Observational Studies

Elena Muñoz Gómez, Marta Aguilar Rodríguez*, Pilar Serra Añó, Núria Sempere Rubio, Sara Mollà Casanova and Marta Inglés

Sex-related differences in migraine clinical features by frequency of occurrence: a cross-sectional study

https://doi.org/10.1515/sjpain-2022-0152
Received October 26, 2022; accepted April 26, 2023; published online May 15, 2023

Abstract

Objectives: The sex-related differences of migraine hold clinical relevance to achieve a better diagnosis and treatment. The purpose of this cross-sectional study was to evaluate sex-related differences in migraine features, the impact, and health care resources for people who suffer from episodic migraine (EM) and chronic migraine (CM).

Methods: 184 patients (72 % women; 61.4 % with EM; mean (SD) age of 38.7 (10.4) years) were assessed through the Migraine Disability Assessment, the Short Form 36 Health Survey, the Beck Depression Inventory II and the State-Trait Anxiety Inventory. Additionally, medication intake and medical assistance were recorded. Multivariate analyses were performed, stratifying by frequency of occurrence (EM and CM) and sex (men and women).

Results: The results showed that women presented a greater number of symptoms ($p=0.03$), pain intensity ($p<0.01$), pain duration ($p=0.03$), disability ($p=0.01$), amount of symptomatic medication ($p=0.04$) and medical visits ($p=0.001$), as well as a worse physical role ($p=0.004$) than men with EM. However, no significant differences between them were found for CM ($p>0.05$). Moreover, it was identified that there was a significant increase in medication intake among people with CM compared to EM ($p<0.001$). It is worth noting that there were no significant differences by diagnosis and sex in emotional status ($p>0.05$).

Conclusions: Migraine features, impact and health care resources were greater in women than men with EM; yet no significant differences between them were found for CM. The findings of the present study may contribute to a better diagnosis and treatment response in people with migraines.

Keywords: chronic pain; diagnosis; gender differences; migraine.

Introduction

Migraines are a common neurological disorder that affects 11.6 % of the adult population [1], and it is the leading cause of disability in the 15–49 age group [2, 3]. Migraines represent a high percentage of consultations with health professionals, as well as limitations in work productivity, thus causing a high socio-health cost [4, 5]. In this regard, chronic migraines (CM) are associated with higher medical resource use and total costs, compared to episodic migraines (EM) [6].

As in many pathological conditions, sex is a very important factor to consider. It is well known that migraines are more prevalent in women than in men [7]. Women are more likely to report higher migraine-related disability [7–9], increased risk of headache recurrence, a longer period of time required to recover [10], and a higher prevalence of migraine trigger factors [11] and associated symptoms [9] than men. However, it is not only hormonal factors have been proposed to explain such differences between men and women [10, 12], but also brain function and structure [13], or even genetic and epigenetic mechanisms [14, 15]. Today, despite the impact of this disabling condition amongst the population, many people have unmet needs related to consultation, diagnosis, and treatment [16]. Indeed, migraines are commonly underdiagnosed in men [10]. Public health efforts should focus on improving diagnostic accuracy in people who suffer from migraines [17]. This further highlights the importance of detecting sex-specific hallmarks of migraines which may allow preventive strategies and individualised therapies.

Migraines have a negative impact on quality of life [18], especially in young patients with a high frequency of

***Corresponding author: Marta Aguilar Rodríguez**, C/Gasco Oliag, Valencia, Spain, E-mail: marta.aguilar@uv.es
Elena Muñoz Gómez, Pilar Serra Añó, Núria Sempere Rubio, Sara Mollà Casanova and Marta Inglés, Research Unit in Clinical Biomechanics (UBIC), Department of Physiotherapy, Faculty of Physiotherapy, University of Valencia, Valencia, Spain

occurrence, who do not take preventive medication and who suffer from other chronic diseases [19]. In addition, comorbidities such as anxiety and depression are common in people who suffer from migraines [20] and may contribute to an increase in migraine symptoms and disability [2, 3], including its chronification [21].

However, sex-related differences regarding emotional status and quality of life have been understudied. Additionally, there is a lack of studies that describe sex-related differences stratifying by migraine frequency of occurrence.

Based on these observations, the aim of the present study was to determine potential sex-related differences in migraine features, frequency of the episodes, pain intensity, disability, quality of life, depression and anxiety levels, and health care resources by migraine frequency of occurrence (i.e., EM and CM).

Materials and methods

Participants and setting

A cross-sectional design was conducted. The recruitment method used was stratified sampling since migraines are two or three times more prevalent in women than in men [22]. Participants were recruited from primary care centres in Valencia (Spain) for one year. Individuals diagnosed according the ICHD-3 criteria [23], with four or more episodes per month, and at least one-year migraine history were included. Patients with another type of primary or secondary headache, psychiatric disorders, or other chronic pain diagnosis different than migraines were excluded.

The assessments were carried out face-to-face by a researcher blinded to the objectives of the study. The study was approved by the Ethics Committee of the University of Valencia (H1509655117217).

Measurements

Migraine diagnosis (episodic or chronic) was provided by a neurologist. Migraine characteristics about family history, migraine duration, pain intensity, pain location, associated symptoms, triggers and relieving factors were collected.

Pain, frequency, and disability relating to migraines were assessed through the Migraine Disability Assessment (MIDAS). It includes questions about days lost or less productive days in terms of paid work, household chores and social activities, pain intensity and number of days with pain in the last three months [24]. The MIDAS has good internal consistency (Cronbach's α=0.73–0.76) and high reliability and validity (Pearson's correlation coefficient (CCI) test-retest r=0.80) [25].

Quality of life was evaluated with the Short Form 36 Health Survey (SF-36) [26]. It consists of 36 items assessing physical function, physical role, bodily pain, and general health (for the physical health subscale), and vitality, social function, emotional role, and mental health (for the mental health subscale). This questionnaire has a good internal consistency (Cronbach's α=0.70), and a CCI of 0.99 on the physical subscale and 0.58 on the mental subscale [27].

Depression level through the Beck Depression Inventory II (BDI-II) which collects psychological and somatic manifestations of depressive episodes in the last two weeks [28]. Internal consistency is rated with a Cronbach's α of 0.90, and test-retest reliability from 0.73 to 0.96 [29].

Anxiety level with the State-Trait Anxiety Inventory (STAI) [30]. It consists of state-anxiety subscale (i.e. emotional state that can vary in intensity over time), and trait-anxiety subscale (i.e. tendency to be anxious and to perceive situations as threatening). It has good internal consistency (Cronbach's α=0.93) [30], and reliability from 0.87 to 0.93 [31].

