</sup> and pain helplessness,<sup>27</sup> in pain intensity. Moreover, negative effect has been associated with poor sleep in individuals with chronic pain.<sup>93-96</sup> Consistent with the results of previous research, the current findings<sup>24,28,29,33</sup> suggest that negative mood in FM patients could affect the association between pain and sleep disturbance, as a covariate. Considering that these patients generally experience greater stress relative to healthy individuals,<sup>97-99</sup> it is not surprising that negative emotional functioning interacts with FM symptoms. Although this review provides important insights into the association between pain and sleep in FM, it was subject to several limitations that should be noted. Most studies included in the review used the Pittsburgh Sleep Quality Index to assess sleep subjectively, while few studies used objective measures such as PSG and

actigraphy. However, some differences were observed between the studies that used objective and subjective sleep assessments. Despite the finding that objective and subjective sleep assessment methods are moderately related,<sup>100,101</sup> they have different functions in sleep assessment.<sup>11,102</sup> Moreover, the observational findings of some studies did not allow inference of a causal relationship between pain and sleep. Although we used the EPHPP, which is a valid, reliable quality assessment tool,<sup>18,19</sup> the studies included in the review were generally of lower quality because of their study designs. Overall, the findings should be considered with caution, as some studies of the same quality reported contradictory results. This could be explained by differences in research methods between the studies or authors' misconceptions regarding the quality assessment process. Furthermore, some studies in the review regarding sleep quality as a sleep dimension, while others considered it an overall sleep score. Therefore, the results were difficult to interpret. In addition, the relationship between pain and sleep could be influenced by other FM symptoms that were not identified in the review. The studies in the review differed in terms of sample size, participants' sociodemographic characteristics, reporting of control variables, and research methods. These differences could have affected both the interpretation and summary of the results.

The review indicated that the relationship between pain and sleep could be bidirectional in FM. In addition, this relationship could interact with depressive symptoms. Findings suggested that several dimensions of sleep, including sleep disturbance, onset latency, and efficiency, were associated with pain in FM. More specifically, sleep disturbance was identified as the most important sleep dimension and should be the focus of FM research. This review is significant, as it sought to enhance understanding of the association between sleep and pain in FM in the context of subjective and objective sleep dimensions. This could guide future research that aims to improve health-related quality of life in FM patients. The enhancement of sleep could reduce pain, and reductions in pain could enhance sleep in FM patients. However, additional studies involving mixed designs are required to determine whether 1) pain drives poor sleep, 2) poor sleep leads to greater pain intensity, and 3) pain and sleep share an indirect relationship that interacts with depression in FM. In addition, further studies examining sleep should use both objective and subjective measurement tools where available, as differences between sleep assessment tools could lead to misconceptions. In light of comprehensive research, multidisciplinary interventions should be



developed to reduce pain and depressive symptoms and enhance sleep quality, which could improve health outcomes for patients with FM.

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