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RESEARCH SUBMISSIONS

Sex differences in migraine attack characteristics: A longitudinal E-diary study

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Abstract

Objective: In this prospective cohort study, characteristics of perimenstrual and non-perimenstrual migraine attacks in women were compared with migraine attacks in men.

Background: Women report longer migraine attacks and more accompanying symptoms than men in cross-sectional questionnaire studies, but this has not been confirmed in longitudinal studies. Supposed differences could result from different characteristics specific to perimenstrual migraine attacks, or of attacks in women in general.

Methods: This cohort study was performed among patients with migraine who were treated at the Leiden Headache Clinic. We assessed differences in migraine attack characteristics between men and women who were prospectively followed by a previously validated electronic headache diary. The primary outcome was "attack" duration. Differences between perimenstrual (Days −2 to +3 of the menstrual cycle) and non-perimenstrual attacks in women versus attacks in men were corrected for age, chronic migraine, and medication overuse headache.

Results: A total of 1347 women and 284 men were included, reflecting the preponderance of women in migraine prevalence. Crude median (first and third quartile [Q1–Q3]) attack duration in men was 32.1 [17.7–53.6] h, compared to 36.7 [21.9–62.4] h for non-perimenstrual migraine attacks and 44.4 [17.9–79.0] h for perimenstrual migraine attacks in women. After correction for confounding, perimenstrual migraine attacks were 1.62 (95% confidence interval [CI] 1.47–1.79; $p < 0.001$) and non-perimenstrual 1.15 (95% CI 1.05–1.25; $p = 0.003$) times longer compared to migraine attacks in men. The mean relapse percentage in men was 9.2%, compared to 12.6% for non-perimenstrual migraine attacks, and 15.7% for perimenstrual migraine

Abbreviations: CES-D, Center for Epidemiologic Studies Depression Scale; CGRP, calcitonin gene-related peptide; CM, chronic migraine; E-diary, electronic diary; GEE, generalized estimating equation; HADS-D, Hospital Anxiety and Depression Scale-Depression subscale; ICHD-3, *International Classification of Headache Disorders*, third edition; MHD, monthly headache days; MMD, monthly migraine days; MOH, medication overuse headache.

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attacks. Relapse risk was greater for perimenstrual (odds ratio [OR] 2.39, 95% CI 1.93–2.95; $p < 0.001$), but not for non-perimenstrual (OR 1.18, 95% CI 0.97–1.45; $p = 0.060$) attacks. Migraine attacks in women were more often accompanied by photophobia, phonophobia, and nausea, but less often aura.

Conclusion: Compared to attacks in men, both perimenstrual and non-perimenstrual migraine attacks are of longer duration and are more often accompanied by associated symptoms. A sex-specific approach to migraine treatment and research is needed.

KEYWORDS
E-diary, gender, menstruation, migraine, sex differences

INTRODUCTION

Sex differences in migraine prevalence are evident with a female-to-male ratio of 3:1.[1] In addition, female sex is suggested to be associated with higher disability, decreased productivity, and increased risk of chronification of migraine.[2–7] A recent meta-analysis assessed sex differences in triptan response.[8] Although there were no differences in initial response rates, female sex was found to be associated with increased relapse risk and higher adverse event frequency.[8]

Differences in migraine between men and women are thought to originate from differences in the effects of sex hormones. Migraine incidence in women strongly increases after menarche and the risk of a migraine attack is highest during the perimenstrual window, which starts 2 days before the menstrual bleeding and lasts until Day 3.[1,3,9,10] These perimenstrual migraine attacks, suggested to be attributed to the drop in estrogen prior to menstruation, are of longer duration, have a higher relapse risk, and are associated with increased triptan intake compared to non-perimenstrual attacks.[11] Sex hormones might also be implicated in male patients with migraine. The testosterone/estradiol ratio is suggested to be lower in male patients with migraine than in males without headache due to increased estradiol levels, reflected by an increased incidence of symptoms consistent with relative androgen deficiency.[12,13]

Women, in general, more often report their migraine attacks to be of higher intensity, longer duration, and more frequently associated with accompanying symptoms, such as photo- and phonophobia, nausea, and vomiting, than men[3,5,14,15]; however, these findings are mainly based on cross-sectional questionnaire studies. Furthermore, in the comparison with men, no distinction has been made between perimenstrual and non-perimenstrual migraine attacks in women, while it may be argued that only perimenstrual migraine attacks in women differ from attacks in men. The present study aimed to prospectively compare migraine attack characteristics between men and perimenstrual and non-perimenstrual migraine attacks in women as registered in an electronic diary (E-diary). We hypothesized that perimenstrual migraine attacks differed from attacks in men and that attack characteristics of non-perimenstrual migraine attacks in women were similar to those of men.