Data related to Health resource use. Medication intake in the last 4 weeks (i.e., acute or preventive medications), and medical assistance (i.e. frequency of visits to a headache specialist, general practitioner over the last year, and other health care professionals) were collected.

Statistical analysis

Statistical analysis was performed using SPSS software v.24 (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was carried out to assess normal distribution. A two-way analysis of variance (ANOVA) was performed with the fixed factors of sex (i.e., men and women) and frequency of occurrence (i.e., EM and CM), and quantitative dependent variables regarding migraine characteristics, psychophysical health, and health care resources. Post hoc analyses were performed using the Bonferroni tests on each set of groups regarding sex and frequency of occurrence. The assumption of homoscedasticity using Levene's test and the sphericity using Mauchly's test were analysed. Chi-square tests were performed for ordinal variables. Size effect was determined using Cohen's d and contingency coefficient (CC) only when statistically significant differences were found. The level of the significance was set at $p<0.05$.

Results

Sex-related differences in sociodemographic characteristics by migraine diagnosis

From the 218 participants initially recruited, 34 participants were excluded because they did not meet the inclusion criteria (i.e. 20 had less than four per month, and 14 suffered from another type of headache). Finally, a total of 184 participants were assessed, of whom 113 participants (61.41 %) were diagnosed with EM and 71 (38.57 %) with CM. Regarding sex, 133 participants were women (72.28 %) and 51 were men (27.72 %). Sociodemographic characteristics by diagnosis and sex are presented in Table 1. The mean age (SD) of the sample was 38.70 (10.39) years, and the average BMI was 23.84 (3.87). Most of the participants were employed (69.57 %). More than half of the participants were physically active (55.43 %). There were no significant differences when stratifying by diagnosis in age, occupation, and level of physical activity ($p>0.05$) between men and women, except for mean BMI in the EM group ($p=0.003$), thus most of the men included

were in the overweight range (42.86 %), while the women belonged to the healthy weight range (70.51 %).

Sex-related differences in migraine clinical characteristics by diagnosis

As shown in Table 2, participants reported being 18.96 (9.39) years old on average when they experienced their first migraine attack, and 19.79 (11.34) years of migraine evolution. Furthermore, 89.67 % of the participants reported having a family history of migraines.

Regarding associated symptoms, 77.13 % of the sample reported suffering from two or more per episodes, being women with EM those with higher number of symptoms (p=0.03, d=0.45) than men. In addition, they reported a higher prevalence of phonophobia than men (60.26 vs. 25.71 %, p=0.001, CC=0.30), and nausea and vomiting (62.82 % vs. 22.86 %, p<0.001, CC=0.35). However, there were no significant differences by diagnosis nor by sex either in the prevalence of photophobia (71.20 % of the sample), pericranial sensitivity (42.39 %), aura (33.70 %), or others (35.87 %, i.e., tears or dizziness) (p>0.05).

Regarding trigger factors, women with CM presented a greater number of triggers than men with CM (p<0.001, d=0.45). Stress was the most reported (74.46 % of the sample) and as expected, menstruation was significantly more reported in women compared to men in both groups (p<0.001, CC=0.44). Sleep deprivation was reported more frequently in women with CM than in men (58.18 % vs. 12.50 %, p=0.001, CC=0.36), yet also differed by diagnosis in men (42.86 % in the EM group vs. 12.50 % in the CM group, p=0.03, CC=0.29). No significant differences by diagnosis nor by sex either were found in other trigger factors (p>0.05).

When analysing sex-related differences by migraine diagnosis, women with EM showed a higher pain intensity (p<0.001, d=0.70) and pain duration (p=0.03, d=0.56) than men with EM. However, there were no significant differences in frequency of onset by sex (p>0.05). Furthermore, no significant differences by sex were found in people with CM in any of the variables (p>0.05).

In addition, regarding diagnosis-related differences by sex, women with CM showed higher frequency of onset (p<0.001, d=1.44), and duration of episodes (p=0.03, d=0.35) than women with EM. Similarly, men with CM had a higher pain intensity (p=0.02, d=0.59), frequency of onset (p<0.001, d=2.01), and duration of episodes (p=0.002, d=1.11) than men with EM.

There were no significant differences by diagnosis nor by sex, either in relieving factors or in pain location (p>0.05) (data not shown). The most common relieving factor was medication intake (82.61 %), rest or sleep (44.02 %) and staying in a dark and quiet place (60.87 %), whereas the most frequent pain locations were temporal (54.89 %), orbicular (44.02 %), frontal (38.58 %) and occipital regions (33.70 %).

Table 1: Sociodemographic characteristics of the participants by diagnosis and sex.

	Episodic migraine		Chronic migraine		
Variable	**Women (n=78)**	**Men (n=35)**	**Women (n=55)**	**Men (n=16)**	**Total (n=184)**
Age, years[a]	35.23 (9.36)	41.83 (10.32)	39.4 (9.57)	46.31 (12.12)	38.70 (10.39)
BMI, kg/cm^{2}[a]	23.15 (3.90)	26.29 (3.68)	23.16 (3.47)	24.19 (3.51)	23.84 (3.87)
Underweight range (<18.5)[b]	4 (5.13 %)	0 (0.00 %)	3 (5.45 %)	0 (0.00 %)	7 (3.80 %)
Healthy weight range (18.5–24.9)[b]	55 (70.51 %)	14 (40.00 %)	41 (74.55 %)	9 (56.25 %)	119 (64.67 %)
Overweight range (25–29.9)[b]	14 (17.95 %)	15 (42.86 %)[c]	7 (12.73 %)	6 (37.5 %)	42 (22.83 %)
Obese range (>30)[b]	5 (6.41 %)	6 (17.14 %)	4 (7.27 %)	1 (6.25 %)	16 (8.70 %)
Occupation					
Employed[b]	53 (67.95 %)	26 (74.29 %)	35 (63.64 %)	14 (87.50 %)	128 (69.57 %)
Studying[b]	18 (23.08 %)	3 (8.57 %)	13 (23.64 %)	2 (12.50 %)	36 (19.57 %)
Unemployed[b]	7 (8.97 %)	5 (14.29 %)	6 (10.91 %)	0 (0.00 %)	18 (9.78 %)
Disabled[b]	0 (0.00 %)	1 (2.86 %)	1 (1.82 %)	0 (0.00 %)	2 (1.09 %)
Physical activity					
Active[b]	42 (53.85 %)	20 (57.14 %)	32 (58.18 %)	8 (50.00 %)	102 (55.43 %)
No active[b]	36 (46.15 %)	15 (42.86 %)	23 (41.82 %)	8 (50.00 %)	82 (44.57 %)

Data shown as [a]mean (SD) and [b]absolute frequency (percentage). [c]Significant differences between men and women (p<0.05). Bonferroni correction was used for the quantitative variables[a].

