Clinical manifestations of sex hormonal influences in migraine

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Sex- and Gender-Specific Aspects of Migraine Treatment

D.S. van Casteren, E.G.M. Couturier, A. MaassenVanDenBrink

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General Introduction

Characteristics of migraine

Migraine is a multifactorial episodic brain disorder characterized by recurrent headache attacks associated with photophobia and phonophobia and/or nausea or vomiting. Migraine headache typically lasts 4-72 hours, is unilaterally located, of pulsating quality and of moderate to severe intensity. Headache intensity often increases with physical exercise, causing avoidance of routine physical activity.[1] Approximately one-third of migraine patients experience auras prior to headaches, which are characterized by transient focal neurological disturbances, such as visual and sensory symptoms and, less frequently, dysphasia or motor symptoms. A typical aura is unilaterally located and develops gradually. Each individual aura symptom generally lasts 5-60 minutes.[2] The majority of migraine patients experience premonitory symptoms, such as fatigue, yawning, cravings for certain foods and neck stiffness up to 48 hours preceding the headache phase and, if present, the aura phase.[3,4]

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.[5,6] Examples of frequently reported external trigger factors are stress, alcohol, certain food-items, skipping meals, and weather changes.[7-10]

Sex differences in migraine prevalence

The ratio of migraine prevalence between males and females varies throughout life. In young childhood the migraine prevalence is slightly higher in boys, while the prevalence is equal in prepubertal boys and girls. This balance turns in to an increased migraine prevalence in girls after the age of menarche. Migraine peaks in prevalence in both sexes between 30 and 39 years of age.[6,11,12] During fertile years, migraine prevalence is three times higher in women than in men, with a peak prevalence of approximately 25% in women.[11] Eventually, the difference in migraine prevalence between men and women becomes smaller in the postmenopausal period, but the prevalence remains slightly higher in women even after the age of 70 years.[11,12]

Migraine prevalence in pregnancy and the postpartum period

About 60-90% of women suffering from migraine without aura report improvement of their migraine attacks during pregnancy.[13-17] Based on a prospective diary study, 47% of women

with migraine reported improvement in the first trimester, 83% in the second trimester, and 87% in the third trimester. Complete remission of migraine attacks was attained by 11% of women in the first trimester, 53% in the second trimester, and 79% in the third trimester.[13] Migraine with aura showed to be less likely to improve during pregnancy with 44%, and more often remains unchanged (49%) or even worsens (8%).[14] A small percentage of women (3-6%) experience their first migraine attack during pregnancy, which usually concerns an attack with aura during the first trimester.[15,18,19] Migraine tends to return soon after delivery. Based on the earlier mentioned prospective diary study, migraine attacks returned within 1 week in 34% of patients and within 1 month in 55%. Bottle feeding was associated with migraine recurrence within the first week in 100% of women, while this was 43% in breastfeeding women.[13] Headache activity, including severity, frequency and duration, appeared to be similar during the first 3 months after delivery in breastfeeding women compared with the second trimester of pregnancy.[20]

Hormonal fluctuations throughout the menstrual cycle

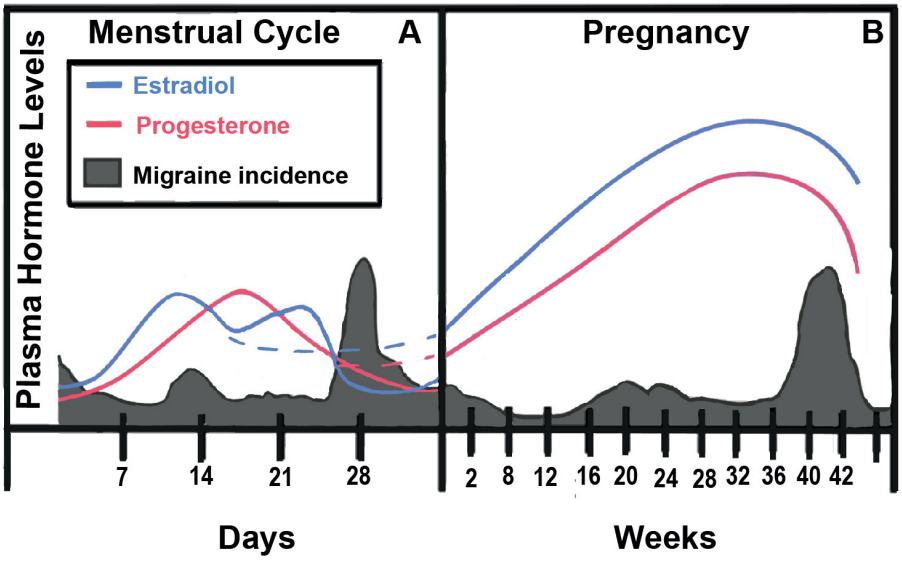
The median duration of a menstrual cycle is 28 days, and most cycle lengths are between 25 and 30 days. By definition, the first day of menstrual flow is called day +1, and there is no day 0. The menstrual cycle can be divided into two phases: [1] follicular or proliferative phase and [2] the luteal or secretory phase. The follicular phase starts on the first day of menstruation and lasts until ovulation. During this phase, the elevation of follicle stimulating hormone (FSH) causes follicles in the ovaries to grow. Ovulation, which is the release of a mature follicle, typically takes place at day 14 of the menstrual cycle and is caused by a sudden increase in luteinizing hormone (LH). This LH surge is initiated by an increase of estradiol produced by the preovulatory follicle and stimulates the synthesis of progesterone responsible for the midcycle FSH surge by luteinization of the granulosa cells. Ovulation is followed by the luteal phase. The remaining of an ovarian follicle that has released a mature oocyte during a previous ovulation is called the corpus luteum. It secretes a moderate amount of estrogen to inhibit further release of gonadotropin-releasing hormone (GnRH) and thus secretion of LH and FSH. The corpus luteum mainly secretes progesterone, which is responsible for the preparation of the uterine lining for pregnancy. If the corpus luteum is not rescued by pregnancy, progesterone withdrawal results in menses.[21]

Hormonal status during pregnancy and the postpartum period

The placenta begins to produce estradiol and progesterone during the sixth to eighth week of pregnancy. Concentrations of estradiol and progesterone continue to gradually

rise during pregnancy toward term. During the third trimester, serum concentrations of estradiol are 30-40 times higher and the level of progesterone is 20 times higher compared to peak levels of normal menstrual cycles.[22] Estrogen levels rapidly decline after delivery to reverse the physiologic changes of pregnancy, which often leads to recurrence of migraine attacks (Figure 1, panel B). Lactation inhibits ovulation by suppressing the hypothalamic–pituitary–ovarian axis, which results in stable low estrogen levels. The return of migraine in breastfeeding women may thus be delayed due to fewer estrogen fluctuations compared with non-breastfeeding women.[23] The frequency of breastfeeding may influence the duration of anovulation, which lasts on average 6 months in 70% of full breastfeeding women. The mean time to ovulation after delivery in non-breastfeeding women is 45 days.[24]

Figure 1. Hormonal fluctuations and migraine incidence throughout the menstrual cycle (panel A) and during pregnancy (panel B). Adapted from Sacco et al.[25]

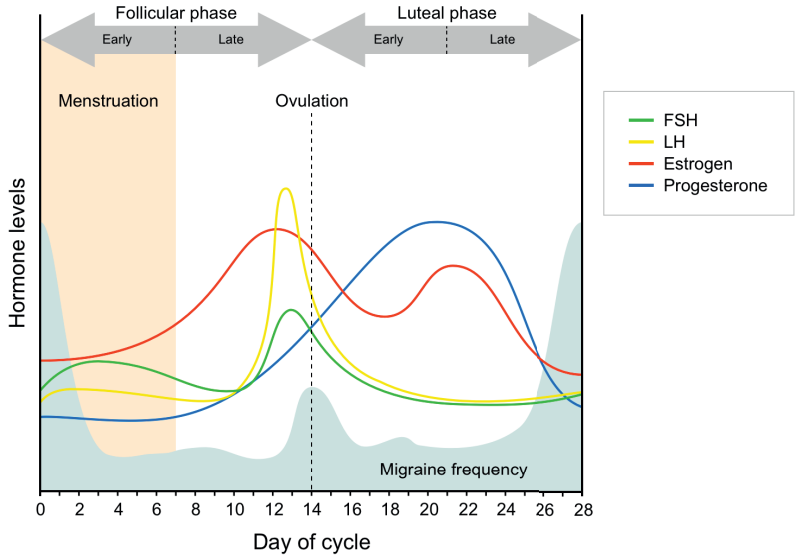


Migraine related to the menstruation

Menstruation is an important factor increasing the susceptibility for an upcoming migraine attack, with the highest risk in the period of 2 days before the menstrual period until the first 3 days of bleeding (days -2 and +3 of the menstrual cycle).[26] In approximately 55% of female migraine patients, the attacks occur not only between days -2 and +3 but can also occur at other times of the menstrual cycle.[1,27] According to the International Classification of Headache Disorders, 3rd edition (ICHD-3), this migraine subtype

is called menstrually related migraine (MRM).[1] A small proportion of female migraine patients, approximately 5.5%, experience migraine attacks exclusively related to the menstruation.[27] This subtype is called pure menstrual migraine (PMM).[1] For research purposes, PMM and MRM are often taken together and defined as menstrual migraine (MM). Menstruation is considered to be endometrial bleeding resulting from either the normal menstrual cycle or from the withdrawal of exogenous progestogens, as in the use of combined oral contraceptives or cyclical hormone replacement therapy (HRT; oral or transdermal conjugated estrogens combined with cyclical oral progestogen). Thus, sex hormonal fluctuations preceding the menstruation are known to affect the susceptibility for migraine attacks, but there is a lack of understanding of the exact underlying pathophysiological mechanism. Perimenstrual migraine attacks are commonly attributed to the sudden drop in estrogen prior to menses. A similar decrease in circulating estrogen occurs at ovulation, but this decline does not seem to be consistently related to increased provocation of migraine attacks.[28,29] Therefore, increasing progesterone levels during ovulation may have migraine-preventive properties (Figure 2).

Figure 2. Hormonal fluctuations and migraine incidence throughout the menstrual cycle. Adapted from Pavlovic et al.[30]



Premenstrual syndrome and migraine

Premenstrual syndrome is characterized by recurrent, moderate-to-severe affective, physical, and behavioural symptoms that develop during the luteal phase and disappear soon after the onset of menstruation. Findings of prospective and retrospective studies

suggest that 5–8% of women with natural menstrual cycles have moderate to severe premenstrual symptoms. However, some other studies suggest that up to 20% of all women of fertile age have premenstrual complaints that could be regarded as clinically relevant.[31]

Since symptoms of premenstrual syndrome also develop during the luteal phase of the menstrual cycle and migrainous headache is often reported as physical symptom, the existence of a possible comorbidity between menstrually related migraine attacks and premenstrual syndrome has been suggested, resulting from a corresponding provoking effect of sex hormonal fluctuations. Previous studies have reported an increased risk of migraine in women with premenstrual syndrome, but results on the prevalence of premenstrual syndrome in women with migraine are inconsistent, ranging from 10-30%.[32-34] Some diary-based pilot studies suggest the existence of a possible comorbidity between menstrually related migraine attacks and premenstrual symptoms, but sample sizes were very low.[32,35,36] Two larger cross-sectional studies found no difference in occurrence of premenstrual syndrome among female migraine patients with MM and non-MM.[33,37]

Migraine during perimenopause and postmenopause

Perimenopause describes the time when a woman's menstrual cycle changes from regular to irregular as a consequence of fluctuating ovarian activity. Early menopausal transition is marked by increased variability in menstrual cycle length and is defined by a difference of 7 days or more in the length of consecutive cycles, which should occur at least twice in a period of 12 menstrual cycles. Late menopausal transition is defined by the occurrence of amenorrhea of 60 days or longer. Menopause is defined as the day of the last menstruation. Perimenopause turns into postmenopause 12 months after the last menstruation.[38] Frequently, perimenopausal migraine patients continue suffering from disabling migraine attacks despite general migraine therapies.[39,40] Fluctuations in estrogen and progesterone levels during perimenopause are associated with increased susceptibility for migraine. This effect is seen on migraine attacks without aura, but not on migraine attacks with aura.[40,41] After menopause, hormonal stability remains with high FSH levels and low estrogen and progesterone levels due to decline of the production of these hormones by the ovaries. The postmenopausal status is associated with an improvement in migraine without aura. The frequency of migraine attacks decreases, and the attacks become less severe or even disappear.[33,42,43] Migraine prevalence in spontaneous menopausal women is 10.5%, which is considerably less than the 25% prevalence that is seen in premenopausal women. However, a migraine prevalence after a surgical menopause of 27% is approximately equal

to the migraine prevalence in premenopausal women.[43,44] In conclusion, migraine usually improves after spontaneous menopause, worsens during perimenopause, and remains the same after surgical menopause.

Sex hormone levels in women with migraine

Results of studies regarding sex hormonal patterns in women with migraine are inconsistent. A previous study showed a faster decline in conjugated urinary estrogens in the late luteal phase compared to healthy controls without a significant difference in estrogen peak levels or mean daily levels between migraine patients and healthy controls.[30] Another study detected a significantly lower mean serum estradiol level on days 19-21 of the menstrual cycle of patients with MRM compared to healthy controls, while no differences in estradiol levels were present at the onset of menstruation.[45] Both studies detected no significant differences in progesterone levels during the luteal phase or at the onset of menstruation. However, other studies showed estrogen levels to be higher in women with MRM compared to controls during most phases of the menstrual cycle,[46-48] and with only small differences between MRM and non-MRM patients.[46,47] No statistically significant differences were found in serum levels of androstenedione, total testosterone, and free testosterone between postmenopausal migraine patients and healthy controls.[49] In addition, a study on salivary testosterone levels in chronic migraine patients, previously affected by medication overuse headache, compared to healthy controls detected no significant differences between both groups.[50] However, in a randomized clinical trial on the management of postmenopausal women with hormone therapy, a combination of 17β-estradiol and tibolone (a tissue-selective steroid with androgenic properties) was more effective in reducing the hours that migraine headache prohibited daily activities, compared to a combination of 17β-estradiol and estrogen-progesterone. These data suggest androgenic steroids might influence the characteristics of migraine headache.[51]

Female-specific acute migraine treatments

Patients with PMM and MRM can be treated with acutely acting drugs according to standard treatment strategy. There are no FDA- or EMA-approved treatments specifically for this group of patients. However, multiple studies have shown the effectiveness of some acutely acting treatments for perimenstrual migraine attacks.

Menstrually related migraine attacks and non-menstrually related migraine attacks can be treated with non-specific analgesics (acetaminophen and NSAIDs) and anti-emetics. However, perimenstrual attacks are generally more resistant to non-specific acute

pharmacological treatment options compared to non-menstrually related migraine attacks.[52]

Triptans (serotonin 5-$HT_{1B/1D}$ receptor agonists) are the treatment of choice for those attacks that do not respond adequately to non-specific analgesics. According to two systematic reviews on acute and prophylactic treatment options for menstrual migraine, almotriptan, sumatriptan, naratriptan, rizatriptan and zolmitriptan have shown a statistically significant higher headache response after 2 and/or 4 hours in triptan users compared to placebo.[53,54] Controlled trials with the objective to compare frovatriptan to other triptans in the acute treatment of menstrually related migraine attacks have shown equal effectiveness in headache response after 2 hours.[55-57] Recurrence rates of headache at 24 and 48 hours were significantly lower with frovatriptan (17% and 21%) than with the comparators (27% and 31%) in patients with oral contraceptive-induced menstrual migraine.[55-57] Due to its sustained antimigraine effect, frovatriptan may be most suitable for the acute treatment of menstrually related migraine attacks.

Acute treatment of migraine during pregnancy

Since women often experience relief of migraine during the second and third trimesters of pregnancy, most of acutely acting migraine medication is used in the first trimester. Preferably, pharmacological treatment of migraine attacks is prevented during this period, as the teratogenic risks of medication are typically highest during the first trimester. Although therapeutic dosages of most acute migraine medication do not increase the risk of fetus malformation or miscarriage, the safest options should be advised.[58-60]

Acetaminophen has been considered the safest acute treatment option for migraine during pregnancy. However, recent studies have raised some new concerns about its safety due to potential adverse neurodevelopmental outcomes in children who are exposed to acetaminophen for more than 28 days in utero. The EMA concluded this potential association to be based on insufficient evidence.[58,59,61]

Sumatriptan is the most hydrophilic triptan compared to other triptans, resulting in a small percentage (about 15%) of a dose crossing the placental membrane.[59] Pregnancy registry studies detected no signal of teratogenicity after maternal use of sumatriptan.[62-64] In addition, a meta-analysis and a large Norwegian Mother and Child Cohort study found no association between triptan use during pregnancy and prematurity, major congenital malformations or spontaneous abortions.[65,66] Mostly sumatriptan was used in both studies.

Only acutely acting treatments that are considered relatively safe are discussed here. Table 1 shows a summary of recommendations and restrictions regarding the use of acetaminophen, sumatriptan and other acutely acting medication during pregnancy.

Table 1. Acute medication: use during pregnancy and lactation.

	1st trimester	2nd trimester	3rd trimester	Lactation	
Acetaminophen	√	√	√	√	
NSAIDs[a]	Avoid	Avoid	Contraindicated	√	Preferably ibuprofen
Ergotamine	Contraindicated	Contraindicated	Contraindicated	Contraindicated	
Sumatriptan	?(√)	?(√)	?(√)	√	
Other triptans[b]	Insufficient data	Insufficient data	Insufficient data	?(√)	
Metoclopramide	√	√	Avoid	(√)	No more than 5 consecutive days
Domperidone	?(√)	?(√)	?(√)	(√)	No more than 7 consecutive days

√: no proof for damage; (√): data suggest unlikely to cause harm; ?(√): insufficient data, probably safe. Recommendations are based on data of several studies.[58-76] [a]Includes diclofenac, ibuprofen and naproxen. [b]Includes almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan and zolmitriptan.

Acute treatment of migraine during lactation

Most drugs transfer into breast milk to some extent. Acetaminophen has been considered a safe acutely acting treatment option for migraine during lactation, as the drug has been used by a large number of breastfeeding women without an increase in adverse effects in the infant.[58,61] Among NSAIDs, the use of ibuprofen during the lactation period is preferred as it has the lowest relative infant dose of 0.1-0.7%. In addition, ibuprofen has been studied extensively in children.[58,61]

Sumatriptan has been categorized as a safe treatment during lactation as it showed a low relative infant dose of 3.5%, even when high plasma concentrations were achieved in mothers after the use of subcutaneous sumatriptan injections.[61,67]

Only acutely acting treatments that are considered relatively safe are discussed here. Table 1 shows a summary of recommendations and restrictions regarding the use of acetaminophen, NSAIDs, sumatriptan and other acutely acting medication during lactation.

Female-specific prophylactic migraine treatments

Patients with PMM and MRM can be treated with prophylactic drugs according to standard treatment strategy. There are no FDA- or EMA-approved treatments specifically for this group of patients. However, multiple studies have shown the effectiveness of some non-specific and specific treatments in the short-term preventive treatment of perimenstrual migraine attacks.

Short-term or intermittent prophylaxis is the daily use of acute medication starting shortly before and during the menstrual period. The occurrence of perimenstrual migraine may be predictable in women with a regular menstrual cycle, allowing initiation of short-term prophylaxis a few days before the onset of an expected menstrually related migraine attack. In general, short lasting preventive medication is taken during 3-5 days before the onset of menstruation and continued during the first few days of bleeding.

Naproxen and estrogens are described as non-migraine specific pharmacological treatment options for this purpose. Naproxen 550 mg administered twice daily is the most commonly used NSAID for perimenstrual migraine prevention. However, this approach is based on a low level of evidence.[77,78] Transdermal estradiol has been studied as short-term prophylactic treatment in patients with PMM and MRM. Estradiol 1.5 mg gel showed to be associated with a higher reduction in perimenstrual migraine days in the estradiol-treated cycles compared to placebo. However, estradiol treatment was followed by deferred estrogen withdrawal, triggering an increase in post-dosing migraine during the 5 days after the gel was stopped.[79]

The highest-quality evidence for the use of triptans as short-term perimenstrual prevention exists for frovatriptan, for zolmitriptan, and to a lesser extent for naratriptan. In a systematic review, six trials involving frovatriptan, zolmitriptan and naratriptan were reviewed as short-term prevention of menstrually related migraine attacks. Frovatriptan 2.5 mg twice per day and zolmitriptan 2.5 mg three times per day appeared to be the preferred regimens.[80] Only frovatriptan 2.5 mg twice per day received a level A rate of evidence and was determined to be effective for prevention of menstrually related migraine attacks according to the guidelines of the American Academy of Neurology and American Headache Society.[81] Importantly, when using triptans as short-term prophylaxis for menstrually related attacks, the amount of medication used per month should not exceed the recommended maximum to prevent medication-overuse headache.[82]

Oral contraceptives as prophylactic migraine treatment

In patients with PMM and MRM, standard prophylactics are often considered ineffective and frequently cause side effects. Clinical data on the preventive effect of combined oral contraceptives or progestogen-only contraceptives on PMM and MRM are scarce. Mainly open-label non-comparative studies are available in the literature, therefore diminishing the strength of the evidence. In general, after introducing a combined oral contraceptive, migraine can become worse (in approximately 25%), stay the same (in approximately 50%), or become less frequent (in approximately 25%).[83] Different types and dosages of combined oral contraceptives do not have a significant influence on this results. The hormone-free interval of combined oral contraceptives can induce estrogen-withdrawal headache, which is reported in up to 70% of women using oral contraception.[84] Therefore, the effect of eliminating or shortening the hormone-free interval has been investigated in combined oral contraceptive treatments. A systematic review suggested possible benefits of an extended regimen of combined oral contraceptives in women with migraine without aura, but the quality of evidence is low.[85] However, extended use of combined oral contraceptives frequently results in breakthrough bleedings. Shortening, instead of eliminating, the hormone-free interval can minimize this risk of breakthrough bleedings. The same systematic review found two studies assessing the role of combined oral contraceptives with a shortened pill-free interval.[85] One study suggested superiority of the shortened pill-free interval treatment (24 active pills + 4 placebo pills) over the conventional one (21 active pills + 7 placebo pills) in women with PMM.[86]

The use of a daily progesterone-only pill inhibits ovulation and results in a stable estrogen production by the ovaries. Theoretically, the use of a progesterone-only pill could be effective as preventive treatment in migraine patients, especially in PMM and MRM. Four observational studies assessed the possible benefits of desogestrel 75 µg in women with migraine. Available data indicated that treatment with oral desogestrel may be associated with improvement in migraine in women with migraine with and without aura.[85]

Prophylactic treatment of migraine during pregnancy

Preferably, pharmacological preventive treatment of migraine should be avoided if a woman is intending to become pregnant, as many drugs are most dangerous during the first trimester when an existing pregnancy may not be known. Therefore, adequate preconception care is needed and women should consider discontinuation of preventive treatments during pregnancy planning. In general it is considered safe when preventive treatments are discontinued at least 5 times the half-life prior to pregnancy. Physicians

should always discuss a potential pregnancy wish with their fertile female migraine patients before starting a preventive treatment.

If preventive migraine treatment is inevitable during pregnancy, propranolol or metoprolol have often been considered the safest options, especially when used after the first trimester. However, fetal growth restriction has been reported for beta-blockers and its use should be stopped prior to labor to avoid reduced uterine contraction and fetal bradycardia. Infants should be monitored for bradycardia, hypotension and hypoglycemia after exposure to propranolol in utero.[58,61,76]

Although there is some controversy on the efficacy of amitriptyline as prophylactic migraine treatment, a causal relationship between reported teratogenic effects and maternal amitriptyline use has not been established.[58] However, the use of amitriptyline should be avoided during the third trimester because neonatal effects, including preterm birth, respiratory distress, drowsiness and hypoglycaemia have been reported.[61,76]

Botulinum toxin A is widely used as treatment of chronic migraine, but its use during pregnancy should be avoided as no adequate and well-controlled studies in humans are available.[58] The efficacy of calcitonin gene-related peptide (CGRP) (-receptor) monoclonal antibodies has been demonstrated for the preventive treatment of migraine in adults. Considerations related to the use of CGRP (-receptor) monoclonal antibodies in human pregnancies should be evaluated.

Table 2 shows a summary of recommendations and restrictions regarding the use of preventive medication during pregnancy.

Table 2. Preventive medication: use during pregnancy and lactation.

	1st trimester	2nd trimester	3rd trimester	Lactation
Propranolol	Avoid	?(√)	?(√)	(√)
Metoprolol	Avoid	?(√)	?(√)	(√)
Candesartan	Contraindicated	Contraindicated	Contraindicated	?(√)
Topiramate	Contraindicated	Contraindicated	Contraindicated	Insufficient data
Valproic acid	Contraindicated	Contraindicated	Contraindicated	Avoid
Amitriptyline	(√)	(√)	Avoid	(√)
Botulinum toxin A	Insufficient data	Insufficient data	Insufficient data	Insufficient data
CGRP(-receptor) monoclonal antibodies	Insufficient data	Insufficient data	Insufficient data	Insufficient data

√: no proof for damage; (√): data suggest unlikely to cause harm; ?(√): insufficient data, probably safe. Recommendations presented in this table are based on data of several studies and only apply when the use of a preventive treatment for migraine is inevitable during pregnancy and lactation.[58,61,75,76,87,88]

Prophylactic treatment of migraine during lactation

The use of propranolol and metoprolol as prophylactic migraine treatment are considered compatible with breastfeeding. Propranolol is preferred due to a low milk/plasma ratio (0.5), resulting in a low infant dose. Additionally, propranolol has shown least pediatric adverse events with various studies. However, infants should be monitored for hypoglycemia and the use of propranolol is contraindicated in mothers with asthma.[58,61] Infant observation for hypoglycemia, hypotension and bradycardia is advised when mothers are using metoprolol during lactation.[58,76]

Although amitriptyline concentrations in breast milk are similar to plasma levels, the use of amitriptyline during lactation has been categorized as relatively safe as no serious pediatric adverse effects are reported in several studies. However, infant monitoring for symptoms of lethargy, dry mouth, constipation and urinary retention should be considered.[58,75,76]

Only preventive treatments that are considered relatively safe are discussed here. Table 2 shows a summary of recommendations and restrictions regarding the use of beta-blockers, amitriptyline and other preventive medication during lactation.