METHODS

We conducted this longitudinal E-diary cohort study among men and women diagnosed with migraine and treated at the Leiden Headache Clinic. Data were collected in the context of standard clinical care between July 2018 and February 2022. Patients completed E-diaries during at least 1 month before their first consultation at the Leiden Headache Clinic, and continued through the entire treatment trajectory, which typically lasted about 3–6 months, although in some patients it could be >1 year. Three subsets of the dataset were previously analyzed and published elsewhere: (i) E-diary data collected between October 2018 and May 2020 were analyzed to compare migraine-related frequency numbers to patients' self-reported estimates[16]; (ii) E-diary data collected between February and April 2020 were analyzed to assess whether migraine-related outcomes changed during coronavirus disease 2019 (COVID-19) lockdown[17]; (iii) E-diary data from menstruating women who registered three or more menstrual cycles between August 2018 and July 2021 were used to validate several aspects of the criteria for menstrual migraine from the *International Classification of Headache Disorders*, third edition (ICHD-3).[18] For aforementioned analyses, an additional research dataset was added to the clinical dataset used in the present study. Ethical consideration for this study was obtained from the Medical Ethics Committee of the Leiden University Medical Center who judged that specific informed consent for this study was not required as all data were accessed and analyzed fully anonymized and therefore could not be traced back to an individual.

No statistical power calculation was conducted prior to the study. The sample size was based on the available data and was considered sufficient based on our previous experience with this study design.

Patients

Patients were considered eligible if they were diagnosed with migraine and had entered data using a previously validated headache E-diary during at least 1 month.[16] The 1 month was defined as a time-period of 28 days. Compliance to the E-diary had to be ≥80% for each individual month. For each patient, the longest period of

consecutive months with ≥80% compliance was selected. Patients with hemiplegic migraine or another primary or secondary headache disorder other than episodic tension-type headache were excluded. Migraine diagnoses were made in consultation with a headache specialist (G.M.T.) according to the ICHD-3 criteria.[19]

Data collection

Data were collected with a daily E-diary, containing detailed questions about headache characteristics, associated symptoms, use of acute pain medication, prophylactic medication, and menstruation.[16–18] Patients received daily email invitations to complete the questionnaire and were, if necessary, reminded by text message. Questionnaires were time-locked after 48 h. All questions had to be completed before the diary could be saved; therefore, diary entries were either filled out completely or missing entirely.

An automated algorithm verified for each headache day whether ICHD-3 criteria for migraine were met.[19] In addition, days with triptan intake or days with aura symptoms were labeled as migraine days. Consecutive migraine days with migraine-free periods with a maximum of 24 h were considered as one "attack". For each migraine attack, attack duration in hours, maximum pain intensity (rated as "mild", "moderate", or "severe"), and minimum pain coping score (rated on a continuous scale from 0–10) was determined.

For each individual migraine day, the occurrence of photophobia, phonophobia, nausea, vomiting, (visual) aura symptoms, use of analgesics and/or triptans, and if applicable, 2-h headache response, 2-h pain-free response and relapse, was retrieved from the E-diary. A 2-h headache response was defined as a decrease in headache intensity from moderate or severe to mild or absent within 2 h after triptan intake.[20] A 2-h pain-free response was defined as the disappearance of moderate or severe headache within 2 h after triptan intake.[20] Relapse was defined as the reoccurrence of migraine within 24 h after triptan intake among patients who were initially pain free.[21] It should be noted that 2-h headache response, 2-h pain-free response, and relapse were only applicable to days with triptan use and not to days with analgesics use.

For each patient, the total number of monthly migraine days (MMD), monthly headache days (MHD), acute medication days, also separated for triptan days and simple analgesics days, were calculated. For calculations on monthly frequency estimates, days with missing data were considered headache free. A distinction between episodic and chronic migraine (CM) was based on the average number of MMD and MHD registered in the E-diary. CM was defined as an average of ≥15 headache days/month with ≥8 migraine days.[19] Medication overuse headache (MOH) was defined as an average of ≥10 acute medication days (≥10 for triptans, ≥15 for analgesics, ≥10 for combination of acute medications) per month.[19] Lifetime depression was determined before the start of the E-diary and was defined as a Hospital Anxiety and Depression Scale-Depression subscale (HADS-D) score ≥8 or Center for Epidemiologic Studies Depression Scale (CES-D) score ≥16 or (past) depression diagnosed by a physician or (past) use of antidepressants for depression.[22]

For women, the total number of menstrual periods and mean menstrual cycle length were calculated. Migraine attacks in women were classified as either perimenstrual or non-perimenstrual. A perimenstrual migraine attack was defined as any attack occurring during the 5-day perimenstrual window, which starts 2 days before the menstruation and lasts until Day 3.[19] All migraine attacks starting outside of this window were defined as non-perimenstrual migraine attacks. Thus, attacks that were already ongoing before Day −2 were considered non-perimenstrual. Women with a perimenstrual migraine attack in two out of the first three menstrual cycles were diagnosed with menstrual migraine. Menstrual migraine diagnosis could, by definition, only be determined in women who completed the E-diary during at least three menstrual cycles. Menstrual migraine diagnosis was considered missing in women who registered less than three menstrual cycles.

