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Brief Research Report

Familial Contributions to Self-Reported Sleep and Pain in Female Twins

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Abstract

Objective. The relationship between sleep quality and pain has been studied in populations with chronic pain and in nonclinical populations using experimental paradigms. Little is known about the familial contributions to this relationship. This study examines self-reported sleep quality and pain in a nonclinical sample and to explore familial (i.e., shared genetic and common family environment) confounding in those relationships.

Design. Cross-sectional.

Subjects. Ninety nine community-based female twin pairs ($N = 198$) with a mean age of 29 years; 72% monozygotic.

Methods. The short form McGill Pain Questionnaire (McGill), a visual analog scale (VAS), a body map, and the Pittsburgh Sleep Quality Index (PSQI) measured self-reported pain and sleep quality. Mixed model regression adjusted for age was used to examine relationships between the pain indices and PSQI in overall and within-pair models.

Results. Higher PSQI total scores were significantly associated with higher scores across the McGill sensory ($B = 0.37$, $p < 0.001$), affective ($B = 0.16$, $p < 0.001$), total scores ($B = 0.54$, $p < 0.001$), the VAS ($B = 2.41$, $p < 0.001$), and number of sites with any pain on the body map ($B = 0.42$, $p = 0.001$). All of these associations were diminished and rendered nonsignificant in within-pair analyses that accounted for genetic and familial factors (all p's ≥ 0.01; Bonferroni $\alpha = 0.01$).

Conclusions. These findings support an association between poor sleep quality and pain and suggest that this relationship may be confounded by shared genetic and environmental factors, which could elucidate biological mechanisms that underlie the development and maintenance of pain and sleep problems.

Key Words. Pain; Sleep; Females; Twins; Genetics; Familial Factors

Introduction

The relationship between poor sleep quality and pain has been well established [1–3]. Experimental paradigms demonstrate that sleep deprivation leads to increased experimental pain sensitivity in healthy individuals [4,5]. Poor sleep is often both a risk factor for and consequence of chronic pain conditions such as chronic widespread pain or fibromyalgia [6]. Individuals with insomnia have demonstrated differences in pain modulation [7]. The link between poor sleep and pain is often characterized as a cycle of reciprocal relationships, whereby poor sleep quality increases pain and increased pain reduces

quality of sleep [2]. However, recent research investigating the directionality of this association suggests that sleep disturbance may be a stronger predictor of pain and that poor sleep temporally preceding pain may be the stronger directional pathway [8]. Little is known about the relationship between sleep and pain in nonclinical samples without diagnosed chronic pain conditions or insomnia, although one study in a nonclinical sample of young adults found that poor quality sleepers reported higher pain symptoms [9]. Further, genes and common family environment (referred to as familial factors) have been implicated in both the experience of poor sleep quality [10] and pain [11,12] separately, but the influence of familial factors on the relationship between poor sleep quality and pain also has not been sufficiently examined and could inform mechanisms involved in this relationship, such as the directionality of this relationship and the specific biopsychosocial factors involved.

This study used data from a genetically informative sample of community twins to study poor sleep quality and nonexperimental pain and poor sleep quality in a nonclinical sample of individuals and to elucidate the role of familial confounding to guide future research to better treat sleep and pain problems. The aims of this study were to: 1) examine self-reported sleep quality and pain and 2) explore familial confounding in those relationships. We hypothesized that poorer sleep quality would be associated with higher pain severity and that these relationships would be confounded by familial factors.

Methods

Participants

This sample contained 99 female twin pairs ($N = 198$) from the University of Washington Twin Registry (UWTR). The UWTR is a community-based registry with identification of twins by the Washington state department of licensing [13,14]. Members of the registry were selected from the UWTR to participate in a study examining psychological, behavioral, and physiological risk factors for medically unexplained chronic pain between 2006 and 2010. The rationale for the study, its methodology, and other outcomes have been previously reported [15–17]. Because the study was focused on examining correlates of medically unexplained chronic pain, exclusion criteria included medical conditions such as autoimmune diseases or cancer that could account for the presence of pain and any medical conditions like uncontrolled allergies or endocrine conditions, heart and lung problems, and sleep disorders that could alter data collection. Participants were excluded if they currently smoked, screened positive for recreational drugs, had a body mass index under 20 or higher than 35 kg/m^2, were pregnant, or had a physical or sensory disability that would make them unable to complete study tasks. Informed written consent was obtained from all participants. The institutional review boards of the University of Washington and the University of California, San Diego approved the study protocol.