Table 2: Migraine clinical characteristics of the participants by diagnosis and sex.

	Episodic migraine		Chronic migraine		
Variable	**Women (n=78)**	**Men (n=35)**	**Women (n=55)**	**Men (n=16)**	**Total (n=184)**
Age of onset, years[a]	18.94 (9.37)	22.06 (10.79)	17.44 (7.79)	17.56 (10.44)	18.96 (9.39)
Time of evolution, years[a]	16.18 (9.03)	20.51 (13.57)	21.89 (10.92)	28.63 (11.59)[d]	19.79 (11.34)
Family history of migraine					
Yes, %[b]	57 (73.08 %)	21 (60.00 %)	34 (61.82 %)	11 (68.75 %)	165 (89.67 %)
No, %[b]	21 (26.92 %)	14 (40.00 %)	21 (38.18 %)	5 (31.25 %)	61 (33.15 %)
Associated symptoms, % yes					
Number of symptoms[a]	2.72 (1.59)	2.09 (1.20)[c]	3.16 (1.38)	2.75 (0.93)	2.73 (1.45)
Photophobia[b]	56 (71.79 %)	22 (62.86 %)	41 (74.55 %)	12 (75.00 %)	131 (71.20 %)
Phonophobia[b]	47 (60.26 %)	9 (25.71 %)[c]	37 (67.27 %)	8 (50.00 %)	101 (54.89 %)
Nausea and vomiting[b]	49 (62.82 %)	8 (22.86 %)[c]	35 (63.64 %)	8 (50.00 %)	100 (54.35 %)
Pericranial sensitivity[b]	30 (38.46 %)	13 (37.14 %)	29 (52.73 %)	6 (37.50 %)	78 (42.39 %)
Presence of aura[b]	22 (28.21 %)	16 (45.71 %)	16 (29.09 %)	8 (50.00 %)	62 (33.70 %)
Other[b]	12 (15.38 %)	5 (14.29 %)	18 (32.73 %)	3 (18.75 %)	38 (20.65 %)
Trigger factors, % yes					
Number of trigger factors[a]	2.41 (1.23)	1.91 (1.04)	2.58 (1.56)	1.25 (1.13)[c]	2.27 (1.35)
Stress[b]	59 (75.64 %)	28 (80.00 %)	41 (74.55 %)	9 (56.25 %)	137 (74.46 %)
Menstruation[b]	40 (51.28 %)	0 (0.00 %)[c]	20 (36.36 %)	0 (0.00 %)[c]	60 (32.61 %)
Sleep deprivation[b]	37 (47.44 %)	15 (42.86 %)	32 (58.18 %)	2 (12.50 %)[c,d]	86 (46.74 %)
Certain food[b]	27 (34.62 %)	9 (25.71 %)	22 (40.00 %)	4 (25.00 %)	62 (33.70 %)
Other[b]	25 (32.05 %)	10 (28.57 %)	27 (49.09 %)	4 (25.00 %)	66 (35.87 %)
Intensity (MIDAS score)[a]	7.43 (1.00)	6.49 (1.68)[c]	7.68 (0.99)	7.31 (1.09)[d]	7.31 (1.23)
Frequency (MIDAS score)[a]	18.24 (8.37)	16.26 (10.23)	36.44 (16.93)[d]	37.75 (11.11)[d]	25.00 (15.21)
Migraine duration, hours[a]	22.63 (19.52)	13.50 (13.34)[c]	30.15 (23.07)[d]	32.19 (20.36)[d]	24.03 (20.60)

Data shown as [a]mean (SD) and [b]absolute frequency (percentage). [c]Significant differences between men and women ($p<0.05$). [d]Significant differences between episodic and chronic migraine ($p<0.05$). Bonferroni correction was used for the quantitative variables[a].

Sex-related differences in disability, impact, quality of life and emotional status by migraine diagnosis

As shown in Table 3, when analysing sex-related differences by migraine diagnosis, women showed a higher disability ($p=0.01$, $d=0.61$) than men with EM. Furthermore, no significant differences by sex were found in people with CM in associated disability ($p>0.05$). In addition, regarding diagnosis-related differences by sex, women with CM showed a higher disability ($p<0.001$, $d=1.14$) than women with EM. Similarly, men with CM had a higher associated disability ($p<0.001$, $d=1.18$) than men with EM.

Regarding quality of life, no significant differences were found between males and females for any of the variables either in EM or CM, except for in regard to a physical role in people with EM, where males showed a higher score ($p=0.004$, $d=0.58$) than women (Table 3). When comparing by diagnosis, the quality of life was significantly reduced in women with CM when compared to women with EM in the following instances: physically functioning ($p<0.001$, $d=0.71$), bodily pain ($p=0.004$, $d=0.54$), general health ($p=0.04$, $d=0.34$), social functioning ($p=0.01$, $d=0.47$), and the physical health subscale ($p=0.01$, $d=0.49$). For men, there were significant differences between EM and CM in physical role ($p=0.01$, $d=0.95$), general health ($p=0.02$, $d=0.76$), and physical health subscale ($p=0.002$, $d=1.02$).

No significant differences by diagnosis and sex were found in emotional status, such as levels of depression and anxiety ($p>0.05$) (Table 3).

Sex-related differences in health care resource use by migraine diagnosis

Regarding medication intake, most of the migraineurs took medication (97.28 %), of whom 46.20 % took preventive medication and 89.10 % took symptomatic medication.

Table 3: Migraine impact, quality of life and emotional status by diagnosis and sex.

