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ORIGINAL ARTICLE

Sex differences in clinical characteristics of migraine and its burden: a population-based study

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Abstract

Background and purpose: Understanding migraine in a sex-specific manner is crucial for improving clinical care, diagnosis and therapy for both females and males. Here, data on sex differences are provided in the presentation of migraine in a large European-based population cohort, which is representative of the general population.

Methods: A population-based study of 62,672 Danish blood donors (both present and previous donors), of whom 12,658 had migraine, was performed. All participants completed a 105-item diagnostic migraine questionnaire sent via an electronic mailing system (e-Boks) between May 2020 and August 2020. The questionnaire allowed for correct diagnosis of migraine according to the International Classification of Headache Disorders, third edition.

Results: The migraine questionnaire was in-cohort validated and had a positive predictive value of 97% for any migraine, a specificity of 93% and a sensitivity of 93%. There were 9184 females (mean age 45.1 years) and 3434 males (mean age 48.0 years). The 3-month prevalence of migraine without aura was 11% in females and 3.59% in males. The

3-month prevalence of migraine with aura was 1.72% in females and 1.58% in males. In females, the age-related 3-month prevalence of migraine without aura increased markedly during childbearing age. In males, migraine both with and without aura showed less age variation. Females had a higher frequency of migraine attacks (odds ratio [OR] 1.22) but a lower frequency of non-migraine headaches (OR = 0.35). Females also had a greater intensity of pain, more unilateral and pulsatile pain, and exacerbation by physical activity (OR = 1.40–1.49) as well as more associated symptoms (OR = 1.26–1.98). Females carried 79% of the total migraine disease burden, which was almost exclusively driven by migraine without aura (77%), whilst there was no sex difference in the disease burden of migraine with aura.

Conclusion: Females have more severe disease, resulting in a much higher migraine disease burden than indicated by prevalence alone.

KEYWORDS
blood donors, burden, migraine, population-based study, sex differences, sex stratification

BACKGROUND

Migraine is predominantly a female disorder because it affects two to three times more females than males [1, 2]. Migraine is the number one cause of years lived with disability in females aged 15–49 years [3, 4] and has a greater impact on the careers of females compared with males [5]. No other disease is responsible for more years of lost healthy life (expressed as disability-adjusted life years) amongst females during the childbearing years [4]. In contrast to females, males are less likely to seek professional medical advice for their migraine [6] and are less likely to be prescribed acute and preventive medication for their migraine [6, 7]. Thus, understanding migraine in a sex-specific manner is crucial for improving clinical care, diagnosis and therapy for both females and males. The high female-to-male ratio in migraine prevalence is well established [1, 8–11], and similar ratios have been reported worldwide. It is also uniformly reported that female patients treated in tertiary headache clinics have a significantly higher burden of disease compared with males [2, 12]. Large-scale, population-based studies with valid migraine diagnoses based on the International Classification of Headache Disorders (ICHD) are, however, rare. Population studies with the primary aim of examining migraine characteristic differences between females and males are absent in European countries [2]. On a small scale, Steiner et al. [13] found migraine characteristics to be significantly different in females and males ($N = 574$). The exact numbers, however, were not reported. In a clinical study based on a Turkish population, age-dependent variations in symptomatology were noted for females, but not for males [14]. Studies based on the US population are common; however, the healthcare system differs significantly from that of many European healthcare systems. There are two main sources for migraine epidemiological studies in the United States, which are internet-based, longitudinal studies of episodic and chronic migraine, using modified ICHD-2 migraine criteria: American Migraine Prevalence and Prevention (AMPP) [15] and Chronic Migraine Epidemiology and Outcomes (CaMEO) [16]. These data showed that females in a US population more often reported severe headache associated with nausea, vomiting, unilateral head pain, pulsing or throbbing pain, photophobia, phonophobia, blurred vision and visual aura, but not sensory aura [7]. More research, specifically from different populations, is needed to increase our understanding of the impact of sex in migraine. This is crucial for improving diagnosis and treatment options [17].

