



Universiteit  
Leiden  
The Netherlands

## **Sex differences in prevalence of migraine trigger factors: a cross-sectional study.**

Casteren, D.S. van; Verhagen, I.E.; Onderwater, G.L.J.; MaassenVanDenBrink, A.; Terwindt, G.M.

### **Citation**

Casteren, D. S. van, Verhagen, I. E., Onderwater, G. L. J., MaassenVanDenBrink, A., & Terwindt, G. M. (2020). Sex differences in prevalence of migraine trigger factors: a cross-sectional study. *Cephalalgia : An International Journal Of Headache*, 41(6), 643-648.  
doi:10.1177/0333102420974362

Version: Publisher's Version

License: [Creative Commons CC BY-NC 4.0 license](#)

Downloaded from: <https://hdl.handle.net/1887/3276105>

**Note:** To cite this publication please use the final published version (if applicable).

# Sex differences in prevalence of migraine trigger factors: A cross-sectional study

Daphne S van Casteren<sup>1,2</sup>, Iris E Verhagen<sup>1,2</sup>,  
Gerrit LJ Onderwater<sup>1</sup>, Antoinette MaassenVanDenBrink<sup>2,\*</sup>  
and Gisela M Terwindt<sup>1,\*</sup>

Cephalalgia

2021, Vol. 41(6) 643–648

© International Headache Society 2020



Article reuse guidelines:

sagepub.com/journals-permissions

DOI: 10.1177/0333102420974362

journals.sagepub.com/home/cep



## Abstract

**Aim:** To examine the effect of sex on migraine trigger factors.

**Methods:** Prevalence of 11 frequently reported trigger factors was determined in a cross-sectional study among migraine patients from a validated migraine database ( $n = 5725$  females and  $n = 1061$  males). Female-to-male odds ratios were calculated for each trigger, using a logistic regression model with attack frequency and migraine subtype (with or without aura) as covariates. Additionally, the effect of sex on total number of triggers per individual was determined.

**Results:** The top three most reported triggers in women were menstruation (78%), stress (77%), and bright light (69%). Men reported stress (69%), bright light (63%), and sleep deprivation (60%) most frequently as provoking factors. The following triggers were more often reported by women than men: Bright light (odds ratio 1.29 [95% CI 1.12–1.48];  $p = 0.003$ ), stress (1.47 [1.27–1.69];  $p < 0.001$ ), skipping a meal (1.24 [1.09–1.42];  $p = 0.015$ ), sleep deprivation (1.37 [1.20–1.57];  $p < 0.001$ ), high altitudes (1.70 [1.40–2.09];  $p < 0.001$ ), and weather changes (1.35 [1.18–1.55];  $p < 0.001$ ). Women reported more triggers than men, even when menstruation was disregarded (mean  $\pm$  SD:  $4.6 \pm 2.3$  and  $4.3 \pm 2.3$ ;  $p < 0.001$ ).

**Conclusion:** Women report migraine trigger factors to be provocative of their attacks more frequently than men, which may be related to a lower migraine threshold due to sex hormonal changes.

## Keywords

Menstruation, stress, light, sleep, primary headache

Date received: 14 July 2020; revised: 24 September 2020; 20 October 2020; accepted: 20 October 2020

## Introduction

Migraine is a multifactorial brain disorder characterised by recurring attacks of severe headaches and neurological features. How attacks exactly are initiated is unknown. Migraine susceptibility seems to be determined by a complex interaction between internal threshold modulating factors and external modifiable factors. Internal threshold modulating components mainly consist of genetic factors and sex hormonal conditions. Differences in sex hormonal conditions may explain why migraine prevalence is three times higher in fertile women than in men. During the fertile period, sex hormonal fluctuations preceding menstruation lower the threshold and thus increase susceptibility to a migraine attack (1–4). External modifiable factors may trigger an attack, especially when the threshold is

already low; for example, during menstruation. Many patients and physicians are convinced that attacks are provoked by external triggers such as certain food items, skipping a meal, alcohol, stress, and weather changes (5–8). In previous migraine trigger-related

<sup>1</sup>Department of Neurology, Leiden University Medical Center, Leiden, The Netherlands

<sup>2</sup>Division of Vascular Medicine and Pharmacology, Erasmus University Medical Center, Rotterdam, The Netherlands

\*These authors are shared last authors.

