



ORIGINAL ARTICLE

Associations between migraine attacks and nightly sleep characteristics among adults with episodic migraine: a prospective cohort study

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Abstract

Study Objectives: Given the unknown immediate impact of migraine on nighttime sleep, we prospectively examined whether migraine headaches were associated with subsequent shorter sleep duration, higher fragmentation, and poorer quality in a cohort of 98 adults with episodic migraine.

Methods: Participants completed twice-daily electronic diaries and wore actigraphs continuously for 6 weeks. We examined whether days with headaches were associated with changes in that night's sleep characteristics compared with headache-free days, using adjusted multivariable linear mixed models with subject-specific intercepts.

Results: Participants were 35 ± 12 years old, 88% women, with an average of five migraine headaches per month. Over 4,406 days, we observed 1,077 headache days, representing 823 discrete headaches. Average nightly objective sleep duration was 7.3 ± 1.2 hr, efficiency $89.5 \pm 3.3\%$, and wake after sleep onset (WASO) 44.8 ± 17.0 min. Objective sleep duration was 7.3 min (95% CI: 1.5, 13.0) longer on nights following a headache day compared with nights on a headache-free day. Objective sleep efficiency, WASO, and reported sleep quality were not significantly different on headache days compared with headache-free days (sleep efficiency: -0.06 min, 95% CI: $-0.3, 0.2$; WASO 1.5 min, 95% CI: 0.0, 3.0; sleep quality: 1.0, 95% CI: 0.8, 1.3).

Conclusions: Sleep periods immediately following migraine headaches are not associated with shorter duration, higher disruption, or poorer sleep quality in patients with episodic migraine. These results suggest that clinical evaluation of sleep disturbance in patients with episodic migraine should be approached independently of their migraine status.

Statement of Significance

Our findings suggest that occurrence of headache is not associated with poorer nightly sleep in adults with episodic migraine. Specifically, subsequent sleep is not characterized by shorter sleep duration, higher sleep disruption, or lower sleep quality. Therefore, occurrence of migraine headaches does not explain sleep disturbances commonly reported by those with episodic migraine. Clinical evaluation and treatment of sleep problems in patients with episodic migraine should occur independently of migraine status; it should not be assumed that treatment of migraine headaches may improve sleep symptoms.

Key words: pain; migraine; actigraphy; epidemiology

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Introduction

Migraine afflicts one billion people worldwide and is the second leading cause of global disability [1]. Migraine attacks are characterized by moderate to severe pain lasting 4–72 hr, sensitivity to light and sound, nausea/vomiting, and may be preceded or followed by changes in mood, concentration, and fatigue [2–5]. Retrospective studies suggest that over half of patients with migraine report sleep disturbances, including difficulty falling asleep and/or staying asleep, poor sleep quality, and inadequate sleep duration [6–16]. Plausible mechanisms underlying this relationship have been identified in neurophysiologic studies of migraine [17]. These include activation of common anatomic structures (such as the hypothalamus early on in a migraine attack) [18], changes in neurotransmitter release (i.e. mobilization of intracellular serotonin during a migraine) [19, 20], and dysfunction of the central nervous system waste removal system, the glymphatic system, in animal models [21].

Given the high prevalence of sleep disturbance reported by patients with migraine, recent work has tried to elucidate the directionality of this relationship [22, 23]. We recently reported that higher nightly sleep fragmentation, but not short sleep duration or poor sleep quality, is associated with higher risk of migraine the following day among patients with episodic migraine [24]. However, despite the commonly held assumption that migraine headaches or their coping mechanisms (e.g. naps; caffeine consumption) negatively affect sleep directly or indirectly [36], and a previous study documenting that 75% of patients with migraine report that a headache forces them to sleep or rest [8], there is sparse prospective data examining the reverse direction—the impact of migraine on subsequent sleep. One study of 18 children with migraine monitored with actigraphy over fourteen nights did not find differences in sleep duration or wakefulness on nights following a migraine attack compared with an interictal night [7]. To the best of our knowledge, there have been no prospective studies in adults utilizing objective sleep measures. Elucidating the temporal association between migraine and subsequent sleep is important because it has direct clinical implications for how sleep disturbances in those with migraine are approached and will inform future research studies.