	Episodic migraine		Chronic migraine		
Variable	**Women (n=78)**	**Men (n=35)**	**Women (n=55)**	**Men (n=16)**	**Total (n=184)**
Disability (MIDAS score)[a]	30.88 (13.69)	22.16 (14.82)[c]	49.48 (18.93)[d]	43.94 (22.00)[d]	35.87 (19.31)
Grade 1 (0–5 points)[b]	0 (0.00 %)	6 (17.14 %)	1 (1.82 %)	0 (0.00 %)	7 (3.80 %)
Grade 2 (6–10 points)[b]	2 (2.56 %)	4 (11.43 %)	0 (0.00 %)	1 (6.25 %)	7 (3.80 %)
Grade 3 (11–20 points)[b]	17 (21.79 %)	7 (20.00 %)	4 (7.27 %)	1 (6.25 %)	29 (15.76 %)
Grade 4 (>21 points)[b]	59 (75.64 %)	18 (51.43 %)[c]	50 (90.91 %)[d]	14 (87.50 %)	141 (76.63 %)
Quality of life (SF36 total score)[a]	60.09 (22.23)	64.12 (17.57)	51.5 (18.17)	54.88 (19.48)	57.84 (20.40)
Physically functioning (SF-36)[a]	85.13 (14.68)	82.86 (19.41)	72.36 (21.10)[d]	75.18 (17.45)	79.93 (18.74)
Physical role (SF-36)[a]	33.97 (36.03)	53.71 (32.16)[c]	30.41 (31.08)	25.94 (26.09)[d]	35.96 (34.05)
Bodily pain (SF-36)[a]	52.31 (23.30)	57.24 (26.76)	40.04 (22.57)[d]	45.44 (25.55)	48.98 (24.66)
General health (SF-36)[a]	57.62 (21.96)	60.20 (17.93)	50.27 (21.11)[d]	44.69 (22.76)[d]	54.79 (21.46)
Vitality (SF-36)[a]	46.86 (22.04)	51.00 (19.99)	41.55 (19.83)	44.69 (24.05)	45.87 (21.29)
Social functioning (SF-36)[a]	64.39 (24.41)	67.93 (22.81)	52.70 (25.88)[d]	60.47 (23.88)	61.23 (25.03)
Emotional role (SF-36)[a]	49.61 (43.58)	57.79 (41.47)	55.15 (43.14)	68.75 (42.98)	54.49 (43.00)
Mental health (SF-36)[a]	55.95 (20.74)	60.87 (17.21)	54.83 (21.20)	54.75 (21.70)	56.45 (20.30)
Physical health subscale (SF-36)[a]	56.90 (17.52)	63.70 (17.07)	48.27 (17.62)[d]	47.52 (14.39)[d]	54.80 (18.06)
Mental health subscale (SF-36)[a]	54.20 (22.74)	59.24 (19.91)	51.06 (21.35)	56.77 (23.80)	54.44 (21.92)
Depression level (BDI-II total score)[a]	10.28 (8.32)	8.40 (8.23)	10.53 (8.55)	10.50 (8.39)	10.02 (8.35)
Minimum (0–13 points)[b]	52 (66.67 %)	29 (82.86 %)	38 (69.09 %)	10 (62.50 %)	129 (70.11 %)
Slight (14–19 points)[b]	16 (20.51 %)	3 (8.57 %)	12 (21.82 %)	2 (12.50 %)	33 (17.93 %)
Moderate (20–28 points)[b]	6 (7.69 %)	1 (2.86 %)	4 (7.27 %)	4 (25.00 %)	15 (8.15 %)
Severe (29–63 points)[b]	4 (5.13 %)	2 (5.71 %)	1 (1.82 %)	0 (0.00 %)	7 (3.80 %)
Anxiety level (STAI total score)[a]	42.71 (12.27)	39.63 (9.62)	42.65 (12.24)	40.91 (13.59)	41.95 (11.89)
Low (<30 points)[b]	12 (15.38 %)	4 (11.43 %)	9 (16.36 %)	5 (31.25 %)	30 (16.30 %)
Moderate (30–44 points)[b]	28 (35.90 %)	16 (45.71 %)	23 (41.82 %)	5 (31.25 %)	72 (39.13 %)
High (>44 points)[b]	38 (48.72 %)	15 (42.86 %)	23 (41.82 %)	6 (37.5 %)	82 (44.57 %)
State anxiety (STAI)[a]	44.33 (13.12)	41.71 (10.41)	43.78 (13.83)	43.94 (14.34)	43.64 (12.92)
Trait anxiety (STAI)[a]	41.08 (12.32)	37.54 (9.69)	41.51 (11.50)	37.88 (13.10)	40.26 (11.71)

Data shown as [a]mean (SD) and [b]absolute frequency (percentage). [c]Significant differences between men and women ($p<0.05$). [d]Significant differences between episodic and chronic migraine ($p<0.05$). Bonferroni correction was used for the quantitative variables[a].

Migraine-specific medicines divided by diagnosis and sex are specified in Table 4. Women with EM took significantly more symptomatic medication than men (p=0.04, d=0.45). Moreover, significant differences in triptans intake were identified (29.49 % among women and 17.14 % among men, p=0.003, CC=0.31). However, there were no significant differences by sex in other specific-migraine drugs (p>0.05), nor between people with CM either (p>0.05). When EM and CM groups were compared, significant differences in medication type were found. Thus, there was an increase in the use of preventive medication in both women (26.92 % with EM vs. 74.55 % with CM, p<0.001, CC=0.38), and men (34.29 % with EM vs. 68.75 % with CM, p=0.002, CC=0.44).

When analysing medical assistance, 51.09 % of the participants visited a headache specialist in the last year, with an average number of visits of 2.01 (3.31) times (Table 4). 36.96 % of participants also visited other health professionals, of whom physiotherapists were the more frequently visited (17.93 %). A higher percentage of women visited a headache specialist in the last year due to migraine than men with EM (55.13 % vs. 22.86 %, p=0.001, CC=0.37), as well as other health professionals (44.87 % vs. 20.00 %, p<0.001, CC=0.37), especially physical therapists (20.51 % vs. 8.57 %, p=0.003, CC=0.34). When comparing by migraine diagnosis, a significantly higher percentage of men with CM visited a headache specialist in the last year than those with EM (22.86 % vs. 68.75%, p=0.002, CC=0.43).

Discussion

Main findings

The main finding of this study was that women with EM presented a greater number of associated symptoms, pain intensity, disability, and duration of episodes, as well as a worse physical role than men with EM, yet those differences are lost in people with CM. Additionally, the use of preventive and symptomatic medication was similar in both men

Table 4: Health care resource in terms of medication intake and medical assistance.