Aims of the Thesis

In this thesis, clinical manifestations of sex hormonal influences in migraine are investigated to increase the understanding of the role of sex hormones and ultimately contribute to the effectuation of sex-specific migraine treatment approaches. The described studies can be divided into two main parts. **Part I** describes studies examining clinical sex differences in migraine. **Part II** describes studies focussing on clinical female-specific characteristics of migraine.

Part I: Clinical sex differences in migraine

Chapter 2 describes a systematic review and meta-analysis aiming to examine the effect of sex on clinical response to triptans and to determine whether these differences are related to sex-specific pharmacokinetics of triptans. In **Chapter 3,** sex differences in the prevalence of migraine trigger factors are evaluated, aiming to determine whether differences between men and women affect the potential of external trigger factors to provoke migraine attacks.

Part II: Clinical female-specific characteristics of migraine

Chapter 4 introduces a self-developed time-locked electronic diary (E-diary), including an automated algorithm differentiating headache and migraine days. The implementation of E-diaries aims to fulfill the need for a high standard in clinical practice and in research regarding the reliability of data on migraine-related outcomes, including the association between migraine attacks and the menstruation. In **Chapter 5**, a prospective E-diary study is described, comparing migraine characteristics between menstrually related migraine attacks and non-menstrually related migraine attacks. In addition, the prevalence of premenstrual syndrome as comorbidity in women with migraine is determined. A large sample of female migraine patients is included in this study, aiming to provide conclusive results since findings of previous smaller diary-based studies and retrospective cross-sectional studies have been inconsistent. In **Chapter 6**, a case-control study is presented, comparing jealousy levels within romantic relationships between women with migraine and non-migrainous controls. Estrogen influences susceptibility to migraine attacks and also has been suggested to affect jealousy in romantic relationships in women.

Chapter 7 provides a general discussion of the thesis and suggestions for future research. Finally, the thesis is summarized in **Chapter 8**.

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PART I

Clinical sex differences in migraine

CHAPTER 2

Sex differences in response to triptans: A systematic review and meta-analysis

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Abstract

Objective To examine the effect of sex on clinical response to triptans in migraine and to determine whether these differences are related to pharmacokinetics of triptans in men and women, we performed a systematic review and meta-analysis.

Methods We searched clinical trials distinguishing clinical response to or pharmacokinetic parameters of triptans between sexes in PubMed, MEDLINE, Cochrane Library, Embase and Web of Science up to Dec 12, 2019. Analysis was based on data extracted from published reports. Male-to-female pooled risk ratios (RR) were calculated for clinical outcomes and pooled ratio of means (RoM) for pharmacokinetic outcomes using random-effects models.

Results Of 1188 publications on clinical trials with triptans, 244 were identified with sex-related search terms. Only 19 publications presented sex-specific results, comprising n = 2280 men and n = 13899 women. No sex differences were revealed for 2-hour headache and pain-free responses, but men had a lower risk for headache recurrence (male-to-female RR 0.64, 95% confidence interval [CI]: 0.55-0.76, Q = 0.81) and adverse events (RR 0.82, 95% CI: 0.72-0.93, Q = 4.93). Men had lower drug exposure with lower area under the curve (RoM 0.69, 95% CI: 0.60-0.81, Q = 18.06) and peak drug concentration (RoM 0.72, 95% CI: 0.64-0.82, Q = 8.24) than women.

Conclusions Remarkably few publications about sex differences in triptan response are available. The limited number of eligible studies show sex differences in adverse event frequency, which may be partly because of drug exposure differences. This higher drug exposure in women is not reflected in different response rates. Despite higher exposure, women have higher headache recurrence rates possibly because of longer attack duration related to sex hormonal changes.

Introduction

Migraine is a common disabling episodic brain disorder, affecting 3 times more women than men.[1] In both sexes, triptans (serotonin 5-$HT_{1B/1D}$ receptor agonists) are the most widely prescribed acute migraine-specific treatments. In contrast to clinical trials in general, where most men are included,[2,3] most trials investigating effectiveness of triptans are performed with approximately 80% women. Because low numbers of men are included, the statistical power to study sex differences in triptan response is limited in individual studies.

Differences between men and women in pharmacokinetics, drug safety and efficacy may be affected by biological components but also behavioral, social, environmental and cultural factors. Because most studies only use a dichotomous variable to distinguish men from women without further distinguishing gender role identity, we use "sex" to describe differences between men and women.

Researchers in other neurologic fields, for example, stroke, multiple sclerosis, and Alzheimer's disease, have also noticed that many clinical trials were not designed to detect sex differences.[4-7] Because sex differences in migraine prevalence are even more striking, there is a clinical need to explore effects of sex on response to antimigraine treatments, starting with the most widely used triptans.

With this systematic review and meta-analysis, we investigated whether sex and sex-related differences in pharmacokinetics are determinants in triptan response. It has been debated whether sex differences in triptan exposure are important for efficacy, although subcutaneous sumatriptan showed highest peak concentrations and bioavailability combined with the most effective response.[8] Taken together, clarity on potential important sex differences in triptan response and its possible association to sex-specific pharmacokinetics is needed.

Methods

Search strategy and selection criteria

Procedures used in this systematic review and meta-analysis were in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[9] A research protocol was written before the start of the study (ZonMw nr. 849100004).

We performed an electronic search for published studies with a last update on December 12, 2019 in PubMed, MEDLINE, EMBASE, Web of Science and the Cochrane Library on clinical trials distinguishing clinical response to triptans for sex or pharmacokinetic parameters of triptans for sex. The search was set up with the assistance of research librarians at the Leiden University Medical Center. The strategy for PubMed is available in figure e-1, doi:10.5061/dryad.6djh9w0zb. In addition, we performed a broad search on clinical trials with triptans in PubMed to demonstrate the attention that has been paid to triptans in general.

Study selection was independently performed by 2 investigators (D.S.v.C. and G.M.T.). Disagreement was resolved by dialogue. We included double-blind randomized controlled trials, randomized crossover trials, open-label trials, and prospective observational studies. Case reports, meeting abstracts, editorials, commentaries, articles with a pediatric population (age <18 years), and articles with incomplete information were not eligible. There were no language or date restrictions. Reference lists of included articles were examined to identify studies that might have been missed by the initial database search.

Data extraction and risk of bias assessment

Data were extracted from all eligible studies using a standardized form. Information was extracted on the following: (1) study design, (2) study population characteristics (sample size, sex, and migraine subtype), (3) type and dose of triptan(s), (4) reported estimates on clinical response outcomes of interest -- headache response after 2 hours, pain free response after 2 hours, headache recurrence within 24 or 48 hours, and adverse event frequency -- and (5) reported estimates on pharmacokinetic parameters of interest -- peak drug concentration (C_{max}), area under the curve from zero to infinite time ($AUC_{0-\infty}$), bioavailability (F), time to reach peak plasma concentration (T_{max}), plasma half-life time ($T_{½}$), and renal clearance (CL_r). The risk of bias of each included study was assessed using the critical appraisal tool -- Joanna Briggs Institute Meta-Analysis of Statistics Assessment and Review Instrument for (pseudo) randomized controlled trials. For all studies, each domain was assigned a score of high, low, or unclear risk of bias. The risk of publication bias was

assessed by visual inspection of funnel plots representing effect estimates on the *X*-axis and standard errors of the effect estimates on the *Y*-axis.

Data analysis

For each clinical response outcome male-to-female pooled risk ratios (RRs) with a 95% confidence interval (CI) were used as the main estimated effect measure. For quantitative syntheses, the Mantel-Haenszel method was applied. For the investigation of sex differences in pharmacokinetic outcomes pooled ratio of means (RoMs) were calculated. A formula described by Friedrich et al.[10] was used to calculate corresponding 95% CIs. For quantitative syntheses of pooled RoMs, the inverse variance method was used. We would have preferred to perform pooled analyses for the different outcome measures separately per triptan. However, because of a limited number of eligible studies per individual triptan, we chose to combine data on different triptans. Especially, sex differences on $T_{½}$ would preferably be calculated separately for different triptans to take relevant differences in drug metabolism into account. As only data of $T_{½}$ on frovatriptan and zolmitriptan were available separated by sex, which are both mainly metabolized by CYP1A2,[11,12] we also chose to perform pooled analyses for these 2 drugs. Furthermore, study arms closest to therapeutic doses were selected from cross-sectional studies to avoid pooling across the same participants. Random-effects models were used to anticipate on clinical between-study heterogeneity. Statistical heterogeneity of the effect between studies was assessed using the χ^2 test of Q. Analyses were conducted using Review Manager version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). A 2-sided *p*-value of ≤ 0.05 was considered statistically significant.

Data Availability Statement

Additional data (table e-1, table e-2, figure e-1, and figure e-2, doi:10.5061/dryad.6djh9w0zb) are available from Dryad**.** Data not published within the article will be shared by request from an investigator.

Results

A search for publications on clinical trials with triptans resulted in 1188 publications, of which 244 remained after adding sex- and gender-related search terms (see flowchart figure 1). Most of these studies were excluded because of the lack of distinguished results for men and women. Sex-specific results were presented in 19 publications, and these were

considered eligible for inclusion in the meta-analysis -- 10 publications with 2187 men and 13805 women concerning clinical response outcome measurements and 9 publications with 93 men and 94 women on pharmacokinetic outcomes.

Six of the included publications on clinical response outcome measurements presented data obtained from multiple trials. In 3 publications, the results on clinical response outcomes were pooled across treatments with different triptans (eletriptan 40/80 mg, sumatriptan 100 mg, rizatriptan 10 mg, zolmitriptan 2.5 mg, almotriptan 12.5 mg). Numbers of participants ranged from 280 to 3714 for women and from 33 to 591 for men, with an 80% female participation frequency. The age of included participants ranged from 18 to 78 years, with a mean age of approximately 40 years. Follow-up duration varied from a single attack treatment to a follow-up of 12 months. From one study, a subgroup was excluded to prevent heterogeneity because it investigated the effect of previous opioid use on response.[13] Sex division in the studies on pharmacokinetic parameters of triptans was nearly equal, with numbers ranging from 6 to 17 per group. The age of included participants in the pharmacokinetic studies also ranged from 18 to 78 years, with a mean age of approximately 35 years. In one study, hypertensive participants received antihypertensive treatment.[14] Table 1 shows characteristics of included studies (for full description see table e-1, doi:10.5061/dryad.6djh9w0zb). The risk of bias of individual publications on clinical response outcomes was mixed with an overall high risk of bias of open-label studies. Blinding of participants, allocators, and outcome assessors was considered to have less influence on the overall risk of bias of studies on pharmacokinetic outcomes (for overview of risk of bias assessments see figure e-2, doi:10.5061/dryad.6djh9w0zb).

Clinical response outcome measurements

The corresponding forest plots and references are shown in figure 2. Sex-specific information on headache response 2 hours after triptan intake (defined as reduction in headache intensity from moderate/severe before treatment to mild/no pain 2 hours after treatment) was reported in 6 studies. No sex differences were revealed for the 2-hour headache response (male-to-female RR 1.04, 95% CI: 0.98-1.11, $p = 0.19$, $Q = 12.16$). Four studies reported sex-specific information on pain-free response 2 hours after the intake of a triptan (defined as a headache reduction of any intensity before treatment to no pain 2 hours after treatment). Men and women had an equal pain-free 2-hour response (male-to-female RR 1.01, 95% CI: 0.96-1.07, $p = 0.68$, $Q = 0.95$). Men had a lower risk for headache recurrence (defined as the return or worsening of headache within 24-48 hours after an initial 2-hour headache response) (3 studies, male-to-female RR 0.64, 95% CI: 0.55-0.76, p

< 0.001, Q = 0.81). No sex-specific results were available on sustained pain-free response (defined as freedom from pain with no recurrence or use of rescue medication 2-24 hours post dose). Four studies presented distinguished data on the frequency of adverse events for men and women. Men had a lower adverse event frequency after the intake of triptans compared with women (male-to-female RR 0.82, 95% CI: 0.72-0.93, p = 0.002, Q = 4.93). Most frequently reported adverse events were asthenia, nausea, somnolence, dizziness, paraesthesia, dry mouth, and warm sensations. A χ^2 test of Q for statistical heterogeneity of the effect between studies was only statistically significant for the 2-hour headache response (p = 0.03) (figure 2). Except for the 2-hour headache response, corresponding funnel plots showed an equal distribution of number of studies on both sides of the pooled RR.

Figure 1. Flowchart of the publication selection process.

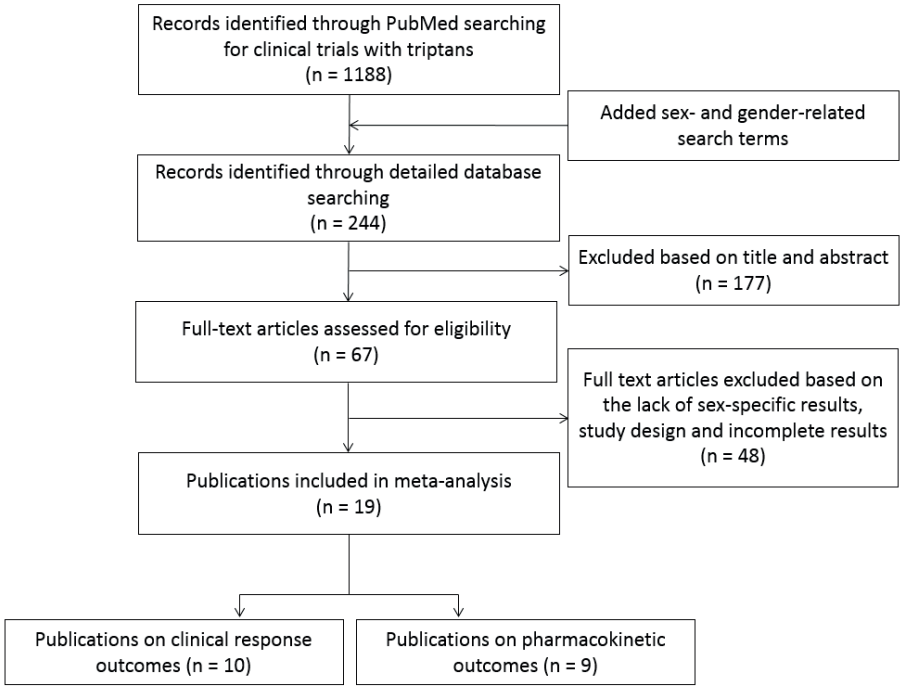


Table 1. Summary characteristics of included studies.

Studies on clinical response outcomes	Publications (n = 10)	Studies on pharmacokinetic outcomes	Publications (n = 9)
Publication year		Publication year	
≤ 2000	5 (50%)	≤ 2000	6 (67%)
2001 – 2010	4 (40%)	2001 – 2010	3 (33%)
2011 – 2018	1 (10%)	2011 – 2018	0 (0%)
Study design		Study design	
Randomized double-blind placebo-controlled study	5 (50%)	Randomized double-blind placebo-controlled study	2 (22%)
Randomized double-blind controlled crossover study	1 (10%)	Randomized double-blind placebo-controlled crossover study	2 (22%)
Non-randomized open-label crossover study	1 (10%)	Randomized open-label crossover study	4 (44%)
Uncontrolled open-label study	2 (20%)	Uncontrolled open-label study	1 (11%)
Prospective observational study	1 (10%)		
Participants		Participants	
Percentage women included > 80%	10 (100%)	Percentage women included 50%	8 (89%)
Migraine without aura + migraine with aura	10 (100%)	Percentage women included 50-55% Healthy volunteers	1 (11%) 9 (100%)
Intervention		Intervention	
Almotriptan (12.5 mg)	1 (10%)	Frovatriptan (2.5 and 40 mg)	1 (11%)
Rizatriptan (10 mg)	1 (10%)	Rizatriptan (2.5, 5, 10, and 15 mg)	3 (33%)
Sumatriptan nasal spray (10 and 20 mg) Zolmitriptan (2.5 and 5 mg)	1 (10%) 4 (40%)	Zolmitriptan (2.5, 5, 10, 15, and 20 mg)	5 (56%)
Combination of triptans	3 (30%)		

Pharmacokinetic outcomes

The corresponding forest plots and references are shown in figure 3. Men had a lower C_{max} (8 studies, RoM 0.72, 95% CI: 0.64-0.82, $p < 0.001$, $Q = 8.24$) and $AUC_{0-\infty}$ (9 studies, RoM 0.69, 95% CI: 0.60-0.81, $p < 0.001$, $Q = 18.06$) than women for frovatriptan, zolmitriptan, and rizatriptan. A pooled analysis on $T_{½}$ for frovatriptan and zolmitriptan showed no sex difference (5 studies, RoM 0.93, 95% CI: 0.80-1.08, $p = 0.34$, $Q = 5.59$). A χ^2 test of Q was only statistically significant for $AUC_{0-\infty}$ ($p = 0.02$) (figure 3). All corresponding funnel plots showed an equal distribution of number of studies on both sides of the pooled RoMs.

Discussion

This systematic review and meta-analysis show that remarkably few publications about sex differences in triptan response are available. Based on the available data, sex differences in adverse event frequency were shown, with men less prone for adverse events, which may be partly because of drug exposure differences. This higher drug exposure in women is not reflected in differences in response rates. Despite higher triptan exposure, women have higher headache recurrence rates possibly because of a longer attack duration related to sex hormonal changes.

In contrast to clinical trials that investigate the effectiveness of triptans, where most women are included, sexes were equally distributed in trials regarding pharmacokinetics of triptans. We observed no sex differences in headache and pain-free response after 2 hours for triptans, which is in line with a prospective open-label study in which no difference in the time to reach pain freedom were found between men and women for acute medication in general.[15]

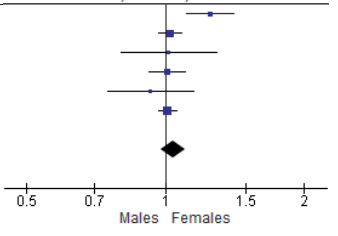
By contrast, women had a higher adverse event frequency compared with men. Using the GRADE criteria (table e-2, doi:10.5061/dryad.6djh9w0zb), we assessed the certainty of this evidence to be moderate. Women generally tend to report adverse drug reactions more frequently than men, which may be related to both biological and social/cultural differences.[16,17] In our study, the sex difference in adverse event frequency may be partly explained by a higher exposure to the drug in women, which seemed from higher C_{max} and $AUC_{0-\infty}$ values for frovatriptan, zolmitriptan, and rizatriptan. The higher drug exposure seems to exist independent of sex differences in body weight because C_{max} and $AUC_{0-\infty}$ for frovatriptan 2.5 mg are shown to be higher in women when assessing results normalized to body weight.[12] This also applies to various other drugs, such as levodopa and sertraline, of which a higher drug exposure in women may only be partially explained by their lower body weight.[18,19] Therefore, researchers and clinicians should be aware of additional factors leading to a higher drug exposure, and potentially more adverse events, in women. The higher triptan exposure in women might probably be explained by a higher bioavailability because of lower first-pass metabolism or because of alterations in receptor number or receptor binding.[12,20-22] In addition, renal clearance of rizatriptan and zolmitriptan seems to be higher in men than in women.[23-25]

Figure 2. Forest plots of the clinical response outcomes.

A. Headache response after 2 hours

		Males		Females				
	Triptan, dosage	Events	Total	Events	Total	Weight	Risk Ratio, 95% CI	Risk Ratio M-H, Random, 95% CI
Ashford et al. 1998[45]	Sumatriptan nasal spray 20 mg	98	136	486	844	14.6%	1.25 [1.11, 1.41]	
Cady et al. 1998[40]	Zolmitriptan 5 mg	239	288	1433	1769	26.2%	1.02 [0.97, 1.08]	
Franconi et al. 2014[47]	Frovatriptan 2.5 mg	37	66	154	280	5.4%	1.02 [0.80, 1.29]	
Pascual et al. 2001[44]	Almotriptan 12.5 mg	79	93	563	669	19.1%	1.01 [0.92, 1.11]	
Schoenen et al. 1997[43]	Zolmitriptan 2.5 mg	38	64	272	425	6.4%	0.93 [0.75, 1.15]	
Tuchman et al. 1999[41]	Zolmitriptan 2.5 mg	298	347	1829	2152	28.4%	1.01 [0.96, 1.06]	
Total (95% CI)			994		6139	100%	1.04 [0.98, 1.11]	
Total events		789		4737				

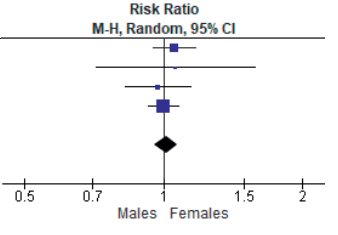
Heterogeneity: Tau² = 0.00; Chi² = 12.16, df = 5 (P = 0.03); I² = 59%
Test for overall effect: Z = 1.30 (P = 0.19)



B. Pain free response after 2 hours

		Males		Females				
	Triptan, dosage	Events	Total	Events	Total	Weight	Risk Ratio, 95% CI	Risk Ratio M-H, Random, 95% CI
Cady et al. 1998[40]	Zolmitriptan 5 mg	167	288	973	1769	28.8%	1.05 [0.95, 1.17]	
Franconi et al. 2014[47]	Frovatriptan 2.5 mg	21	66	84	280	2.1%	1.06 [0.71, 1.58]	
Ho et al. 2009[13]	Rizatriptan 10 mg	97	237	646	1538	12.3%	0.97 [0.83, 1.15]	
Tuchman et al. 1999[41]	Zolmitriptan 2.5 mg	239	347	1485	2152	56.8%	1.00 [0.92, 1.08]	
Total (95% CI)			938		5739	100.0%	1.01 [0.96, 1.07]	
Total events		524		3188				

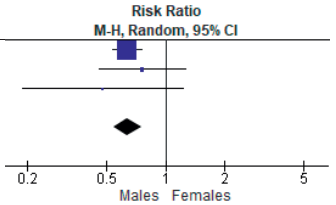
Heterogeneity: Tau² = 0.00; Chi² = 0.95, df = 3 (P = 0.81); I² = 0%
Test for overall effect: Z = 0.42 (P = 0.68)



C. Headache recurrence rate after 24 hours or 48 hours

		Males		Females			Risk Ratio,
	Triptan, dosage	Events	Total	Events	Total	Weight	95% CI
Dodick et al. 2008[46]	Eletriptan, sumatriptan, placebo	113	591	1114	3714	86.7%	0.64 [0.54, 0.76]
Franconi et al. 2014[47]	Frovatriptan 2.5 mg	14	66	78	280	10.3%	0.76 [0.46, 1.26]
Sheftell et al. 2010[48]	Triptans in general	4	33	82	326	3.0%	0.48 [0.19, 1.23]
Total (95% CI)			690		4320	100%	0.64 [0.55, 0.76]
Total events		131		1274			

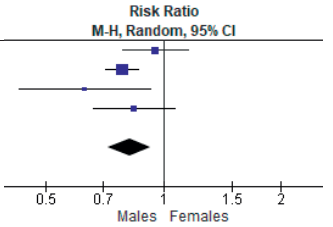
Heterogeneity: Tau² = 0.00; Chi² = 0.81, df = 2 (P = 0.67); I² = 0%
Test for overall effect: Z = 5.36 (P < 0.00001)



D. At least one adverse event

		Males		Females			Risk Ratio,
	Triptan, dosage	Events	Total	Events	Total	Weight	95% CI
Ashford et al. 1998[45]	Sumatriptan nasal spray 20 mg	64	140	418	871	25.3%	0.95 [0.79, 1.16]
Cady et al. 1998[40]	Zolmitriptan 5 mg	176	288	1380	1769	46.6%	0.78 [0.71, 0.86]
Edmeads et al. 1997[42]	Zolmitriptan 2.5 mg	19	63	239	498	9.0%	0.63 [0.43, 0.93]
Pascual et al. 2001[44]	Almotriptan 12.5 mg	41	93	350	669	19.1%	0.84 [0.66, 1.07]
Total (95% CI)			584		3807	100.0%	0.82 [0.72, 0.93]
Total events		300		2387			

Heterogeneity: Tau² = 0.01; Chi² = 4.93, df = 3 (P = 0.18); I² = 39%
Test for overall effect: Z = 3.14 (P = 0.002)

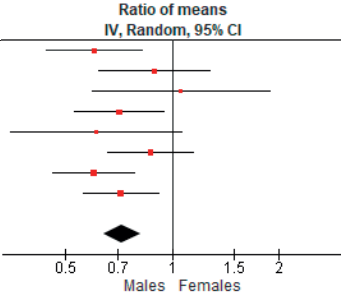


Headache response after 2 hours (A), pain-free response after 2 hours (B), headache recurrence rate after 24 hours or 48 hours (C), and the incidence of at least one adverse event after the intake of a triptan in male and female migraine patients (D). M-H = Mantel-Haenszel method; random = random effects model. The squares represent effect sizes of the individual studies (size reflects the weight of the study) and the horizontal lines indicate the 95% confidence intervals (CI). The filled diamonds represent the overall effect size (horizontal width indicates the 95% CI).