To examine whether headache attacks are associated with subsequent worse sleep characteristics among adults with episodic migraine, we conducted a 6-week prospective cohort study of daily lifestyle and headache information collected via actigraphy and electronic diaries. We hypothesized that the sleep period on the night of a headache day would be shorter duration compared with nights on headache-free days (primary outcome) and would have longer sleep latency, higher sleep fragmentation, and poorer sleep quality.

Methods

Study setting

The detailed methodology for this study has been published [24]. Briefly, participants were recruited through three academic centers in Boston, MA (Beth Israel Deaconess Medical Center [BIDMC], Massachusetts General Hospital and Brigham and Women's Hospital [BWH]), as well as local college student health clinics, between March 2016 and August 2017. Potential participants were screened by telephone and then completed

1 week of “run-in” diaries, with final determination based on physician interview at the baseline visit. Participants completed baseline questionnaires and then completed twice-daily web-based electronic diaries and wore an actigraph for at least 6 weeks. Diary data were collected and managed using REDCap (Research Electronic Data Capture) [25] unless a participant preferred paper diaries ($n = 5$). All visits were conducted at BIDMC. The BIDMC Committee on Clinical Investigations approved the study and all participants provided written informed consent.

Study population

Participants with episodic migraine were enrolled if they were ≥ 18 years of age, reported history of migraine for at least 3 years with at least two migraine headaches per month during the past 3 months, were able to communicate in English, and give informed consent. Enrolled participants met the criteria for International Classification of Headache Disorders - β for migraine with or without aura [26] based on an in-person physician interview at the baseline visit. Exclusion criteria included: ≥ 15 headache days per month for the previous 3 months, chronic pain condition, current opioid use, high-risk of obstructive sleep apnea [27] or known untreated obstructive sleep apnea, pregnancy, uncontrolled medical problems that precluded participation, or failure to complete at least 4 out of 7 days of run-in diaries. Among the 126 individuals expressing interest in the study, 101 met inclusion criteria and agreed to participate. Three withdrew with < 21 days of data, resulting in a sample of 98 participants who completed the study and provided 4,406 days of data.

Baseline sample characteristics

We collected information on socio-demographics, medical and headache history, medication use, headache-associated disability, and sleep symptoms. We used standardized questionnaires to capture global sleep quality, depressive symptoms, and stress. In this analysis, we report data from the Pittsburgh Sleep Quality Index (PSQI) [28], a 19-item questionnaire assessing sleep quality and disturbance in the last month. To assess depressive symptoms, we used the 20-item Center for Epidemiological Studies Depression scale (CES-D) [29], and to assess stress we used the 10-item Perceived Stress Scale [30], which reflects self-perceived stress over the last month. Migraine-related quality of life was assessed using the Headache Impact Test-6 (HIT-6) [31].

Sleep assessments

Every morning participants completed the electronic Consensus Sleep Diary [32], which includes questions on sleep timings, quality (very poor, poor, fair, good, very good), awakenings, and medications. To capture objectively measured sleep duration, wake after sleep onset (WASO), and sleep efficiency in a naturalistic setting, actigraphy was utilized. Participants wore an actigraph (Actiwatch Spectrum; Philips Respironics, Murrysville, PA) on their nondominant wrist for 24 hr a day for 42 consecutive days [33]. The actigraphs recorded data on activity and light in 30 s intervals and indicated any “off wrist” time. Data were transmitted to the BWH Sleep Reading Center for scoring by a trained technician

blinded to daily headache status [33, 34]. The technician manually identified the start and stop of the rest period using a hierarchical approach, which has been described previously [24, 35]. Using the actigraphy and diary data, we calculated total sleep time, WASO, and sleep efficiency (proportion of total sleep duration/duration of rest period). We defined low sleep quality as self-reported poor or very poor sleep quality on the morning diary, and sleep latency was quantified from the daily sleep diary.