The distinction between sex and gender was first noted in the 1950s, and social and scientific understanding of sex and gender has evolved over decades. Whilst definitions may vary, for the purpose of this paper the currently accepted definitions from the American Physiological Association guidelines on sexual orientation and gender diversity are used [18]. Here, *sex* refers to "a person's biological status and is typically categorized as male, female, or intersex, i.e., atypical combinations of features that usually distinguish male from female", and *gender* refers to "the attitudes, feelings, and behaviors that a given culture associates with a person's biological sex". A majority of studies cited used these terms interchangeably, and their methodology did not clearly indicate whether gender or sex was studied. In the present study, sex assigned at birth was studied, which is a biological construct and is assigned based on physical appearance at birth. In consideration of space limitations, the terms of female and male will refer to cis-gender females and males.

The aim of the study was to understand the sex differences in the presentation of migraine in a large European-based population cohort which is representative of the general population and consists of 62,672 individuals who have answered an extensive, validated diagnostic headache questionnaire of whom 12,658 had migraine based on the third edition of the ICHD (ICHD-3).

MATERIALS AND METHODS

The Danish Blood Donor Study

The Danish Blood Donor Study (DBDS) started in 2010 and is an ongoing nationwide multicenter, epidemiological cohort and biobank. The demographics of the DBDS have been described in

detail elsewhere [19]. All participants from the DBDS who were connected to the Danish public electronic mailing system (e-Boks) between May 2020 and August 2020 ($n = 127{,}802$) were recontacted. All participants were asked to fill out an extensive migraine questionnaire regardless of whether they were still blood donors. Sex was defined by the unique Danish Civil Registration System number. The diagnostic migraine questionnaire consisted of 105 questions assessing migraine diagnosis, headache frequency, duration, pain characteristics, accompanying symptoms, aura symptoms, autonomic symptoms, allodynia, family history, and treatment response of triptans and over-the-counter simple analgesics (i.e., paracetamol, Pamol, Panodil, Pinex, Ipren, Ibumax, ibuprofen, Kodimagnyl, Codipar, acetylsalicylic acid and Treo). Acute treatment effect was scaled from 0 to 10, and efficacy was defined as the interval from 50% pain relief to pain freedom, that is, the standard effect measurement in clinical trials. In total, 62,672 participants answered the questionnaire and entered our case–control study with the primary aim to study sex differences in the presentation of migraine. Diagnosis of migraine was made by applying the criteria of the ICHD-3 (M.A.C. and J.O.). Individuals with missing data regarding migraine characteristics, not allowing for assessment of a migraine diagnosis, were excluded from the main analysis and set as controls. In total, 12,618 participants fulfilled an ICHD-3 defined migraine diagnosis (Figure S1). The questionnaire was in-cohort validated using a validated semi-structured telephone interview [20, 21] performed by a specially trained neurology resident (M.A.C.) in 500 randomly selected responders. The semi-structured interview assessed migraine with aura (MA) and migraine without aura (MO) separately in detail, including frequency, duration, pain, aura, accompanying and autonomic symptoms. Blood donors enter a quarantine period if they used analgesics of any form; thus, the risk of an overestimation of medication overuse amongst blood donors is very small.

Migraine disease burden

The median migraine disease burden (MDB) was based on the Migraine Headache Index Score (MHIS). The MHIS has been described in detail elsewhere [22, 23] and is calculated by multiplying the migraine frequency within the last 3 months (days per month) by the pain intensity (scaled from 0 to 10) and migraine attack duration (fraction of 24 h). The MDB was calculated by multiplying the median MHIS by the 3-month prevalence of migraine.

Statistical analyses

Analyses were performed using R version 4.0.0 and R Studio version 1.3.1073. Differences in clinical parameters between sexes were analyzed with logistic regression, adjusting for age. Males were used as reference in the adjusted logistic regression analyses.