Figure 3. Forest plots of pharmacokinetic outcomes.

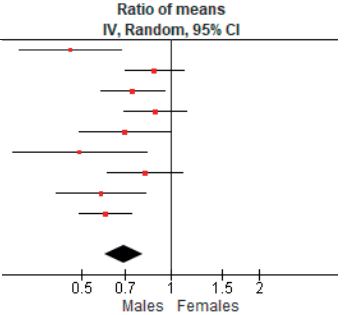
A. C_{max}, ng/ml	Triptan, dosage	Ln[Ratio of means]	Total	Total	Weight	Ratio of means, 95% CI
Buchan et al. 2002[12]	Frovatriptan 2.5 mg	-0.5037	6	6	13.2%	0.60 [0.44, 0.83]
Lee et al. 1999[23]	Rizatriptan 10 mg	-0.1154	12	12	10.4%	0.89 [0.62, 1.28]
Musson et al. 2001[24]	Rizatriptan 10 mg	0.0562	8	8	4.3%	1.06 [0.59, 1.88]
Peck et al. 1998[25]	Zolmitriptan 5 mg	-0.3425	12	12	14.7%	0.71 [0.53, 0.95]
Seaber et al. 1997[21]	Zolmitriptan 10 mg	-0.4943	6	6	4.7%	0.61 [0.35, 1.06]
Seaber et al. 1998[22]	Zolmitriptan 2.5 mg	-0.1393	10	10	16.1%	0.87 [0.66, 1.15]
Smith et al. 1998[14]	Zolmitriptan 5 mg	-0.5108	16	17	17.1%	0.60 [0.46, 0.78]
Yates et al. 2002[11]	Zolmitriptan 2.5 mg	-0.3352	15	15	19.5%	0.72 [0.56, 0.91]
Total (95% CI)			85	86	100.0%	0.72 [0.64, 0.82]

Heterogeneity: Tau² = 0.00; Chi² = 8.24, df = 7 (P = 0.31); I² = 15%
Test for overall effect: Z = 5.15 (P < 0.00001)



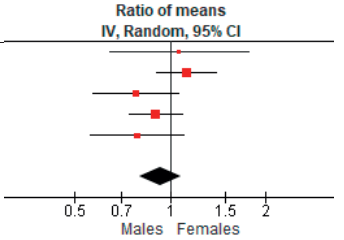
B. $AUC_{0-\infty}$, ng/h/ml	Triptan, dosage	Ln[Ratio of means]	Males Total	Females Total	Weight	Ratio of means, 95% CI
Buchan et al. 2002[12]	Frovatriptan 2.5 mg	-0.7844	6	6	8.4%	0.46 [0.31, 0.68]
Goldberg et al. 2000[49]	Rizatriptan 10 mg	-0.125	8	8	13.8%	0.88 [0.70, 1.12]
Lee et al. 1999[23]	Rizatriptan 10 mg	-0.298	12	12	13.1%	0.74 [0.58, 0.95]
Musson et al. 2001[24]	Rizatriptan 10 mg	-0.1157	8	8	13.3%	0.89 [0.70, 1.14]
Peck et al. 1998[25]	Zolmitriptan 10 mg	-0.3567	12	12	9.5%	0.70 [0.49, 1.00]
Seaber et al. 1997[21]	Zolmitriptan 10 mg	-0.7133	6	6	5.8%	0.49 [0.29, 0.83]
Seaber et al. 1998[22]	Zolmitriptan 2.5 mg	-0.1984	10	10	11.4%	0.82 [0.61, 1.10]
Smith et al. 1998[14]	Zolmitriptan 5 mg	-0.5447	16	17	9.8%	0.58 [0.41, 0.82]
Yates et al. 2002[11]	Zolmitriptan 2.5 mg	-0.5067	15	15	14.9%	0.60 [0.49, 0.74]
Total (95% CI)			93	94	100.0%	0.69 [0.60, 0.81]

Heterogeneity: Tau² = 0.03; Chi² = 18.06, df = 8 (P = 0.02); I² = 56%
Test for overall effect: Z = 4.82 (P < 0.00001)



C. $T_{1/2}$, h	Triptan, dosage	Ln[Ratio of means]	Males Total	Females Total	Weight	Ratio of means, 95% CI
Buchan et al. 2002[12]	Frovatriptan 2.5 mg	0.0641	6	6	7.8%	1.07 [0.64, 1.76]
Peck et al. 1998[25]	Zolmitriptan 10 mg	0.1222	12	12	28.3%	1.13 [0.91, 1.40]
Seaber et al. 1997[21]	Zolmitriptan 10 mg	-0.2485	6	6	17.1%	0.78 [0.57, 1.07]
Seaber et al. 1998[22]	Zolmitriptan 2.5 mg	-0.1054	10	10	31.8%	0.90 [0.74, 1.09]
Smith et al. 1998[14]	Zolmitriptan 10 mg	-0.2384	16	17	15.0%	0.79 [0.56, 1.11]
Total (95% CI)			50	51	100.0%	0.93 [0.80, 1.08]

Heterogeneity: Tau² = 0.01; Chi² = 5.59, df = 4 (P = 0.23); I² = 28%
Test for overall effect: Z = 0.95 (P = 0.34)



Peak drug concentration (Cmax, ng/ml) (A), area under the curve from time zero to infinite time (AUC0-∞, ng/h/ml) (B) and plasma half-life times (T1/2) (C). IV = inverse variance method; random = random effects model. The squares represent effect sizes of the individual studies (size reflects the weight of the study) and the horizontal lines indicate the 95% confidence intervals (CI). The filled diamonds represent the overall effect size (horizontal width indicates the 95% CI). There are a few minor discrepancies with the original studies, at the most two hundredths of decimals, in the calculation of the ratio of means and upper/lower limit of the 95% CIs because of differences in the rounding of decimals.

We expected $T_{½}$ for frovatriptan and zolmitriptan to be higher in women because both triptans are mainly metabolized by CYP1A2, which has a higher activity in men.[11,12,26] Surprisingly, no sex differences were revealed on $T_{½}$ for frovatriptan and zolmitriptan. In addition, 2 independent studies did not find sex differences for $T_{½}$ for N-desmethylzolmitriptan, the most active metabolite of zolmitriptan.[14,22] A possible explanation for this finding is the fact that a substantial proportion of female participants in the studies used an oral contraceptive pill. As ethinyl steroid-containing oral contraceptive pills are inhibitors of CYP1A2,[27] this usage might have decreased the clearance of frovatriptan and zolmitriptan in these female participants.

Contrary to what was to be expected based on the higher drug exposure, women did not have higher response rates to triptans and experienced even higher headache recurrence rates compared with men (evidence estimated as moderate based on GRADE, see table e-2, doi:10.5061/ dryad.6djh9w0zb). In the included studies, headache recurrence is consistently defined based on a previous definition as the return or worsening of headache within 24 or 48 hours after an initial response (instead of an initial pain-free response). In general, headache recurrence occurs several hours after the half-life time point of triptans. Although frovatriptan has demonstrated lower headache recurrence rates compared with most other triptans, probably because of its long half-life time of 26 hours, recurrence rates are not negligible ranging from 11 to 15% at 24-48 hours.[28] Hence, we conclude that headache recurrence is not directly related to triptan plasma levels because we even showed that women have higher total drug exposure than men and both sexes have similar plasma half-life times. The higher headache recurrence in women despite their higher drug exposure may be explained by the longer attack duration related to sex hormonal changes, such as menstrually related migraine attacks or perimenopausal attacks. Previous studies showed that menstrually related migraine attacks have a longer duration, are less responsive to acute therapy, and are more prone to headache recurrence after treatment with triptans compared with migraine attacks occurring outside the menstrual period.[29-31] In addition, major fluctuations in estrogen levels during perimenopausal transition are associated with an increased prevalence of migraine and an increased risk of high frequency headache.[32-34] Although data regarding attack duration and the risk of headache recurrence specifically in perimenopausal women are lacking, we hypothesize that sex hormonal changes during perimenopause may be of influence on these outcomes.

Our study also has some limitations. Important methodological differences were found across clinical trials, including the approach of blinding, type and dose of treatment, follow-

up duration, and the use of headache recurrence after 24 and/or 48 hours as outcome parameter. Based on the χ^2 test of Q, statistical heterogeneity of the effect between studies was observed for headache response after 2 hours and $AUC_{0-\infty}$, so results of these analyses should be interpreted with caution. Although no significant statistical heterogeneity arose from methodological diversity between studies in the other outcome measures, this limitation of our study should be kept in mind when interpreting the results. We chose to pool all triptans because separated meta-analyses per triptan could not be performed. Although triptans roughly have the same mechanism of action, it must be stressed that there are pharmacodynamic and pharmacokinetic differences between triptans. Pharmacodynamic differences between triptans may include variation in lipophilicity, the ability to cross the blood-brain barrier, and differences in 5-$HT_{1B,}$ 5-$HT_{1D,}$ and 5-HT_{1F} receptor affinities.[35] Pharmacokinetic differences between oral triptans are $T_{½}$ differences ranging from 2 to 26 hours (exceptionally long for frovatriptan with 26 hours) and T_{max} ranging from 1 to 4 hours, main excretion route through hepatic drug metabolism (by cytochrome P450 and monoamine oxidase enzymes) except for naratriptan, which is partly metabolized by renal excretion.[12,36-38] We have tried to take these limitations into account by using random-effects models for our analyses. Furthermore, in modern meta-analytical approaches, it is unusual to conduct pooled analyses across few studies. Nevertheless, in some analyses, we chose to pool across only a few studies because limited data were available, and one of our aims was to address that results are currently rarely presented separately for men and women. Although we have performed random-effects meta-analyses, which weight the studies relatively more equally than fixed-effect analyses, most weight was given to one study in pooled analyses on adverse event rates and headache recurrence rates. However, it is reassuring that also smaller, medium-sized clinical trials presenting results on these outcomes point in the same direction as the larger studies. The included studies on sex differences in pharmacokinetic outcomes of triptans are performed in healthy volunteers. However, migraine attacks may be of influence on drug absorption because of delayed gastric emptying and thereby may cause additional variability in pharmacokinetic parameters.[39] Gender differences could not be specifically addressed because corresponding information was not presented in the included studies. Finally, publication bias might be an issue in the reporting of clinical trials because negative findings are less likely to get published. However, it concerned mainly large clinical trials investigating the efficacy and tolerability of triptans, which are less likely to be unpublished. Indeed, visual inspection of funnel plots was unsuspected for publication bias; however, it cannot be excluded. Tests for funnel plot asymmetry were not used because test power is usually too low to distinguish chance from real asymmetry when less than 10 studies are included in the meta-analysis.

We encourage physicians treating patients with migraine to be aware that their female migraine patients will likely report more adverse events after the intake of triptans and more headache recurrences compared with male migraine patients. Physicians should be aware that dose reduction to reduce adverse events seems undesirable because this might further increase the risk for headache recurrence in women and might also affect initial efficacy. Instead, menstrually related attacks and nonmenstrually related attacks should be assessed separately. We also want to underline the importance of prescribing preventive treatments in migraine patients to diminish frequency, duration, and severity of attacks. As we hypothesize that the longer attack duration in women relates to sex hormonal changes, there is an urgent need for clear evidence whether preventive hormonal treatments are effective (ClinicalTrials.gov NCT04007874). In addition, dedicated studies on gender-related differences in migraine are needed. Finally, we would like to call on headache researchers to present data by sex and, if information is collected, also by gender when performing clinical trials on the efficacy and tolerability of acute and preventive migraine treatments. So far, this has only occasionally been performed for today's important clinical trials on migraine prevention with monoclonal antibodies acting on calcitonin gene-related peptide or on its receptor.

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Table e-1. Description of individual characteristics of included studies.

	Name	Year	Study design	Intervention with separate results	Sample size (males/females)	Population	Follow-up duration
Studies on clinical response outcomes	Cady et al.[40]	1998	Uncontrolled open-label study	Zolmitriptan 5 mg	n=288 / n=1769	Migraine without aura + with aura	One attack - >12 months
	Tuchman et al.[41]	1999	Non-randomized open-label cross-over study	Zolmitriptan 2.5 mg and zolmitriptan 5 mg	n=347 / n=2152 n=347 / n=2152	Migraine without aura + with aura	6 months
	Edmeads et al.[42]	1997	Randomized double-blind placebo-controlled studies and uncontrolled open-label studies	Zolmitriptan 2.5 mg Zolmitriptan 5 mg Placebo	n=63 / n=498 n=158 / n=854 n=62 / n=339	Migraine without aura + with aura	Single attack or multiple attacks
	Schoenen et al.[43]	1997	Randomized double-blind placebo-controlled studies	Zolmitriptan 2.5 mg	n= 64 / n=425	Migraine without aura + with aura	Single attack
	Pascual et al.[44]	2001	Uncontrolled open-label study	Almotriptan 12.5 mg	n=93 / n=669	Migraine without aura + with aura	One attack - >12 months
	Ho et al.[13]	2009	Randomized double-blind placebo-controlled studies	Rizatriptan 10 mg Placebo	n=237 / n=1538 n=154 / n=939	Migraine without aura + with aura	Treatment of single attack
	Ashford et al.[45]	1998	Randomized double-blind placebo-controlled studies	Sumatriptan nasal spray 10 mg Sumatriptan nasal spray 20 mg Placebo	n=107 / n=709* n=140 / n=871* n=82 / n=486*	Migraine without aura + with aura	Single attack or three attacks
	Dodick et al.[46]	2008	Randomized double-blind placebo-controlled studies	Eletriptan 40 mg, eletriptan 80 mg, sumatriptan 100 mg and placebo	n=591 / n=3714	Migraine without aura + with aura	Single attack
	Franconi et al.[47]	2014	Randomized double-blind controlled cross-over studies	Frovatriptan 2.5 mg Comparator: rizatriptan 10 mg, zolmitriptan 2.5 mg and almotriptan 12.5 mg	n=66 / n=280 n=66 / n=280	Migraine without aura + with aura	6 months
	Sheftell et al.[48]	2010	Prospective observational study	Triptans in general	n=33 / n=326	Migraine without aura + with aura	6 months

*Represents sample sizes for the evaluation of frequency of adverse events as outcome measurement. The headache response 2 hours after treatment was calculated based on smaller sample sizes.

	Name	Year	Study design	Intervention with separate results	Sample size (males/females)	Population	Follow-up duration
Studies on pharmacokinetic outcomes	Peck et al.[25]	1998	Randomized double-blind placebo-controlled cross-over study	Zolmitriptan 5 mg Zolmitriptan 10 mg Zolmitriptan 15 mg	n=12 / n=12 n=12 / n=12 n=12 / n=12	Healthy adult + elderly volunteers	-
	Smith et al.[14]	1998	Randomized double-blind placebo-controlled cross-over study	Zolmitriptan 5 mg Zolmitriptan 10 mg Zolmitriptan 20 mg	n=16 / n=17 n=16 / n=17 n=16 / n=17	Healthy adult volunteers	-
	Seaber et al.[21]	1997	Randomized open-label cross-over study	Zolmitriptan 10 mg	n=6 / n=6	Healthy adult volunteers	-
	Seaber et al.[22]	1998	Randomized open-label cross-over study	Zolmitriptan 2.5 mg Zolmitriptan 5 mg	n=10 / n=10 n=10 / n=10	Healthy adult volunteers	-
	Yates et al.[11]	2002	Uncontrolled open-label study	Zolmitriptan 2.5 mg	n=15 / n=15	Healthy adult Japanese volunteers	-
	Musson et al.[24]	2001	Randomized double-blind placebo-controlled study	Rizatriptan 10 mg	n=8 / n=8	Healthy elderly volunteers	-
	Lee et al.[23]	1999	Randomized open-label cross-over study	Rizatriptan 2.5 mg Rizatriptan 5 mg Rizatriptan 10 mg Rizatriptan 15 mg	n=12 / n=12 n=12 / n=12 n=12 / n=12 n=12 / n=12	Healthy adult volunteers	-
	Goldberg et al.[49]	2000	Randomized double-blind placebo-controlled study	Rizatriptan 10 mg	n=8 / n=8	Healthy adult volunteers	-
	Buchan et al.[12]	2002	Review including results of a randomized open-label cross-over study	Frovatriptan 2.5 mg Frovatriptan 40 mg	n=6 / n=6 n=6 / n=6	Healthy adult volunteers	-

*Represents sample sizes for the evaluation of frequency of adverse events as outcome measurement. The headache response 2 hours after treatment was calculated based on smaller sample sizes.

Table e-2. GRADE assessments for two outcomes: adverse event frequency after the intake of triptans (A) and risk for headache recurrence (B).

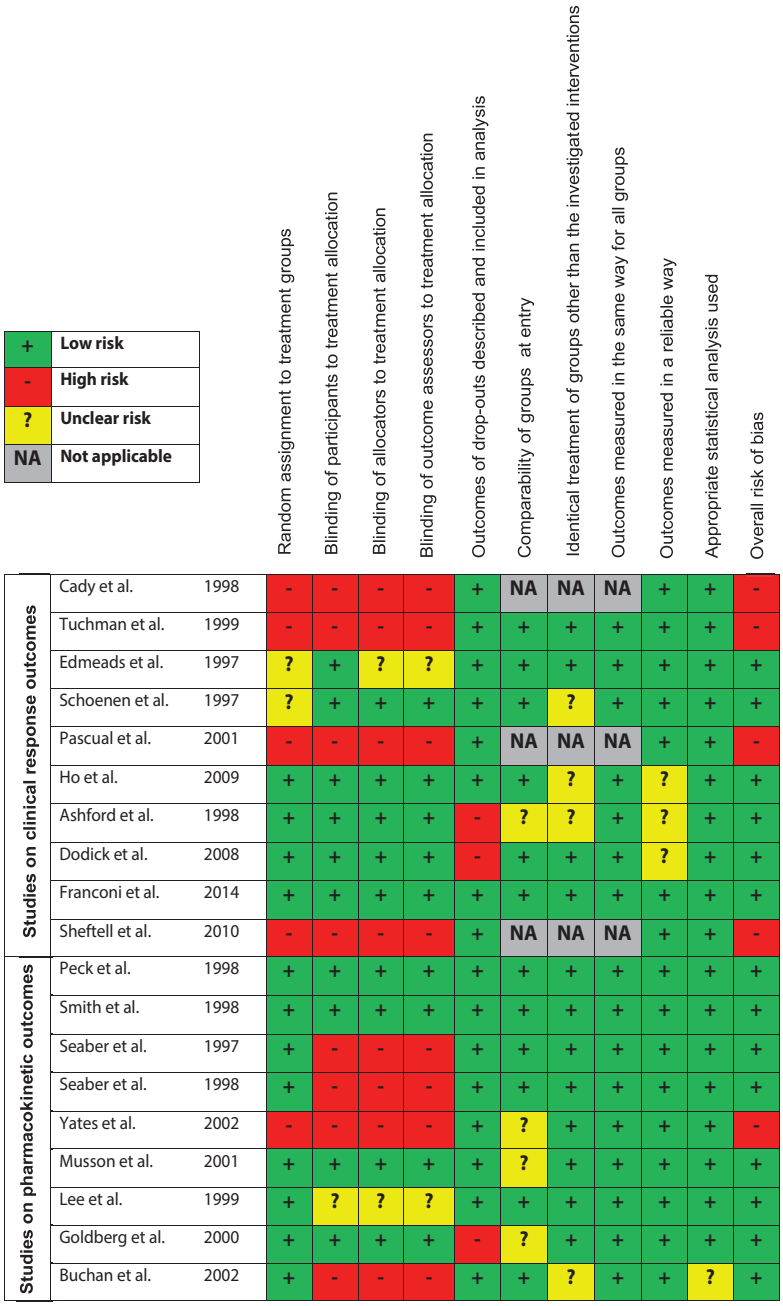
A. GRADE criteria	Rating	Quality of evidence (high, moderate, low or very low)
Outcome: Adverse event frequency after the intake of triptans		
Study design	RCTs and non-RCTs – high score	
Risk of Bias	Serious (-1)	
Inconsistency	No	Moderate
Indirectness	No	
Imprecision	No	
Publication Bias	Undetected	

B. GRADE criteria	Rating	Quality of evidence (high, moderate, low or very low)
Outcome: Risk of headache recurrence		
Study design	RCTs and non-RCTs – high score	
Risk of Bias	No	
Inconsistency	No	Moderate
Indirectness	No	
Imprecision	Serious (-1)	
Publication Bias	Undetected	

Figure e-1. Search strategy for PubMed.

(("rizatriptan"[Supplementary Concept] OR "rizatriptan"[tw] OR rizatriptan*[tw] OR "MK 0462"[tw] OR "MK-0462"[tw] OR "MK-462"[tw] OR "MK 462"[tw] OR "maxalt"[tw] OR "almotriptan"[Supplementary Concept] OR "almotriptan"[tw] OR almotriptan*[tw] OR "Almogran"[tw] OR "eletriptan"[Supplementary Concept] OR "eletriptan"[tw] OR eletriptan*[tw] OR "UK 166,044"[tw] OR "UK-166044"[tw] OR "UK 166044"[tw] OR "UK-166,044"[tw] OR "Relpax"[tw] OR "UK-116044-04"[tw] OR "UK-116,044-04"[tw] OR "Sumatriptan"[Mesh] OR "sumatriptan"[tw] OR sumatriptan*[tw] OR "GR-43175"[tw] OR "GR 43175"[tw] OR "GR43175"[tw] OR "Imigran"[tw] OR "sumatriptan-naproxen"[Supplementary Concept] OR "zolmitriptan"[Supplementary Concept] OR "zolmitriptan"[tw] OR zolmitriptan*[tw] OR "Zomig"[tw] OR "311C90"[tw] OR "frovatriptan"[Supplementary Concept] OR "frovatriptan"[tw] OR frovatriptan*[tw] OR "VML-251"[tw] OR "VML251"[tw] OR "SB 209509"[tw] OR "fromirex"[tw] OR "naratriptan"[Supplementary Concept] OR "naratriptan"[tw] OR naratriptan*[tw] OR "GR 85548A"[tw] OR "Naramig"[tw] OR "triptans"[tw] OR "triptan"[tw] OR triptan*[tw] OR "Tryptamines"[Mesh:NoExp]) AND (("female"[tiab] OR "females"[tiab] OR "woman"[tiab] OR "women"[tiab]) AND ("male"[tiab] OR "males"[tiab] OR "man"[tiab] OR "men"[tiab])) OR "Sex Characteristics"[mesh] OR "Sex"[mesh] OR "Sex Factors"[mesh] OR "Sex Ratio"[mesh] OR gender*[tw] OR sex differenc*[tw] OR "sex"[ti] OR ("Female"[mesh] AND "Male"[mesh] AND ("sex"[tw] OR gender*[tw]))) AND ("Clinical Trial"[Publication Type] OR "Randomized Controlled Trial"[Publication Type] OR random*[tiab] OR double blind*[tiab] OR "RCT"[tiab] OR "trial"[tiab] OR "systematic"[sb] OR "Meta-Analysis"[Publication Type] OR "Meta-Analysis"[ti] OR "Metaanalysis"[ti] OR Meta-Analy*[ti] OR Metaanaly*[ti] OR placebo*[ti]) AND ("Migraine Disorders"[mesh] OR "migraine"[tw] OR migrain*[tw] OR anti-migrain*[tw] OR antimigrain*[tw]))

Figure e-2. Risk of bias assessments based on JBI Critical Appraisal Checklist for Randomized Controlled/ Pseudo-randomized Trials.



CHAPTER 3

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

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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 ± SD: 4.6 ± 2.3 and 4.3 ± 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.

Key words: menstruation, stress, light, sleep, primary headache

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 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) 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 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 ± SD: 41.9 ± 12.1 vs. 45.7 ± 13.1, p < 0.001), with a lower body mass index (BMI) (24.5 ± 6.4 vs 25.8 ± 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.

Table 1. Baseline characteristics of the study population.

	Female (n = 5725)	Male (n = 1061)
Age in years, mean ± SD	41.9 ± 12.1	45.7 ± 13.1
Age range in years	18.0 : 82.7	18.0 : 83.6
BMI, mean ± SD	24.5 ± 6.4	25.8 ± 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 ± SD	7.6 ± 8.8	7.6 ± 9.6
Other headache days per month, mean ± SD	7.3 ± 12.2	7.0 ± 12.3

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).

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

	Percentage(%)			
	Female (n = 5725)	Male (n = 1061)	Odds ratio 95% CI	Adjusted p-value
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.

Additional analyses

Women reported a larger total number of migraine trigger factors than men (mean ± SD: 4.6 ± 2.3 and 4.3 ± 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 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 (β = 0.32, p < 0.001). The number of triggers was positively associated with migraine attack frequency (β = 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 (β = 0.04, p = 0.508) (Table 3).

Most postmenopausal women reported four or five trigger factors (13.7% and 13.9% respectively, mean ± SD: 4.4 ± 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).