Headache

Participants completed twice-daily diaries about presence of headache, and if present, time of onset and whether the headache was ongoing. When the participant reported headache resolution, they reported additional information on time of resolution, duration, maximum pain intensity, use of headache medications, associated symptoms and whether the headache was “similar to a usual migraine headache?”. When patients reported two headaches within the same day ($n = 79$ days), headache duration was defined as the start of the first headache and the end of the second headache, maximum pain was the defined as the highest of the two scores and associated symptoms or medication use included those reported for either headache.

Daily covariates

Participants also reported on the following measures daily: number of servings of alcoholic beverages, use of hypnotic medications, menstrual cycle status (if applicable), servings of caffeinated beverages, and minutes of moderate and vigorous physical activity performed. Daily stress was rated using a visual analog scale of 0–100 on the evening diary.

Statistical analysis

In this prospective cohort study, we estimated the associations between daily headache status and that evening's sleep duration (primary outcome), fragmentation, and quality (secondary outcomes). We compared a participant's sleep characteristics on the night of a headache day with sleep on headache-free days, using multivariable linear mixed models with subject-specific intercepts. In the primary models, we adjusted for age, sex, daily number of alcohol and caffeinated beverages (continuous), daily minutes of self-reported physical activity (continuous), and daily stress levels (continuous). We used generalized linear mixed models with logit link function and binary distribution to compare low sleep quality following a headache day compared with a headache-free day, with the same covariates as above. In secondary analyses, we further adjusted for evening use of pharmacologic sleep aids, menstrual cycle status, and naps, separately. We conducted sensitivity analyses excluding headaches not reported to be “similar to a usual migraine headache” and headaches of long duration (>24 hr and >72 hr, separately), respectively. Two-sided p -values of <.05 were considered statistically significant. Analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC).

Table 1. Baseline characteristics, mean \pm standard deviation, or frequency (%) among 98 participants with episodic migraine

	n (%) or mean (\pm SD)
Sample size (N=)	98
Age (years)	35.1 \pm 12.1
Women	86 (88%)
Premenopausal	60 (79%)
Race	
White/Caucasian	81 (83%)
Black/African-American	4 (4%)
Asian	4 (4%)
Other	9 (9%)
Smoking status	
Never	81 (84%)
Past	13 (14%)
Current	2 (2%)
Age at migraine onset (years)	16.3 \pm 8.3
Self-reported headache frequency (attacks/month)	5.0 \pm 3.6
Migraine subtype	
Without aura	50 (51.0%)
With aura	48 (49.0%)
Any migraine preventive	26 (26.5%)
HIT-6	61.0 \pm 6.2
PSQI	4.7 \pm 3.0
CES-Depression	9.9 \pm 7.8
Perceived Stress Scale	14.7 \pm 6.4

Categorical variables are expressed as percentages and continuous variables are expressed as mean \pm standard deviation. PSQI = Pittsburgh Sleep Quality Index, total score (ranging from 0–21, with a score of ≥ 5 indicating poor sleep quality). HIT-6 = Headache Impact Test – 6 item total score, (ranges from 36 to 78, with a higher score indicating a greater impact of headache on daily life). CES-D = Center for epidemiological studies depression scale total score (range of 0–60, higher score indicates more depressive symptoms). Perceived Stress Scale total score (range 0–40, 0–13 low; 13–26 moderate stress over the last month).

Results

The 98 participants who completed the study were a mean age of 35 \pm 12 years, 88% women and had an average of five headaches per month (see Table 1). The sample was primarily white/Caucasian (83%) and a majority of women were premenopausal (79%). Only 2% of participants reported active smoking. Use of daily migraine preventive medication was reported by 27% of the sample. Overall, HIT-6 scores were on average 61.0 \pm 6.2, consistent with severe impact. The average Pittsburgh Sleep Quality Index (PSQI) score (4.7 \pm 3.0) indicates that our sample had on a normal to modestly reduced sleep quality. Mean CES-D score indicated a low level of depression symptoms and mean perceived stress scale total score was consistent with low–moderate stress. Of note, rates of adherence to daily data capture were excellent (93.5 \pm 6.0% diary; 92.1 \pm 11.9% actigraphy).