	Episodic migraine		Chronic migraine		
Variable	**Women (n=78)**	**Men (n=35)**	**Women (n=55)**	**Men (n=16)**	**Total (n=184)**
Medication use, % yes					
Preventive medication[b]	21 (26.92 %)	12 (34.29 %)	41 (74.55 %)[d]	11 (68.75 %)[d]	85 (46.20 %)
Antidepressants[b]	5 (6.41 %)	2 (5.71 %)	7 (12.73 %)	1 (6.25 %)	15 (8.15 %)
Anti-seizure drugs[b]	3 (3.85 %)	4 (11.43 %)	12 (21.82 %)	3 (18.75 %)	22 (11.96 %)
CGRP monoclonal antibodies[b]	9 (11.54 %)	5 (14.29 %)	12 (21.82 %)	3 (18.75 %)	29 (15.79 %)
Botox injections[b]	4 (5.13 %)	1 (2.86 %)	10 (18.18 %)[d]	4 (25.00 %)[d]	19 (10.33 %)
Acute medication[b]	76 (97.44 %)	32 (91.43 %)	43 (78.18 %)	13 (81.25 %)	164 (89.13 %)
NSAIDs[b]	39 (50.00%)	20 (57.14 %)	18 (32.73 %)	6 (37.50 %)	83 (45.11 %)
Ergotamine[b]	7 (8.97 %)	5 (14.29 %)	4 (7.27 %)	2 (12.5 %)	18 (9.78 %)
Triptans[b]	23 (29.49 %)	6 (17.14 %)[c]	18 (32.73 %)	5 (31.25 %)	52 (28.26 %)
Opioid medications[b]	7 (8.97 %)	1 (2.86 %)	3 (5.45 %)	0 (0.00 %)	11 (5.98 %)
Number of pills per month[a]	6.14 (4.47)	4.41 (3.19)[c]	12.49 (12.67)	11.13 (5.51)	8.23 (8.50)
No medication use[b]	2 (2.56 %)	3 (8.57 %)	0 (0.00 %)	0 (0.00 %)	5 (2.72 %)
Medical assistance in the last year					
Yes, %[b]	43 (55.13 %)	8 (22.86 %)[c]	32 (58.18 %)	11 (68.75 %)[d]	94 (51.09 %)
No, %[b]	35 (44.87 %)	27 (77.14 %)	23 (41.82 %)	5 (31.25 %)	90 (48.91 %)
Number of medical visits in the last year[a]	1.41 (1.98)	1.14 (2.81)	3.75 (5.10)[d]	2.54 (2.29)	2.01 (3.31)
Type of health professional, % yes					
Headache specialist[b]	43 (55.13 %)	8 (22.86 %)[c]	32 (58.18 %)	11 (68.75 %)[d]	94 (51.09 %)
General practitioner[b]	35 (44.87 %)	7 (20.00 %)[c]	21 (38.18 %)	5 (31.25 %)	68 (36.96 %)
Physical therapist[b]	16 (20.51 %)	3 (8.57 %)[c]	12 (21.82 %)	2 (12.50 %)	33 (17.93 %)
Nutritionist[b]	6 (7.69 %)	0 (0.00 %)	5 (9.09 %)	0 (0.00 %)	11 (5.98 %)
Ophthalmologist[b]	3 (3.85 %)	1 (2.86 %)	0 (0.00 %)	2 (12.50 %)	6 (3.26 %)
Acupuncture[b]	4 (5.13 %)	1 (2.86 %)	0 (0.00 %)	1 (6.25 %)	6 (3.26 %)
Maxillofacial[b]	3 (3.85 %)	1 (2.86 %)	1 (1.82 %)	0 (0.00 %)	5 (2.72 %)
Otorhinologist[b]	1 (1.28 %)	0 (0.00 %)	2 (3.64 %)	0 (0.00 %)	3 (1.63 %)
Psychologist[b]	1 (1.28 %)	1 (2.86 %)	1 (1.82 %)	0 (0.00 %)	3 (1.63 %)

Data shown as [a]mean (SD) and [b]absolute frequency (percentage). NSAIDs: Nonsteroidal anti-inflammatory drugs. [c]Significant differences between men and women ($p<0.05$). [d]Significant differences between episodic and chronic migraine ($p<0.05$). Bonferroni correction was used for the quantitative variables[a].

and women. However, women with EM visited migraine-related health professionals more frequently than men.

Interpretation of results in relation to current knowledge/literature

Changes in brain structure are described in migraine patients, such as reduced microstructural integrity in the thalamus, corpus callosum, longitudinal fasciculus, and cingulum [32]. Recent studies suggest that there are structural brain differences between EM and CM according to cortical surface area, cortical thickness, and regional volumes [33]. For example, more streamlines have been found between the left caudal anterior cingulate and right superior frontal gyri in CM compared to EM [34], as well as decreased axial diffusivity in white matter regions, that might reflect a set of maladaptive plastic changes after the onset of CM [35].

Previously it has been highlighted that females display greater associated disability [7–9, 36], more frequency (i.e., days per month) [9], longer attack duration and more associated symptoms [36] than men, which is consistent with our results among people with EM. In contrast, others did not find significant differences by sex [37]. In addition, it is interesting stratifying by frequency of occurrence as CM is much more disabling [6, 25, 38–44]. Surprisingly, we found that the differences found in our study between men and women with EM were lost in the CM group, since the impact of migraine chronicity affects both men and women equally. This may be explained because the aforementioned changes in CM in brain structure and function may occur in men and women indistinctly. In contrast to our results, previous

studies reported that female migraineurs with CM experience higher levels of headache-related disability [45]. However, further analysis in men are warranted to elucidate disability levels since men are less likely to receive a diagnosis than women with migraine [46]. In addition, data obtained in previous studies are self-reported and not verified physician diagnoses or medical records, which could be misleading. For example, in the study by Buse et al. [47], disability values were lower than usually experienced in people with CM (i.e., 41.30 % of women with CM reported having severe headache-related disability vs. 28.10 % of men). In this regard, in the International Burden of Migraine Study [40], 78 % of the people with CM were classified as MIDAS grade IV (i.e., severe disability), even with an adjustment for sex, which is more similar to the values reported in the present study.

The increase in disability may influence quality of life [44]. In the present study, poorer physical functioning, physical role, bodily pain, general health, and social functioning was observed in people with CM compared with people with EM. The worse physical condition may be due to the fact that migraine chronification leads to difficulties in physical activity engagement, mainly because physical exertion is a trigger factor for migraines [23], and some people avoid physical activity as a prevention strategy [48]. It is worth noting that women with EM reported lower scores in the physical role item than men with EM. This could be explained precisely by the fact that women have traditionally exercised less, and consequently are in worse physical condition. Despite all this, the increase of beta-endorphin, endocannabinoid and brain-derived neurotrophic factor levers released in plasma after exercise may have prophylactic effect on migraine frequency [49]. It is worth noting that previous studies have not only highlighted the impairment of quality of life at the physical level, but also have found significant differences between diagnosis at the emotional level [44], specifically in the vitality, role emotional and mental health items [43, 50].

Regarding emotional status, the participants included in our study reported low levels of depression and anxiety, with no significant differences between men and women either in EM or in CM. This is consistent with the results obtained by Song et al. [37], since almost 30 % of the sample presented anxiety and 16 % presented symptoms of depression, without significant differences by sex. However, regarding potential differences by migraine subtypes, we did not find any differences between EM and CM either in men or in women. The disagreement with previous studies showing a higher prevalence of mental disorders in people with CM than people with EM [43] may be due to the high heterogeneity of the data found in our study. Thus, these results must be taken with caution. Overall, emotional status-related conditions should be considered in the clinical practice as they may increase the burden in patients with episodic and chronic headaches [51].