Data analysis

Baseline characteristics were compared between men and women stratified for age (<50 or ≥50 years) with the use of independent *t*, chi-square, and Mann–Whitney *U* tests. Variables are denoted as absolute number (%), mean (±SD) or median (with first and third quartile [Q1–Q3]). Stratification for age was used as a proxy for menopause because we hypothesized that sex differences result from sex hormonal influences, which may be limited after menopause.

We primarily assessed whether there were differences in attack duration between migraine attacks in men and perimenstrual and non-perimenstrual migraine attacks in women using a linear model, where generalized estimating equation (GEE) with exchangeable correlation was used to account for correlations between repeated observations within patients. The model ignored missing E-diary days, which we consider appropriate for a selection of E-diaries with >80% compliance. Based on what patients reported, we assumed missing data to be disregardable in E-diaries with high adherence (>80%), but not in E-diaries with low adherence (patients who entered data exclusively on headache days). Assumptions of normal distribution were visually evaluated with histograms. Attack duration was log transformed to achieve a normal distribution. Independent variables included sex, relation to the menstruation (perimenstrual vs. non-perimenstrual), and age dichotomized at 50 years; CM and MOH were added as covariates. Previous research suggested that female sex is associated with an increased risk of MOH and conversion from episodic to CM, both of which are likely to be associated with longer attack duration and more severe symptoms.[6,7] We included CM and MOH as covariates to obtain the effect of sex adjusted for potential differences in prevalence of CM and MOH. The coefficients from the model on the log scale were exponentiated to obtain percent differences in geometric means of attack duration.

We secondarily assessed differences in minimum pain coping using a linear GEE model and the occurrence of photophobia, phonophobia, nausea, vomiting, visual aura, maximum headache intensity, use of analgesics, use of triptans, 2-h headache response,

2-h pain-free response, and relapse, using logistic GEE models. Maximum headache intensity for each attack was dichotomized as severe versus mild/moderate.

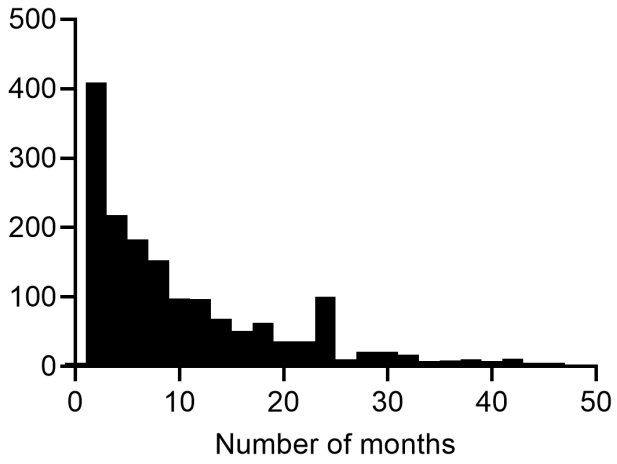

FIGURE 1 Histogram of total follow-up duration in months (men and women pooled).

A sensitivity analysis was performed for the primary outcome (attack duration) including all patients regardless of their compliance to the E-diary.

A two-sided $p < 0.05$ was considered statistically significant. All analyses were performed in R version 4.0.5.

RESULTS

A total of 1756 patients were diagnosed with migraine and were followed with E-diaries during at least 1 month, of whom 125 were excluded due to insufficient compliance to the E-diary, yielding 1631 patients (1347 women and 284 men). The median (Q1–Q3) follow-up duration was 196 (83–419) days with a compliance of 97%. A histogram of the follow-up duration in months is shown in Figure 1. A total of 80,274 E-diary days in men, 343,577 non-perimenstrual days and 20,625 perimenstrual days in women were evaluated.

Baseline characteristics, stratified for age, are presented in Table 1. Numbers of MMD and MHD were similar in men and women aged <50 years, while women aged ≥50 years had significantly more MMD than men (median [Q1–Q3]: 7.1 [4.7–10.6] vs.

TABLE 1 Patient characteristics for men and women stratified for age.