Over 4,406 days, we observed 1,077 headache days, representing 823 discrete headaches (see Table 2). Average headache duration was 11.1 \pm 9.4 hr and average pain severity 46 \pm 14 (0–100 scale). The most common migrainous feature reported was photophobia, which was present during 61.9% of headaches. Two-thirds of headaches were treated with an acute medication. Headaches were more likely to start during the day (47.5% starting between 8 am and 4 pm) compared with the evening (28.7% starting between 4 pm and midnight and 23.8% starting between midnight and 8 am).

Table 2. Migraine, sleep, and health habits during the study period (4,406 nights)

Migraine	
Number of headache attacks	823
Number of headache days	1077
Duration of headache (hr)	11.1 ± 9.4
Pain severity (0–100)	46 ± 14
Presence of aura (% of headaches)	8.8
Presence of migrainous features (% of headaches)	
Photophobia	61.9
Phonophobia	48.4
Nausea	36.1
Vomiting	3.2
Treatment with acute medication (% of headaches)	
Any	66.7
NSAID	32.5
Triptan	26.4
Acetaminophen-aspirin-caffeine	11.3
Acetaminophen	5.3
Butalbital—analgesic combination	3.3
Anti-emetic	2.0
Isometheptene-analgesic	0.3
Muscle relaxant	0.7
Timing of headache onset (% of headaches)	
Midnight—3:59 am	3.9
4 am–7:59 am	16.5
8 am–11:59 am	23.7
12 pm–3:59 pm	23.8
4 pm–7:59 pm	19.1
8 pm–11:59 pm	13.0
Timing of headache resolution (% of headaches)	
Midnight—3:59 am	6.1
4 am–7:59 am	8.5
8 am–11:59 am	14.8
12 pm–3:59 pm	21.6
4 pm–7:59 pm	25.2
8 pm–11:59 pm	23.8
Sleep	
Actigraphy	
Average sleep duration (min)	436.7 ± 71.7
Sleep Efficiency (%)	89.5 ± 3.3
WASO (min)	44.8 ± 17.0
Naps (% of days)	9.4
Naps duration (min)	74.9 ± 41.9
Diaries	
Estimated sleep duration	464.4 ± 78.6
Estimated sleep latency	27.7 ± 30.0
Sleep quality	
Very poor	3.0
Poor	11.0
Fair	32.4
Good	44.1
Very good	9.5
Use of a sleep aid (% of nights)	16.7
Health habits	
Alcohol (servings/day, % of days)	
0	69.9
1	14.3
2	8.2
3 or more	7.6
Caffeine (servings/day)	
0	28.2
1–2	59.3
3 or more	12.5
Moderate to vigorous exercise (minutes/day)	
0 minutes	53.3
0–60 minutes	35.1
>60 minutes	11.6

Categorical variables are expressed as percentages and continuous variables are expressed as mean ± standard deviation. Use of sleep aid includes prescription and over the counter medications, as reported on diaries.

Table 3. Sleep characteristics following a day on which headache was reported compared with a headache-free day

	Actigraphy	Diaries
Total sleep time (min) β (95%CI)	7.3 (1.5, 13.0)	7.4 (0.9, 13.9)
Sleep efficiency (%) β (95%CI)	−0.1 (−0.3, 0.2)	0.2 (−0.4, 0.7)
WASO (min) β (95%CI)	1.5 (0.0, 3.0)	–
Sleep latency (min) β (95%CI)	–	0.2 (−2.7, 3.2)
Sleep quality OR (95% CI)	–	1.0 (0.8, 1.3)

Mixed-effects linear regression was performed for total sleep time, sleep efficiency, wake after sleep onset (WASO) and sleep latency. A repeated measure logistic regression (Glimmix procedure) was performed for sleep quality such that the Odds Ratio represents the likelihood of reporting poor/very poor sleep quality (vs. fair/good/very good) on days with migraine. All models adjusted for sex, age, daily servings of alcohol and caffeine intake, self-reported physical activity and psychological stress.