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

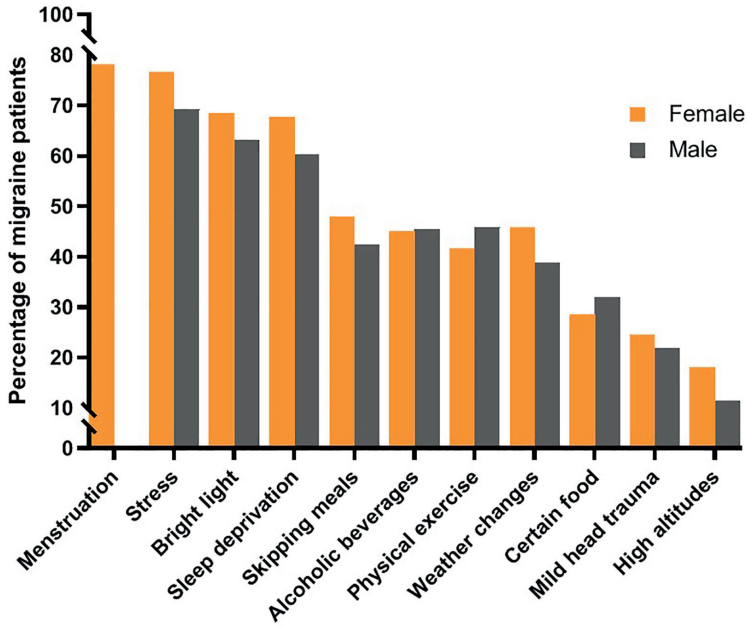

Table 3. Linear model of predictors of the number of reported trigger factors.

	Estimate (β)	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

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.

Supplementary data availability: Data not published within the article will be shared by request from any qualified investigator.

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Online supplementary information

LUMINA Background information

Dutch migraine patients aged 18-80 years were recruited via nationwide public announcement, advertising in lay press and our research website (www.lumc.nl/hoofdpijn). They were considered eligible after a two-step inclusion process using validated questionnaires via the dedicated Leiden University MIgraine Neuro-Analysis (LUMINA) website. Additionally, patients attending our outpatient headache clinic were invited to participate by a letter. Patients were first asked to fill out a validated web-based screening questionnaire with a sensitivity of 0.93 and specificity of 0.36.[1] Patients who fulfilled the screening criteria, were sent a validated web-based extended migraine questionnaire[2], based on the International Classification of Headache Disorders criteria (previously ICHD-2, now ICHD-3 version) criteria.[3] The specificity of the second questionnaire was 0.95 and sensitivity was 0.45.[2] This questionnaire is accessible for patients via our research website and is described in English in detail by van Oosterhout et al. 2011.[2] We consider the cohort a well-defined web-based cohort. Four percent of subjects were included from our headache outpatient clinic and 87% of the participants were previously diagnosed with migraine by a physician. In addition to questions that were necessary to diagnose migraine accurately, the extended questionnaire also included items on demographic factors, aura and headache characteristics, acute and prophylactic headache medication use, and allodynia. Participants unable to use the web-based questionnaires due to lack of the needed internet skills were allowed to fill out the questionnaires on paper.

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PART II

Clinical female-specific characteristics of migraine

CHAPTER 4

E-diary use in clinical headache practice: A prospective observational study

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Abstract

Aim We determined whether our E-diary can be used to diagnose migraine and provide more reliable migraine-related frequency numbers compared to patients' self-reported estimates.

Methods We introduced a self-developed E-diary including automated algorithms differentiating headache and migraine days, indicating whether a patient has migraine. Reliability of the E-diary diagnosis in combination with two previously validated E-questionnaires was compared to a physician's diagnosis as gold standard in headache patients (n = 596). In a subset of migraine patients (n = 484), self-estimated migraine-related frequencies were compared to diary-based results.

Results The first migraine screening approach including an E-headache-questionnaire and the E-diary revealed a sensitivity of 98% and specificity of 17%. In the second approach, an E-migraine-questionnaire was added, resulting in a sensitivity of 79% and specificity of 69%. Mean self-estimated monthly migraine days, non-migrainous headache days and days with acute medication use were different from E-diary-based results (absolute mean difference ± SD respectively 4.7 ± 5.0, 6.2 ± 6.6 and 4.3 ± 4.8).

Conclusion The E-diary including algorithms differentiating headache and migraine days showed usefulness in diagnosing migraine. The use emphasized the need for E-diaries to obtain reliable information as patients do not reliably recall numbers of migraine days and acute medication intake. Adding E-diaries will be helpful in future headache telemedicine.

Key words: telemedicine, electronic diary, data reliability, migraine

Introduction

The gold standard for diagnosing migraine is based on information obtained from a clinical interview and physical and neurological examination. Due to the episodic nature of the disease, most patients experience difficulties in recalling details on frequency and specific characteristics of each individual attack. Daily prospective electronic diaries (E-diaries) may reduce recall bias and increase the reliability of patients´ descriptions of migraine attack characteristics.[1] Therefore, E-diaries may have an added value both in clinical practice and for research purposes. In addition, the need for telemedicine was recently emphasized due to the coronavirus outbreak (COVID-19), which made it impossible for certain groups of patients to visit their general practitioner or the hospital. Various telemedicine approaches are already being used in other chronic neurological disorders.[2]

There is growing attention for self-monitoring mobile phone E-applications that allow patients with chronic disorders, including migraine, to monitor their own disease-related symptoms or health parameters.[3,4] Keeping a headache E-diary may help to discover unrecognized trigger factors, but it can also show that some perceived trigger factors are not as reliable as believed.[5] As an example, the need for diary-based information in migraine has emerged from studies showing inaccuracy of self-reported menstrual migraine diagnoses and menstrual cycle lengths.[6,7] Although a headache E-diary is not mandatory in clinical practice, its use can be helpful in diagnosing specific headache disorders, such as chronic migraine, menstrual migraine, and medication-overuse headache. In addition, responses to preventive and acute medications could be closely monitored. However, most available daily E-diaries for migraine lack specificity as often only one simple question is asked, such as "Did you suffer from headache today?" or "Did you suffer from migraine today?", with reporting on drug intake but failing to determine whether a reported day was fulfilling the criteria of the International Classification of Headache Disorders (ICHD-3) for migraine.[8]

We have developed a time-locked headache E-diary enabling the collection of accurate data for clinical and research purposes based on detailed daily characteristics and an automated algorithm. Additionally, migraine patients and their physicians receive visual summary reports of registered E-diary data on a daily basis, which provides insight in the course of detailed characteristics over time.

With the current study, we aimed to determine the usefulness of our E-diary in diagnosing migraine in a large group of headache patients referred to the Leiden Headache Clinic of

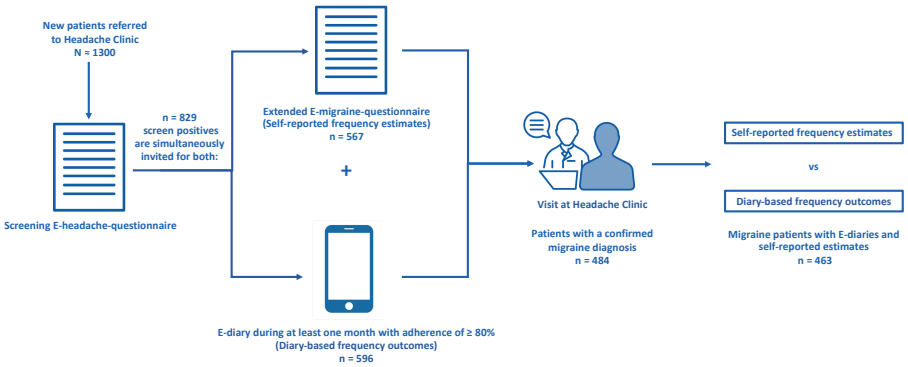
the Leiden University Medical Center by comparing the reliability of the E-diary diagnosis in combination with previously validated E-questionnaires to a physician's diagnosis as gold standard. In addition, we assessed the added value of E-diaries in the subset of clinically diagnosed migraine patients, by comparing patients' self-reported estimates on mean numbers of monthly migraine days, non-migrainous headache days and days with acute medication use to numbers based on E-diaries. Lastly, various criteria on headache duration (e.g. at least 4 hours or at least 30 min) are currently used in randomized clinical trials when defining a migraine day if no migraine-specific acute treatment had been taken. We aimed to determine the consequence of using different criteria on headache duration in the definition of migraine days by comparing mean monthly numbers of migraine days based on both time criteria.

Methods

Study population and study flow

For this study we identified new patients referred to the Leiden Headache Clinic of the Leiden University Medical Center between October 2018 and May 2020. Study flow is shown in Figure 1. Firstly, headache patients had to fulfill the screening criteria for migraine based on an adapted version of a validated web-based screening E-headache-questionnaire (Supplementary information).[9] Using an automated algorithm, screen positives (potential migraine patients) received an invitation to complete an extended E-migraine-questionnaire, after which also a validated automated algorithm determined migraine (subtype) according to ICHD-3 criteria (Supplementary information).[10] Additionally, screen positives were simultaneously asked to complete a daily headache E-diary, starting at least one month prior to their first consultation at the Leiden Headache Clinic. Patients that were screen positive on both migraine and cluster headache were excluded. Only registered E-diaries preceding a first consultation at the Headache Clinic were used for this study. To be eligible for this study, adherence to the E-diary had to be at least 80% of the total registration period. Final diagnosis of patients was made based on the ICHD-3 criteria[8] after a clinical interview and physical and neurological examination by a neurology-resident with consultation of a headache specialist (G.M.T. and/or R.F.) or by one of the other neurologists with headache expertise at the Leiden Headache Clinic. The study was approved by the medical ethics committee of the Leiden University Medical Center. Since data collection was embedded in clinical practice, patients provided a temporally informed consent at the start of data collection. After their first consultation, they were additionally asked for written informed consent.

Figure 1. Visual representation of the study flow.



Headache E-diary

The Leiden Headache Center has developed a web-based and time-locked E-diary. Patients received a daily link at 9.00 am by email to access the E-diary covering the previous 24 hours (from midnight to midnight), consisting of 6 to 31 questions depending on a negative/positive reply regarding the presence of headache including its detailed characteristics and associated symptoms (one sided / throbbing / intensity / increasing with physical activities / photophobia / phonophobia / nausea / vomiting), presence of aura symptoms including its characteristics and duration, use of acute (headache-specific) pain medication, (changes in) prophylactic headache medication, presence of menstruation, general well-being and pain coping. Completion of the E-diary took approximately 3 minutes per day. Once monthly, up to 8 additional questions were asked regarding the type and dose of used acute and prophylactic (specific) headache medication, menstrual cycle regularity and (post)menopausal status. If an E-diary was not completed at 6.00 pm, an alert with the same link was sent by text message as reminder. No adjustments could be made after completion of an E-diary. When E-diaries were not completed, they were time-locked after 48 hours. The E-diary could be filled in by mobile phone (mobile phone E-diary).

An automatic algorithm calculated for each day whether it was a headache day. A headache day was defined as a day with a headache lasting for at least 1 hour and/or for which acute (pain or headache) medication (analgesics or triptans) was used. If a headache was present, the algorithm verified diagnostic criteria for migraine according to the ICHD-3 criteria. Therefore, the registration of migraine days could be used as indication for a migraine diagnosis. The default algorithm in the E-diary calculated migraine days based on the headache duration criterion of at least 4 hours if no migraine-specific acute treatment had been taken. Days on which a triptan was used and/or days with aura symptomatology

lasting 5-60 minutes were also interpreted as migraine days (Supplementary information). By definition, each migraine day was also considered a headache day. Headache days not fulfilling criteria of migraine days were labelled as non-migrainous headache days. Days with aura symptomatology lasting 5-60 minutes were additionally labelled as aura days. Efficacy of triptans was determined by comparing pre-dose headache intensity to 2 hours post-dose headache intensity. Triptan intake was considered effective when a moderate or severe pre-dose headache reduced to mild or no pain 2 hours post-dose.
Additionally, migraine days were determined based on the duration criterion of at least 30 minutes to enable the comparison to the 4 hours duration criterion.

Eventually, the total number of migraine days, headache days, aura days and days with acute (headache) medication use were calculated for the registered months. These total numbers were reported to physicians by presentation in the electronic patient records together with a visualized summary of registered E-diary data for each day, i.e. detailed headache characteristics, associated symptoms, aura symptoms, intake of analgesics, intake of triptans, menstrual bleeding, and change in preventive medication. Once a week, a simplified visualized summary including headache symptoms, intake of acute medication and a general well-being score was reported to patients by e-mail.

Mean numbers of monthly migraine days, non-migrainous headache days and days with acute medication use were calculated based on the total number of invited E-diary days. Therefore, missing days were considered headache-free. An E-diary month was set at 28 days.

Self-reported outcomes

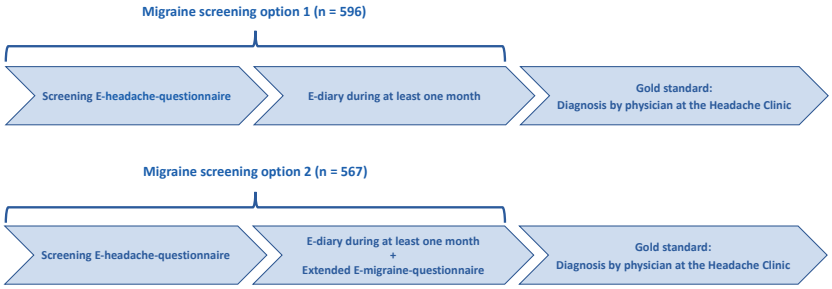
Self-reported estimates on mean numbers of monthly migraine days, non-migrainous headache days and days with acute medication use were extracted from the extended E-migraine-questionnaire. The corresponding questions asked for estimates per month when looking at the past 3 months. Outcomes were divided by 3 months when patients misunderstood the question and reported estimates > 31 days per month. Thereafter, estimates between 29 and 31 were converted to 28 days as these outcomes were compared to diary-based results with a maximum of 28 days.

Data analysis and statistics

Descriptive statistics were used to present characteristics of the selected headache population. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated as measures of reliability of the two different migraine screening

approaches. Firstly, we compared the derived diagnosis based on the combination of the screening E-headache-questionnaire and the E-diary to the physicians' diagnosis as gold standard (Figure 2, option 1). Secondly, we compared the derived diagnosis based on the combination of the screening E-headache-questionnaire, the E-diary and the extended E-migraine-questionnaire to the physicians' diagnosis as gold standard (Figure 2, option 2). To fulfill migraine screening criteria of option 2, both the E-diary and the extended E-migraine-questionnaire had to indicate a migraine diagnosis. Similar screening approaches were used to assess reliability of aura diagnoses.

Figure 2. Flow chart of the two options for migraine screening approaches.



Mean differences and absolute mean differences were calculated to compare self-reported outcomes and diary-based outcomes (i.e. number of monthly migraine days, non-migrainous headache days, and days with acute medication use). The absolute difference was calculated by abs(self-reported value - diary-based value) for each patient as self-reported estimates were both higher and lower compared to diary-based results, nullifying the mean difference. Linear regression models were fitted to investigate the relationship between self-reported outcomes and diary-based outcomes. In addition, Bland-Altman plots were constructed including a linear regression line to evaluate the agreement between self-reported outcomes and diary-based outcomes. No covariates were included because no variables were known or expected to be of influence on self-reported frequency estimates or diary-based frequency results. Lastly, the mean difference in number of monthly migraine days based on two different criteria of headache duration (at least 4 hours vs. at least 30 minutes) was calculated for episodic and chronic migraine patients. Chronic migraine was defined based on E-diary data by a mean of ≥ 15 headache days per month, from which ≥ 8 days had the features of a migrainous headache and/or triptan intake. Two-sided *p*-values < 0.05 were considered statistically significant. All analyses were performed in R version 3.6.1 (https://www.r-project.org/).

Results

Participants

Of approximately 1300 new patients who were referred to the Leiden Headache Clinic, a total of 829 screen-positives on the E-headache-questionnaire were invited to complete the E-diary, of whom 596 started at least one month preceding their first consultation and adhered to the E-diary for a minimum of 80% of the total registration period. Of these 596 patients with appropriate E-diary registrations, 507 patients completed the extended E-migraine-questionnaire about the same day as they started to complete E-diaries, 60 patients completed the extended E-migraine-questionnaire after the start of E-diary registrations, and 29 did not complete the extended E-migraine-questionnaire. At the Headache Clinic, 484 of headache patients were diagnosed with migraine by a physician (Figure 1). Only 14 of the screen-negative patients started E-diary registrations after their first consultation, and therefore, appeared to be wrongly screened as non-migraine patient based on the screening E-headache-questionnaire. Baseline characteristics of the included population are shown in Table 1. Main diagnoses made by physicians consisted mostly of migraine (81%, of which 39% experienced auras), followed by tension-type headache (8%) and cluster headache (3%). Of the 484 migraine patients, 154 met criteria of chronic migraine based on E-diary data. The mean number of completed E-diary days preceding first consultations at the Headache Clinic was 57.8, reflecting a mean E-diary adherence of 96%.

Table 1. Baseline characteristics of included headache population.

	Headache population (n = 596)
Age, years, mean (SD)	44.8 (13.6)
Female sex, n (%)	484 (81%)
Main diagnosis by physician at headache clinic	
Migraine, n (%)	484 (81%)
Without aura, n (%)	297 (61%)
With aura, n (%)	187 (39%)
Tension-type headache, n (%)	45 (8%)
Cluster headache, n (%)	20 (3%)
Chronic daily persistent headache	7 (1%)
Other headache or no conclusion	40 (7%)
Number of invited E-diary days, mean (SD)	60.1 (24.8)
Number of completed E-diary days, mean (SD)	57.8 (23.1)

Diagnostic aspects

The migraine screening approach consisting of the combination of the screening E-headache-questionnaire and our E-diary (Figure 2, option 1) revealed a sensitivity of 98%, specificity of 17%, PPV of 84% and NPV of 68% for migraine (Table 2). The approach including the combination of the screening E-headache-questionnaire, the E-diary and the extended E-migraine-questionnaire (Figure 2, option 2) resulted in a sensitivity of 79%, specificity of 69%, PPV of 92% and NPV of 43% for migraine (Table 2). Similar screening approaches were used to assess reliability of aura diagnoses. Option 1 resulted in a sensitivity of 60%, specificity of 78%, PPV of 58% and NPV of 80%. Option 2 revealed a sensitivity of 39%, specificity of 98%, PPV of 84% and NPV of 83% (Table 2).

Table 2. Cross tables regarding the validation of migraine (with and without aura) and aura symptoms separately, based on two screening approaches.

Migraine validation

		Gold standard		
		+	-	
Option 1	+	475	93	568
	-	9	19	28
		484	112	596

Sensitivity:	475/484	=	0.98
Specificity:	19/112	=	0.17
PPV:	475/568	=	0.84
NPV:	19/28	=	0.68

Aura validation

		Gold standard		
		+	-	
Option 1	+	118	87	205
	-	79	312	391
		197	399	596

Sensitivity:	118/197	=	0.60
Specificity:	312/399	=	0.78
PPV:	118/205	=	0.58
NPV:	312/391	=	0.80

		Gold standard		
		+	-	
Option 2	+	366	33	399
	-	95	73	168
		461	106	567

Sensitivity:	366/461	=	0.79
Specificity:	73/106	=	0.69
PPV:	366/399	=	0.92
NPV:	73/168	=	0.43

		Gold standard		
		+	-	
Option 2	+	54	10	64
	-	85	418	503
		139	428	567

Sensitivity:	54/139	=	0.39
Specificity:	418/428	=	0.98
PPV:	54/64	=	0.84
NPV:	418/503	=	0.83

Gold standard: Diagnosis by physician at headache clinic. ***Option 1***: Screening E-headache-questionnaire + E-diary. ***Option 2***: Screening E-headache-questionnaire + E-diary + extended E-migraine-questionnaire. *PPV*: Positive predictive value. *NPV*: Negative predictive value. For the first approach 596 headache patients were suitable to be included. The number of included patients for the second approach was 567 due to missing extended migraine questionnaires.

Frequency estimates

Crude data on mean self-reported and diary-based outcomes regarding monthly migraine days, non-migrainous headache days and days with acute medication use, including mean differences and absolute mean differences are shown in Table 3. The absolute mean difference for monthly migraine days was 4.7 ± 5.0, meaning that self-estimated numbers of monthly migraine days were on average 4.7 days lower or higher compared to diary-based numbers. Similarly, self-estimated monthly non-migrainous headache days and days with acute medication use were on average 6.2 days and 4.3 days lower or higher compared to diary-based numbers.

Linear regressions were calculated to assess the correlation between diary-based outcomes and self-reported outcomes. Scatter plots and Bland-Altman plots including linear regression lines for the three outcomes are presented in Figure 3. The majority of data points on the three scatter plots are located far away from the fitted regression lines, resulting in low correlation coefficients, which indicates a weak linear relationship between self-reported and diary-based outcomes. For monthly migraine days, a correlation coefficient of $r = 0.44$ (95% CI: 0.36 - 0.51, $p < 0.001$) was observed, indicating a low positive correlation. Similar results were found for monthly non-migrainous headache days ($r = 0.47$, 95% CI: 0.40 - 0.54, $p < 0.001$) and for monthly days with acute medication use ($r = 0.50$, 95% CI: 0.43 - 0.57, $p < 0.001$). The linear regression models showed wide 95% prediction intervals, implying that a future individual observation is predicted to fall within a large range of values. The three Bland-Altman plots showed wide ranges of agreement within which 95% of the differences between self-reported and diary-based measurements are located, indicating large discrepancy between the outcomes. When comparing linear regression lines to reference lines ($x = y$) and to equality lines (mean difference = 0), we carefully suggest that numbers of objectively diary-based monthly migraine days and days with acute medication use were underestimated when less than 8 days per month were reported and overestimated when more than 8 days per month were reported. The number of monthly non-migrainous headache days seemed to be overestimated when more than 4 days per month were reported.

Migraine day duration criterion

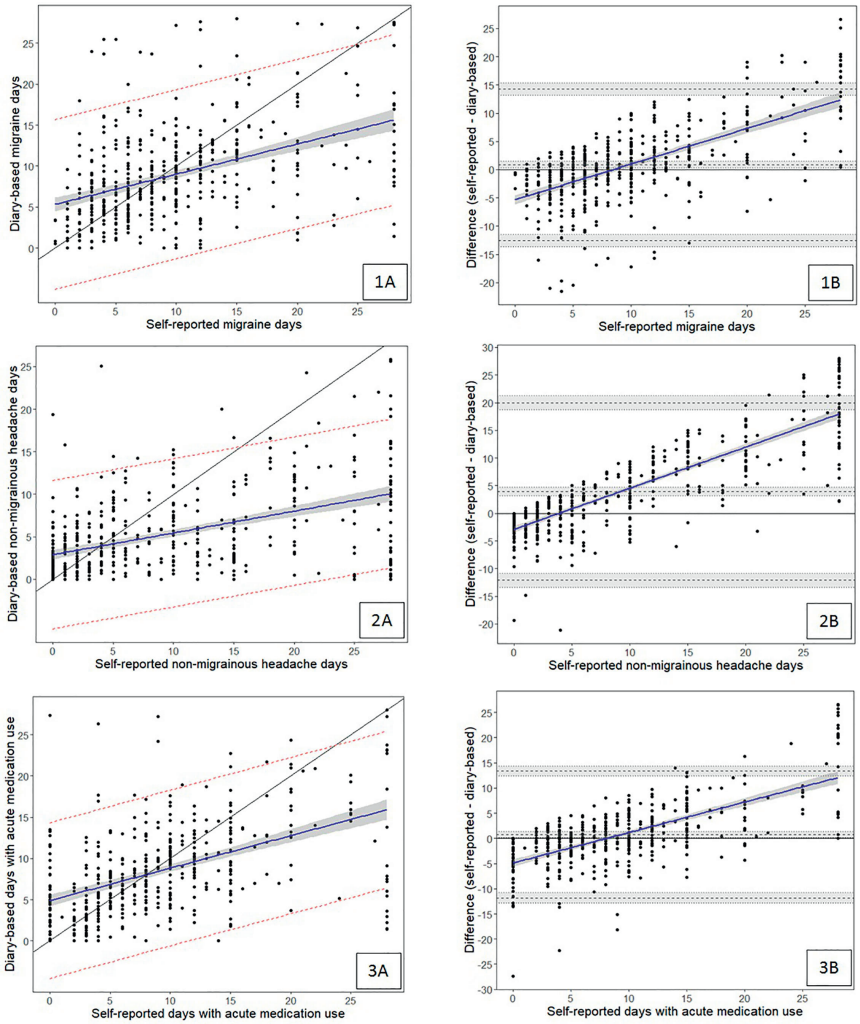
The number of mean monthly migraine days calculated based on the 30 minutes criterion on headache duration was 0.5 days higher in episodic migraine patients (95% CI: 0.3-0.6) and 0.7 days higher in chronic migraine patients (95% CI: 0.4-0.9) compared to calculations based on the 4 hours criterion.

Table 3. Crude data on self-reported and diary-based outcomes.

	Self-reported	Diary-based	Mean difference	Absolute mean difference
Migraine days/month (mean ± SD)	9.9 ± 7.0	9.0 ± 5.8	0.9 ± 6.8	4.7 ± 5.0
Non-migrainous headache days/month (mean ± *SD*)	9.2 ± 9.3	5.2 ± 5.0	3.9 ± 8.2	6.2 ± 6.6
Days with acute medication use/month (mean ± *SD*)	9.4 ± 7.1	8.6 ± 5.5	0.8 ± 6.4	4.3 ± 4.8

Absolute difference was calculated by abs(self-reported value - diary-based value) for each patient as self-reported estimates were both higher and lower compared to diary-based outcomes, nullifying the mean difference.