### Corresponding author:

Gisela M Terwindt, Department of Neurology, Leiden University Medical Center, PO Box 9600, 2300 RC, Leiden, The Netherlands.  
Email: G.M.Terwindt@lumc.nl

research, remarkably little attention has been paid to sex differences, which is surprising given the large influence of sex on migraine prevalence. The aim of this study was to investigate sex differences in trigger factors in a large, well-defined cohort of migraine patients. Although behavioural, social, environmental and cultural factors are expected to be of influence as well, we chose to use the term “sex” to comprehensibly describe differences between men and women in this study.

## Methods

### Study design and population

This study is a cross-sectional, web-based questionnaire study among female and male migraine patients. This study was conducted as part of the Leiden University MIgraine Neuro-Analysis (LUMINA) project, a validated migraine population (9). Participants in the LUMINA project are Dutch adults suffering from migraine with or without aura based on the International Classification of Headache Disorders (ICHD-3) criteria (10). An elaborate description of LUMINA participants and procedures is found as supplemental material. The study was approved by the medical ethics committee of Leiden University Medical Center (METC number P12.201). All participants provided written informed consent. Recruitment for the LUMINA study population is still ongoing, but for the current study we included participants recruited between 2008 and 2018.

### LUMINA questionnaire

All participants completed an extended online questionnaire (accessible via [www.lumc.nl/hoofdpijn](http://www.lumc.nl/hoofdpijn)) that incorporated 11 items on trigger factors. The prevalence of frequently reported trigger factors was assessed by the question: Which of the following factors can provoke migraine attacks? 1. Bright (sun)light. 2. Stress. 3. Physical exercise and/or sexual activity. 4. Mild head trauma. 5. Skipping a meal. 6. Certain food or non-alcoholic beverages. 7. Alcoholic beverages. 8. Sleep deprivation. 9. High altitudes (for instance in the mountains). 10. Weather changes. Answer possibilities were No/Yes/Don't know. Participants were motivated to answer positively when a certain factor inconsistently provokes severe headaches. Additionally, women were asked to indicate the relation between migraine attacks and menstruation, defined as attacks occurring on  $-2$  days of the onset of menstruation to  $+2$  days from the end of menstruation, using the following answer possibilities: 1. There is no association between my headache and the menstrual period; 2. My headache exclusively occurs

related to the menstrual period and at no other times of the cycle; 3. My headache occurs related to the menstrual period and additionally at other times of the cycle, or 4. Not applicable. Data on current use of contraceptives was not collected.

### Data analysis and statistics

Independent-samples *t* tests and Chi-square tests were used to compare baseline characteristics between female and male migraine patients. Logistic regression models were conducted to calculate female-to-male odds ratios for each trigger factor. Migraine attack frequency was included as covariate, as we expect this to influence the recall of trigger factors. Migraine subtype (migraine without aura (MO) or migraine with aura (MA)) was also included as covariate, as knowledge regarding its influence on the role of trigger factors is insufficient. *p*-values were adjusted for multiple testing with a Bonferroni correction. Additionally, a linear regression model was conducted to compare the total number of trigger factors between females and males, including migraine attack frequency and migraine subtype as covariates. Menstruation as a trigger factor was disregarded in these analyses. The frequency of “don't know” answers to the questions regarding migraine trigger factors was compared between men and women and appeared to be similar.

## Results

### Participants

A total of 6786 patients completed the LUMINA questionnaire. Baseline characteristics of female ( $n = 5725$ ) and male ( $n = 1061$ ) participants are shown in Table 1. Women were younger (mean age in years  $\pm$  SD:  $41.9 \pm 12.1$  vs.  $45.7 \pm 13.1$ ,  $p < 0.001$ ), with a lower body mass index (BMI) ( $24.5 \pm 6.4$  vs.  $25.8 \pm 13.3$ ,  $p < 0.001$ ), and a higher percentage of migraine without aura diagnoses ( $64.5\%$  vs.  $57.2\%$ ,  $p < 0.001$ ). Fourteen percent of the female population was 55 years of age or older and likely postmenopausal ( $n = 825$ ). Men more often experienced low frequency migraine (1–6 attacks/year) and very high frequency migraine ( $>54$  attacks/year) compared to women ( $18.7\%$  vs.  $13.7\%$  and  $23.0\%$  vs.  $16.6\%$  respectively). Mean number of migraine days per month and mean number of headache days per month did not differ between men and women.