Procedures

Self-report measures were collected via a questionnaire packet completed at home to ensure sufficient time to complete questionnaires before the lab visit. The study also involved at-home collection of saliva samples and a two-day laboratory session at the University of Washington General Clinical Research Center for physical examinations and other study tasks, which are not included in the present analyzes but are reported elsewhere [15–17]. Participants were asked to avoid taking all medications that might impact sleep, pain, the hypothalamic–pituitary–adrenal (HPA) axis, or the autonomic nervous system during the study period and for the 2 weeks prior to the study. Participants were restricted to having only as many as two alcoholic drinks per week and one cup of coffee per day while in the study. Urine drug tests were done during the study's laboratory portion to ensure no recreational drug use. Zygosity of twin pairs was determined with genetic testing using either the AmpFlSTR® Identifiler® Plus PCR amplification kit, or the PowerPlex® 16 HS System with all assays conducted according to manufacturer's instructors at the University of Washington center for clinical genomics.

Measures

Demographic information included age, race/ethnicity, marital status, highest level of education, and total household income. The Pittsburgh Sleep Quality Index (PSQI; 18) was used to assess sleep quality in the past 4 weeks; the measure was scored according to standard procedures with higher numbers indicating worse sleep quality (range 0–21). Pain in the past 4 weeks was assessed with the short-form McGill pain questionnaire (McGill; 19), which results in the sensory (range 0–33) and affective (range 0–12) subscales, a total score (range 0–45), a visual analog scale (VAS), and an overall pain rating. The VAS was a 100 mm line anchored at "no pain" and "worst possible pain." A body map with 21 sites was used to gather information on the location of pain. Both the PSQI and McGill are standardized self-report measures and have good psychometric properties [18,19].

Statistical Analyses

Descriptive statistics were calculated and provided. Analyses were performed in line with recommended procedures for regression models with twin studies [20]. Overall mixed model regressions were run with sleep quality (PSQI) as a predictor, the McGill pain, VAS, and total number of pain sites as the response variables, twin pair as the random factor, and age as a covariate. For relationships with significant overall models, within-pair models were conducted that control for the familial (shared genetic and common family environmental) confounding within twin pairs. Twins share between 50 and 100% of their genetics and 100% of their family environment when reared together in the same household.

These within-pair models naturally account for these familial factors that could influence the sleep-pain relationship. A Bonferroni adjusted alpha of ($0.05/5 = 0.01$) was used for all analyses because each pain variable was run in a separate model. The statistical methods are comparable to those previously used [15–17]. Data analyses were performed using statistical package for social sciences version 20 (IBM, Armonk, NY).

Results

Participants

Demographic, sleep, and pain characteristics for the entire sample are presented in Table 1. Participants were female and mostly (72%) monozygotic. The average age was 29 years ($SD = 10$); 88% were white; 50% had a bachelor's degree or higher, and 24% were married or cohabitating; 33% of participants had an income greater than $80,000, and 28% reported an income less than $20,000. The sample demonstrated good sleep quality (mean PSQI Total < 5), had little to no difficulty across all seven PSQI component scores, and had a mean sleep efficiency of 93% ($SD = 23$). Figure 1 displays the prevalence of self-reported pain across body map sites. The most common reported pain sites were upper back, lower back, neck, and knee. Table 2 provides detailed pain characteristics for the overall sample. The most commonly endorsed (i.e., a McGill rating of 1–3) sensory items were aching, cramping, throbbing, tender, and sharp. Tiring-exhausting was the most frequently rated affective item. The majority of the sample had mild pain on the VAS and on the overall pain rating. Upper back, lower back, neck, and knees were the most common areas of pain on the body map.

Sleep and Pain

Results of overall and within-pair mixed model regressions are presented in Table 3. Poorer sleep quality was significantly associated with higher pain across all of the pain variables (p's ≤ 0.001). A one unit increase in the PSQI total score was linked to 0.36, 0.16, and 0.53 increases in McGill sensory, affective, and total scores, respectively. The McGill VAS increased by 2.37 and the number of total pain sites on a body map increased by 0.41 for every one unit increase in PSQI total score. After controlling for familial factors in the within-pair analyses, these relationships were attenuated and rendered nonsignificant with a Bonferroni adjusted alpha (p's ranging from 0.01 to 0.39).