Acute medication was prescribed in 89.13 % of the patients, and preventive medication in 46.20 % of them. This is consistent with the results reported by Ford et al. [52], who described that >90 % of migraine patients were prescribed an acute treatment and >50 % a preventive one. In addition, triptans were the most commonly used drugs, as they were in our study after NSAIDs. However, they reported that opioids were significantly more frequently prescribed in patients with CM than in EM, whereas we found only significant differences between diagnosis subgroups in Botox injections prescription. It should be considered that the utilisation of migraine-specific medications varies between countries [53]. Nevertheless, since this pathology continues to affect people's daily lives, it is claimed that migraine drugs are used inadequately [52–54]. Difficulty in finding an appropriate migraine treatment may be justified because the drug response differs among individuals. In this regard, we observed that the use of triptans was significantly higher in women than in men with EM. According to Van Casteren et al. [55], even though response rates of triptans are similar in males and females regarding headache and pain-free responses, men had a lower risk for headache recurrence, thus the need for triptan intake may be reduced. Furthermore, we observed that the amount of medication used per month was 28.30 % higher in women than in men. This may be due to the higher frequency of episodes in women, and in some cases it may lead to the phenomenon of medication overuse [56]. Therefore, more tailored and specific non-pharmacologic treatments such as those proposed by our group [57–59], are needed to lower polypharmacy among patients with migraine.

Regarding health care resource use, one half of the participants reported having visited a headache specialist in the previous year. Interestingly, we found that men with EM visited the doctor significantly less often than women with EM, while they experienced an increase in medical visits up to three times when they get to CM. This is consistent with the well-known higher health care resource use and direct and indirect costs associated to CM [60, 61]. Despite this, many people with migraine have unmet needs related to consulting for migraine, migraine diagnosis, and getting potentially beneficial migraine treatment [16], which may be due to the lack of accuracy in migraine diagnosis, probably due to sex-related underdiagnosed differences.

The novelty of our study is that multiple areas of clinical interest (i.e. migraine characteristics, psychophysical health

and health care resource) are analysed by sex and frequency of occurrence in individuals that suffer from four or more migraine episodes per month. In this regard, most of the published articles that compare EM vs. CM included people with at least one migraine day per month [8, 20, 40–43, 51, 61]. It is of interest to study this population since associated disability is higher than in people with less frequency of occurrence [52], and there is still a need to find effective prophylactic treatments for them to lessen the migraine burden [54]. In addition, in contrast to previous cross-sectional studies [7, 9, 40, 41, 43, 52, 54], individuals with other comorbidities (i.e., another type of primary or secondary headache, psychiatric disorders, or other chronic pain diagnosis) were excluded in our study. Thus, a more specific analysis of the impact of migraine on patients' daily lives is performed. Notably, most studies assessing gender differences assess migraine patients without distinguishing between episodic and chronic migraines [7, 36, 37]. Furthermore, in some cases respondents did not have a medical diagnosis [8, 9, 20, 40, 41, 54, 60]. In this regard, correct diagnosis of migraines according to the ICHD-3 criteria [23], as well as understanding the patient's needs, is important to design individualised treatment protocols. In addition, an early therapeutic approach, as well as control of risk factors for migraine progression (i.e., increased daily headache frequency, acute medication overuse/high frequency use and depression) will prevent the transition from EM to CM [21]. This, in turn, will improve the patient's quality of life, and will result in reduced costs to the health care system. Finally, the use of reliable, validated, easy-to-use and low-cost assessment tools, such as those presented in this study, are easy to implement in clinical practice, thus allowing health professionals to improve both diagnostic accuracy and response to treatment monitoring.

Limitations

The main limitation of the study was that the sample included much more women than men, yet migraines occur much more often in women than in men. Another limitation was that our sample comprised of mostly people between 18 and 50 years old, thus these results may not be generalisable to other populations. However, it is important to study the young population since migraines are the leading cause of disability in this age group [2, 3]. In addition, the fact that the participants were young and relatively healthy decreased the possibility of comorbidities that could influence the analysis. In this regard, although the groups were comparable with respect to age, sex, and race, significant differences in BMI between men and women with EM were considered as a potential confounder. However, when this variable was controlled for in the analyses, there was no significant changes in the results for any of the main outcomes. Finally, the evaluations consisted in questionnaires, so more objective measures would be desirable.

Conclusions

In conclusion, considering the aforementioned limitations, women display a greater number of associated symptoms, pain intensity, disability, and duration of episodes, as well as a worse physical role than men with EM; yet no significant differences between them were found for CM. These findings may contribute to a better diagnosis and treatment response in people who suffer from migraines.

Acknowledgments: The authors would like to thank Milda Žukauskienė and Tadas Mikelionis for their assistance during the recruitment process.
Research funding: This work was partially supported by Grants from the Spanish Government (PID2021-125694OB-I00; co-financed by EU FEDER funds;), Generalitat Valenciana, Conselleria d'Innovació, Universitats, Ciència i Societat (CIAICO/2021/215); and from Universitat de València (INV19-01-13-07).
Author contributions: Conceptualization, EMG, PAS and MI; methodology, EMG and MI; formal analysis, EMG and PAS; investigation, SMC, NSR and MAR.; writing—original draft preparation, EMG and MI; writing—review and editing, EMG, MAR, NSR, SMC, PAS and MI. All authors have read and agreed to the published version of the manuscript. All authors discussed the results and commented on the manuscript.
Competing interest: The authors declare no conflict of interest.
Informed consent: Informed consent was obtained from all individuals included in this study.
Ethical approval: All procedures were performed in accordance with the ethical standards of the Declaration of Helsinki and the protocols were approved by the Ethics Committee of the University of Valencia (H1509655117217).

References

1. Woldeamanuel YW, Cowan RP. Migraine affects 1 in 10 people worldwide featuring recent rise: a systematic review and meta-analysis of community-based studies involving 6 million participants. J Neurol Sci 2017;372:307–15.