	Age <50 years			Age ≥50 years		
	Women	Men	*p*	Women	Men	*p*
Number of patients	880	165		467	119	
Age, years, mean (SD)	35.7 (9.1)	37.4 (8.6)	**0.029**	56.8 (5.9)	58.0 (6.2)	0.055
Migraine with aura, *n* (%)	349 (39.7)	69 (41.8)	0.665	142 (30.4)	53 (44.5)	**0.005**
Chronic migraine, *n* (%)	206 (23.4)	46 (27.9)	0.257	93 (19.9)	22 (18.5)	0.825
Medication overuse headache, *n* (%)	64 (7.3)	9 (5.5)	0.500	47 (10.1)	5 (4.2)	0.068
Prophylactic medication use, *n* (%)	332 (37.7)	55 (33.3)	0.325	154 (33.0)	42 (35.3)	0.712
Age of migraine onset, years, mean (SD)	17.6 (8.5)	17.0 (9.9)	0.442	24.7 (14.0)	23.6 (15.7)	0.449
Lifetime depression, *n* (%)	423 (48.1)	101 (61.2)	**0.003**	222 (47.5)	58 (48.7)	0.859
Number of menstrual cycles, median (IQR)	2.0 (0.0–6.0)	NA	NA	0.0 (0.0–1.0)	NA	NA
Cycle length, days*						
Natural menstrual cycle, median (IQR)	28.0 (26.0–31.0)	NA	NA	37.7 (27.3–53.5)	NA	NA
Hormonal contraceptives, median (IQR)	40.0 (28.4–63.5)	NA	NA	72.8 (45.9–105.0)	NA	NA
Hormonal contraceptive use, *n* (%)	446 (50.7)	NA	NA	75 (16.1)	NA	NA
Menstrual migraine diagnosis**, *n* (%)	236 (59.6)	NA	NA	31 (50.8)	NA	NA
Follow-up duration, days, median (IQR)	168 (56–336)	168 (56–388)	0.996	249 (112–532)	280 (111–502)	0.927
E-diary compliance, %, median (IQR)	96 (92–99)	97 (93–99)	0.218	98 (96–100)	98 (95–100)	0.542

Note: Variables are denoted as absolute number (%), mean (SD) or median (IQR). A month was defined as a time period of 28 days. Bold values statistically significant at $p < 0.05$.

*Mean menstrual cycle length was calculated in 497 women aged <50 years and 80 women aged ≥50 years, who registered two or more menstruations.

**Menstrual migraine diagnosis was evaluated in 396 women aged <50 years and 61 women aged ≥50 years, who registered three or more menstruations during the entire follow-up. Chronic migraine was defined as an average of ≥15 headache days per month with ≥8 migraine days.[19] Medication overuse headache was defined as an average of ≥10 acute medication days (≥10 for triptans, ≥15 for analgesics, ≥10 for combination of acute medications) per month.[19] Lifetime depression was defined as a Hospital Anxiety and Depression Scale-Depression subscale score of ≥8 or Center for Epidemiologic Studies Depression Scale score of ≥ 16 or (past) depression diagnosed by a physician or (past) use of antidepressants for depression.[22]