Figure 3. Scatter plots (1A, 2A, 3A) and Bland-Altman plots (1B, 2B, 3B) including regression lines for the comparison of self-reported outcomes and diary-based outcomes, respectively number of monthly migraine days (1), non-migrainous headache days (2) and days with acute medication use (3).



Scatter plots (1A, 2A, 3A): Blue line = linear regression; black line = reference (x = y); interval in grey = 95% confidence interval; interval between red dotted lines = 95% prediction interval. Bland-Altman plots (1B, 2B, 3B): Blue line = linear regression; black line = equality (mean difference = 0); black dotted lines = limits of agreement from -1.96*s* to +1.96*s*.

Discussion

In this study we introduced our self-developed time-locked E-diary including an automated algorithm differentiating headache and migraine days based on detailed characteristics according to ICHD-3 criteria. A new era of telemedicine is emerging, in which a diagnosis has already been made prior to a consultation at the Headache Clinic. Making clinical decisions based on information from patients' memory is not recommended since patients showed to unreliably recall migraine-related frequencies. The same high standard as for clinical trials should apply to clinical practice regarding reliability of data as important decisions are made based on clinical outcome parameters.

We determined reliability of two migraine screening approaches including our E-diary, mainly focussing on sensitivity and specificity since these are characteristics of the tests and unaffected by the prevalence of the outcome. Both approaches showed to be useful in screening for migraine. The first approach, consisting of the screening E-headache-questionnaire combined with the E-diary is suitable when all true migraine patients need to be identified and the additional identification of false positives is acceptable. The low specificity may partly be explained by patients who are convinced of having migraine but for whom an official diagnosis has never been made. Since these headache patients probably have more knowledge on symptomatology of migraine, they may be more likely to report these symptoms. The second approach, in which additionally another previously validated extended E-migraine-questionnaire is included, appeared to be suitable when only migraine patients need to be identified and missing some migraine patients is not problematic. Therefore, a specific approach could be chosen depending on the aim of the screening. Both screening approaches showed to have a high specificity in diagnosing auras, indicating that they are able to identify mainly true-positive patients. However, patients with auras could be missed due to lower sensitivity of the screening approaches. This shows that using E-tools for aura diagnoses will likely always remain a challenge and will never completely meet up to a direct clinical interview, even though we showed examples of images of visual auras in our E-tools. Our findings apply to headache patients referred to a neurology practice. When the screening approaches would be implemented in a general practitioner population, PPV may be lower and NPV higher, however, sensitivity and specificity are test-characteristics and will be unaffected.

In clinical practice, we would recommend to use the second approach as tool to screen for a migraine diagnosis because this will mainly identify true migraine patients, which enables

physicians to appropriately prepare for consultations. Missing some migraine patients will not have major consequences since the correct diagnosis still will be made by the physician. When a migraine diagnosis has already been established by a neurologist or general practitioner, the E-diary may be used for clinical follow-up without completion of additional E-questionnaires. Our E-diary is different from a recently published E-diary study, which evaluated the accuracy of an automated tool for the classification of headache attacks. A substantial level of agreement (kappa 0.74) was found in the classification of 102 attacks as migraine (with or without aura) or tension-type headache by a neurologist with specialization in headache and the algorithm.[11] Their classification tool could not be used for diagnostic screening since only single attacks were classified. Additionally, the classification of auras was based on self-reported aura symptomatology as no characteristics and duration criterion were incorporated in the E-diary.

Most importantly, the need for E-diaries to obtain reliable information was emphasized in our study as patients did not reliably recall migraine-related frequency numbers. Monthly migraine days and days with acute medication use were tended to be underestimated in case of < 8 self-reported migraine days and overestimated in case of high frequent (> 8) self-reported migraine days. Another recently published study using E-diary data from an dietary intervention trial with 182 participants, concluded that migraine patients may underestimate headache frequency based on retrospective estimation,[12] whereas our patients mainly overestimated non-migrainous headache days and underestimated migraine days up to 8 self-reported days.

Migraine patients underestimating their acute medication intake might have major consequences for diagnosing and treating medication-overuse headache. The automatic calculation of monthly total numbers of days with use of analgesics, use of triptans, and use of a combination of both will enable us to perform research on medication-overuse (headache) in the future. Furthermore, with the upcoming new prophylactic treatments it may be that health-care insurance companies will require information on effectiveness to reimburse these prophylactic treatments. Therefore, reliable data are necessary for the decision making whether to stop or continue medication. Nevertheless, treating physicians should continue to pay attention to the subjective assessment of a patient's satisfaction during consultation. Information on general well-being and coping, as incorporated in our E-diary, could be helpful in shared decision making.

Missing E-diary days were considered headache-free, which is expected to have a negligible influence on numbers of monthly migraine days since mean E-diary adherence was 96% in the selected population. In addition, patients report that they are more likely to register days with headache than days without headache.

We also calculated monthly migraine days based on different duration criteria (30 minutes versus 4 hours). The similarity between the calculated monthly migraine days can be explained by the intake of triptans because most migraine patients (n = 341) used triptans and all days with headache for which a triptan was taken were interpreted as migraine days independent of headache duration or other characteristics. However, the seemingly small differences may have scientific relevance as various criteria (e.g. 4 hours, 2 hours, 30 min) are currently used in outcome measures of randomized clinical trials. In these prophylactic treatment trials, differences in decrease of mean monthly migraine days between active drugs and placebo treatments are approximately between -1 and -4 days/month.[13-17] Therefore, researchers should be aware of the consequence of a chosen criterion on headache duration when defining migraine days both in clinical trials and clinical practice when following patients and assess efficacy of therapies.

Our study has some limitations. Physicians were given insight into the registered E-diary data before diagnosing, which may have affected their diagnosis. However, this insight has never stopped them from making different diagnoses based on the interpretation of complete clinical interviews and physical and neurological examinations, and diagnoses were made in consultation with a headache specialist or by headache specialists themselves who were unaware of the E-diagnoses. In patients with a life-time migraine with aura diagnosis, but with low frequency auras, a diary-based aura diagnosis could have been missed, resulting in an underestimation of the sensitivity of the screening approaches. Lastly, self-reported migraine-related frequency estimates preferably would have been collected at the end of the period with E-diary registrations, since it can be expected that the estimation would have been most accurate at that time point. In addition, the screening E-headache-questionnaire asks about mean migraine-related frequency estimates per month when looking at the past 3 months, whereas the mean monthly E-diary estimates were calculated based on an average duration of approximately 2 months. However, in the earlier mentioned dietary intervention trial, concordance between the number of headache days based on an E-diary and retrospective recall questionnaires was assessed on a monthly basis during four months, which only showed a mild increase in concordance over time.[12] This finding suggests that specifying a limited and more recent period does not significantly affect the degree of recall bias.

The recent experience in using our E-diary showed usefulness in clinical follow-up and evaluation of effectiveness of migraine treatments. Its use has become common practice at the Headache Clinic to which physicians adjust their treatment strategies. In addition, it enables physicians and patients to prepare for consultations. In migraine patients, its use may potentially improve understanding of their own disease as they are given insight in the course of symptoms over time. This is also why patients at our Headache Clinic appreciate the E-diary. The E-diary has been implemented in our investigated-initiated clinical trials and real-life-data collection of new treatments and offers opportunities for (ad hoc) research and telemedicine. During the recent COVID-19 outbreak, we were able to assess the effect of Dutch intelligent lockdown measures on migraine-related outcomes (Verhagen et al, Cephalalgia in press). More importantly, we were able to start and/or continue consultations with our patients by visualizing E-questionnaires and E-diary data in the electronic patient records during video-consultation. E-diaries added to E-questionnaires for headache using automated algorithms can thus be helpful in telemedicine. In the future, new research questions and/or clinical outcome measures can easily be implemented since we have developed a flexible E-diary. A new era begins for headache care.

Clinical implications

- A new era of telemedicine is emerging, which increases the need for a similar high standard in clinical practice as in clinical trials regarding the reliability of data.
- E-diaries need to include detailed headache characteristics to be able to differentiate between headache and migraine days.
- The use of E-diaries in clinical practice should be encouraged, since migraine patients do not reliably recall migraine-related frequencies.

Ethics or Institutional Review Board Approval: The study was approved by the medical ethics committee of the LUMC.

Supplementary data availability: Data not published within the article will be shared by request from any qualified investigator.

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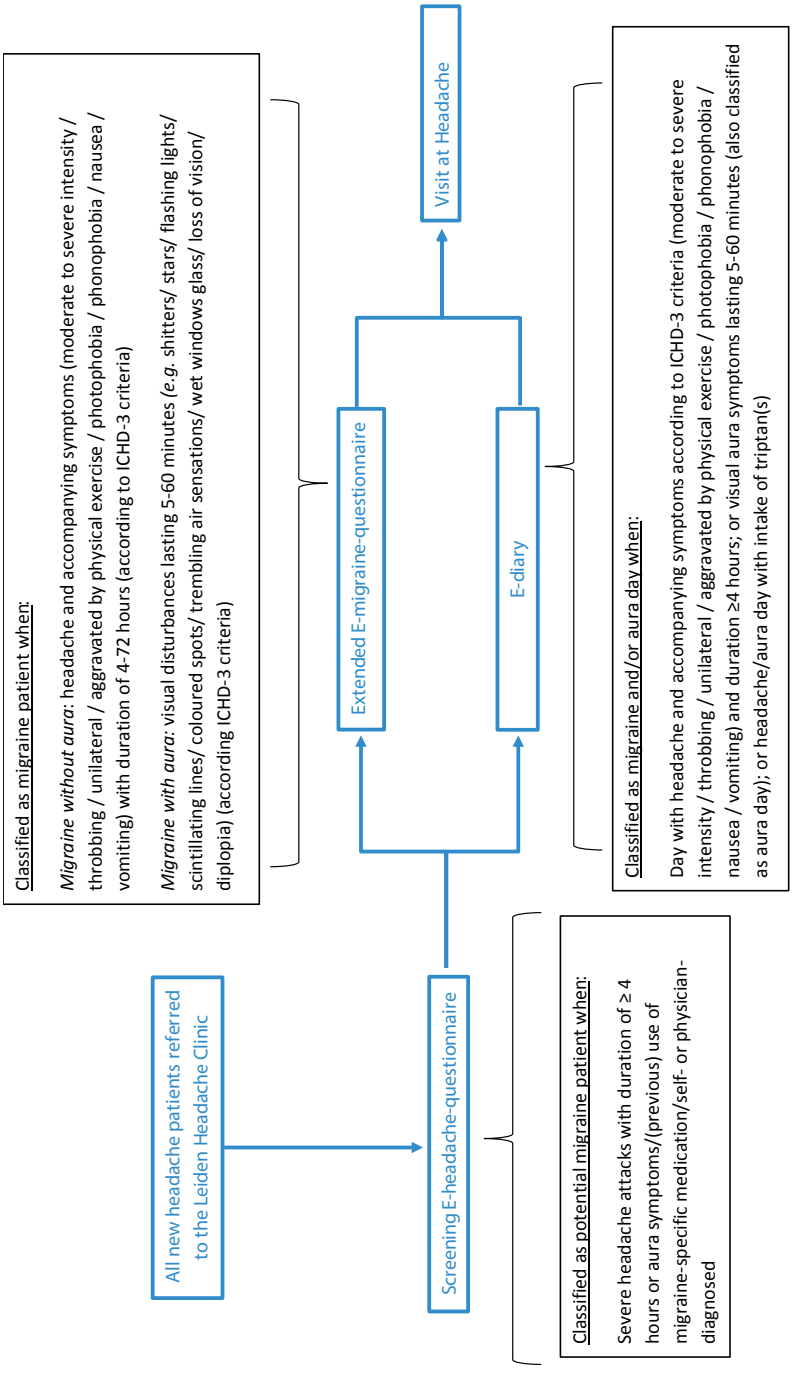
Online supplementary information



CHAPTER 5

Menstrually related and non-menstrually related migraine attacks compared: An E-diary study

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Submitted

Abstract

Aim To compare menstrually related and non-menstrually related migraine attack characteristics and to assess premenstrual syndrome (PMS) symptomatology in women with migraine.

Methods In 500 women with migraine, from the validated migraine LUMINA database, menstrually related attacks and non-menstrually related attacks were compared using a self-developed time-locked E-diary. Women using continuous sex hormonal therapies were excluded. Attack duration (including recurrences) was defined as primary outcome. Secondary outcomes were headache intensity, accompanying symptoms, acute medication intake and pain coping. Results were analyzed with mixed effects models to account for the correlation between multiple migraine attacks within the same patient. PMS was assessed only in those women who did not use oral contraceptives, and compared between women with menstrually related migraine (n = 187 women) and non-menstrual migraine (n = 157 women).

Results Menstrually related migraine attacks (n = 998 attacks) compared with non-menstrually related attacks (n = 4097 attacks) were associated with a longer duration (20.0 vs 16.1 hours, 95% CI [0.2-0.4]), and higher recurrence risk (OR 2.4 [2.0-2.9]), increased triptan use (OR 1.2 [1.1-1.4]), higher headache intensity (OR 1.4 [1.2-1.7]), less pain coping (mean difference -0.2 [-0.3- -0.1]), more pronounced photophobia (OR 1.3 [1.2-1.4]) and phonophobia (OR 1.2 [1.1-1.4]), but less aura (OR 0.8 [0.6-1.0]). PMS was not different for women with menstrually related migraine (11%) compared to women with non-menstrual migraine (15%).

Conclusion The longer duration of menstrually related migraine attacks is associated with a higher recurrence risk and increased triptan use, which increases the risk of medication overuse and emphasizes the need to develop female-specific prophylactic treatment.

Key words: migraine, menstruation, premenstrual syndrome

Introduction

Menstruation is the most reported migraine trigger factor in women.[1] The exact underlying pathophysiological mechanism is suggested to be the drop in estrogen level prior to the menstruation leading to increased brain excitability and triggering the trigeminovascular system.[2-5] The rate of estrogen decline seems important in attack provocation.[6,7] Although previous (small) diary-based studies cautiously suggested that menstrually related migraine attacks have a longer duration and are associated with higher disability compared to non-menstrually related attacks, they showed conflicting results on acute therapy efficacy, pain intensity, and associated symptoms.[8-13]

Many migraine patients report prodromal symptoms before the headache phase. It is hypothesized that a mechanism of subcortical and diencephalic brain activation at the start of an attack and prior to the headache, including that of basal ganglia, hypothalamus, and thalamus, causes a top-down effect on brainstem structures involved in trigeminovascular nociception.[14] Interestingly, the affective, behavioral and physical symptoms, belonging to the premenstrual syndrome (PMS) show many similarities with the prodromal migraine phase.[15-17] Previous studies suggested an increased risk of migraine in women with PMS of approximately 60%.[17,18] Due to the strictly defined temporal relationships between menstrual related migraine, PMS, and the menstruation, prospective diaries are needed to reliably confirm diagnoses.[19-21]

With this prospective electronic diary (E-diary) study, we aimed to study menstrually related and non-menstrually related migraine attack characteristics in a large group of female migraine patients. Furthermore, we assessed PMS in women fulfilling criteria of menstrually related migraine and compared this to women in which attacks were non-menstrually related.

Methods

Study design and population

This study is a longitudinal prospective cohort study among women with migraine, conducted between February 2019 and October 2020. Dutch adults diagnosed with migraine were recruited by the Leiden Headache Clinic group.[22] An elaborate description of LUMINA participants and procedures is found as Appendix e-1. Final diagnoses were

made based on the ICHD-3 criteria[23] after a clinical interview by a neurology resident with consultation of a headache specialist or a researcher with headache expertise. Pregnant, breastfeeding and postmenopausal women were excluded from participation. Additionally, women using continuous sex hormonal therapies (e.g. hormone-releasing intrauterine device, progesterone-only pill, etonogestrel implant, medroxyprogesterone injection, oral estradiol/dydrogesterone) were excluded. When using combined oral contraceptives, patients had to be willing to insert a pill-free period every month. Lastly, women with a current gynecological malignancy or a history of oophorectomy and/or hysterectomy were excluded. The study was approved by the medical ethics committee of Leiden University Medical Center (METC number P18.181). All participants provided written informed consent.

E-diary

For this study we used our self-developed time-locked E-diary. Patients received a daily link at 9.00 am by email to access the E-diary covering the previous 24 hours (from midnight to midnight), consisting of 6 to 31 questions depending on the absence or presence of headache including its detailed characteristics and associated symptoms (one sided/ throbbing/ intensity/increasing with physical activities/photophobia/phonophobia/ nausea/vomiting/ pain coping), presence of aura symptoms including its characteristics and duration, acute and prophylactic medication, and menstruation. Up to five additional questions were asked depending on the absence or presence of menstruation, including intensity of the bleeding, menstrual pain and associated use of analgesics. Lastly, questions regarding the presence of PMS based on the Daily Record of Severity of Problems (DRSP) scale were incorporated in the E-diary.[19] The DRSP scale consists of 21 items regarding affective and physical symptoms and three items on associated functional impairment, all rated on a 6-point severity scale. If an E-diary was not completed at 11.00 am, an alert with the same link was sent by text message as reminder. An additional check on E-diary adherence was performed twice a week, and if necessary, a final reminder was sent by email to avoid missing E-diaries. No adjustments could be made after completion of an E-diary. When E-diaries were not completed, they were time-locked after 6 days. Patients were followed for 105 days, aiming to register at least three menstrual cycles. Patients who completed the E-diary for less than one month were excluded. Missing days were considered headache-free. Single days with spotting or bleeding were not considered to belong to a menstruation period. In patients with a natural menstrual cycle, menstrual bleedings with a gap up to a maximum of three days were interpreted as one continuous menstruation. Finally, cycle lengths with a duration < 14 days were visually inspected and adjusted when accidentally wrong answers were suspected (n = 27).

An automatic algorithm calculated for each day whether it was a headache day. A headache day was defined as a day with a headache lasting for at least 1 hour and/or for which acutely acting medication (analgesics or triptans) was used. If a headache was present, the algorithm verified diagnostic criteria for migraine according to the ICHD-3 criteria.[23] Days on which a triptan was used and/or days with aura symptomatology lasting 5-60 minutes were also interpreted as migraine days. By definition, each migraine day was also considered a headache day. Headache days not fulfilling criteria of migraine days were labelled as non-migrainous headache days.

Outcome measures

All registered migraine attacks were divided into menstrually related attacks and non-menstrually related attacks according to the ICHD-3 criteria.[23] The primary outcome was the difference in migraine attack duration in hours between menstrually related attacks and non-menstrually related attacks. A migraine attack that was temporarily remitted, regardless of the intake and effectivity of acutely acting medication, and then recurred within 24 hours was considered as one attack. Time in between was also included in the attack duration. The secondary outcomes were differences in attack duration when migraine-free periods of < 48 hours are included in the duration, maximum headache intensity (rated as mild, moderate or severe), associated symptoms (i.e. photophobia, phonophobia, nausea, vomiting, all rated as mild, moderate or severe), aura symptoms, use of acute medication (analgesics/triptans), 2-hour headache response, 2-hour pain free response, recurrence of migraine within 24 hours, recurrence of migraine within 48 hours, and minimum pain coping (rated on a continuous scale from 0.0 to 10.0; lower score means less coping). A 2-hour headache response was defined by a reduction of moderate or severe pre-dose headache to mild or no pain 2 hours after the intake of a triptan. A 2-hour pain free response was defined by a reduction of moderate or severe pre-dose headache to no pain 2 hours after the intake of a triptan. Recurrence was defined as migraine that recurred after the intake of a triptan among patients who were pain free 2 hours post-dose. Diagnosis of chronic migraine, medication overuse and the use of oral combined contraceptives were considered potential confounders for all outcomes. The use of analgesics due to menstrual pain was additionally considered a potential confounder for differences in headache intensity and for differences in the use of analgesics during migraine attacks. Chronic migraine was defined as a mean of ≥ 15 headache days per month, from which ≥ 8 days fulfilled criteria of a migrainous headache or triptan intake.[23] Medication overuse was defined based on the average use of acutely acting treatment (analgesics ≥ 15 days per month or triptans ≥ 10 days per month or a combination of analgesics and triptans ≥ 10 days per month).[23]

In addition, PMS was assessed in women with menstrually related migraine and non-menstrual migraine who were not using combined oral contraceptives. Menstrually related migraine was defined based on the ICHD-3 criteria as migraine attacks that occur between day 1 of menstruation ± 2 days, during at least two of three menstrual cycles, additional attacks may occur at other times of the cycle.[23] A minimum of two registered menstrual cycles is required to reliably assess PMS.[19] This criterium was automatically met, since only those women who completed E-diaries during three menstrual cycles, which was needed to assess criteria of menstrually related migraine, were included in the analyses on PMS. Women with depressive, anxiety symptoms, or both were not excluded, since there are strong associations between migraine and depression and we aimed for a representative group of migraine patients.[24-26] The PMS criteria of the American College of Obstetricians and Gynecologists (ACOG) are far less strictly defined compared to the highly specified criteria of the American Psychiatric Association (DSM-IV).[27] We chose to combine these two criteria (ACOG and DSM-IV) into a definition that we considered clinically relevant. The late luteal phase is represented by the 5 days prior to the onset of menstruation, while the mid-follicular phase is represented by the period of 6 to 10 days from the start of menstruation. The following criteria needed to be met for PMS in our study: (1) 30% higher mean total symptom score in late luteal phase compared to mid-follicular phase; (2) Higher mean total functional impairment score in late luteal phase compared to mid-follicular phase.

Data analysis and statistics

Descriptive statistics were used to present characteristics of the included women with migraine. To account for the correlation between the repeated observations of the same patient, we used mixed effects regression models with a random intercept per patient for all our analyses. The relation between migraine attacks and menstruation and potential confounders were added as fixed effects. Migraine attack duration was log transformed to achieve a normal distribution. Linear mixed effects models were used to assess the difference in continuous outcome measures (i.e. attack duration and pain coping) between menstrually related migraine attacks and non-menstrually related migraine attacks. Ordinal logistic mixed effects models were used to investigate differences in ordinal outcome measures (i.e. headache intensity, nausea, vomiting, photophobia and phonophobia) and logistic mixed effects models were used to assess differences in binary outcome measures (i.e. aura symptoms, use of analgesics, use of triptans, 2-hour headache response, 2-hour pain free response and recurrence of migraine). Two-sided p-values < 0.05 were considered statistically significant. All analyses were performed in R, version 3.6.1.

Results

A total of 518 women with migraine started with the study, of whom 500 completed the E-diary for at least one month. In this group, E-diary adherence was high with 249 women who completed 100%, 190 women who completed 90-99% , 13 women who completed 80-89% , and 3 women who completed < 80%. Few women (n = 45) prematurely ended their participation due to the start of a continuous sex hormonal therapy or pregnancy or personal (health-related) circumstances. Baseline characteristics of the study population are shown in Table 1.

Table 1. Baseline characteristics of the included migraine population.

	Women with migraine (n = 500)
Age in years, (mean ± SD)	40.5 ± 8.9
BMI, (mean ± SD)	24.1 ± 4.1
Migraine subtype, n (%)	
Migraine without aura, n (%)	267 (53%)
Migraine with aura, n (%)	187 (37%)
Chronic migraine,[a] n (%)	46 (9%)
Migraine attacks/month, (mean ± SD)	2.8 ± 1.5
Migraine days/month, (mean ± SD)	5.5 ± 4.2
Non-migrainous headache days/month, (mean ± SD)	3.8 ± 3.6
Headache days/month, (mean ± SD)	9.3 ± 5.7
Days with use of analgetics/month, (mean ± SD)	4.7 ± 4.2
Days with use of triptans/month, (mean ± SD)	2.7 ± 2.9
Use of preventive medication, n (%)	149 (30%)
Medication overuse,[b] n (%)	80 (16%)
Use of combined oral contraceptives, n (%)	65 (13%)
Menstrual cycle length, median (IQR)	
Women with a natural menstrual cycle	27.5 (25.5-29.5)
Women using combined oral contraceptives	28.0 (28.0-28.7)
Association between migraine attacks and menstruation (n = 396)[c]	
Menstrually related migraine, n (%)	221 (56%)
Non-menstrual migraine, n (%)	175 (44%)
Depressive/anxiety symptoms (n = 422)[d]	
HADS-D ≥ 8 and/or CESD ≥ 16 and/or HADS-A ≥ 8, n (%)	173 (41%)

[a] Chronic migraine was defined as a mean of ≥15 headache days per month, from which ≥8 days fulfilled criteria of a migrainous headache or triptan intake.[23]

[b] Medication overuse was defined based on the average use of acutely acting treatment (analgesics ≥ 15 days per month or triptans ≥ 10 days per month or a combination of analgesics and triptans ≥ 10 days per month).[23]

[c] The association between migraine attacks and menstruation was determined in 396/500 patients with ≥ 3 documented menstruations.

[d] The presence of depressive and/or anxiety symptoms could be determined in 422/500 patients.

Primary outcome

The median attack duration was 20.0 hours for menstrually related migraine attacks and 16.1 hours for non-menstrually related migraine attacks when migraine-free periods of less than 24 hours were included in the duration (Figure 1 and Table 2). The average attack duration of menstrually related attacks was 35% longer compared to non-menstrually related attacks ($\beta = 0.30$, 95% CI: 0.2-0.4, $p < 0.001$). Chronic migraine was associated with a longer attack duration ($\beta = 0.75$, 95% CI: 0.6-0.9, $p < 0.001$), but medication overuse had no additional effect. Use of combined oral contraceptives did not affect duration.