2. Vos T, Alemu-Abajobir A, Hassen-Abate K, Abbafati C, Abbas KM, Abd-Allah F, et al. GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Lond Engl 2017;390:1211–59.
3. Steiner TJ, Stovner LJ, Vos T, Jensen R, Katsarava Z. Migraine is first cause of disability in under 50s: will health politicians now take notice? J Headache Pain 2018;19:17.
4. Linde M, Gustavsson A, Stovner LJ, Steiner TJ, Barré J, Katsarava Z, et al. The cost of headache disorders in Europe: the Eurolight project. Eur J Neurol 2012;19:703–11.
5. Volcy-Gómez M. The impact of migraine and other primary headaches on the health system and in social and economic terms. Rev Neurol 2006;43:228–35.
6. Bloudek LM, Stokes M, Buse DC, Wilcox TK, Lipton RB, Goadsby PJ, et al. Cost of healthcare for patients with migraine in five European countries: results from the International Burden of Migraine Study (IBMS). J Headache Pain 2012;13:361–78.
7. Buse DC, Loder EW, Gorman JA, Stewart WF, Reed ML, Fanning KM, et al. Sex differences in the prevalence, symptoms, and associated features of migraine, probable migraine and other severe headache: results of the American Migraine Prevalence and Prevention (AMPP) study. Headache 2013;53:1278–99.
8. Lipton RB, Manack Adams A, Buse DC, Fanning KM, Reed ML. A comparison of the chronic migraine epidemiology and outcomes (CaMEO) study and American migraine prevalence and prevention (AMPP) study: demographics and headache-related disability. Headache 2016;56:1280–9.
9. Lipton RB, Munjal S, Alam A, Buse DC, Fanning KM, Reed ML, et al. Migraine in America Symptoms and Treatment (MAST) Study: baseline study methods, treatment patterns, and gender differences. Headache 2018;58:1408–26.
10. Vetvik KG, MacGregor EA. Sex differences in the epidemiology, clinical features, and pathophysiology of migraine. Lancet Neurol 2017;16:76–87.
11. van Casteren DS, Verhagen IE, Onderwater GL, MaassenVanDenBrink A, Terwindt GM. Sex differences in prevalence of migraine trigger factors: a cross-sectional study. Cephalalgia Int J Headache 2021;41:643–8.
12. Pavlović JM, Allshouse AA, Santoro NF, Crawford SL, Thurston RC, Neal-Perry GS, et al. Sex hormones in women with and without migraine: evidence of migraine-specific hormone profiles. Neurology 2016;87:49–56.
13. Maleki N, Linnman C, Brawn J, Burstein R, Becerra L, Borsook D. Her versus his migraine: multiple sex differences in brain function and structure. Brain J Neurol 2012;135:2546–59.
14. Allais G, Chiarle G, Sinigaglia S, Airola G, Schiapparelli P, Benedetto C. Gender-related differences in migraine. Neurol Sci Off J Ital Neurol Soc Ital Soc Clin Neurophysiol 2020;41:429–36.
15. Finocchi C, Strada L. Sex-related differences in migraine. Neurol Sci Off J Ital Neurol Soc Ital Soc Clin Neurophysiol 2014;35:207–13.
16. Lipton RB, Nicholson RA, Reed ML, Araujo AB, Jaffe DH, Faries DE, et al. Diagnosis, consultation, treatment, and impact of migraine in the US: results of the OVERCOME (US) study. Headache 2022;62:122–40.
17. Lipton RB, Serrano D, Holland S, Fanning KM, Reed ML, Buse DC. Barriers to the diagnosis and treatment of migraine: effects of sex, income, and headache features. Headache 2013;53:81–92.
18. Abu Bakar N, Tanprawate S, Lambru G, Torkamani M, Jahanshahi M, Matharu M. Quality of life in primary headache disorders: a review. Cephalalgia Int J Headache 2016;36:67–91.
19. AlHarbi FG, AlAteeq MA. Quality of life of migraine patients followed in neurology clinics in Riyadh, Saudi Arabia. J Fam Community Med 2020; 27:37–45.
20. Goulart AC, Santos IS, Brunoni AR, Nunes MA, Passos VM, Griep RH, et al. Migraine headaches and mood/anxiety disorders in the ELSA Brazil. Headache 2014;54:1310–9.
21. Buse DC, Greisman JD, Baigi K, Lipton RB. Migraine progression: a systematic review. Headache 2019;59:306–38.
22. Russell MB, Rasmussen BK, Thorvaldsen P, Olesen J. Prevalence and sex distribution of different forms of migraine. Ugeskr Laeger 1996;158: 1369–72.
23. Headache Classification Committee of the International Headache Society (IHS). The international classification of headache disorders. Cephalalgia Int J Headache 2018;38:1–211.
24. Stewart W, Lipton R, White J, Dowson A, Kolodner K, Liberman J, et al. An international study to assess reliability of the Migraine Disability Assessment (MIDAS) score. Neurology 1999;53:988–94.
25. Stewart W, Lipton R, Dowson A, Sawyer J. Development and testing of the migraine disability assessment (MIDAS) questionnaire to assess headache-related disability. Neurology 2001;56:S20–8.
26. Ware J, Sherbourne C. The MOS 36-item short form health survey (SF-36). Med Care 1992;30:473–83.
27. Vilagut G, Ferrer M, Rajmil L, Rebollo P, Permanyer-Milada G, Quintana J, et al. El Cuestionario de Salud SF-36 español: una década de experiencia y nuevos desarrollos. Gac Sanit 2005;19:135–50.
28. Beck A, Steer R, Brown G. Manual for the Beck Depression Inventory-II. San Antonio, TX: Psychological Corporation; 1996.
29. Wang YP, Gorenstein C. Psychometric properties of the Beck depression inventory-II: a comprehensive review. Rev Bras Psiquiatr Sao Paulo Braz 1999. 2013;35:416–31.
30. Spielberger C, Gorsuch R, Lushene R, Vagg P, Jacobs G. Manual for state-trait anxiety inventory. Palo Alto: Consulting Psychologist Press; 1983.
31. Guillén-Riquelme A, Buela-Casal G. Meta-analysis of group comparison and meta-analysis of reliability generalization of the State-Trait Anxiety Inventory Questionnaire (STAI). Rev Esp Salud Publica 2014;88:101–12.
32. Rahimi R, Dolatshahi M, Abbasi-Feijani F, Momtazmanesh S, Cattarinussi G, Aarabi MH, et al. Microstructural white matter alterations associated with migraine headaches: a systematic review of diffusion tensor imaging studies. Brain Imaging Behav 2022;16:2375–401.
33. Schwedt TJ, Chong CD, Wu T, Gaw N, Fu Y, Li J. Accurate classification of chronic migraine via brain magnetic resonance imaging. Headache 2015;55:762–77.
34. Planchuelo-Gómez Á, García-Azorín D, Guerrero ÁL, Aja-Fernández S, Rodríguez M, de Luis-García R. Structural connectivity alterations in chronic and episodic migraine: a diffusion magnetic resonance imaging connectomics study. Cephalalgia 2020;40:367–83.
35. Planchuelo-Gómez Á, García-Azorín D, Guerrero ÁL, Aja-Fernández S, Rodríguez M, de Luis-García R. White matter changes in chronic and episodic migraine: a diffusion tensor imaging study. J Headache Pain 2020;21:1.
36. Akarsu E, Baykan B, Ertas M, Zarifoglu M, Orhan E, Saip S, et al. Sex differences of migraine: results of a nationwide home-based study in Turkey. Noro Psikiyatr Ars 2019;57:126–30.
37. Song TJ, Cho SJ, Kim WJ, Yang KI, Yun CH, Chu MK. Sex differences in prevalence, symptoms, impact, and psychiatric comorbidities in migraine and probable migraine: a population-based study. Headache 2019;59:215–23.