On average, nightly actigraphically assessed sleep duration was 7.3 ± 1.2 hr, sleep efficiency was 89.5 ± 3.3%, and WASO was 44.8 ± 17.0 min. Self-reported sleep duration was approximately 30 min longer compared with actigraphy (464.4 ± 78.6 vs. 436.7 ± 71.7 min). Participants reported their sleep quality as fair, good, or very good the majority of the time, with 14% of nights reported as poor or very poor quality. There were 399 naps recorded over the 4,406 days, with an average duration of 74.9 ± 41.9 min. There was no alcohol consumption on the majority of days (69.9%), consumption of 1–2 caffeinated beverages was reported in about half of days (53.3%), and vigorous exercise was reported on about half of days (see Table 2).

In adjusted models, actigraphically assessed sleep duration was 7.3 min (95% CI: 1.5, 13.0) longer on nights following a headache day compared with nights on headache-free days (see Table 3). Results were similar for diary-reported sleep duration. Actigraphically assessed sleep efficiency and WASO did not differ on nights following headache days compared with nights following headache-free days (sleep efficiency: −0.06%, 95% CI: −0.3, 0.2; WASO 1.5 min, 95% CI: 0.0, 3.0). Diary-reported sleep latency and sleep quality were also not significantly different on nights following headache days compared with nights following headache-free days. High stress levels were associated with a 12 min shorter actigraphically assessed sleep duration on that day. Of note, our results were similar to those in our unadjusted models and were not substantively altered when we further adjusted for nightly hypnotic use, menstrual cycle status, or naps on that day, separately. Inclusion of only headache days reported to be “similar to a usual migraine” (895 of 1,077 days) and separate exclusion of headaches of >24 hr duration did not change our results substantively. Lastly, truncating our analysis to the first six weeks of monitoring did not change our results.

Discussion

In this prospective cohort study of participants with episodic migraine, the presence of a headache was associated with small increases in objectively assessed sleep duration (average of 7 min). There was no association between headache and subsequent sleep efficiency, WASO, sleep latency, or sleep quality. Our results did not differ after accounting for daily naps or nightly pharmacologic sleep aid use. These results indicate that in individuals with episodic migraine, occurrence of headache attack is

not associated with a subsequent sleep period characterized by shorter sleep duration, higher sleep disruption, or poorer sleep quality. Therefore, occurrence of headache attacks is unlikely to explain the high rates of retrospectively reported sleep disturbances in a relatively healthy cohort of individuals with high frequency episodic migraine [22, 36].

In one prior study of 18 children with episodic migraine followed for 2 weeks, there were no differences in sleep duration on the nights following an attack compared to an interictal night [7]. Given that our sample was larger (98 adults with migraine) and captured a longer period of actigraphic sleep data (6 weeks), it was better powered to detect subtle variations in sleep duration, which may account for our finding of a modest increase in sleep duration. It is also possible that adults with episodic migraine may differ from children and adolescents with episodic migraine regarding their sleep behaviors on days with a headache attack. Furthermore, differences in standardization of scoring actigraphy, which is partially dependent on device-specific algorithms and methods for determining the rest interval, may limit comparison of results between studies [37].

Our findings are similar to other studies examining the relationship between episodic pain conditions and actigraphically assessed sleep outcomes. In a demographically similar sample of pre- and peri-menopausal women with episodic generalized pain, participants were asked to rate global pain immediately prior to sleep every night for one menstrual cycle [38]. Higher pain rating was associated with 5–12 min longer actigraphy-assessed sleep duration [38]. Other studies in children with diverse episodic pain etiologies, including musculoskeletal pain [39], postsurgical pain [40], and crisis in sickle cell disease [41] indicate that the occurrence of pain was not associated with subsequent shorter actigraphically assessed sleep duration. Despite varied pain conditions and populations, these studies did not report shortened sleep duration following exposure to episodic pain, similar to our results. This suggests that reported associations between sleep disturbances and pain are unlikely to be explained by the occurrence of pain attacks in those with an episodic pain condition.