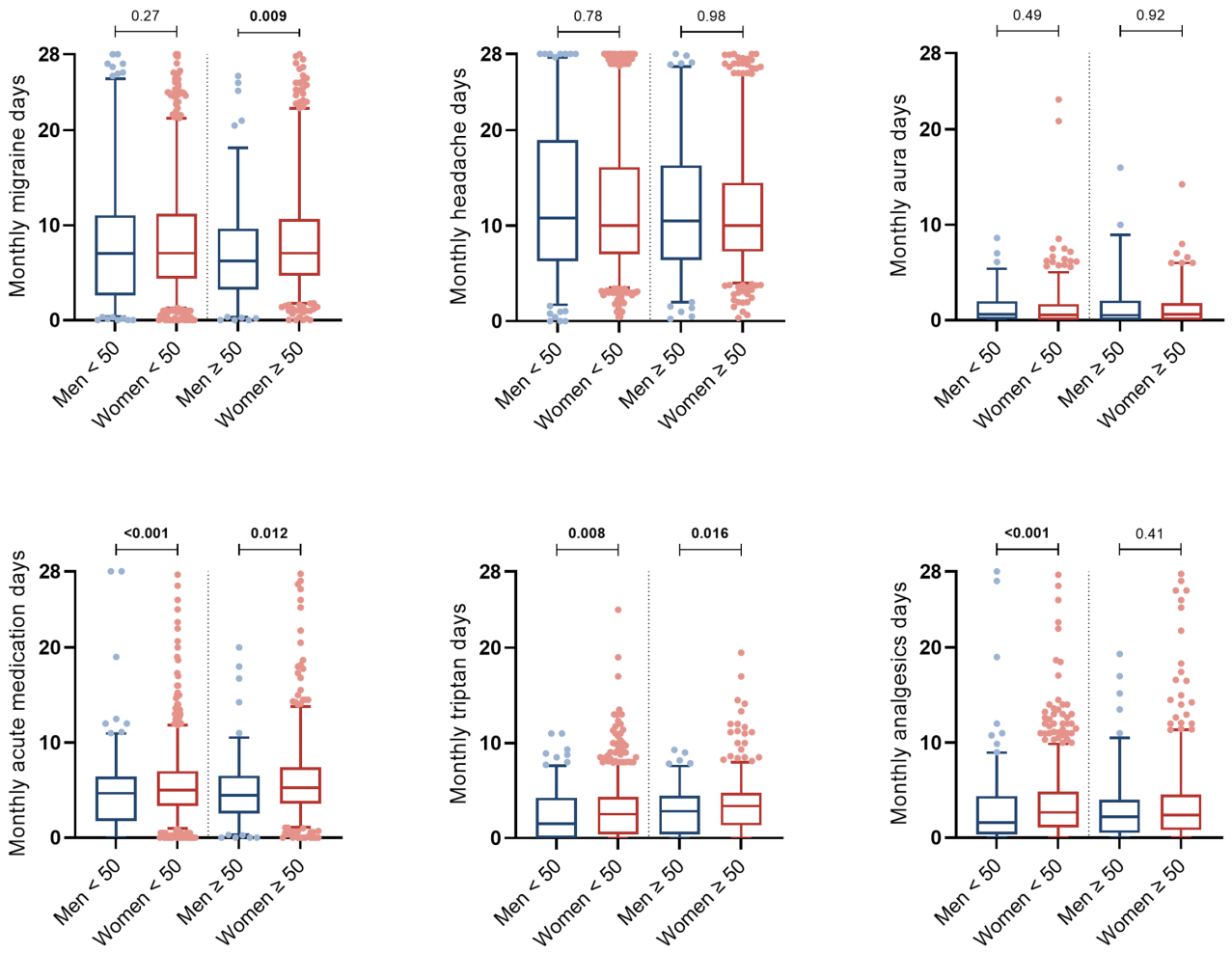

FIGURE 2 Box plots of average number of migraine days, headache days and acute medication days per month in men and women stratified for age. Mean occurrence per month for a patient was calculated by dividing the total number of migraine days, headache days and medication days by the follow-up time. Whiskers indicate the 5%–95% percentile. [Color figure can be viewed at wileyonlinelibrary.com]

6.3 [3.4–9.6], $p = 0.009$) (Figure 2). In both strata, women used acute medication slightly more often than men (Figure 2). No statistically significant differences in prevalence of CM and MOH were found between men and women in both strata. Lifetime depression was more prevalent in men aged <50 years (61% vs. 48% in women, $p = 0.003$) (Table 1).

Crude median (Q1–Q3) migraine attack duration in men was 32.1 (17.7–53.6) h, compared to 36.7 (21.9–62.4) h for non-perimenstrual migraine attacks and 44.4 (17.9–79.0) h for perimenstrual migraine attacks in women (Figure 3). After correction for age < or ≥50 years, CM, and MOH, non-perimenstrual migraine attacks were 1.15 (95% confidence interval [CI] 1.05–1.25, $p = 0.003$) and perimenstrual migraine attacks were 1.62 (95% CI 1.47–1.79, $p < 0.001$) times longer than migraine attacks in men, despite that women were more likely to use long-acting triptans (defined as eletriptan, naratriptan, or frovatriptan; 37% vs. 27%, $p = 0.006$). The median (Q1–Q3) attack duration in patients aged <50 years without CM and MOH was 14.0 (12.9–15.2) h in men, 16.1 (15.4–16.8) h for non-perimenstrual migraine attacks, and 22.7 (21.3–24.2) h for perimenstrual migraine attacks. Perimenstrual migraine attacks (odds ratio [OR] 1.47, 95% CI 1.25–1.74; $p < 0.001$), but not non-perimenstrual migraine attacks (OR 1.04, 95% CI 0.88–1.22; $p = 0.660$), were more likely to be associated with severe pain intensity (vs. mild/moderate pain intensity) than migraine attacks in men (Figure 4). There were no differences in minimal pain coping (rated on a continuous scale from 0–10) between non-perimenstrual (adjusted mean difference 0.13, 95% CI −0.06 to 0.33; $p = 0.177$) or perimenstrual (adjusted mean difference −0.11, 95% CI −0.31 to 0.10; $p = 0.315$) migraine attacks compared to men.