Discussion

Summary of Findings

We found that poorer sleep quality was significantly related to higher pain on all of our pain indicators in a nonclinical community sample of female twins. These associations appeared to be influenced by shared

Table 1 Demographic, sleep, and pain characteristic for all twins

Demographics	Total ($n = 186$)
Age, *M* (*SD*)	28.7 (9.8)
Race/Ethnicity	
White, %	87.6
Asian, %	5.9
Native Hawaiian or Pacific Islander, %	1.6
Biracial, %	1.6
Hispanic, %	6.5
Education	
Less than high school education, %	1.1
High school or GED, %	5.9
Some college or technical school, %	43.1
Bachelor's degree or higher, %	40.9
Graduate or professional degree, %	9.1
Marital status	
Single, %	72.6
Married, %	19.9
Widowed, %	0.5
Divorced, %	3.2
Cohabitating, %	3.8
Income	
Less than $20,000, %	28.1
$20,000–$29,999, %	13.5
$30,000–$39,999, %	7.0
$40,000–$49,999, %	8.6
$50,000–$59,999, %	3.8
$60,000–$69,999, %	3.2
$70,000–$79,999, %	2.7
$80,000 and more, %	33.0
Sleep	
PSQI subjective sleep quality, *M* (*SD*)	1.0 (0.7)
PSQI sleep latency, *M* (*SD*)	0.9 (0.9)
PSQI sleep duration, *M* (*SD*)	0.3 (0.7)
PSQI habitual sleep efficiency, *M* (*SD*)	0.0 (0.0)
PSQI sleep disturbance, *M* (*SD*)	1.1 (0.5)
PSQI use of sleeping medication, *M* (*SD*)	0.3 (0.8)
PSQI daytime dysfunction, *M* (*SD*)	0.7 (0.7)
PSQI total, *M* (*SD*)	4.3 (2.7)
PSQI percent sleep efficiency, *M* (*SD*)	92.7 (23.4)
Pain	
McGill sensory, *M* (*SD*)	3.6 (3.4)
McGill affective, *M* (*SD*)	0.8 (1.2)
McGill total, *M* (*SD*)	4.4 (4.2)
McGill VAS, *M* (*SD*)	18.5 (18.5)
Total pain sites from body map, *M* (*SD*)	4.6 (4.3)

Note. PSQI is the Pittsburg Sleep Quality Index. PSQI total scores range from 0 to 21, and the percent sleep efficiency ranges from 0 to 100. All other PSQI subscales range from 0 to 3. McGill is the short-form McGill pain questionnaire. McGill total scores range from 0 to 45, sensory scores range from 0 to 33, and affective scores range from 0 to 12. VAS is visual analog scale (100 mm line anchored at "no pain" and "worst possible pain"). The body map had a total of 21 sites. Demographics exclude six participants with missing PSQI data and their twin pair for a total of 12 participants excluded.