### Primary analysis

The top three most reported trigger factors in women were menstruation ( $78.1\%$ ), stress ( $76.7\%$ ), and exposure to bright light ( $68.5\%$ ) (Table 2 and Figure 1). The large majority of women with a menstrual cycle stated

their attacks to be related to their menstrual cycle. Only 4.7% of women reported attacks to be exclusively related to menstruation (pure menstrual migraine) (10), most (73.4%) indicated that besides the menstruation period, attacks also occur at other time periods in the cycle (menstrually related migraine) (10). Men reported stress (69.2%), exposure to bright light (63.2%), and sleep deprivation (60.3%) most frequently as migraine provoking factors (Table 2 and Figure 1). The following trigger factors were more often reported by women than men after correction for attack frequency and migraine subtype: Exposure to bright light (odds ratio 1.29 [95% CI 1.12–1.48];  $p = 0.003$ ), stress (1.47 [1.27–1.69];  $p < 0.001$ ), skipping a meal (1.24 [1.09–1.42];  $p = 0.015$ ), sleep deprivation (1.37 [1.20–1.57];  $p < 0.001$ ), high altitudes (1.70 [1.40–2.09];  $p < 0.001$ )

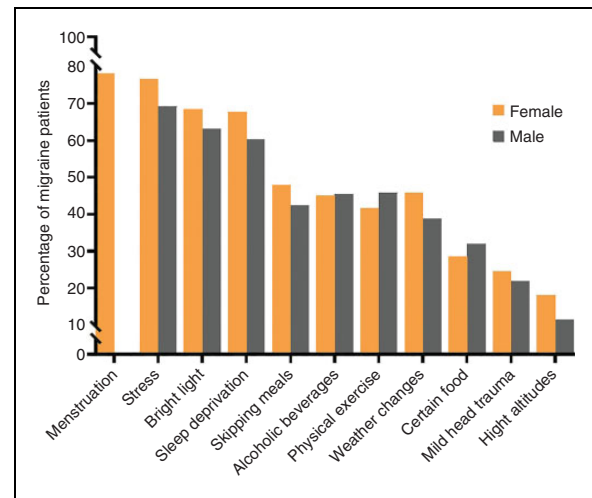
and weather changes (1.35 [1.18–1.55];  $p < 0.001$ ) (Table 2 and Figure 1). Prevalence of physical exercise/sexual activity, mild head trauma, certain food/non-alcoholic beverages, and alcoholic beverages as migraine trigger factors did not differ significantly between men and women (Table 2 and Figure 1).

**Additional analyses**

Women reported a larger total number of migraine trigger factors than men (mean  $\pm$  SD:  $4.6 \pm 2.3$  and  $4.3 \pm 2.3$  respectively), with most women reporting five trigger factors (16.9%) compared to four trigger factors in men (17.2%). A significant regression equation was found after correcting for attack frequency and migraine subtype (see Table 3,  $p < 0.001$ ). Female

**Table 1.** Baseline characteristics of the study population.

	Female (n = 5725)	Male (n = 1061)
Age in years, mean $\pm$ SD	41.9 $\pm$ 12.1	45.7 $\pm$ 13.1
Age range in years	18.0 : 82.7	18.0 : 83.6
BMI, mean $\pm$ SD	24.5 $\pm$ 6.4	25.8 $\pm$ 13.3
Migraine without aura, n (%)	3694 (64.5)	607 (57.2)
Migraine attack frequency per year, n (%)		
1–2	167 (2.9)	47 (4.4)
3–6	617 (10.8)	152 (14.3)
7–12	1395 (24.4)	216 (20.4)
13–54	2593 (45.3)	402 (37.9)
>54	951 (16.6)	244 (23.0)
Migraine days per month, mean $\pm$ SD	7.6 $\pm$ 8.8	7.6 $\pm$ 9.6
Other headache days per month, mean $\pm$ SD	7.3 $\pm$ 12.2	7.0 $\pm$ 12.3



**Figure 1.** Prevalence of migraine trigger factors in females and males.

**Table 2.** Prevalence of migraine trigger factors separately for both sexes and female-to-male odds ratios for all triggers.