Migraine attacks in women, both perimenstrual and non-perimenstrual, were more often accompanied by photophobia, phonophobia, and nausea compared to men (Table 2). Aura symptoms were less prevalent in women, both during perimenstrual and non-perimenstrual migraine attacks. No differences were found in use of triptans, 2-h headache response, and 2-h pain-free response. Relapse rate was higher for perimenstrual migraine attacks compared to men (OR 2.39, 95% CI 1.93–2.95; $p < 0.001$). For non-perimenstrual migraine attacks the difference was smaller (OR 1.18, 95% CI 0.97–1.45; $p = 0.060$).

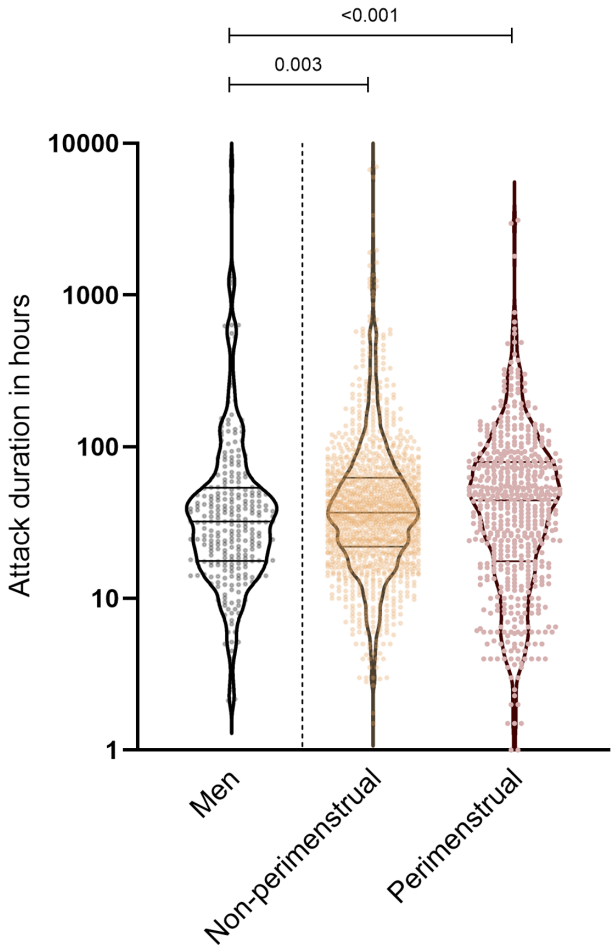

FIGURE 3 Violin plots of crude migraine attack duration in men and perimenstrual and non-perimenstrual attacks in women. The horizontal lines indicate the median and interquartile range. Mean attack duration was first calculated for perimenstrual and non-perimenstrual migraine attacks in each patient, and subsequently mean attack duration per group was calculated. [Color figure can be viewed at wileyonlinelibrary.com]

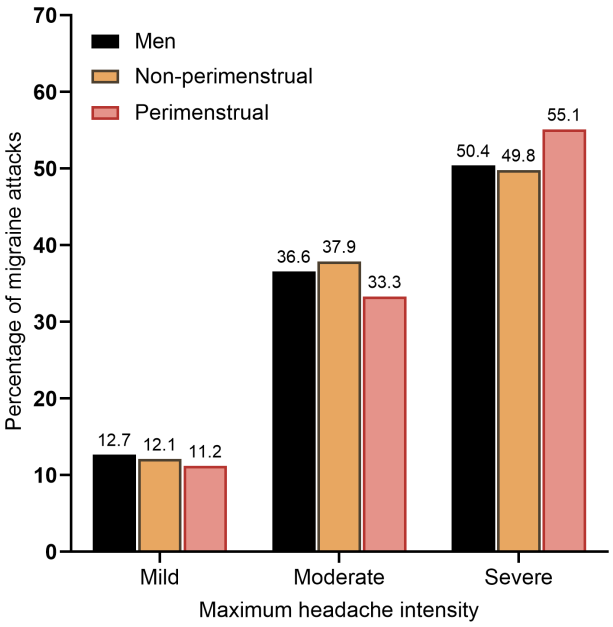

FIGURE 4 Maximum pain intensity scores in men versus perimenstrual and non-perimenstrual attacks in women. The percentage of migraine attacks in each category ("mild", "moderate", or "severe") was first calculated for perimenstrual and non-perimenstrual migraine attacks in each patient, and subsequently mean percentages per group were calculated. [Color figure can be viewed at wileyonlinelibrary.com]

Sensitivity analyses

A total of 125 patients were excluded from all analyses due to insufficient compliance to the E-diary (<80% for each month). Inclusion of these patients yielded similar effect estimates as the initial analysis for attack duration. Non-perimenstrual migraine attacks were found to have a mean (95% CI) 18% (9%–28%, $p < 0.001$) longer attack duration and perimenstrual migraine attacks 65% (50%–80%, $p < 0.001$) than migraine attacks in men.