Secondary outcomes

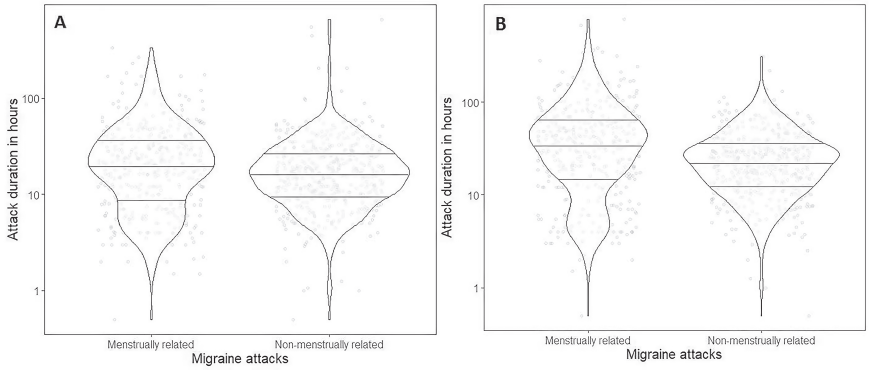
The average attack duration of menstrually related attacks was 84% longer than the duration of non-menstrually related attacks when migraine-free periods of less than 48 hours were included in the duration ($\beta = 0.61$, 95% CI: 0.5-0.7, $p < 0.001$) (Figure 1 and Table 2). Pain coping (rated 0-10) was lower (adjusted mean difference -0.2, 95% CI: -0.3- -0.1, $p < 0.001$) and headache intensity (rated mild-moderate-severe) higher during menstrually related migraine attacks compared to non-menstrually related attacks (OR 1.4, 95% CI: 1.2-1.7, $p < 0.001$) (Figure 2). Menstrually related migraine attacks were more often associated with triptan intake (OR 1.2, 95% CI: 1.1-1.4, $p = 0.004$). Associated symptoms of photophobia and phonophobia were more pronounced ($p < 0.001$), but nausea and vomiting were not (Table 3). The 2-hour headache and pain free response were not different but attacks recurred more often during menstrually related migraine attacks ($p < 0.001$). There was a trend that menstrually related migraine attacks were less likely to be associated with aura (OR 0.8, 95% CI: 0.6-1.0, $p = 0.054$) (Table 3).

Table 2. Descriptive statistics on the continuous outcomes duration (hours) and pain coping (0-10, lower score means less coping) for menstrually related and non-menstrually related migraine attacks.

	Menstrually related attacks (n = 998)	Non-menstrually related attacks (n = 4097)
Duration (hours) - incl. 24 h migraine-free, median (IQR)	20.0 (8.5-37.0)	16.1 (9.7-26.6)
Duration (hours) - incl. 48 h migraine-free, median (IQR)	35.4 (16.0-63.0)	22.7 (12.3-35.2)
Pain coping score (0-10 scale), mean ± SD	5.1 ± 1.6	5.4 ± 1.3

Intra-individual means were calculated for menstrually related attacks and non-menstrually related attacks prior to group calculations to account for the correlation between migraine attacks within the same participant. Numbers of attacks included in the analyses on duration when migraine-free periods of less than 48 hours were included in the duration were lower than presented in the table (n = 894 and n = 3253 respectively). Note: the adjusted mean difference on pain coping presented in the text is calculated with a linear mixed effects model corrected for potential confounders, and therefore, slightly deviates from the result presented in this table.

Figure 1. Violin plots of migraine attack duration visualizing distribution and probability density, respectively duration when migraine-free periods of less than 24 hours are included (A) and duration when migraine-free periods of less than 48 hours are included (B).



Intra-individual mean duration was calculated for menstrually related attacks and non-menstrually related attacks to account for the correlation between migraine attacks within the same participant.

Table 3. Prevalence of ordinal and binary outcomes separately for menstrually related and non-menstrually related migraine days with corresponding results of mixed effects models.

	Percentage (%)		Adjusted odds ratio 95%CI	Adjusted p-value
	Menstrually related migraine days (n = 2272)	Non-menstrually related migraine days (n = 7399)		
Photophobia	86.3	82.9	1.3 (1.2-1.4)	**< 0.001**
Phonophobia	82.7	79.5	1.2 (1.1-1.4)	**< 0.001**
Nausea	63.6	60.9	1.0 (0.9-1.1)	0.850
Vomiting	7.2	7.7	0.9 (0.7-1.1)	0.205
Aura symptoms	7.3	9.4	0.8 (0.6-1.0)	0.054
Use of analgesics	44.8	41.9	1.3 (0.7-2.2)	0.370
Use of triptans	53.7	48.8	1.2 (1.1-1.4)	**0.004**
2 hour headache response	61.2	62.4	0.9 (0.8-1.1)	0.414
2 hour pain-free response	29.7	29.2	1.0 (0.8-1.2)	0.993
Recurrence < 24 hours	16.3	8.3	2.4 (2.0-2.9)	**< 0.001**
Recurrence < 48 hours	17.2	7.5	2.8 (2.4-3.3)	**< 0.001**

The associated symptoms photophobia, phonophobia, nausea and vomiting were rated on a ordinal scale (no-mild-moderate-severe), all other outcomes presented in the table are rated on a binary scale (no-yes). To obtain frequency numbers on associated symptoms, a comparison was made between negative replies and positive replies (i.e. mild, moderate or severe were rated as yes). Odds ratios for associated symptoms were calculated based on the ordinal results with ordinal logistic mixed effects models and for all other outcomes with logistic mixed effects models, adjusted for chronic migraine, medication overuse and the use of combined oral contraceptives. Analgesics use was additionally corrected for use because of menstrual pain. Prevalence of 2-hour responses are calculated based on migraine days with triptan intake (respectively n = 1244 and n = 3699 days). Recurrence is calculated based on days with triptan intake including respectively 24 hours and 48 hours.

Premenstrual syndrome (PMS)

PMS symptom scores and functional impairment scores were slightly higher in women with menstrually related migraine compared to women with non-menstrual migraine, but differences within groups between the late luteal phase and the mid-follicular phase were small (Table 4). PMS was observed in 11% of women with menstrually related migraine and in 15% of women with non-menstrual migraine, which was a statistically non-significant difference (Table 4).

Table 4. Crude data on DRSP scale scores during the late luteal phase and mid-follicular phase of the menstrual cycle and premenstrual syndrome (PMS).

	Total population (n = 344)	Menstrually related migraine (n = 187)	Non-menstrual migraine (n = 157)	p-value
Luteal total symptom score, median (IQR)	31.4 (26.0-38.8)	31.8 (27.4-39.6)	30.4 (24.9-37.6)	0.053
Follicular total symptom score, median (IQR)	28.5 (24.6-35.2)	28.8 (25.1-38.5)	27.4 (23.8-34.5)	0.012
Luteal total impairment score, median (IQR)	4.3 (3.5-6.2)	4.4 (3.7-6.4)	4.1 (3.3-6.0)	0.021
Follicular total impairment score, median (IQR)	4.4 (3.5-6.0)	4.5 (3.6-6.5)	4.0 (3.3-5.7)	0.013
Premenstrual syndrome diagnosis, n (%)	44 (13%)	20 (11%)	24 (15%)	0.268

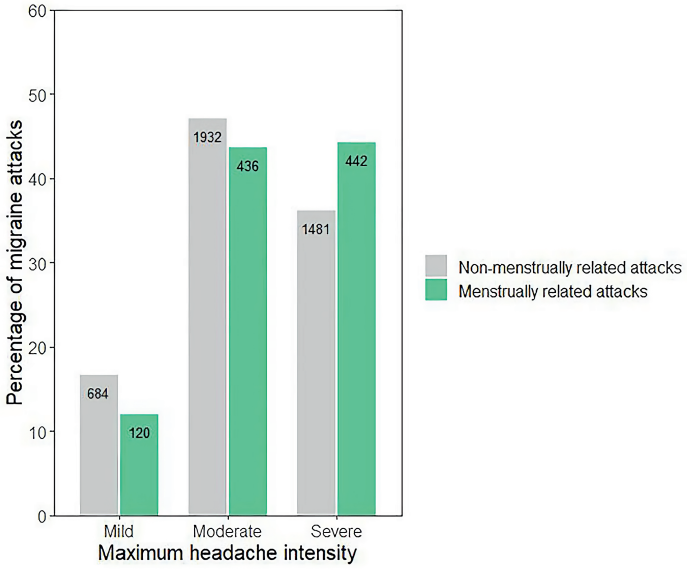
Inclusion: women with migraine who were not using combined oral contraceptives and with at least three registered menstrual cycles. DRSP= Daily Record of Severity of Problems; total symptom score (range 21-126), total functional impairment score (ranges 3-18). The following criteria needed to be met for PMS: (1) 30% higher mean total symptom score in late luteal phase compared to mid-follicular phase; (2) Higher mean total functional impairment score in late luteal phase compared to mid-follicular phase. Group differences on symptom scores and impairment scores were calculated with Wilcoxon rank sum tests and on PMS diagnoses with a Chi-squared test.

Discussion

This large prospective E-diary study clearly showed that menstrually related migraine attacks have a longer duration and are more severe compared to non-menstrually related attacks, with a higher recurrence risk leading to the need for repeated triptan intake during these attacks. This fits with our recent systematic review and meta-analysis where we found that despite the higher drug exposure of triptans in women, they have higher headache recurrence rates and we suggested that this might be due to longer attack duration related to sex hormonal changes.[28] In the current study we show that this is indeed the case for the menstrually related migraine attacks as opposed to the non-menstrually related attacks. This has practical implications for migraine treatment in women.

The longer attack duration of menstrually related attacks and higher risk of recurrence are consistent with results of previous small studies.[8-13] The sex hormonal triggering effect, which is hypothetically due to estrogen changes that modulate neuronal brain excitability and the trigeminovascular system[2-5] seems to result in a longer attack duration with failure of effectiveness after an initial adequate triptan response. Thus, in contrast to what has been suggested about acute migraine treatments that would be less effective for menstrually related migraine attacks,[8,9] our E-diary study showed similar 2-hour response rates after triptan use, but higher recurrence rates. This finding fits our expectations since we recently showed that women have a higher triptan exposure compared to men and similar 2-hour response rates.[28] The prolonged attack duration of menstrually related migraine attacks in our study was found in a population that consisted of women with natural menstrual cycles and women using combined oral contraceptives. A small diary-based study in n = 28 women specifically studied pill use and also found that attacks during the hormone-free interval lasted longer.[29]

Figure 2. Prevalence of headache intensity scores separately for menstrually related and non-menstrually related migraine attacks.



Cortical spreading depression (CSD), which is thought to be the underlying mechanism of the migraine aura, is also suggested to be affected by estrogen levels. High estrogen levels were shown to increase CSD susceptibility, whereas estrogen withdrawal and low estrogen levels appeared to decrease the risk for CSD,[30-32] which may explain why menstrually related migraine attacks seemed less likely to be associated with aura in our study. The

observed more pronounced photophobia during menstrually related migraine attacks seems noteworthy in that light because previous studies suggested photophobia to be associated with visual aura.[33,34] A greater visual cortex hyperexcitability in migraine with aura may induce abnormal processing of light sensitivity and may be the link between symptoms of photophobia and CSD susceptibility.[35-38]

Women with menstrually related migraine did not have a higher PMS prevalence compared to women with non-menstrual migraine, in contrast to what some small diary-based pilot studies suggested.[15,39-41] The prevalence of PMS in our large cohort of women with migraine is comparable to the prevalence in the general population, which ranges between 5 and 20%.[21] Our finding corresponds with previous studies reporting PMS in 10-30% of women with migraine and we did not find a difference in PMS between women with and without menstrually related migraine.[15-17,42] However, as there is important overlap in symptomology between PMS and the prodromal phase of migraine it is conceivable that women with menstrually related migraine are less likely to differentiate between these two phenomena. Importantly, we did find slightly higher PMS symptom scores and functional impairment scores in women with menstrually related migraine compared to women with non-menstrual migraine. Previously, the potential comorbidity between PMS and migraine was suggested to be due to the involvement of serotonin in both disorders and cyclical changes in its levels resulting from estrogen fluctuations.[43-45] However, growing evidence suggests that affective symptoms of PMS reflect suboptimal GABA(A) receptor sensitivity to fluctuating levels of the positive modulator allopregnanolone,[46] which is a neuroactive metabolite of progesterone with an inhibitory effect on neuronal excitability.[47] Reduced levels of allopregnanolone have been associated with the development of depressive disorders and menstrual cycle-related disorders such as PMS.[48] However, conflicting results were observed in small studies for serum allopregnanolone concentrations between women with and without migraine.[49,50]

Strengths of the current study include the large sample of well-defined female migraine patients and the use of our self-developed and validated time-locked E-diary with an automated algorithm differentiating headache and migraine days based on detailed characteristics according to ICHD-3 criteria. In almost all currently available daily E-diaries, migraine days are defined based on whether the patient reports a day as a migraine and/or headache day just stating yes or no. Missing E-diary days were considered free of symptoms, which is expected to have a negligible influence on our results since E-diary adherence was very high and patients report that they are more likely to register days

with complaints than days without complaints. The Leiden E-headache diary is time-locked, meaning that no adjustments can be made after completion of a day or the diary is locked when it is not filled out after a predefined time period, which prevents patients from changing their input. The study also has some limitations. Firstly, we defined recurrences only after the intake of triptans, and not after intake of painkillers or NSAIDs, as we considered this to be more robust. However, in the definition of migraine attack duration, migraine-free periods of 24 hours or 48 hours were included regardless of the intake and effectivity of acutely acting medication. Secondly, the lack of uniformity in the interpretation of what is substantial PMS made us choose to combine the strictly defined criteria of DSM-IV with the less strictly defined criteria of ACOG into a definition that we considered clinically relevant.[27] In addition, research on PMS in women with migraine is complicated by overlapping symptomatology of PMS, the premonitory phase of migraine attacks, and depression and anxiety, which are strongly associated with migraine.[24-26] In our study we chose that premenstrual symptoms did not have to remit completely following onset of menstruation in order to meet our definition of PMS.

Physicians treating women with menstrually related migraine should be aware of a long duration of menstrually related attacks with a high risk of recurrence. Although women are more likely to report adverse events after the intake of triptans than men,[28] they often need to take triptans repeatedly during their menstrually related attacks. Consequently, women with menstrually related migraine are at increased risk for medication overuse. Physicians should be encouraged to prescribe preventive treatments in women with disabling menstrually related migraine attacks to diminish duration and severity of attacks, because this may prevent the need for these women to use triptans during multiple subsequent days. In addition, physicians should consider to prescribe long-acting triptans such as eletriptan or frovatriptan for the acute treatment of migraine attacks, aiming to reduce the risk of recurrence. Alternatively, long-acting NSAIDS such as etoricoxib or naproxen could be added to a triptan with a short half-life time such as sumatriptan or rizatriptan. The intake of etoricoxib or naproxen should be timed based on the expected timing of recurrence (e.g. before going to sleep if the recurrences normally are the next morning or on awakening). Short-term prophylaxis with frovatriptan or etoricoxib starting 1 to 2 days prior to the onset of menstruation with a maximum of 7 subsequent days should only be considered in women with pure menstrual migraine, because it can easily induce medication overuse in women who have additional attacks at other times of the cycle.

The long duration of menstrually related migraine attacks with a high risk of recurrence highlights the need to improve understanding of the role of sex hormones in the provocation of attacks in women with migraine. Ultimately, this knowledge will contribute to the development of an urgently needed female-specific prophylactic treatment intervening with sex hormones. To begin with, the potential efficacy of existing hormonal treatments, such as combined oral contraceptives, in the prevention of migraine attacks should be clarified (WHAT! Study - ClinicalTrials.gov NCT04007874). In addition, future large scale daily E-diary studies are needed to assess symptoms belonging to the premonitory phase in women with migraine and to determine their contribution in the prediction of an upcoming migraine attack.

Standard Protocol Approvals and Patient Consents: The study was approved by the medical ethics committee of Leiden University Medical Center (METC number P18.181). All participants provided written informed consent.

Data Availability Statement: Data not published within the article will be shared by request from an investigator.

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Online Supplementary information

LUMINA Background information

Dutch migraine patients aged 18-80 years were recruited via nationwide public announcement, advertising in lay press and our research website (www.lumc.nl/hoofdpijn). They were considered eligible after a two-step inclusion process using validated questionnaires via the dedicated Leiden University MIgraine Neuro-Analysis (LUMINA) website. Additionally, patients attending our outpatient headache clinic were invited to participate by a letter. Patients were first asked to fill out a validated web-based screening questionnaire with a sensitivity of 0.93 and specificity of 0.36.[1] Patients who fulfilled the screening criteria, were sent a validated web-based extended migraine questionnaire[2], based on the International Classification of Headache Disorders criteria (previously ICHD-2, now ICHD-3 version) criteria.[3] The specificity of the second questionnaire was 0.95 and sensitivity was 0.45.[2] This questionnaire is accessible for patients via our research website and is described in English in detail by van Oosterhout et al. 2011.[2] We consider the cohort a well-defined web-based cohort. Four percent of subjects were included from our headache outpatient clinic and 87% of the participants were previously diagnosed with migraine by a physician. In addition to questions that were necessary to diagnose migraine accurately, the extended questionnaire also included items on demographic factors, aura and headache characteristics, acute and prophylactic headache medication use, and allodynia. Participants unable to use the web-based questionnaires due to lack of the needed internet skills were allowed to fill out the questionnaires on paper.

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CHAPTER 6

Jealousy in women with migraine: A cross- sectional case-control study

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Abstract

Background Estrogen influences susceptibility to migraine attacks and it has been suggested to affect jealousy in romantic relationships in women. Therefore, we hypothesized that migraine women may be more jealous.

Methods Jealousy levels and hormonal status were determined based on a cross-sectional, web-based, questionnaire study among female migraine patients and controls. A random sample of participants was selected from a validated migraine database. Participants with a serious and intimate monogamous relationship were included (n = 498) and divided into the following subgroups: menstrual migraine (n = 167), non-menstrual migraine (n = 103), postmenopausal migraine (n = 117), and premenopausal (n = 57) and postmenopausal (n = 54) controls. The primary outcome was the difference in mean jealousy levels between patients with menstrual migraine, non-menstrual migraine and premenopausal controls. Results were analyzed with a generalized linear model adjusting for age, relationship duration and hormonal status (including oral contraceptive use). Additionally, the difference in jealousy levels between postmenopausal migraine patients and controls was assessed. Previous research was replicated by evaluating the effect of combined oral contraceptives on jealousy.

Results Jealousy levels were higher in menstrual migraine patients compared to controls (mean difference ± SE: 3.87 ± 1.09, $p = 0.001$), and non-menstrual migraine patients compared to controls (4.98 ± 1.18, $p < 0.001$). No difference in jealousy was found between postmenopausal migraine patients and controls (-0.32 ± 1.24, $p = 0.798$). Women using combined oral contraceptives were more jealous compared to non-users with a regular menstrual cycle (2.32 ± 1.03, $p = 0.025$).

Conclusion Young women with migraine are more jealous within a romantic partnership.

Keywords: migraine, jealousy, estrogen

Background

Sex hormones have a major influence on migraine, appearing from a three times higher migraine prevalence in premenopausal women compared to men, an increase in attack frequency during menopausal transition, and a postmenopausal decrease of symptoms.[1-3] Furthermore, the fluctuation of estrogen prior to menstruation is evidently linked to an increased susceptibility to an upcoming attack.[4] Two subtypes of migraine with menstruation-associated attacks exist: pure menstrual migraine (PMM) and menstrually-related migraine (MRM). In MRM, attacks occur additionally at other times of the cycle. For research purposes, PMM and MRM are often taken together and defined as menstrual migraine (MM).[5] Although the exact pathophysiological underlying mechanism remains unclear, previous research has suggested that fluctuations in estrogen levels, possibly the rate of decrease in estrogen, may affect the susceptibility to migraine attacks in women and/or higher estrogen levels may be implicated in both sexes.[2,6-9]

Problems within a romantic relationship, such as jealousy, divorce, and bereavement after the suicide of a partner potentially have a large impact on quality of life.[10,11] Knowledge on potential associations between relationship problems and disabling chronic diseases, such as migraine, may increase our understanding, reduce stigma, and improve disease outcomes. Relationship jealousy can be defined as thoughts, emotions, or behaviors that occur as a result of the perceived threat of losing a partner to an actual or imagined rival.[12] In the fertile phase, when estrogen levels are high, women tend to report higher jealousy levels compared to other times of the menstrual cycle.[13] Furthermore, jealousy seems to be affected by the use of combined oral contraceptives. Especially using formulations with higher doses of ethinyl estradiol are associated with significantly higher jealousy scores.[13-15] These findings indicate that estrogen plays a role in jealousy within a romantic relationship, but the exact underlying mechanism is unknown.

That biological factors may affect mental health has been illustrated by previous research concluding that alterations in prolactin and thyroid hormone levels are associated with suicide attempts in psychiatric patients.[16]

We hypothesized that women with migraine, especially those fulfilling the criteria of MM, would have higher jealousy levels compared to women with non-menstrual migraine (non-MM) and premenopausal controls due to a corresponding provoking effect of estrogen in migraine and jealousy. Secondarily, we hypothesized that postmenopausal

migraineurs and controls report low and similar jealousy levels due to stabilization of sex hormones.[3,17] Lastly, we investigated the effect of using combined oral contraceptives on jealousy, aiming to replicate previous results on this topic.

Methods

Study Design

This study is a cross-sectional, web-based, questionnaire study among female migraine patients and healthy controls, performed in November and December 2018.

Participants

The Leiden University Medical Center MIgraine Neuro Analysis (LUMINA) cohort was used to select women who met the ICHD-3 criteria for migraine and healthy controls.[5] An elaborate description of LUMINA participants and procedures is found in a previous publication and in additional file 1.[18] The study was approved by the medical ethics committee of Leiden University Medical Center. All subjects provided written informed consent prior to the study. A random selection of n = 1024 female migraine patients and controls was made from the LUMINA cohort for this present study.

As inclusion criterium participants were required to have a serious and intimate monogamous relationship, assuming that contributions are equally divided among the partners and both partners have a concern for the welfare of the other, and will therefore respond to each other's needs.[19] Pregnant and breastfeeding women were excluded. Additionally, women with a permanent primary amenorrhea, and therefore lifelong absence of menses, were excluded. Participants received a web-based questionnaire consisting of questions concerning relationship duration, jealousy feelings and thoughts, menstrual cycle status and exogenous sex hormone use. Jealousy scores were determined using the validated Buunks Jealousy scale (Cronbach's alpha = 0.843).[12] This questionnaire consists of five statements for each of the three sub-types of jealousy, i.e. reactive jealousy (a negative response to the emotional or sexual involvement of the partner with someone else), preventive jealousy (efforts to prevent intimate contact of the partner with someone else) and anxious jealousy (obsessive anxiety and worrying about the possibility of infidelity of the partner). A 5-point Likert scale was used to rate how strongly the participants agreed with the statements. Premenopausal migraine patients were categorized as MM or non-MM according to the ICHD-3 criteria.[5]

Covariates

The covariates age, relationship duration and hormonal status were chosen a-priori based on previous studies. Relationship duration was categorized as shorter or longer than 1 year. Although the effect of relationship duration on jealousy levels is inconsistent in previous studies, this covariate was reasoned to be important, and therefore, was included in this study.[20,21] Hormonal status was defined as the use of combined oral contraceptives (COC), use of other hormonal contraceptives or no use of hormonal contraceptives (i.e. naturally menstruating). Other hormonal contraceptives included desogestrel-only pills, levonorgestrel intrauterine devices, etonogestrel subcutaneous implants, medroxyprogesterone injections and an ethinylestradiol/etonogestrel ring. The naturally menstruating group consisted of women with a regular menstrual cycle (i.e. duration of 21 to 35 days) or irregular menstrual cycle (i.e. shorter than 21 days, longer than 35 days or irregular). The use of hormonal contraceptives has been shown to increase jealousy levels and was an important covariate to include in our analyses.[13,14]

Statistical analyses

One-way ANOVA or Chi-square tests were used to compare the characteristics between the different groups. For our primary analysis we performed a generalized linear model to assess the mean difference between the total self-reported jealousy scores of MM, non-MM and premenopausal controls. Age, relationship duration and hormonal status were included as covariates. In a secondary analysis, we compared the mean total jealousy levels of postmenopausal migraine patients and controls using a generalized linear model, adjusting for age and relationship duration. The same statistical model was used to compare mean jealousy levels between women using COC and women with a regular menstrual cycle, controlling for age, relationship duration and migraine status. Mean differences in sub-type jealousy levels were analyzed for the premenopausal groups as exploratory analyses. A p-value of < 0.05 was considered statistically significant.

Results

Participants

A total of 1024 patients were invited to participate in this study, of which 498 were eligible and completed the questionnaire (see Figure 1). The characteristics of the premenopausal and postmenopausal study populations are shown in Tables 1 and 2, respectively. The majority of premenopausal migraine patients was classified as MM (62%), of which 38% fulfilled the criteria of migraine with aura. In the non-MM group, 60% of patients had

migraine with aura. The number of migraine days per month was higher in women with MM compared to women with non-MM, with at least one migraine day per week in 38% of the MM group compared to 20% in the non-MM group. In the postmenopausal migraine group, 39% experienced at least one migraine day per week.