	Percentage (%)		Odds ratio 95% CI	Adjusted $p$ -value
	Female (n = 5725)	Male (n = 1061)		
Menstruation	78.1	–	–	–
Stress	76.7	69.2	1.47 (1.27–1.69)	<0.001
Bright (sun)light	68.5	63.2	1.29 (1.12–1.48)	0.003
Sleep deprivation	67.7	60.3	1.37 (1.20–1.57)	<0.001
Skipping meals	47.9	42.4	1.24 (1.09–1.42)	0.015
Alcoholic beverages	45.0	45.5	0.96 (0.84–1.10)	1
Physical exercise/sexual activity	41.7	45.8	0.84 (0.74–0.96)	0.114
Weather changes	45.9	38.7	1.35 (1.18–1.55)	<0.001
Certain food/non-alcoholic beverages	28.6	31.9	0.86 (0.75–1.00)	0.424
Mild head trauma	24.5	21.9	1.15 (0.98–1.35)	0.794
High altitudes	18.0	11.5	1.70 (1.40–2.09)	<0.001

Note: The included number of participants per trigger slightly differs from the numbers mentioned at the top of the table.

**Table 3.** Linear model of predictors of the number of reported trigger factors.

	Estimate ( $\beta$ )	SE	t-value	p-value
Constant	2.69	0.141	19.03	<0.001
Sex (female)	0.32	0.076	4.30	<0.001
Migraine attack frequency	0.42	0.026	16.00	<0.001
Migraine subtype (MO/MA)	0.04	0.057	0.66	0.508

sex appeared to be associated with a higher total number of reported trigger factors compared to men, even when menstruation was disregarded in the analysis ( $\beta=0.32$ ,  $p<0.001$ ). The number of triggers was positively associated with migraine attack frequency ( $\beta=0.42$ ,  $p<0.001$ ). On the contrary, migraine subtype (with or without aura) appeared to have no effect on the total number of reported triggers ( $\beta=0.04$ ,  $p=0.508$ ) (Table 3).

Most postmenopausal women reported four or five trigger factors (13.7% and 13.9% respectively, mean  $\pm$  SD:  $4.4 \pm 2.5$ ), which appeared to be comparable to the total number of trigger factors reported by men after correcting for attack frequency and migraine subtype ( $p=0.371$ ).

## Discussion

Menstruation, stress and exposure to bright light are the most reported migraine trigger factors in our large validated migraine population. Women have a higher self-reported prevalence of migraine trigger factors than men, especially concerning skipping a meal, sleep deprivation, stress, exposure to bright light, weather changes and high altitudes.

The susceptibility to migraine attacks is suggested to be determined by natural fluctuations in neuronal excitability in the brain. The brain may be much more susceptible to triggers at the peak of these neuronal excitability fluctuations. We hypothesise that migraine susceptibility is determined by a complex interaction between internal threshold modulating factors and external modifiable factors. These internal threshold components are partly stable, such as genetic predisposition factors, and partly fluctuating, such as sex hormonal conditions (1,11,12). When internal threshold factors decrease the threshold at a certain point in time, susceptibility to an attack will be high. At this point, external trigger factors may provoke an attack whereas at other time points, when the internal threshold is high and susceptibility to an attack is low, these external factors are not able to provoke a migraine attack.

We also hypothesise that sex hormonal differences between males and females may contribute to a different pattern of fluctuations in neuronal brain excitability and the internal threshold, and therefore, to an increased potential of external trigger factors to provoke migraine in women. Our hypothesis is supported by the finding that the total number of trigger factors reported by postmenopausal women with stabilised sex hormones was comparable to the results in men. Additionally, previous clinical and experimental pain research demonstrated a lower pain threshold and greater pain sensitivity in women than in men. Although the exact pathophysiological underlying mechanism is unknown, the influence of sex hormones on nociceptive processing is suggested to be of great importance (13,14).