DISCUSSION

This large longitudinal E-diary study showed that not only perimenstrual, but also non-perimenstrual migraine attacks in women have a longer duration than migraine attacks in men. These results build on findings from previous research showing differences between perimenstrual and non-perimenstrual migraine attacks in women.[11] Perimenstrual migraine attacks, suggested to result from changes in sex hormone levels prior to menstruation, are known to have a longer duration and increased relapse risk compared to non-perimenstrual migraine attacks.[23] The present study confirmed that similar differences exist between perimenstrual migraine attacks and migraine attacks in men. These differences may be most pronounced in a subgroup of women with menstrual migraine, as was the case in previous studies.[11,18] In addition, we found differences, although smaller, in attack duration between non-perimenstrual migraine attacks and attacks in men. These results contribute to the notion that migraine in women is associated with more severe symptoms than migraine in men. Differences in attack duration were found despite women being more likely to use long-acting triptans compared to men.

Both perimenstrual and non-perimenstrual migraine attacks were more often associated with accompanying symptoms, such as photophobia, phonophobia, and nausea. Photophobia and phonophobia are hypothesized to result from cortical hyperresponsiveness of the visual and auditory cortices respectively, which are suggested to be activated by craniovascular nociceptive information that relays directly from thalamic neurons.[24] Increased calcitonin gene-related peptide (CGRP) levels have also been linked to photophobia, indicating that promotion of a trigeminal nociceptive pathway could be the underlying pathophysiological mechanism.[24] CGRP release may be increased in women with migraine, as was suggested in a study evaluating dermal blood flow after topical application of capsaicin on the forearm. Women with migraine showed a higher CGRP-dependent dermal blood flow response than healthy women, independent of

TABLE 2 Mean prevalence of outcomes in men and women for perimenstrual and non-perimenstrual migraine days with corresponding results of generalized estimating equation models adjusted for age < or ≥50 years, chronic migraine, and medication overuse headache.

		Women, %		Adjusted OR (95% CI) non-perimenstrual vs. men		Adjusted OR (95% CI) perimenstrual vs. men	
	Men, %	Non-perimenstrual	Perimenstrual		Adjusted *p*		Adjusted *p*
Photophobia	77.2	84.2	84.5	1.67 (1.38–2.01)	**<0.001**	1.70 (1.40–2.06)	**<0.001**
Phonophobia	67.5	80.1	81.4	1.99 (1.66–2.40)	**<0.001**	2.15 (1.78–2.61)	**<0.001**
Nausea	46.7	59.3	57.8	1.66 (1.39–1.97)	**<0.001**	1.69 (1.41–2.01)	**<0.001**
Vomiting	7.4	9.2	8.4	1.23 (0.96–1.59)	0.119	1.25 (0.97–1.63)	0.104
Aura symptoms*	30.4	20.2	15.6	0.59 (0.45–0.78)	**<0.001**	0.54 (0.41–0.71)	**<0.001**
Use of analgesics	25.7	28.2	29.7	1.08 (0.94–1.23)	0.404	1.21 (1.06–1.39)	**0.036**
Use of triptans	38.9	41.5	46.3	1.03 (0.90–1.17)	0.758	1.10 (0.96–1.26)	0.300
2-h headache response**	53.7	58.1	59.1	1.17 (0.99–1.38)	0.104	1.11 (0.93–1.32)	0.312
2-h pain-free response**	24.1	28.7	29.1	1.19 (0.97–1.47)	0.101	1.12 (0.90–1.40)	0.326
Relapse <24 h**	9.2	12.6	15.7	1.18 (0.97–1.45)	0.060	2.39 (1.93–2.95)	**<0.001**

Note: The reported mean percentages result from descriptive statistics, where the percentage of migraine days with occurrence of the symptom per individual was calculated first and subsequently the mean percentage per group. ORs and *p* values were retrieved from GEE models adjusted for age < or ≥50 years, chronic migraine, and medication overuse headache. Bold values statistically significant at $p < 0.05$.

Abbreviations: CI, confidence interval; GEE, generalized estimating equation; MA, migraine with aura; OR, odds ratio.

*The percentage of migraine days with aura symptoms was calculated in patients with MA only.