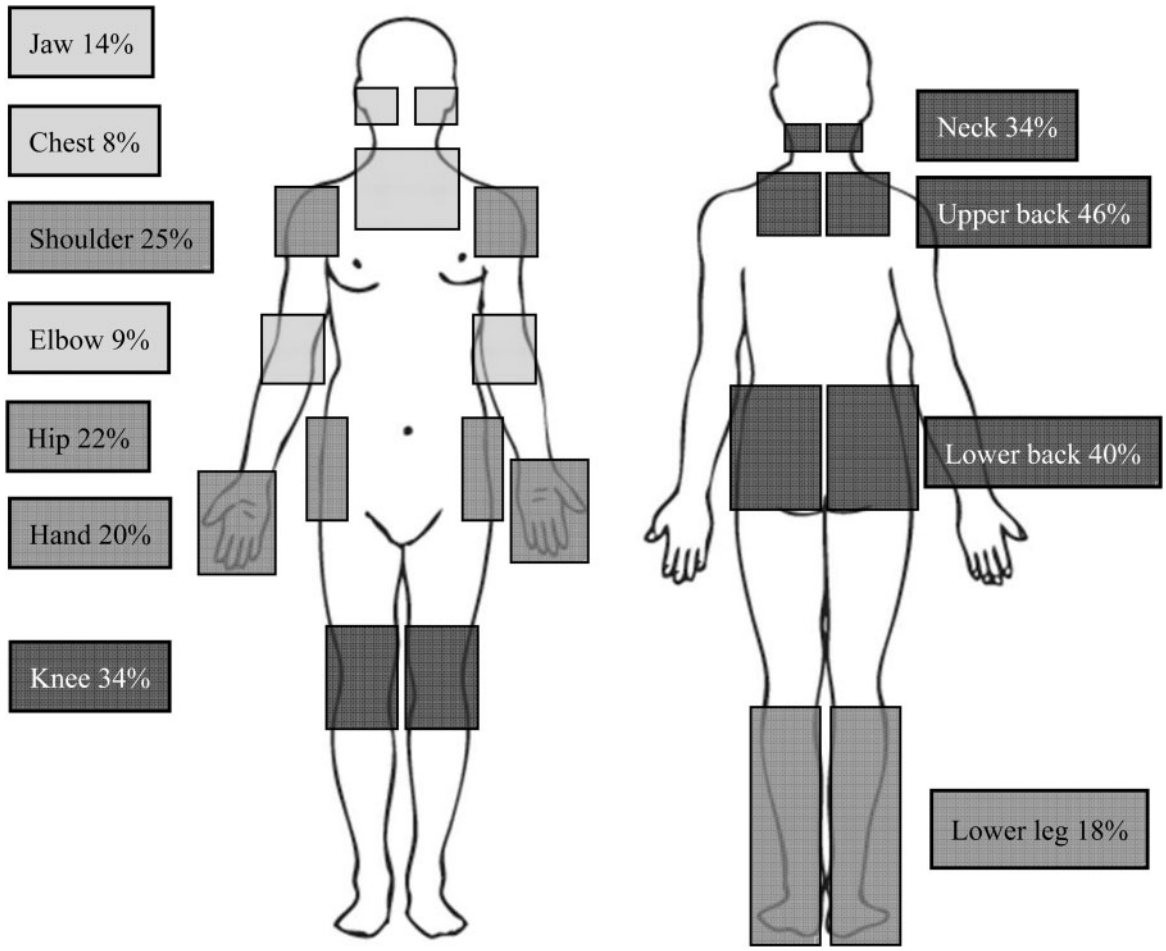

Figure 1 Prevalence of self-reported pain across body map sites. A total of 21 sites were presented but distinct right and left locations assessed were combined for current prevalence rates. Dark gray areas are the most prevalent, medium gray areas are second most prevalent, and the light gray areas are the least prevalent pain areas. Descriptive exclude six participants with missing PSQI data and their twin pair for a total of 12 participants excluded.

Table 2 Pain characteristics from the McGill

Sensory Subscale, (% Endorsing Item)	Affective Subscale, (% Endorsing Item)	VAS, (% Within Range)	Overall Pain Rating, (% in Pain Rating Categories)
68% Aching	42% Tiring-exhausting	0–4: 28% none	21% No pain
50% Cramping	11% Sickening	5–44: 61% mild	53% Mild
31% Throbbing	4% Fearful	45–74: 9% moderate	24% Discomforting
30% Tender	4% Punishing-cruel	75+: 1% severe	2% Distressing
26% Sharp			0% Horrible
13% Splitting			0% Excruciating
12% Shooting			
10% Stabbing			
10% Gnawing			
7% Hot-burning			
6% Heavy			

McGill is the short-form McGill pain questionnaire. VAS is visual analog scale. Descriptives exclude six participants with missing PSQI data and their twin pair for a total of 12 participants excluded.

Table 3 Results from overall and within-pair analyses of sleep quality related to pain

Response Variable	Analysis	*B*	(95% *CI*)	*p*
McGill sensory	Overall	0.36	0.97, 4.22	<0.001*
	Within-pair	0.12	−0.15, 0.39	0.39
McGill affective	Overall	0.16	0.09, 0.22	<0.001*
	Within-pair	0.11	0.002, 0.22	0.05
McGill total	Overall	0.53	0.30, 0.76	<0.001*
	Within-pair	0.23	−0.012, 0.57	0.20
McGill VAS	Overall	2.37	1.38, 3.36	<0.001*
	Within-pair	1.47	0.002, 2.94	0.05
Total pain sites from body map	Overall	0.42	0.18, 0.65	0.001*
	Within-pair	0.41	0.10, 0.73	0.01

*Statistically significant at Bonferroni adjusted alpha of 0.01.
B is the change in pain response variable for a one unit increase in PSQI total score from mixed model regression analyses. Analyses exclude six participants with missing PSQI data and their twin pair for a total of 12 participants excluded.

familial factors. This is the first study to examine the relationship between the number of pain sites on a body map and sleep quality in a nonclinical pain sample. We also found that our sample of female twins endorsed mild pain mostly located in back, neck, and knee regions that were described mostly as being aching, cramping, throbbing, tender, sharp, and tiring-exhausting.