Premenopausal controls and MM patients were more likely to have a regular menstrual cycle than to use hormonal contraceptives. Non-MM patients more frequently used combined oral contraceptives or other hormonal contraceptives. Migraine and/or headache was in 38% of MM patients and in 30% of non-MM patients a reason to start using combined oral contraceptives. MM patients mentioned more frequently headache and/or migraine as reason for starting other hormonal contraceptives compared to non-MM patients (respectively 61% and 45%). Furthermore, women with MM were more likely to be irregularly cycling (20%) compared to controls (9%) and non-MM patients (7%).

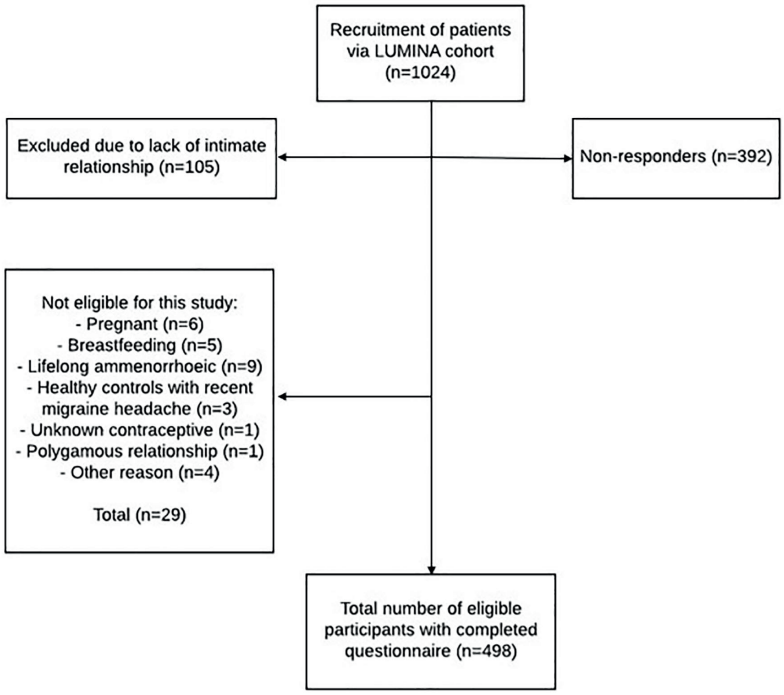
Women using combined oral contraceptives (COC) were younger than women who were regularly cycling (mean 34.9 and 38.5 years, respectively). The percentage of women with a relationship duration of at least 1 year in the COC group was 89%, which was comparable to the group with a regular menstrual cycle (96%). Furthermore, 82% of participants in the COC group had migraine, compared to 79% of the women with a regular menstrual cycle.

Table 1. Characteristics of the premenopausal study population.

	Control (n = 57)	non-MM (n = 103)	MM (n = 167)	p-value
Age, y, mean (SD)	37.2 (9.7)	37.5 (10.3)	38.8 (9.3)	0.401
Relationship duration > 1 year, n (%)	50 (87.7)	89 (86.4)	160 (95.8)	0.015
BMI, mean (SD)	23.1 (3.7)	23.5 (4.1)	23.7 (4.0)	0.594
Menstrual cycle, n (%)	29 (50.9)	31 (30.1)	102 (61.1)	< 0.001
Regular menstrual cycle	24 (42.1)	24 (23.3)	68 (40.7)	
Irregular menstrual cycle	5 (8.8)	7 (6.8)	34 (20.4)	
COC	15 (26.3)	30 (29.1)	37 (22.2)	
Other hormonal contraceptive	13 (22.8)	42 (40.8)	28 (16.8)	
Migraine frequency, n (%)				< 0.001
≤ 1 day/month	-	40 (38.8)	23 (13.8)	
1-4 days/month	-	42 (40.8)	80 (47.9)	
≥ 5 days/month	-	21 (20.4)	64 (38.3)	
Type of migraine, n (%)				< 0.001
Without aura	-	41 (39.8)	103 (61.7)	
With aura	-	62 (60.2)	64 (38.3)	

Non-MM = non-menstrual migraine, MM = menstrual migraine, COC = combined oral contraceptive. A relationship is defined as a serious and intimate monogamous relationship. A regular menstrual cycle is defined as a menstrual cycle duration of 21 to 35 days. Irregular menstrual cycle duration is defined as shorter than 21 days, longer than 35 days or an irregular duration.

Figure 1. Flow diagram of recruitment of participants.



Primary analysis

There was a significant difference in mean total self-reported jealousy levels between MM, non-MM and premenopausal control groups, $X^2(2) = 18.05$, $p < 0.001$. After adjusting for age, relationship duration and hormonal status, the difference between groups remained statistically significant, $X^2(2) = 18.67$, $p < 0.001$. A pairwise comparison with Bonferroni correction revealed that the mean jealousy levels were higher in patients with MM compared to controls (mean difference ± SE: 3.87 ± 1.09, $p = 0.001$), and in non-MM patients compared to controls (4.98 ± 1.18, $p < 0.001$). There was no difference in jealousy levels between the MM and non-MM group (-1.11 ± 0.93, $p = 0.705$) (see Figure 2). Age was negatively correlated with jealousy levels, resulting in a decline of 0.49 points per 5 years, $X^2(1) = 5.1$, $p = 0.024$. The homogeneity of variance, tested with a Levene's test of equality of error variances, was violated in this primary analysis ($F(2,324) = 8.94$, $p < 0.001$). However, using a robust model did not alter the outcome, therefore no adjustments were made to correct for this violation.

Table 2. Characteristics of the postmenopausal study population.

	Postmenopausal control (n = 54)	Postmenopausal migraine (n = 117)	p-value
Age, y, mean (SD)	59.9 (6.2)	58.1 (6.7)	0.093
Relationship duration > 1 year, n (%)	54 (100)	115 (98.3)	0.334
BMI, mean (SD)	24.8 (3.6)	24.6 (4.4)	0.731
Migraine frequency, n (%)			
≤ 1 day/month	-	26 (22.2)	
1-4 days/month	-	45 (38.5)	
≥ 5 days/month	-	46 (39.3)	
Type of migraine, n (%)	-		
Without aura	-	68 (58.1)	
With aura		49 (41.9)	

A relationship is defined as a serious and intimate monogamous relationship.

Secondary analyses

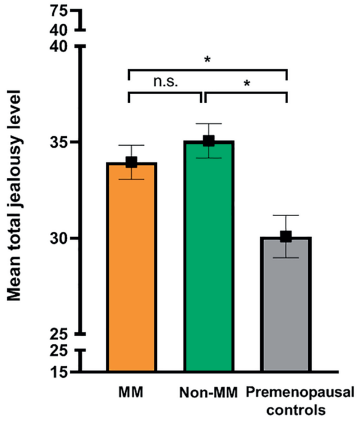
Mean total jealousy levels were similar in postmenopausal migraine patients and controls (mean difference ± SE: -0.41 ± 1.23, p = 0.737). Adjusting for age and relationship duration did not influence the outcome (-0.32 ± 1.24, p = 0.798) (see Figure 3). Women using COC reported higher jealousy levels compared to women with a regular menstrual cycle (2.32 ± 1.03, p = 0.025). After adding age and relationship duration as covariates, this effect became borderline significant (1.86 ± 1.04, p = 0.073). Women with a relationship duration of at least 1 year scored 4.9 points lower compared to women with a relationship duration of less than 1 year, $X^2(1) = 5.6$, p = 0.018. The presence of migraine was associated with an increase of 3.6 points in jealousy levels ($X^2(1) = 8.6$, p = 0.003). However, adding migraine status as covariate did not alter the overall effect of using COC on jealousy levels (1.77 ± 1.02, p = 0.081) (Table 3). Migraine attack frequency was not added as covariate as it did not affect jealousy levels in both, the total group of migraine patients ($X^2(5) = 3.14$, p = 0.678) and the subgroup of premenopausal migraine patients ($X^2(5) = 5.53$, p = 0.355).

Exploratory analyses

Mean differences in the three sub-type jealousy levels (reactive jealousy, preventive jealousy and anxious jealousy) were analyzed for the premenopausal groups as exploratory analyses. A pairwise comparison with Bonferroni correction revealed that both MM and non-MM groups reported higher levels compared to the premenopausal control group for the reactive jealousy sub-type (mean difference ± SE: 1.89 ± 0.64, p = 0.010 and 1.97 ± 0.70, p = 0.014, respectively). Similarly, both MM and non-MM groups reported higher anxious jealousy levels compared to premenopausal controls (1.24 ± 0.49, p = 0.035 and

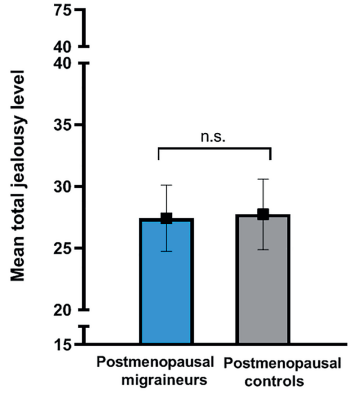
1.83 ± 0.53, p = 0.002, respectively). No statically significant difference was found in mean preventive jealousy levels between premenopausal controls and MM patients (-0.74 ± 0.35, p = 0.104). Non-MM patients reported higher mean preventive jealousy scores compared to premenopausal controls (1.18 ± 0.38, p = 0.005).

Figure 2. Mean of total jealousy levels controlled for age, relationship duration and hormonal status.



Premenopausal women: MM = menstrual migraine; non-MM = non-menstrual migraine; Premenopausal non-migraine controls. Jealousy levels were determined using the validated Buunks Jealousy scale (score between 15 and 75). Depicted levels are mean ± SEM. * = statistically significant difference, n.s. = non-statistically significant difference.

Figure 3. Mean of total jealousy levels controlled for age and relationship duration.



Postmenopausal women: Postmenopausal migraine patients; Postmenopausal non-migraine controls. Jealousy levels were determined using the validated Buunks Jealousy scale (score between 15 and 75). Depicted levels are mean ± SEM. n.s. = non-statistically significant difference.

Table 3. Comparison of jealousy levels between women using COCs and women with a regular menstrual cycle.

	Combined oral contraceptive (n = 82)	Regular menstrual cycle (n = 116)	p-value
Unadjusted (mean ± SE)	34.3 ± 0.79	31.9 ± 0.67	0.025
Adjusted for age and relationship duration (mean ± SE)	36.1 ± 1.16	34.2 ± 1.13	0.073
Adjusted for age, relationship duration and migraine status (mean ± SE)	35.1 ± 1.18	33.4 ± 1.14	0.081

Discussion

Premenopausal women with migraine in a relationship have significantly higher jealousy scores than controls in this study. This is independent from whether they experience menstrually-related attacks and the effect disappears after menopause. Our hypothesis is that this association between migraine and increased jealousy is due to the effect of estrogen. Previous research showed estrogen levels to be higher in women with MM compared to controls during most phases of the menstrual cycle, and with only small differences between MM and non-MM patients.[7,8] As estrogen levels will be low in the postmenopausal stage of life we expected that difference in jealousy levels would diminish and indeed we did not find differences when comparing postmenopausal female migraine patients with controls supporting our hypothesis. Interestingly, we did not find a significant difference in jealously between patients with menstrually-related attacks (MM) and those without menstrually-related attacks (non-MM). We imagine that there might be one important explanation for this, namely the inaccuracy of non-diary self-reported MM or non-MM diagnosis. In a recent study, we asked 104 female migraine patients whether their attacks were associated with the menstruation and then collected prospective E-diaries. In this study, we showed women's self-reported diagnoses had a positive predictive value of 65% and negative predictive value of 50%. Sensitivity was 80% and specificity 33%.[22] Accurate MM diagnoses are difficult to obtain even when prospective diaries are collected. Previous research has shown that current ICHD-3 diagnostic criteria for MM reached maximum sensitivity only for three menstrual cycles, although specificity increased with more cycles of data collection.[23] Thus, accuracy of self-reported menstrual-related migraine diagnosis is poor in female migraine patients and we suggest to reconsider the IHCD-3 criteria for menstrual migraine where no prospective diary data is required anymore to confirm MM.

Are there alternative explanations for our findings? The effect of a disabling chronic disease on the quality of life might explain the higher jealousy response within romantic relationships in female migraine patients. The most recent Global Burden of Disease study ranked migraine as the second most disabling disease worldwide.[24] Previous studies showed that migraine patients scored lower on health-related quality of life domains than controls, such as social functioning and mental health.[25,26] Female migraine patients might have less social interaction compared to their partners, both during a migraine attack due to severe headache and disabling associated symptoms, but also outside migraine attacks due to an adjusted lifestyle trying to prevent migraine attacks. One could imagine that a disbalance in social interactions in a romantic relationship may induce jealousy towards a partner. Studying the association between other disabling chronic diseases and jealousy within romantic relationships may be of interest in this light. Although postmenopausal women with migraine are limited in social activities, their jealousy response is comparable to that of postmenopausal controls, suggesting that impaired social functioning only partially contributes to the difference in jealousy between younger migraine patients and controls. Several population-based studies have analysed the prevalence of disabling pain disorders and associated risk factors. Separated or divorced status is consistently associated with an increased risk of (chronic) pain in women.[27-29] Additionally, separation and divorce have been suggested to be a risk factor for worsening outcomes in pain disorders with persisting pain.[30] This knowledge might be helpful in understanding the potential adverse effects of migraine on the relationships of patients, such as jealousy and potentially divorce.

A recent meta-analysis on personality of migraine patients has shown higher risk for neuroticism and harm avoidance, and for low self-directedness and extraversion in migraineurs,[31] which hypothetically may be involved in more pronounced reactive and anxious jealousy scores than preventive scores for MM patients.

Women using combined oral contraceptives reported higher jealousy compared to non-using women with a regular menstrual cycle, which is congruent with previous studies.[13,20] With this, our study contributes to the existing literature by using a different study population and adjusting for relevant covariates, which limits potential confounders and increases the validity. Participants in our study were older and had a longer relationship duration compared to participants in other studies, who were students between the age of 22 and 33 years with a mean relationship duration of one year.[13,20] The higher jealousy levels in women using combined oral contraceptives might be caused by an effect of estrogen, which is suggested to influence jealous behavior.[14,15] Progesterone dose in combined

oral contraceptives is shown to be unrelated to reported jealousy, but combined oral contraceptives with higher doses of ethinyl estradiol are associated with higher jealousy compared with formulations with lower ethinyl estradiol doses.[14,15]

This study has a number of strengths. A large number of participants from the reliable LUMINA cohort were recruited. Furthermore, a validated jealousy scale was used, with a Cronbach's alpha of 0.843 indicating a very good internal consistency. However, some limitations of our study should be mentioned. Firstly, a considerable part of invited women were classified as non-responders. The non-response rate could partially be explained by women who were not eligible for participation, e.g. as they had no romantic partnership at the time of the study but refrained from informing the investigators. Secondly, as indicated the MM and non-MM diagnoses in this study were not based on diary data as this is not a requirement anymore in the ICHD-3 classification. In addition, the phase of the menstrual cycle at the time of completing the questionnaire is unknown. In a prior study, higher jealousy levels were found in the fertile phase compared to the non-fertile phase of the menstrual cycle. However, this effect became marginally significant when comparing the menstrual cycle phases in partnered women.[13] Since we included only partnered women, this is thus thought to be of less importance for our results. Additionally, since the percentage of women with a regular menstrual cycle in the MM and control group is comparable (41% vs. 42% respectively), the amount of women in the fertile and non-fertile phase is expected to be equally distributed in these groups.

Conclusions

Our study is the first to show that young migraine women are more jealous within a romantic partnership than non-migraine women. We suggest estrogen to play an important role in this relationship. Future research is needed on establishing the role of estrogen in women with migraine as this may provide important treatment options for this incapacitating disorder. We encourage physicians treating patients with migraine to pay attention to aspects of social functioning.

Abbreviations: COC: combined oral contraceptives; LUMINA: Leiden University Medical Centre MIgraine Neuro Analysis; MM: menstrual migraine; MRM: menstrually-related migraine; non-MM: non-menstrual migraine; PMM: pure menstrual migraine

Authors' contributions: DvC and GT contributed to the study design. DvC and FvW were responsible for running the study. DvC carried out the statistical analyses with help from

FvW. All authors contributed to the interpretation of the results. DvC made the figures and wrote the initial draft of the manuscript. FvW, GT and AMvdB critically revised the article, and all authors approved the final version for submission.

Ethics approval and consent to participate: The study was approved by the medical ethics committee of Leiden University Medical Center (METC number P12.201). All subjects provided written informed consent prior to the study.

Availability of data and material: Data not published within the article is available from the corresponding author on reasonable request.

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Online supplementary information

LUMINA Background information

Dutch migraine patients aged 18-80 years were recruited via nationwide public announcement, advertising in lay press and our research website (www.lumc.nl/hoofdpijn). They were considered eligible after a two-step inclusion process using validated questionnaires via the dedicated Leiden University MIgraine Neuro-Analysis (LUMINA) website. Additionally, patients attending our outpatient headache clinic were invited to participate by a letter. Patients were first asked to fill out a validated web-based screening questionnaire with a sensitivity of 0.93 and specificity of 0.36.[1] Patients who fulfilled the screening criteria, were sent a validated web-based extended migraine questionnaire[2], based on the International Classification of Headache Disorders criteria (previously ICHD-2, now ICHD-3 version) criteria.[3] The specificity of the second questionnaire was 0.95 and sensitivity was 0.45.[2] This questionnaire is accessible for patients via our research website and is described in English in detail by van Oosterhout et al. 2011.[2] We consider the cohort a well-defined web-based cohort. Four percent of subjects were included from our headache outpatient clinic and 87% of the participants were previously diagnosed with migraine by a physician. In addition to questions that were necessary to diagnose migraine accurately, the extended questionnaire also included items on demographic factors, aura and headache characteristics, acute and prophylactic headache medication use, and allodynia. Participants unable to use the web-based questionnaires due to lack of the needed internet skills were allowed to fill out the questionnaires on paper.

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CHAPTER 7

General Discussion

In this thesis, clinical manifestations of sex hormonal influences in migraine are investigated by examining clinical sex differences and female-specific characteristics.

Part I: Clinical sex differences in migraine

Only little attention has been paid to sex differences in previous migraine-related research, which seems surprising given the large influence of sex on migraine prevalence. However, analysing results separately for men and women is often complicated by a lack of statistical power in individual studies due to low numbers of included men. This obstacle should be overcome since knowledge on differences in migraine characteristics and treatment response between men and women may increase understanding of underlying pathophysiological mechanisms such as the role of sex hormones and may contribute to sex-specific migraine treatment approaches. In this thesis, two studies are described on migraine-related sex differences, one on the effect of sex on the clinical response to triptans and another on sex differences in the prevalence of migraine trigger factors.

Sex differences in clinical response to triptans

Triptans are the most widely prescribed acutely acting migraine-specific treatments in both sexes. As a majority of women have been included in clinical trials evaluating the efficacy of triptans, the statistical power to study the effect of sex on triptan response has often been limited in individual studies. Chapter 2 describes a systematic review and meta-analysis investigating whether sex is an important determinant in the clinical response to triptans. In addition, sex differences in clinical response outcomes were related to sex-specific values of pharmacokinetic parameters.

Remarkably few studies presented the results of clinical trials with triptans separately for men and women. The available studies showed that women had a higher drug exposure, appearing from a higher peak drug concentration and area under the curve, which was reflected by equally good 2 hour response rates in men and women. The higher drug exposure in women was also reflected by a higher adverse event frequency after the intake of triptans than men. Despite higher drug exposure, women had higher headache recurrence rates, which was hypothesized to be due to menstrually related migraine attacks that are provoked by sex hormonal changes and tend to have a longer duration. This hypothesis was confirmed by the comparison of menstrually related migraine attacks and non-menstrually related migraine attacks based on an electronic diary (E-diary) study

presented in **chapter 5**, showing that menstrually related migraine attacks indeed had a longer duration and a higher risk of migraine recurrence within 24 and 48 hours. It can also be hypothesized that migraine attacks provoked by sex hormonal changes during perimenopause may contribute to the observed higher headache recurrence rates in women.

Physicians treating patients with migraine should be aware that dose reduction in order to reduce adverse events is undesirable, because this might further increase the risk for headache recurrence in women and might also affect initial efficacy.

Sex differences in prevalence of migraine trigger factors

The susceptibility to migraine attacks is suggested to be determined by natural fluctuations in neuronal excitability in the brain due to a complex interaction between internal threshold modulating factors and external modifiable factors. The internal threshold components are partly stable, such as genetic predisposition factors, and partly fluctuating, such as sex hormonal conditions.[1,2] External modifiable factors may trigger an attack especially when the threshold is already low, e.g. during a menstruation or after a period of sleep deprivation. **Chapter 3** presents a large cross-sectional study investigating sex differences in the prevalence of migraine trigger factors.

The top three most reported trigger factors in women were menstruation, stress, and exposure to bright light. Men reported stress, bright light, and sleep deprivation most frequently as provoking factors. Women reported more migraine trigger factors than men, even when menstruation was disregarded. It can be hypothesized that sex hormonal differences between men and women contribute to a different pattern of fluctuations in neuronal brain excitability and the internal migraine threshold, and therefore, to an increased potential of external trigger factors to provoke migraine in women. This hypothesis is supported by the finding that the total number of reported trigger factors by postmenopausal women with stabilized sex hormones was comparable to that in men.

For future studies it may be interesting to incorporate detailed information on triggers and attack occurrence as migraine patients may wrongly interpreted premonitory symptoms for triggers. As an example, migraine patients may perceive factors as bright sunlight and stress more intensely during the premonitory phase as a result of an enhanced neuronal susceptibility.[3]

The pathophysiological role of sex hormones in women with migraine

Besides obviously important peripheral neurovascular effects, estrogen and progesterone have opposite effects on neuronal excitability, with estrogen being excitatory and progesterone being inhibitory, which may have a role in modulating susceptibility to menstrual cycle-related disorders, such as menstrually related migraine and premenstrual syndrome.[4,5] Therefore, the observation that the onset of menstrually related migraine attacks is correlated with falling levels of estrogen seems counterintuitive.[1,6] Possibly, the rate of estrogen decline is implicated and estrogen withdrawal may only provoke a migraine attack after several days of high levels.[7,8] The exact underlying mechanisms remain unknown, but it is hypothesized that fluctuations in estrogen levels influence several regions of the trigeminovascular system, which is the main pathway involved in migraine.[5,9,10]

High concentrations of estrogen and progesterone receptors are located in the hypothalamus,[11] and sex hormonal fluctuations are suggested to induce an abnormal hypothalamic activation during migraine in women.[12,13] Although the pathophysiological role of the hypothalamus as generator of the trigeminal pain system is not undisputed, several hypothalamic descending projections have been shown to modulate trigeminovascular nociceptive processing.[14] In addition, imaging studies revealed that the hypothalamus is activated during the premonitory and headache phase of migraine attacks, and typical migraine premonitory symptoms such as fatigue and yawning, but also the association of attacks to circadian and menstrual cycles could be explained by involvement of the hypothalamus.[13,15-19] Fluctuations of estrogen levels also were shown to modulate calcitonin gene-related peptide (CGRP) in the trigeminovascular system.[20] CGRP is believed to play a key role in migraine pathophysiology by causing vasodilation of dural and pial vessels, mediating neurogenic inflammation, and transmission of nociceptive information from intracranial blood vessels to the central nervous system.[14,21] The periaqueductal gray is another region of the trigeminovascular system that is involved in the modulation of nociceptive responses, of which the output is enhanced by excitatory effects of estrogens that act on GABA-ergic neurons.[10,14]

Also cortical spreading depression (CSD), which is thought to be the underlying mechanism of the migraine aura is suggested to be affected by estrogen levels. High estrogen levels were shown to increase CSD susceptibility, whereas estrogen withdrawal and low estrogen levels appeared to decrease the risk for CSD.[22] This may explain why menstrually related migraine attacks are less likely to be associated with an aura as described in **chapter 5**.

The menopausal transition phase is also associated with an increased migraine prevalence, which is hypothesized to be provoked by estrogen withdrawal due to prolonged periods of amenorrhoea.[23-26] In this estrogen-deficient state, there is increased expression of neuropeptides within the infundibular nucleus of the hypothalamus, such as neurokinin B, which increases the pulsatile secretion of gonadotropin-releasing hormone (GnRH) and is involved in the susceptibility to vasomotor symptoms.[27-29] Pathophysiological involvement of neuropeptides such as neurokinin B in women with migraine during perimenopause might also be suggested because these hormones seem to be expressed in the trigeminovascular system and vasomotor symptoms have been reported to be more common in women with migraine.[23,27,30] Interestingly, targeting neurokinin B might thus be helpful in perimenopausal women with migraine, as it has also been shown to be effective in hot flushes.[31]

Part II: Clinical female-specific characteristics of migraine

The second part of this thesis focuses on the investigation of clinical female-specific characteristics of migraine. Sex hormonal changes during the luteal phase of the menstrual cycle increase the risk for menstrually related migraine attacks and also have been suggested to provoke symptoms of premenstrual syndrome.[32,33] Due to the strictly defined temporal relationships between both disorders and the menstruation, prospective diaries are needed to reliably confirm diagnoses of menstrually related migraine and premenstrual syndrome.[34,35] Moreover, there is a need for a high standard regarding the reliability of data in research and in clinical practice, which also requires daily diary registrations to reduce recall bias.[36] Therefore, a self-developed E-diary was introduced, which enabled obtaining reliable data on migraine-related outcomes, comparing migraine characteristics between menstrually related attacks and non-menstrually related attacks and determining the prevalence of premenstrual syndrome in women with migraine. Lastly, the association between romantic relationship jealousy and migraine was assessed in women since estrogen is suggested to play a major role in both conditions.