An alternative explanation for our findings may be related to behavioural, social and cultural differences between men and women in reporting health-related outcomes. Epidemiological pain research has shown that women are more likely than men to report symptoms of pain, such as headaches, musculoskeletal pain and abdominal pain (15). Women also tend to report adverse drug reactions more frequently than men (16,17). However, the reported number of migraine days and headache days per month was comparable in men and women in our study, suggesting that in our study there were no sex differences in reporting pain-related outcomes.

The most important strength of the current study includes the large cohort of well-defined patients suffering from migraine with and without aura. In contrast to previous studies, our study is sufficiently powered to investigate sex differences regarding the prevalence of trigger factors. A possible limitation of the current study is the self-reported nature, which makes it susceptible to recall bias. Furthermore, frequently reported trigger factors were selected for investigation in this study, but more factors are suggested as potential migraine triggers, such as odours, noise and smoking (18). However, trigger-related research is complicated by overlap of trigger factors and premonitory symptoms. Many putative trigger factors might in fact be part of the premonitory symptom phase, reflecting an attack that has already started rather than true inducers of migraine attacks. Thus, migraine patients may perceive factors such as odours, noise, and bright sunlight more intensely during the premonitory phase as a result of an enhanced neuronal susceptibility (5). Therefore, we selected mostly trigger factors that are not also among the most frequently reported premonitory symptoms (19,20). Nevertheless, the uncertainty associated with overlapping trigger factors and premonitory symptoms should be born in mind when interpreting results on perceived triggers, especially

regarding bright light, stress, sleep deprivation and skipping meals. Lastly, the temporal window used to consider a migraine attack related to the peri-menstrual period was expanded compared to the current ICHD-3 criteria (10), which may have affected the prevalence of women reporting menstruation as trigger factor. The lack of uniform criteria for the definition of the peri-menstrual period in the past has demonstrated prevalence differences (21). Additionally, accuracy of self-reported menstrual migraine diagnoses has shown to be poor in female migraine patients (22). However, accurate menstrual migraine diagnoses are difficult to obtain even when prospective diaries are collected, since the current ICHD-3 diagnostic criteria for menstrual migraine have shown to reach maximum sensitivity for three menstrual cycles, although specificity increased with more cycles of data collection (23).

To further study the role of trigger factors in male and female migraine patients, a prospective electronic headache-trigger diary may be applied to screen for a close temporal relationship between the suspected trigger and attack onset. Electronic registration of objective measurements, such as weather changes and sleeping patterns, in combination with headache diaries would increase the reliability of trigger research even

further. Additionally, it would be interesting to investigate suspected external trigger factors at different time points of the menstrual cycle in order to assess the influence of menstrual cycle status on the triggering effect. Two pilot questionnaire studies were performed at our Headache clinic to assess patients' willingness to participate in future detailed trigger-related research. The first group comprised 53 male and female migraine patients who were asked about multiple trigger factors and willingness to participate in a prospective headache-trigger diary study. The second group included 48 female migraine patients who were asked about the influence of sex-hormonal changes on migraine and their willingness to participate in a diary study. In the first group, 92% of male and female migraine patients indicated that more research needs to be performed addressing trigger factors in migraine and 64% were willing to participate in a headache-trigger diary study. In the second group, 85% of women stated that the role of sex hormones in migraine should be further investigated and 77% of patients with sex-hormonal related migraine were willing to participate in a diary study. These results are promising when it comes to future inclusion of participants in detailed and prospective trigger-related studies.

### Clinical implications

- Women report more migraine trigger factors than men.
- Menstruation, stress and exposure to bright light are the most reported migraine trigger factors.

### Ethics approval

The study was approved by the medical ethics committee of Leiden University Medical Center (METC number P12.201). All subjects provided written informed consent.

### Declaration of conflicting interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: GMT reports consultancy support from Novartis, Lilly, Teva, and independent support from Dutch Organization for Scientific Research, and the Dutch Heart & Brain Foundations. AMvdB reports consultancy or industry support from Novartis, Lilly and Teva, and independent support from the Dutch Organization for Scientific Research and the Dutch Heart & Brain Foundations. DSvC and IEV report independent support from the Dutch Organization for Scientific Research and the Dutch Brain Foundation. GLJO has no conflict of interest to declare.

### Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this

article: The Netherlands Organisation for Health Research and Development (ZonMw).

### References

1. Vetvik KG and MacGregor EA. Sex differences in the epidemiology, clinical features, and pathophysiology of migraine. *Lancet Neurol* 2017; 16: 76–87.
2. Victor TW, Hu X, Campbell JC, et al. Migraine prevalence by age and sex in the United States: A life-span study. *Cephalalgia* 2010; 30: 1065–1072.
3. Buse DC, Loder EW, Gorman JA, et al. Sex differences in the prevalence, symptoms, and associated features of migraine, probable migraine and other severe headache: Results of the American Migraine Prevalence and Prevention (AMPP) study. *Headache* 2013; 53: 1278–1299.
4. MacGregor EA, Frith A, Ellis J, et al. Incidence of migraine relative to menstrual cycle phases of rising and falling estrogen. *Neurology* 2006; 67: 2154–2158.
5. Hoffmann J and Reuber A. Migraine and triggers: Post hoc ergo propter hoc? *Curr Pain Headache Rep* 2013; 17: 370.

6. Marmura MJ. Triggers, protectors, and predictors in episodic migraine. *Curr Pain Headache Rep* 2018; 22: 81.
7. Martin VT and Behbehani MM. Toward a rational understanding of migraine trigger factors. *Med Clin North Am* 2001; 85: 911–941.
8. Kelman L. The triggers or precipitants of the acute migraine attack. *Cephalalgia* 2007; 27: 394–402.
9. van Oosterhout WP, Weller CM, Stam AH, et al. Validation of the web-based LUMINA questionnaire for recruiting large cohorts of migraineurs. *Cephalalgia* 2011; 31: 1359–1367.
10. Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders, 3rd edition. *Cephalalgia* 2018; 38: 1–211.
11. de Boer I, van den Maagdenberg A and Terwindt GM. Advance in genetics of migraine. *Curr Opin Neurol* 2019; 32: 413–421.
12. de Boer I, Terwindt GM, van den Maagdenberg A. Genetics of migraine aura: An update. *J Headache Pain* 2020; 21: 64.
13. Maurer AJ, Lissounov A, Knezevic I, et al. Pain and sex hormones: A review of current understanding. *Pain Manage* 2016; 6: 285–296.
14. Bartley EJ and Fillingim RB. Sex differences in pain: A brief review of clinical and experimental findings. *Brit J Anaesth* 2013; 111: 52–58.
15. Unruh AM. Gender variations in clinical pain experience. *Pain* 1996; 65: 123–167.
16. Martin RM, Biswas PN, Freemantle SN, et al. Age and sex distribution of suspected adverse drug reactions to newly marketed drugs in general practice in England: Analysis of 48 cohort studies. *Brit J Clin Pharmacol* 1998; 46: 505–511.
17. Montastruc JL, Lapeyre-Mestre M, Bagheri H, et al. Gender differences in adverse drug reactions: Analysis of spontaneous reports to a regional pharmacovigilance centre in France. *Fund Clin Pharmacol* 2002; 16: 343–346.
18. Rose FC. Trigger factors and natural history of migraine. *Funct Neurol* 1986; 1: 379–384.
19. Schoonman GG, Evers DJ, Terwindt GM, et al. The prevalence of premonitory symptoms in migraine: A questionnaire study in 461 patients. *Cephalalgia* 2006; 26: 1209–1213.
20. Kelman L. The premonitory symptoms (prodrome): A tertiary care study of 893 migraineurs. *Headache* 2004; 44: 865–872.
21. Vetvik KG, Macgregor EA, Lundqvist C, et al. Prevalence of menstrual migraine: A population-based study. *Cephalalgia* 2014; 34: 280–288.
22. Verhagen IE, van Casteren DS, MaassenVanDenBrink A, et al. Menstrually-related migraine: A comparison between self-reported diagnosis and prospective headache diaries. *Cephalalgia* 2019; 39: 87–88.
23. Barra M, Dahl FA, MacGregor EA, et al. Identifying menstrual migraine – improving the diagnostic criteria using a statistical method. *J Headache Pain* 2019; 20: 95.