Standard protocol approval, registrations and patient consents

Written informed consent was obtained from all participants. The DBDS study is an on-going, national study and was approved by the Danish Ethical Standards Committees in the relevant regions of Denmark (DESC) (1-10-72-95-13, SJ-740, 1-90-09-88 and 1-70-04-07) and the Danish Data Protection Agency (DDPA) (P-2019-99). Studies from the Danish Headache Center were approved by the DESC (H-2-2010-122) and the DDPA (01080/GLO-2010-10).

RESULTS

The Danish Migraine Population Cohort compared with the general population regarding migraine

The questionnaire response rate was 49% (62,672/127,802), with 33,450 female responders with a mean age of 46.3 years (SD = 13.9) and 29,238 male responders with a mean age of 49.8 years (SD = 13.5). Responders had marginally fewer contacts to the hospital system ($n = 15.2$ times) compared with non-responders ($n = 16.6$ times) when adjusted for age and sex ($p = 3.6 \times 10^{-6}$). The use of triptans was similar in responders and non-responders. Participants who fulfilled a migraine diagnosis ($N = 12{,}618$) constituted the Danish Migraine Population Cohort (DaMP). For parameters relevant to the present study such as self-reported, health-related quality of life and socio-economic factors, the DaMP cohort was representative of the general Danish population; however, there were fewer participants with severe comorbidities [24, 25]. In DaMP, the lifetime prevalence of migraine was 20.1% (12,618/62,672), 27.5% in females and 11.8% in males, which corresponds to the lifetime migraine prevalence in the Danish population [10]. It was found that 7.95% of the participants had tried a triptan, which corresponded to the general population in Denmark [26]. The prevalence of proposed chronic migraine [27] was 2.01% for females and 1.93% for males; it was not possible to assess chronic migraine. Thus, DaMP was largely representative of the Danish migraine population regarding prevalence, use of triptans, age and sex ratio.

Validity of the diagnostic migraine questionnaire and migraine prevalence

The sensitivity and the specificity of the migraine questionnaire were assessed. Sensitivity refers to the ability of the self-reported questionnaire to detect all cases with migraine. Specificity refers to the ability of the questionnaire to discriminate all cases with migraine from subjects who did not suffer from migraine. The overall migraine diagnosis, that is, all migraine, had a specificity of 93%

(specificity = [number of true negatives]/[number of true negatives + number of false positives] = 96/[96 + 7] = 0.93) and a sensitivity of 93% (sensitivity = [number of true positives]/[number of true positives + number of false negatives] = 241/[241 + 19] = 0.93), giving a positive predictive value (PPV) of 97% (positive predictive value [precision] = [true positives]/[true positives + false positives] = 241/[241 + 7] = 0.97). For MA, the specificity was 97% (100/[100 + 3] = 0.97) and sensitivity was 89% (93/[93 + 12] = 0.89), giving a PPV of 97% (93/[93 + 3] = 0.97). For MO, the specificity was 95% (98/[98 + 5] = 0.95) and sensitivity was 85% (88/[88 + 16] = 0.85), giving a PPV of 95% (88/[88 + 5] = 0.95). Validation of probable MO showed a slight drop in specificity from 95% to 91% (94/[94 + 9] = 0.91) and sensitivity from 85% to 73% (250/[250 + 91] = 0.73). Therefore, it was decided not to include probable migraine in the main analysis in the present study.

The 3-month prevalence of migraine without aura amongst females was significantly age dependent

Although probable migraine was not included in the main analysis, Table 1 provides the prevalence of migraine and its subtypes for each sex for transparency and since such data have been lacking in the literature. Amongst all participants in DaMP, there were 9184 females (72.8%) and 3434 (27.2%) males. The female predominance was greater for MO than MA, whilst the proportion of probable MO and MA was greater for males (Table 1). The mean age of females with migraine was 45.1 years (SD = 13.0), and the mean age of males with migraine was 48.0 years (SD = 13.1). Age distributions of overall migraine and migraine subtypes, MA, MO and migraine with and without aura (MAMO), amongst females and males are presented in Figures 1 and 2. It has been reported that assessment of 3-month prevalence of migraine instead of 1-year prevalence may reduce variability in the data [28]. The 3-month prevalence was defined as migraine during the 3 months prior to assessment. The 3-month prevalence of overall migraine was markedly age dependent amongst females and less age dependent amongst males (Figure 1).