We also found that migraine headache occurrence was not associated with subsequent changes in nightly actigraphically assessed sleep fragmentation or diary-determined sleep latency or quality. These results are consistent with the previously mentioned actigraphy study performed in children with migraine [7] and with prospective studies of sleep and pain utilizing actigraphy in children with acute musculoskeletal pain (<1 month duration) [39], acute postsurgical pain [40], and pain occurrence from sickle cell disease [41]. Our finding that a discrete headache attack is not associated with subsequent disturbed sleep is similar to results from a growing body of literature examining the bidirectionality of sleep and pain relationships, which has found a stronger effect of sleep on pain than vice versa in both short-term longitudinal studies, such as our own and longer-term studies [42].

We found that migraine headache attacks are associated with small increases in objectively measured nightly sleep duration, suggesting that retrospective reports of shorter sleep, reduced sleep quality, or higher fragmentation by those with episodic migraine are unlikely to be explained by discrete attacks. One explanation may be that variation in sleep may be related to attack physiology in the premonitory phase and not the headache pain phase which we studied. Indeed, activation of structures

integral in sleep physiology (hypothalamus and brainstem) has been found in fMRI studies of the premonitory phase of a migraine attack [18, 43]. Alternatively, there may be a migraine-sleep endophenotype which reflects a manifestation of shared underlying predisposing factors, such as a particular set of genetic or environmental factors. It is also possible that more habitual sleep patterns monitored over a longer time period are more likely to predict development/worsening of migraine than more immediate reports [42].

A distinction between our work and that of studies of sleep and migraine or other pain conditions is that our participants had episodic migraine (of high frequency) and had relatively healthy sleep. Sleep disturbances, poor sleep, and excessive daytime sleepiness are more commonly reported in those with chronic rather than episodic migraine [8, 45–47] and for those with high frequency rather than low frequency episodic migraine [48]. This suggests that sleep disturbances may be a marker of migraine chronification. However, a 12-year community-based prospective study in participants with episodic headache found that insomnia symptoms at baseline predicted chronification of tension-type headache but not migraine [49]. Taken together with our findings that a migraine headache is not associated with sleep disturbance that night in those with episodic migraine, the current state of the literature suggests that the nuanced relationship between migraine chronification and worsening sleep disturbance is neither easily predictable by patient report at baseline, nor clearly explained by individual attacks. Future longitudinal studies utilizing multiple nights of polysomnography and actigraphy (e.g. for brief epochs every year or few years) in patients at high risk for development of chronic migraine may help provide a clearer understanding of these relationships.

To the best of our knowledge, our study of 98 participants followed for at least 6 weeks is the largest study using objective assessments of sleep among adults with episodic migraine. With >4,000 days of data across the participants, we had sufficient statistical power to prospectively examine the association between migraine headache days and subsequent sleep in a naturalistic setting. Our study had some limitations. Our definition of a migraine attack was limited to the pain phase of migraine because this is a more clearly defined and typically the most disabling phase of a migraine attack when compared with the pre- or post-monitory phases. A more comprehensive analysis that includes pre- and post-monitory phases may capture changes to sleep parameters that were not possible in our analyses. These results may not be generalizable to other populations, as our sample was mostly white/Caucasian premenopausal women with relatively healthy sleep habits and modest sleep disturbances.

Our findings suggest that occurrence of headache is not associated with poorer nightly sleep in adults with episodic migraine. Specifically, subsequent sleep is not characterized by shorter duration, higher disruption, or lower quality. Therefore, occurrence of migraine headaches does not explain sleep disturbances commonly reported by those with episodic migraine. Clinical evaluation and treatment of sleep problems in patients with episodic migraine should occur independently of migraine status; it should not be assumed that treatment of migraine headaches may improve sleep symptoms.

Future research should focus on a potentially shared common endophenotype between insomnia and migraine, which may be more apparent in those with chronic migraine.

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