**2-h headache response, 2-h pain-free response and relapse were evaluated in migraine days with triptan intake.

the menstrual cycle, while no differences were found between men with migraine and healthy men.[25]

Altered dopamine levels in the hypothalamus are likely to be involved in nausea and vomiting in migraine. Patients with migraine present with increased symptoms of yawning, nausea, vomiting, and dizziness after treatment with a dopamine agonist, suggesting a hypersensitivity to dopamine.[24] Whether there are sex differences in dopamine (hyper)sensitivity or regulation remains to be elucidated. Interictal sex differences in brain structure of the insula and precuneus have also been reported.[26] The insula is involved in multiple functional processes such as pain, interoception, autonomic function, sensation, and affective processing. Based on these findings, it has been suggested that sensory and emotional circuitries differ between men and women with migraine.

Whether differences between men and women are solely the result of biological or psychosocial and cultural factors, or a combination of both, is difficult to determine. Gender differences in pain experience and willingness to report pain have been well established.[27,28] Persons with more feminine personality traits tend to report more severe symptoms of pain than persons with typical masculine traits, especially in questionnaire studies and interviews.[27] The same could be true for other subjective symptoms, such as photophobia, phonophobia, and nausea. As participants' gender was not assessed in the present study, we were unable to assess to what extent sex, gender, or a combination of both, was implicated; however, it is noteworthy that gender differences in pain experience and reporting are less pronounced in studies of patients with (chronic) pain in a clinical setting.[29] This may be explained by the instrumental purpose of pain reporting in a clinical setting, necessary for receiving the right treatment, which was also the case for the present study. Moreover, we found no differences in maximum headache intensity scores or pain coping between men and non-perimenstrual migraine attacks in women, indicating that the idea that women are merely more likely to report more frequent and more severe symptoms is too simplistic.

Migraine headache in women was less frequently accompanied by aura symptoms than migraine attacks in men. Importantly, the absolute number of migraine auras or prevalence of migraine with aura diagnoses (a patient is labeled as migraine with aura when he/she experienced at least two aura attacks) did not differ between the groups, but the proportion of migraine attacks accompanied by aura symptoms in patients diagnosed with migraine with aura was higher in men. A sudden drop in estrogen levels is hypothesized to increase susceptibility to migraine attacks without aura.[5,18,30–32] This could explain the relatively lower prevalence of aura symptoms in women, particularly for perimenstrual attacks.

Strengths of the present study include the longitudinal study design using a previously well-validated headache E-diary tool.[16] Patients provided daily information about detailed headache symptoms and menstruation, which enabled us to distinguish perimenstrual from non-perimenstrual migraine attacks and allowed us to prospectively compare migraine attack characteristics over a long time-period. A limitation of this study was that we had to make assumptions about the mechanism of missing data. In general, compliance to the E-diary was high, but 125 patients were excluded due to <80% compliance; however, a sensitivity analysis of the

primary outcome, including all patients independent of compliance, showed similar results. Moreover, no detailed data were available for menopausal status and exact type of hormonal contraception use (combined hormonal contraception vs. progestogen only methods). Defining menopause based on a questionnaire is very imprecise, and therefore far too little research is being done on the influence of the menopausal transition phase and postmenopausal status on migraine symptoms. Future studies addressing migraine during menopause would benefit from defining menopause based on a detailed clinical interview and/or follicle-stimulating hormone levels consistent with the Stages of Reproductive Aging Workshop (STRAW) criteria.[33] Furthermore, it may be interesting to assess whether sex differences are specific to women with menstrual migraine. This could not be determined in the present study because not all women were followed for three or more menstrual cycles. Finally, this study was not population-based, but has the advantages of a well-defined cohort in which attack frequency was virtually comparable between sexes, which allowed us to look at migraine characteristics irrespective of the number of migraine attacks.

CONCLUSION

Both perimenstrual and non-perimenstrual migraine attacks in women differ from migraine attacks in men. Treating physicians should be aware of a longer attack duration in women, despite the use of long-acting triptans, and particularly the increased risk of relapse during the perimenstrual window. Women in general are more likely to experience accompanying symptoms during a migraine attack, but less often aura than men. To what extent differences between men and women have a biological basis or result from psychosocial and cultural factors requires further research, but it seems too simplistic to assume that women are merely more likely to report more frequent and more severe symptoms than men. Our results highlight the need for a sex- and gender-informed approach in migraine treatment and research.

AUTHOR CONTRIBUTIONS

Iris E. Verhagen, Britt W.H. van der Arend, Antoinette MaassenVanDenBrink and Gisela M. Terwindt contributed to the study design. Iris E. Verhagen, Britt W.H. van der Arend and Daphne S. van Casteren contributed to acquisition of data. Iris E. Verhagen, Britt W.H. van der Arend, Daphne S. van Casteren and Saskia le Cessie performed the statistical analyses. Iris E. Verhagen drafted the manuscript. All authors revised the manuscript and approved the final version for submission.

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CONFLICT OF INTEREST STATEMENT

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