For the migraine subtypes, the 3-month prevalence of MO in females was highly correlated with age and had two phases: the 3-month prevalence was rapidly increasing and peaked at age 40 with a rapid decrease after the age of 40. The 3-month prevalence of MAMO was also age dependent for females; however, it was less pronounced compared with MO, whilst the prevalence of MA did not show any correlation with age. Amongst males, the 3-month prevalence of MO was also age dependent but less markedly compared with females. After 40 years the 3-month prevalence of MO and MAMO decreased for males, whilst there was a slight increase of the prevalence of MA after 40 years (Figure 2).

Females had more frequent and severe migraine attacks compared with males

Females had a higher frequency of migraine attacks (odds ratio [OR] = 1.22, $p = 0.033$, Table 2) but a lower frequency of non-migraine headaches (OR = 0.35, $p < 0.001$) compared with males. The duration of migraine attacks was longer for females (OR = 2.56, $p < 0.001$). The intensity of pain during migraine attacks, measured by the visual analogue scale (VAS), was higher in females (mean VAS [SD] = 7.45 [1.98]) than males (mean VAS [SD] = 6.71 [2.37]) ($p < 0.001$). Females also had more unilateral pain, pulsatile pain and pain exacerbated by physical activity during attack (OR = 1.40–1.49, $p < 0.001$). The associated symptoms such as nausea, vomiting, photophobia, phonophobia, osmophobia, allodynia and cranial autonomic symptoms were also frequent (OR = 1.26–1.98, $p < 0.001$). This was also reflected in mental health, where the 12-item mental health component scale was lower in females (mean = 52.1, SD = 7.78) than males (mean = 53.7, SD = 6.71, OR = 0.97, 95% CI [0.97–0.98], $p < 0.001$) and to a less degree in the self-perceived physical health between females (mean = 54.7, SD = 5.49) and males (mean = 54.9, SD = 4.89, OR = 0.99, 95% CI [0.98–1.00], $p = 0.002$).

TABLE 1 Prevalence of migraine subtypes

	Females		Males				
Variables	***n***	**%**	***n***	**%**	**OR**	**95% CI**	***p* value**
Migraine subtypes							
MA	1764	17.0	1236	35.6	0.63	0.57–0.70	<0.001
pMA	40	0.39	44	1.0	0.38	0.25–0.59	<0.001
MAMO	2739	26.4	711	16.1	1.83	1.65–2.02	<0.001
MO	4681	45.2	1487	33.7	1.62	1.50–1.74	<0.001
pMO	1100	10.6	902	20.5	0.47	0.43–0.52	<0.001

Note: Males were used as reference in the adjusted logistic regression analysis. Results are presented as numbers (*n*), percentages (%) and odds ratios (OR) with corresponding 95% confidence intervals (CI).

Abbreviations: MA, migraine with aura; MO, migraine without aura; MAMO, migraine with and without aura; pMA, probable migraine with aura; pMO, probable migraine without aura.