Relevance to Nonclinical Samples

Our findings suggesting a link between poor sleep quality and pain are in line with findings from previous research using nonclinical samples [4] and further describe the association to include links between poor sleep quality and higher pain severity on a VAS, more sensory and affective descriptors on the McGill, and higher number of pain sites on a body map. Studies with healthy participants have demonstrated that poor sleep quality and experimentally induced sleep restriction are associated with higher pain ratings and hyperalgesia in response to an evoked pain sensitivity paradigm [5,21]. Further, there is some evidence suggesting that the stress response system or HPA axis functioning may mediate the relationship between sleep quality and evoked pain [21].

Relevance to Clinical Samples

Our findings also are consistent with studies on the relationship of sleep quality and pain in samples with chronic pain or serious medical conditions where higher clinical pain and pain sensitivity in response to evoked pain tasks are associated with poorer sleep quality [22–25]. Interestingly, the sleep-pain relationship found in this study has been supported in clinical samples that have notably higher pain ratings and poorer sleep quality compared with our nonclinical sample. The association of sleep quality and pain may apply broadly beyond populations with chronic pain or medical conditions. However, the exact nature of these relationships in clinical samples could differ based on the measure of pain used. For example, one study found that duration of pain symptoms in months and highest VAS 2-week pain rating accounted for more variance in poor sleep quality than average VAS 2-week pain ratings [26]. Research on sleep and pain in clinical samples may need to carefully consider how pain is assessed given the potentially dynamic nature of pain symptoms and the relationship with sleep in a chronic pain population. An added complication is that commonly comorbid depression or anxiety symptoms may better account for poor sleep quality in individual with chronic pain than pain symptoms [27]. However, populations with insomnia [28] or migraine [29] maintain the pain-poor sleep quality relationship after controlling for depression so the influence of depression and anxiety on the association between poor sleep quality and pain may depend on the clinical population being studied [8].

Familial Factors and Future Directions

Results from our study supporting that familial factors confound the relationship between poor sleep quality and pain suggest that poor sleep quality and pain may have common familial origins. These findings are in line with previous work identifying the role of familial or genetic components of poor sleep and pain independently [10–12]. Our findings extend that literature to provide more evidence that the sleep quality-pain relationship is influenced by shared familial factors. Recent research using bivariate genetic analyses found that 98% of the phenotypic association between poor sleep quality and pain can be explained by genetic factors with a more limited influence of shared environment [28]. Although some research has identified genetic polymorphisms involved in insomnia, more research is needed to better understand the influence of genes and shared environment on the relationship between poor sleep quality and pain and the potential epigenetic mechanisms that might contribute to the development and maintenance of both poor sleep and pain as a result of life events such as acute and chronic stress [30]. Identification of

candidate genes may provide insight into biological mechanisms and treatment targets shared familial mechanisms like learning and culture could also underlie the association between sleep quality and pain and could also provide information for prevention and treatment of poor sleep quality and pain.

Limitations

This study has several limitations. The sample consisted of young female twin pairs so our findings may not generalize to men, older populations, or to individuals with current chronic pain. Our design was cross-sectional, so we cannot further disentangle the directionality of the sleep-pain relationship.

Conclusions

In conclusion, we found that poorer sleep quality was significantly associated with higher pain across multiple pain indices in a nonclinical community sample of female twins and that familial factors appeared to play a role in the sleep-pain relationship. More research is needed to better understand the role of poor sleep in the experience of pain naturalistically and the development and maintenance of chronic pain, as well as the biological, psychological, and social mechanisms at work. This line of research can ultimately lead to better prevention and treatment strategies for both sleep problems and pain.

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References

1 Foley D, Ancoli-Israel S, Britz P, Walsh J. Sleep disturbances and chronic disease in older adults: Results of the 2003 national sleep foundation sleep in America survey. J Psychosom Res 2004;56:497–502.

2 Smith MT, Haythornthwaite JA. How do sleep disturbance and chronic pain inter-relate? Insights from the longitudinal and cognitive-behavioral clinical trials literature. Sleep Med Rev 2004;8:119–32.

3 Menefee LA, Cohen MJM, Anderson WR, et al. Sleep disturbance and nonmalignant chronic pain: A comprehensive review of the literature. Pain Med 2000;1:156–72.