Introduction of an electronic headache diary

Most available daily E-diaries for migraine lack specificity as they fail to determine whether a reported day was fulfilling the ICHD-3 criteria for migraine and/or headache. In **chapter 4** a self-developed time-locked E-diary is described, including an automated algorithm differentiating headache and migraine days based on detailed characteristics

according to ICHD-3 criteria. The E-diary showed usefulness in diagnosing migraine when added to two previously validated headache E-questionnaires. Making diagnoses prior to a first consultation at the Headache Clinic has great relevance in a new era of emerging telemedicine. Additionally, the need for E-diaries to obtain reliable information was emphasized as patients did not reliably recall migraine-related frequency numbers, indicating that clinical decision making based on information from patients' memory is not recommended. The implementation of E-diaries in clinical headache practice could be indicative for other health care providers (e.g. GP's, general neurology practices and specialized headache clinics) that recently have been confronted with the need for telemedicine approaches and offers opportunities for research.

Differences between menstrually related and non-menstrually related attacks

Although some small and medium-sized diary-based studies suggested that menstrually related migraine attacks have a longer duration, are less responsive to acute therapy and are more likely associated with disability compared to non-menstrually related migraine attacks, the results of different studies have been inconsistent.[37-40] Therefore, in **chapter 5** the self-developed E-diary was used to perform a large prospective observational study aiming to provide conclusive results on differences in migraine characteristics between menstrually related attacks and non-menstrually related attacks. Menstrually related migraine attacks showed to have a longer duration with a higher risk of migraine recurrence compared to non-menstrually related attacks, which probably explains the observed higher recurrence rates after the use of triptans in women than in men as described in **chapter 2.** Additionally, menstrually related attacks were associated with a higher headache intensity, more pronounced photophobia and phonophobia, and decreased pain coping. The longer duration of menstrually related attacks with higher recurrence rates probably resulted in the observed increased use of triptans. Lastly, menstrually related migraine attacks were less frequently accompanied by auras, but no differences were observed on 2 hour triptan response rates, nausea, vomiting and the use of analgesics. Results of **chapter 2** showed that women have a higher triptan exposure compared to men, which is reflected by equally good 2 hour response rates in both sexes. Therefore, the similar 2 hour response rates in menstrually related and non-menstrually related attacks were in accordance with expectations.

Premenstrual syndrome and migraine

Several hypotheses have been formulated on an important role of the hypothalamic–pituitary–gonadal axis in premenstrual syndrome. It has been suggested to be triggered

by decreasing progesterone levels during the late luteal phase because progesterone regulates the expression of the GABA(A) receptor.[41] Others suggest that premenstrual symptoms are provoked by the preovulatory peak in estradiol and/or by the postovulatory increase in progesterone.[42,43] The sex hormone sensitivity hypothesis suggests that women with premenstrual syndrome have an altered sensitivity to normal sex hormonal fluctuations at the receptor level.[44-47] Growing evidence suggests that affective symptoms of premenstrual syndrome reflect suboptimal GABA(A) receptor sensitivity to fluctuating levels of the positive modulator allopregnanolone.[48] Allopregnanolone is a neuroactive metabolite of progesterone and has an inhibitory effect on neuronal excitability.[49] Reduced levels of allopregnanolone have been associated with the development of depressive disorders and menstrual cycle-related disorders.[50] However, lower allopregnanolone levels following antidepressant treatment for severe premenstrual syndrome were shown to be associated with improvement of mood and behavioural symptoms.[51] In addition, subcutaneous injections with allopregnanolone antagonists during the luteal phase have shown promising results as a potential treatment for premenstrual dysphoric disorder, which is a severe form of premenstrual syndrome.[52] Recently, attention has also been paid to the role of allopregnanolone in women with menstrually related migraine. So far, conflicting results were observed regarding differences in serum allopregnanolone concentrations between women with migraine and women without migraine.[53,54] Allopregnanolone as a potential target in premenopausal women with migraine should be explored, especially in women who are also suffering from premenstrual syndrome.

Findings of previous small diary-based studies and retrospective cross-sectional studies on the existence of a comorbidity between menstrually related migraine attacks and premenstrual syndrome have been contradictory.[55-58] The large prospective observational E-diary study from **chapter 5** was also used to determine the prevalence of premenstrual syndrome as comorbidity in women with migraine. Premenstrual syndrome prevalence in women with migraine appeared to be comparable to the prevalence in the general population. Fulfilling criteria of menstrually related migraine did not affect premenstrual syndrome prevalence, which suggests that the provoking factor of sex hormonal changes during the luteal phase of the menstrual cycle is different in both disorders. Research on premenstrual syndrome in women with migraine is complicated by corresponding symptomatology of premenstrual syndrome, the premonitory phase of migraine attacks and symptoms of depression, which is strongly associated with migraine.

Jealousy in women with migraine

Estrogen plays a role in the susceptibility to migraine attacks and it has been suggested to affect jealousy in romantic relationships in women. In the fertile phase, when estrogen levels are high, women tend to report higher jealousy levels compared to other times of the menstrual cycle.[59] Furthermore, jealousy seems to be affected by the use of combined oral contraceptives. Especially using formulations with higher doses of ethinyl estradiol are associated with significantly higher jealousy scores.[60] Therefore, it could be hypothesized that women with migraine may be more jealous than women without migraine. In **chapter 6**, the association between romantic relationship jealousy and migraine is evaluated based on a validated jealousy questionnaire in premenopausal and postmenopausal women who were in a heterosexual or homosexual relationship. Premenopausal women with migraine showed to be more jealous in a romantic relationship compared to controls. This seemed independent from whether they experienced menstrually related attacks, although it should be noted that menstrually related migraine was not assessed with an E-diary. The difference in jealousy levels disappeared after menopause, which was hypothesized to be due to low and stabilized estrogen levels. However, another explanation may be that postmenopausal women have more long-lasting romantic relationships than younger migraine women who might be at the start of their relationships and still have to build trust in their partners.

Conclusions

Female-specific sex hormonal conditions are suggested to contribute to a lower internal migraine threshold, increasing the risk for menstrually related migraine attacks and potentiating the provoking effect of external trigger factors. Daily E-diary registrations are needed to correctly define menstrually related migraine attacks and to reliably determine migraine-related frequencies. Based on E-diary data, menstrually related migraine attacks were shown to have a longer duration with a higher risk of migraine recurrence, increased headache intensity, and decreased pain coping compared to non-menstrually related attacks. While women more often experienced adverse events after the intake of triptans than men due to a higher drug exposure, an increased intake was seen during menstrually related attacks compared to non-menstrually related attacks. The long attack duration of menstrually related migraine attacks with a high risk of recurrence may be the explanation for higher migraine recurrence rates after the use of triptans in women compared to men.

Future perspectives

The long duration of menstrually related migraine attacks with high risk of recurrence and reduced pain coping abilities emphasize the need to improve the understanding of the provoking role of sex hormones in women with migraine. The change in estrogen levels prior to the menstruation, possibly the rate of decrease in estrogen, is implicated in an increased susceptibility to migraine attacks,[8] but the exact provoking effect of sex hormonal changes remains unknown since the association with the occurrence of migraine attacks has often been undefined. A large case-control study is needed, not only examining absolute sex hormone levels during several time points of the luteal phase, but also ratios of sex hormones and the rate and amplitude of changes in sex hormone levels. Levels of metabolites of estrogen and progesterone, such as allopregnanolone and pregnenolone (sulfate), should also be investigated during the same time points to explore its potential role in women with migraine. Furthermore, CGRP measurements should not me omitted, because of its important role in the pathophysiology of migraine and results of previous studies have suggested that levels might be affected by sex hormones.[61-63] Apart from the above-mentioned hormone measurements, which all focus on sex aspects, also measurements of gender are of importance, since gender-related factors may influence the way symptoms are reported by patients. Such measurements should be accompanied by daily E-diary registrations in order to provide insight in the temporal relationship between specific sex hormonal findings and the occurrence of menstrually related migraine attacks. A similar case-control study with perimenopausal women could contribute to an increased understanding of the role of changing sex hormonal conditions in women with migraine during menopausal transition. In this group, it would be interesting to obtain information on the presence of climacteric symptoms and to add neurokinin B measurements, because of its involvement in the pathophysiology of vasomotor symptoms, and potentially, in migraine during perimenopause. Ultimately, all this knowledge will contribute to the development of an urgently needed female-specific prophylactic treatment intervening with sex hormones. To begin with, the potential efficacy of existing hormonal treatments, such as combined oral contraceptives, in the prevention of migraine attacks should be clarified.

Female migraine patients appeared to be poor at indicating whether the menstruation is a consistent trigger for their migraine attacks,[35] which suggests that confirmation of a close temporal relationship between other suspected trigger factors and the onset of migraine attacks based on E-diary registrations will improve the accuracy of trigger-related research.

Additionally, it would be interesting to investigate the triggering effect of perceived trigger factors throughout the menstrual cycle in order to test the hypothesis that sex hormonal fluctuations related to the menstruation and ovulation contribute to a lower internal migraine threshold, increasing the potential of external trigger factors to provoke migraine in women.

Trigger-related research is complicated by overlap of trigger factors and premonitory symptoms as some putative trigger factors might in fact be part of the premonitory symptom phase reflecting an already started attack. Symptomatology of premenstrual syndrome and the premonitory phase also partly correspond, which further complicates research on these topics. Large scale collection of daily E-diary data on the exposure to trigger factors and the experience of symptoms belonging to the premonitory phase and/or premenstrual syndrome offers possibilities for artificial intelligence approaches to determine their contribution in the prediction of an upcoming migraine attack. An algorithm may detect a pattern of features that specifically occur prior to the headache phase of menstrually related migraine attacks. However, the interpretation of obtained results and defining its implications will probably remain challenging.

Understandably, a majority of women is included in clinical trials on the efficacy and tolerability of acute and preventive migraine treatments. However, migraine researchers should be encouraged to analyze and present data by sex, because that will eventually enable researchers to perform meta-analyses investigating whether sex is an important determinant in the clinical response to these treatments.

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CHAPTER 8

Summary

Nederlandse Samenvatting

Summary

This thesis explores clinical manifestations of sex hormonal influences in migraine with the ultimate goal to increase the understanding of the role of sex hormones in women and to contribute to the effectuation of sex-specific migraine treatment approaches. The research is divided in two parts. **Part I** describes studies examining clinical sex differences in migraine, and **Part II** describes studies focussing on clinical female-specific characteristics of migraine.

Part I starts with a description of a systematic review and meta-analysis in **chapter 2**, investigating sex differences in the efficacy of triptans. Remarkably, few authors presented their results of clinical trials with triptans separately for men and women. Based on the available data, a higher adverse event frequency after the intake of triptans was observed in females compared to males, which may be due to a combination of a higher drug exposure and a larger tendency to report adverse drug reactions. Despite higher drug exposure, women more often experienced headache recurrence after an initially adequate triptan response, which is probably due to the occurrence of menstrually related migraine attacks that generally have a longer duration. Physicians are advised not to apply a dose reduction in order to reduce adverse events in women, because this might further increase the risk for headache recurrence and may also affect initial efficacy.

Chapter 3 describes a large cross-sectional study investigating sex differences in the prevalence of migraine trigger factors. The top three most reported trigger factors in women were menstruation, stress, and exposure to bright light. Men reported stress, bright light, and sleep deprivation most frequently as provoking factors. Furthermore, women reported more migraine trigger factors than men, also after disregarding menstruation. It is suggested that female-specific sex hormonal fluctuations contribute to a lower internal migraine threshold, and therefore, to an increased potential of external trigger factors to provoke migraine attacks in women.

Part II starts with an introduction of a self-developed electronic diary (E-diary) in **chapter 4**, including an automated algorithm differentiating headache and migraine days based on detailed characteristics according to ICHD-3 criteria. The E-diary showed usefulness in diagnosing migraine prior to a first consultation at the Headache Clinic when added to two previously validated headache E-questionnaires. In addition, the need for E-diaries

to obtain reliable information is emphasized as patients did not reliably recall monthly migraine-related frequency numbers.

Chapter 5 describes a large prospective observational E-diary study, investigating differences in migraine characteristics between menstrually related attacks and non-menstrually related attacks. In addition, the prevalence of premenstrual syndrome as comorbidity in women with migraine is determined. Menstrually related migraine attacks showed to have an increased headache intensity and a longer duration with a higher risk for headache recurrence compared to non-menstrually related attacks, which probably explains the increased use of triptans during menstrually related attacks. Menstrually related attacks were less frequently associated with auras, but no differences were observed on 2 hour triptan response rates, nausea, vomiting and the use of analgesics. The prevalence of premenstrual syndrome in women with migraine was comparable to the prevalence in the general population. Fulfilling criteria of menstrually related migraine did not affect premenstrual syndrome prevalence, which suggests that the provoking factor of sex hormonal changes during the luteal phase of the menstrual cycle is different in both disorders.

Estrogen plays a role in the susceptibility to migraine attacks and it has been suggested to affect jealousy in romantic relationships in women. In Chapter 6 a case-control study is presented, comparing jealousy levels within romantic relationships between women with migraine and controls. Premenopausal women with migraine showed to be more jealous compared to controls, which was independent from whether they experienced menstrually related attacks. The difference in jealousy levels disappeared after menopause, possibly due to low and stabilized estrogen levels. It is suggested that estrogen plays an important role in the relationship between migraine and jealousy, which stresses the need to elucidate the exact role of estrogen in women with migraine.

Finally, chapter 7 provides a general discussion and suggests possibilities for future research.

Nederlandse Samenvatting

In dit proefschrift worden de klinische uitingen van de invloed van geslachtshormonen in migraine onderzocht, met als uiteindelijk doel de kennis over de rol van geslachtshormonen bij vrouwen te vergroten en bij te dragen aan het realiseren van sekse-specifieke behandelstrategieën. Het onderzoek is opgesplitst in twee delen. **Deel I** beschrijft studies waarin klinische sekse verschillen in migraine worden onderzocht, en **deel II** beschrijft studies over klinische vrouwspecifieke kenmerken van migraine.

Deel I begint met een beschrijving van een systematische review en meta-analyse in **hoofdstuk 2,** waarbij is gekeken naar sekse verschillen in de effectiviteit van triptanen. Opmerkelijk weinig auteurs hebben de resultaten van klinische onderzoeken met triptanen gescheiden voor mannen vrouwen gepresenteerd. Op basis van de beschikbare gegevens werd geconcludeerd dat vrouwen vaker bijwerkingen ervaren na de inname van triptanen dan mannen, wat mogelijk komt door een combinatie van een grotere blootstelling aan het geneesmiddel en een grotere neiging om bijwerkingen te rapporteren. Ondanks de grotere blootstelling kwam de hoofdpijn bij vrouwen vaker terug nadat een triptan tijdelijk goed effect had, wat waarschijnlijk komt door het optreden van menstruatie-gerelateerde migraine aanvallen die over het algemeen langer duren. Dokters worden geadviseerd niet de dosis te verlagen om bijwerkingen bij vrouwen te verminderen, omdat dit het risico op terugkeer van hoofdpijn verder kan verhogen en mogelijk ook de initiële effectiviteit kan beïnvloeden.

Hoofdstuk 3 beschrijft een groot cross-sectioneel onderzoek naar sekse verschillen in de prevalentie van migraine triggerfactoren. De drie meest gerapporteerde triggerfactoren bij vrouwen waren de menstruatie, stress en blootstelling aan fel licht. Mannen rapporteerden stress, fel licht en slaapgebrek als meest voorkomende uitlokkende factoren. Verder rapporteerden vrouwen meer migraine triggerfactoren dan mannen, ook wanneer de menstruatie buiten beschouwing gelaten werd. Er wordt gesuggereerd dat vrouwspecifieke schommelingen in geslachtshormonen bijdragen aan een lagere interne migraine drempel, waardoor externe triggerfactoren makkelijker een migraine aanval kunnen uitlokken bij vrouwen.

Deel II begint met een introductie van een zelfontwikkeld elektronisch dagboek (E-dagboek) in **hoofdstuk 4**, dat met een geautomatiseerd algoritme onderscheid maakt tussen hoofdpijn- en migrainedagen op basis van gedetailleerde kenmerken volgens de ICHD-3 criteria. Het E-dagboek bleek bruikbaar te zijn voor het stellen van een migraine diagnose

voorafgaand aan een eerste consult op de Hoofdpijnpolikliniek wanneer het samen met twee eerder gevalideerde hoofdpijn E-vragenlijsten wordt toegepast. Bovendien wordt benadrukt dat het gebruik van E-dagboeken noodzakelijk is om betrouwbare informatie te verkrijgen, omdat patiënten zich maandelijkse migraine gerelateerde aantallen niet goed konden herinneren.

Hoofdstuk 5 beschrijft een grote prospectieve observationele E-dagboekstudie waarin de verschillen in klinische migraine kenmerken tussen menstruatie-gerelateerde aanvallen en niet-menstruatie-gerelateerde aanvallen worden onderzocht. Daarnaast werd de prevalentie van het premenstrueel syndroom als comorbiditeit bij vrouwen met migraine bepaald. Menstruatie-gerelateerde aanvallen hadden een hogere hoofdpijnintensiteit en een langere duur met een hogere kans op terugkeer van hoofdpijn dan niet-menstruatie-gerelateerde aanvallen, wat waarschijnlijk het hogere gebruik van triptanen tijdens de menstruatie-gerelateerde aanvallen verklaart. Menstruatie-gerelateerde migraine aanvallen gingen minder vaak gepaard met aura's, maar er werden geen verschillen gevonden in de effectiviteit van triptanen na 2 uur, misselijkheid, braken en het gebruik van analgetica. De prevalentie van premenstrueel syndroom in vrouwen met migraine was vergelijkbaar met de prevalentie in de algemene bevolking. Het voldoen aan de criteria van menstruatie-gerelateerde migraine had geen effect op de premenstrueel syndroom prevalentie, wat suggereert dat de uitlokkende factor van de veranderingen in geslachtshormoonlevels tijdens de luteale fase van de menstruatiecyclus bij beide aandoeningen verschillend is.

Oestrogeen speelt een rol in de gevoeligheid voor migraine aanvallen en het lijkt bij vrouwen ook invloed te hebben op de mate van jaloezie in een romantische relatie. In **hoofdstuk 6** wordt een case-control onderzoek gepresenteerd waarin de mate van jaloezie in een romantische relatie wordt vergeleken tussen vrouwen met migraine en vrouwen zonder migraine. Premenopauzale vrouwen met migraine bleken jaloerser te zijn dan vrouwen zonder migraine, wat onafhankelijk was van het optreden van menstruatie-gerelateerde migraine aanvallen. Het verschil in de mate van jaloezie verdween na de menopauze, mogelijk door lage en gestabiliseerde oestrogeenlevels. Er wordt gesuggereerd dat oestrogeen een belangrijke rol speelt in de relatie tussen migraine en jaloezie, wat benadrukt dat de exacte rol van oestrogeen in vrouwen met migraine opgehelderd moet worden.

Ten slotte wordt in **hoofdstuk 7** een algemene discussie gepresenteerd en worden mogelijkheden voor toekomstig onderzoek voorgesteld.

APPENDICES

List of Publications

PhD Portfolio

Curriculum Vitae

Dankwoord

List of Publications

I.E. Verhagen, D.S. van Casteren, S. de Vries Lentsch, G.M. Terwindt. Effect of lockdown during COVID-19 on migraine: a cohort study. *Cephalalgia 2021;* [Epub ahead of print].

D.S. van Casteren, T. Kurth, A.H.J. Danser, G.M. Terwindt, A. MaassenVanDenBrink. Sex differences in response to triptans: a systematic review and meta-analysis. *Neurology* 2021;96:162-170

D.S. van Casteren, I.E. Verhagen, G.L.J. Onderwater, A. MaassenVanDenBrink, G.M. Terwindt. Sex differences in prevalence of migraine trigger factors: a cross-sectional study. *Cephalalgia* 2020; [Epub ahead of print].

K.M. Linstra, K. Ibrahimi, D.S. van Casteren, M.J.H. Wermer, G.M. Terwindt, Antoinette MaassenVanDenBrink. Pain perception in women with menstrually-related migraine. *Cephalalgia* 2020; [Epub ahead of print].

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PhD Portfolio

PhD student	Daphne S. van Casteren
Department	Internal Medicine
	Division of Vascular Medicine and Pharmacology
Promotors	Prof. dr. A.H.J. Danser and Prof. dr. G.M. Terwindt
Copromotor	Dr. A. Maassen van den Brink

General academic and research skills	Year	5.2 ECTS
Introductory Meeting for PhD Candidates, LUMC, Leiden	2016	0.2
Basiscursus Regelgeving en Organisatie voor Klinisch onderzoekers (BROK)	2016	1.0
Statistics and Journal clubs, department of Neurology, LUMC, Leiden	2016-2020	2.5
Basic Methods and Reasoning in Biostatistics, LUMC, Leiden	2017	1.5

In-depth courses		7.7 ECTS
Systematic reviews and meta-analysis, EpidM VUmc, Amsterdam	2017	1.2
Hoofdpijn IN-zicht, LUMC, Leiden	2017	0.3
iHead Meeting, The International Headache Society, London	2016	1.0
Regression Analysis, LUMC, Leiden	2019	1.5
Repeated Measurements, LUMC, Leiden	2019	1.5
iHead Meeting, The International Headache Society, Dublin	2019	1.0
Using R for Data Analysis, LUMC, Leiden	2019	1.2

Presentations		4.0 ECTS
Gender en Gezondheid, WOMEN Inc congress, Amersfoort *The Migraine-WHAT! Study - Women, Hormones, Attacks and Treatment* (Poster presentation)	2017	0.4
12th European Headache Federation Congress, Florence, Italy *Gender differences in clinical and pharmacological response to triptans* (Poster presentation)	2018	0.4
Science Days, Internal Medicine, Sint-Michielsgestel *Gender differences in clinical and pharmacological response to triptans* (Poster presentation)	2019	0.4
Iedere patiënt is anders, WOMEN Inc congress, Amsterdam *Gender differences in response to triptans* (Oral presentation)	2019	0.5
13th European Headache Federation Congress, Athens, Greece *Differences in sex hormone levels between female migraine patients and healthy controls* (Poster presentation)	2019	0.4
Hoofdpijn patiëntendag, LUMC, Leiden *The use of electronic headache diaries at the outpatient clinic* (Oral presentation)	2019	0.7
Gender Summit, Amsterdam *Self-reported prevalence of migraine trigger factors and patients willingness to participate in future trigger research* (Poster presentation)	2019	0.4

19th Congress of the International Headache Society, Dublin, Ireland *Gender differences in clinical and pharmacological response to triptans* (Poster presentation)	2019	0.4
Science Days Internal Medicine, Sint-Michielsgestel *Differences in sex hormone levels between female migraine patients and healthy controls* (Poster presentation)	2020	0.4

International conferences		3.0 ECT
12th European Headache Federation Congress, Florence, Italy	2018	1.0
13th European Headache Federation Congress, Athens, Greece	2019	1.0
19th Congress of the International Headache Society, Dublin, Ireland	2019	1.0

Seminars and workshops		3.5 ECTS
Wetenschappelijke jaarvergaderingen van de Nederlandse Hoofdpijn Vereniging (NHV)	2016-2019	1.0
Gender en Gezondheid, WOMEN Inc congress, Amersfoort	2017	0.3
Science Days Neurology, LUMC, Leiden	2017-2019	1.0
Sex, Drugs and Science congress, NVG&G, Rotterdam	2018	0.3
Iedere patiënt is anders, WOMEN Inc congress, Amsterdam	2019	0.3
Gender Summit, Amsterdam	2019	0.6

Teaching activities		9.0 ECTS
Minor Translational Neuroscience, LUMC, Leiden Practical teaching course - How to interview a headache patient	2017-2019	1.5
Scientific internship of bachelor medical students	2018-2019	4.0
Bachelor Medicine - Hersenen en Aansturing, LUMC, Leiden Interactive teaching courses	2019-2020	3.5

Curriculum Vitae

Daphne van Casteren was born on December 23, 1988 in Heemstede, the Netherlands. After finishing secondary school (Atheneum College Hageveld, Heemstede) in 2007, she moved to Amsterdam and started studying Biomedical Sciences at the University of Amsterdam. She passed her propaedeutic year. In 2008, she started to study Medicine at the University of Amsterdam. During medical school she completed elective internships at the Department of Paediatric Neurology of the Academic Medical Center in Amsterdam and at the Department of Neurology at Spaarne Gasthuis in Haarlem. After obtaining the degree of medical doctor in 2015 she worked as a resident (ANIOS) at the Department of Neurology at Tergooi ziekenhuis in Blaricum. From 2016 to 2020 she worked as a PhD candidate at the Department of Internal Medicine of the Erasmus Medical Center in Rotterdam and the Department of Neurology of the Leiden University Medical Center in Leiden under the supervision of Prof. dr. G.M. Terwindt, Prof. dr. A.H.J. Danser, and Dr. A. Maassen van den Brink. The results of this work are described in this thesis. From January 2021 she is working as a resident (ANIOS) at the Department of Neurology of the Leiden University Medical Center.

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