38. Adams AM, Serrano D, Buse DC, Reed ML, Marske V, Fanning KM, et al. The impact of chronic migraine: the Chronic Migraine Epidemiology and Outcomes (CaMEO) Study methods and baseline results. Cephalalgia 2015;35:563–78.
39. Berra E, Sances G, De Icco R, Avenali M, Berlangieri M, De Paoli I, et al. Cost of chronic and episodic migraine. A pilot study from a tertiary headache centre in northern Italy. J Headache Pain 2015;16:532.
40. Blumenfeld AM, Varon SF, Wilcox TK, Buse DC, Kawata AK, Manack A, et al. Disability, HRQoL and resource use among chronic and episodic migraineurs: results from the International Burden of Migraine Study (IBMS). Cephalalgia Int J Headache 2011;31:301–15.
41. Buse DC, Reed ML, Fanning KM, Bostic RC, Lipton RB. Demographics, headache features, and comorbidity profiles in relation to headache frequency in people with migraine: results of the American Migraine Prevalence and Prevention (AMPP) Study. Headache J Head Face Pain 2020;60:2340–56.
42. Di Antonio S, Castaldo M, Ponzano M, Bovis F, Torelli P, Finocchi C, et al. Disability, burden, and symptoms related to sensitization in migraine patients associate with headache frequency. Scand J Pain 2021;21:766–77.
43. Torres-Ferrús M, Quintana M, Fernandez-Morales J, Alvarez-Sabin J, Pozo-Rosich P. When does chronic migraine strike? A clinical comparison of migraine according to the headache days suffered per month. Cephalalgia Int J Headache 2017;37:104–13.
44. Wang SJ, Wang PJ, Fuh JL, Peng KP, Ng K. Comparisons of disability, quality of life, and resource use between chronic and episodic migraineurs: a clinic-based study in Taiwan. Cephalalgia Int J Headache 2013;33:171–81.
45. Tsai CK, Tsai CL, Lin GY, Yang FC, Wang SJ. Sex differences in chronic migraine: focusing on clinical features, pathophysiology, and treatments. Curr Pain Headache Rep 2022;26:347–55.
46. Scher AI, Wang SJ, Katsarava Z, Buse DC, Fanning KM, Adams AM, et al. Epidemiology of migraine in men: results from the chronic migraine epidemiology and outcomes (CaMEO) study. Cephalalgia Int J Headache 2019;39:296–305.
47. Buse DC, Manack AN, Fanning KM, Serrano D, Reed ML, Turkel CC, et al. Chronic migraine prevalence, disability, and sociodemographic factors: results from the American Migraine Prevalence and Prevention Study. Headache J Head Face Pain 2012;52:1456–70.
48. Farris SG, Thomas JG, Abrantes AM, Lipton RB, Burr EK, Godley FA, et al. Anxiety sensitivity and intentional avoidance of physical activity in women with probable migraine. Cephalalgia Int J Headache 2019;39:1465–9.
49. Amin FM, Aristeidou S, Baraldi C, Czapinska-Ciepiela EK, Ariadni DD, Di Lenola D, et al. The association between migraine and physical exercise. J Headache Pain 2018;19:83.
50. Meletiche DM, Lofland JH, Young WB. Quality-of-life differences between patients with episodic and transformed migraine. Headache 2001;41:573–8.
51. Zebenholzer K, Lechner A, Broessner G, Lampl C, Luthringshausen G, Wuschitz A, et al. Impact of depression and anxiety on burden and management of episodic and chronic headaches – a cross-sectional multicentre study in eight Austrian headache centres. J Headache Pain 2016;17:15.
52. Ford JH, Jackson J, Milligan G, Cotton S, Ahl J, Aurora SK. A real-world analysis of migraine: a cross-sectional study of disease burden and treatment patterns. Headache 2017;57:1532–44.
53. Katsarava Z, Mania M, Lampl C, Herberhold J, Steiner TJ. Poor medical care for people with migraine in Europe – evidence from the Eurolight study. J Headache Pain 2018;19:10.
54. Vo P, Fang J, Bilitou A, Laflamme AK, Gupta S. Patients' perspective on the burden of migraine in Europe: a cross-sectional analysis of survey data in France, Germany, Italy, Spain, and the United Kingdom. J Headache Pain 2018;19:82.
55. van Casteren DS, Kurth T, Danser AHJ, Terwindt GM, MaassenVanDenBrink A. Sex differences in response to triptans: a systematic review and meta-analysis. Neurology 2021;96:162–70.
56. Diener HC, Dodick D, Evers S, Holle D, Jensen RH, Lipton RB, et al. Pathophysiology, prevention, and treatment of medication overuse headache. Lancet Neurol 2019;18:891–902.
57. Muñoz-Gómez E, Inglés M, Serra-Añó P, Espí-López GV. Effectiveness of a manual therapy protocol based on articulatory techniques in migraine patients. A randomized controlled trial. Musculoskelet Sci Pract 2021;54:102386.
58. Muñoz-Gómez E, Inglés M, Aguilar-Rodríguez M, Mollà-Casanova S, Sempere-Rubio N, Serra-Añó P, et al. Effect of a craniosacral therapy protocol in people with migraine: a randomized controlled trial. J Clin Med 2022;11:759.
59. Muñoz-Gómez E, Serra-Añó P, Mollà-Casanova S, Sempere-Rubio N, Aguilar-Rodríguez M, Espí-López GV, et al. Potential add-on effects of manual therapy techniques in migraine patients: a randomised controlled trial. J Clin Med 2022;11:4686.
60. Burch RC, Buse DC, Lipton RB. Migraine: epidemiology, burden, and comorbidity. Neurol Clin 2019;37:631–49.
61. Stokes M, Becker WJ, Lipton RB, Sullivan SD, Wilcox TK, Wells L, et al. Cost of health care among patients with chronic and episodic migraine in Canada and the USA: results from the International Burden of Migraine Study (IBMS). Headache J Head Face Pain 2011;51:1058–77.