4 Lautenbacher S, Kundermann B, Krieg JC. Sleep deprivation and pain perception. Sleep Med Rev 2006;10:357–69.

5 Roehrs T, Hyde M, Blaisdell B, Greenwald M, Roth T. Sleep loss and REM sleep loss are hyperalgesic. Sleep 2006;29:145.

6 Moldofsky H. Sleep and pain. Sleep Med Rev 2001; 5:385–96.

7 DelVentura JL, Terry EL, Bartley EJ, Rhudy JL. Emotional modulation of pain and spinal nociception in persons with severe insomnia symptoms. Ann Behav Med 2014;47:303–15.

8 Finan PH, Goodin BR, Smith MT. The association of sleep and pain: An update and a path forward. J Pain 2013;14:1539–52.

9 Goodin BR, Smith MT, Quinn NB, King CD, McGuire L. Poor sleep quality and exaggerated salivary cortisol reactivity to the cold pressor task predict greater acute pain severity in a non-clinical sample. Biol Psychol 2012;91:36–41.

10 Gregory AM, Buysse DJ, Willis TA, et al. Associations between sleep quality and anxiety and depression symptoms in a sample of young adult twins and siblings. J Psychosom Res 2011;71: 250–5.

11 Nyman T, Mulder M, Iliadou A, Svartengren M, Wiktorin C. High heritability for concurrent low back and neck-shoulder pain: A study of twins. Spine 2011;36:E1469–76. Epub 2010/12/31.

12 Norbury TA, MacGregor AJ, Urwin J, Spector TD, McMahon SB. Heritability of responses to painful stimuli in women: A classical twin study. Brain 2007;130: 3041–9.

13 Afari N, Noonan C, Goldberg J, et al. University of Washington twin registry: Construction and characteristics of a community-based twin registry. Twin Res Hum Genet 2006;9:1023–9.

14 Strachan E, Hunt C, Afari N, et al. University of Washington twin registry: Poised for the next generation of twin research. Twin Res Hum Genet 2012;455–62.

15 Afari N, Mostoufi S, Noonan C, et al. C-reactive protein and pain sensitivity: Findings from female twins. Ann Behav Med 2011;42:277–83.

16 Godfrey KM, Strachan E, Dansie E, et al. Salivary cortisol and cold pain sensitivity in female twins. Ann Behav Med 2014;47:180–8.

17 Strachan E, Poeschla B, Dansie E, et al. Clinical and evoked pain, personality traits, and emotional states: Can familial confounding explain the associations? J Psychosom Res 2015;78:58–63.

18 Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index: A new instrument for psychiatric practice and research. Psychiatry Res 1989;28:193–213.

19 Melzack R. The short-form McGill pain questionnaire. Pain 1987;30:191–7.

20 Carlin JB, Gurrin LC, Sterne JAC, Morley R, Dwyer T. Regression models for twin studies: A critical review. Int J Epidemiol 2005;34:1089–99.

21 Sariyildiz M, Batmaz I, Budulgan M, et al. Sleep quality in patients with systemic sclerosis: Relationship between the clinical variables, depressive symptoms, functional status, and the quality of life. Rheumatol Int 2013;33:1973–9.

22 Flume PA, Ciolino J, Gray S, Lester MK. Patient-reported pain and impaired sleep quality in adult patients with cystic fibrosis. J Cyst Fibros 2009;8:321–5.

23 Ulus Y, Akyol Y, Tander B, et al. Sleep quality in fibromyalgia and rheumatoid arthritis: Associations with pain, fatigue, depression, and disease activity. Clin Exp Rheumatol 2011;29:S92–S6.

24 Agargün MY, Tekeoglu I, Güneş A, et al. Sleep quality and pain threshold in patients with fibromyalgia. Compr Psychiatry 1999;40:226–8.

25 Affleck G, Urrows S, Tennen H, Higgins P, Abeles M. Sequential daily relations of sleep, pain intensity, and attention to pain among women with fibromyalgia. Pain 1996;68:363–8.

26 Menefee LA, Frank ED, Doghramji K, et al. Self-reported sleep quality and quality of life for individuals with chronic pain conditions. Clin J Pain 2000;16:290–7.

27 Sayar K, Arikan M, Yontem T. Sleep quality in chronic pain patients. Can J Psychiatry 2002;47:844–8.

28 Zhang J, Lam S-P, Li S, et al. Insomnia, sleep quality, pain, and somatic symptoms: Sex differences and shared genetic components. Pain 2012;153:666–73.

29 Vgontzas A, Cui L, Merikangas KR. Are sleep difficulties associated with migraine attributable to anxiety and depression? Headache 2008;48:1451–9.

30 Palagini L, Biber K, Riemann D. The genetics of insomnia–evidence for epigenetic mechanisms? Sleep Med Rev 2014;18:225–35.