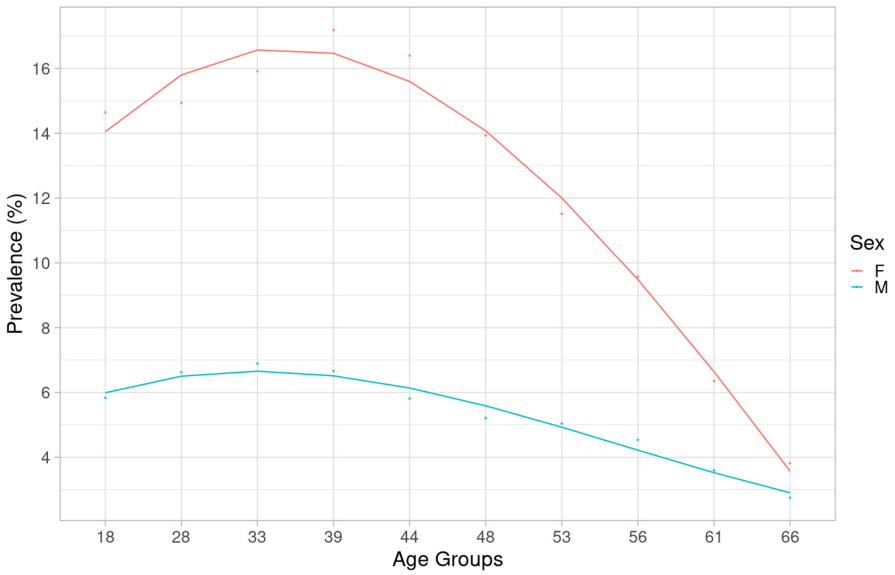

FIGURE 1 Sex- and age-related 3-month prevalence of overall migraine. 3-month prevalence of migraine stratified by sex within the DBDS cohort ($n = 62{,}672$) in 15 age groups. Each age group consists of an equal number of participants. Red, females; blue, males.

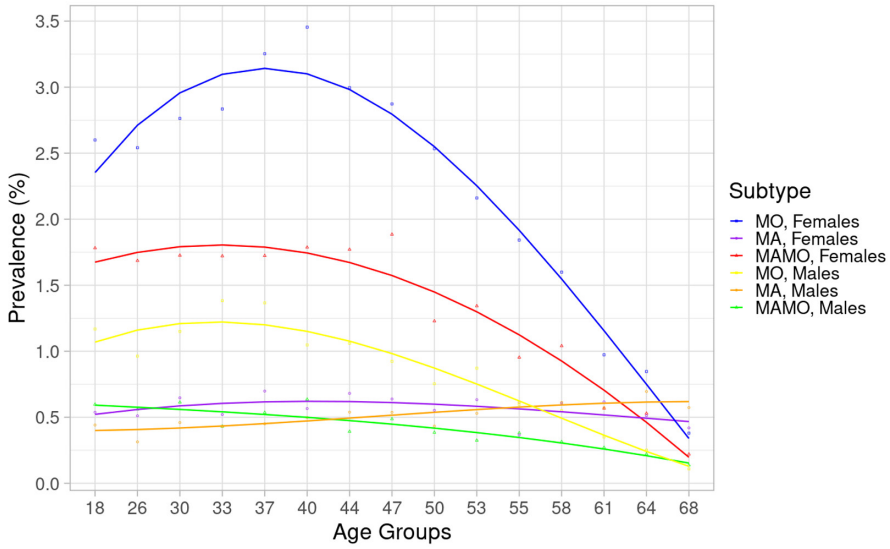

FIGURE 2 Sex- and age-related 3-month prevalence of migraine subtypes. 3-month prevalence of migraine with aura (MA), migraine without aura (MO) and migraine with and without aura (MAMO) stratified by sex within the DBDS cohort ($n = 62{,}672$) in 15 age groups. Each age group consists of an equal number of participants. Red, $MO_{females}$; green, $MA_{females}$; blue, MO_{males}; purple, MA_{males}.

Females carried 79% of the migraine disease burden

The MHIS was calculated by multiplying the migraine frequency by the intensity of pain and the migraine attack duration for attacks within the last 3 months, stratified by migraine subtype. For females with MO, the median MHIS (interquartile range, IQR) was 240 (384) and for males with MO the median MHIS (IQR) was 192 (174). For females with MA, the median MHIS (IQR) was 32 (148) and for males the median MHIS (IQR) was 28 (174). The median MDB, stratified by migraine subtype and sex, was calculated by multiplying the median MHIS by the 3-month prevalence of MO for females (11%) and males (3.59%) and the 3-month prevalence of MA for females (1.72%) and males (1.58%). For females with MO, the MDB (IQR) was 2652 (4243) and for males with MO the MDB (IQR) was 688 (624). For females with MA, the MDB (IQR) was 55 (254) and for males with MA the MDB (IQR) was 44 (164). The total MDB for all migraine for both sexes was 3439 (2652 + 688 + 55 + 44); thus, females carried 79% of the total MDB ([55 + 2652]/3439). Females with MO alone carried 77% (2652/3439) of the total MDB. Males carried 20% (688/3439) of the total MDB. Females with MA carried 1.6% (55/3439) of the total MDB, which was similar to males with MA, who carried 1.3% (44/3439) of the total MDB.

Sex differences in drug treatment

Males ($n = 1509$, 59.0%) had a better effect of over-the-counter simple analgesics than females ($n = 4095$, 54.0%) (OR = 0.86, 95% CI [0.76–0.91], $p < 0.001$), whilst there was no difference in the treatment effect of migraine-specific treatment by triptans between males ($n = 309$, 73.4%) and females ($n = 1565$, 76.4%) (OR = 1.15, 95% CI [0.87–1.51], $p = 0.33$). Regarding prophylactic treatment,

TABLE 2 Clinical migraine characteristics amongst females and males with migraine

Variables	Females (*N* = 9184)		Males (*N* = 3435)		OR	95% CI	*p* value
	N	%	*N*	%			
Migraine frequency							
No migraine attacks in the last 3 months	4865	53.3	1903	55.8	Ref	–	–
1–3 days/month	3531	38.7	1278	37.5	1.01	0.93–1.10	0.73
4–7 days/month	555	6.08	165	4.84	1.22	1.02–1.47	0.033
≥8 days/month	184	2.01	66	1.93	1.04	0.78–1.39	0.79
Non-migraine headache frequency							
Never	462	5.08	88	2.60	Ref	–	–
<1 day/year	2291	25.2	720	21.3	0.59	0.46–0.75	<0.001
≥1 day/year	4632	51.0	1602	47.4	0.55	0.43–0.70	<0.001
≥1 day/month	1233	13.6	691	20.4	0.35	0.28–0.45	<0.001
≥1 day/week	472	5.19	281	8.31	0.35	0.26–0.45	<0.001
Migraine attack duration							
<4 h[a]	1245	13.7	929	27.5	0.53	0.48–0.59	<0.001
4–24 h	5547	61.2	2099	62.2	Ref	–	–
25–72 h	2213	24.4	336	9.95	2.56	2.26–2.91	<0.001
>72 h[a]	64	0.71	12	0.35	2.09	1.17–4.08	0.002
Characteristics							
Unilateral pain	3535	39.5	1142	34.5	1.22	1.12–1.33	<0.001
Pulsatile pain	7628	84.3	2540	75.3	1.66	1.50–1.83	<0.001
Routine activities exacerbate pain	6836	76.3	2138	63.8	1.73	1.59–1.89	<0.001
Accompanying symptoms							
Nausea	6574	72.6	1730	51.5	2.45	2.25–2.66	<0.001
Vomiting	4410	48.8	1199	35.7	1.74	1.61–1.89	<0.001
Photophobia	8138	89.7	2833	83.9	1.59	1.42–1.78	<0.001
Phonophobia	7266	80.2	2211	65.7	2.06	1.88–2.25	<0.001
Photophobia and phonophobia	6916	76.4	2085	62.0	1.93	1.77–2.10	<0.001
Osmophobia	3164	35.1	502	15.0	3.10	2.80–3.45	<0.001
Allodynia	1834	20.4	393	11.6	1.89	1.68–2.12	<0.001
Cranial autonomic symptoms[b]	2614	30.6	1049	32.2	0.90	0.83–0.99	0.002

Note: Males were used as reference in the adjusted logistic regression analysis. Results are presented as numbers (*n*), percentages (%) and odds ratios (OR) with corresponding 95% confidence intervals (CI). Migraine with cranial autonomic symptoms (CAS) was defined by the proposed diagnostic criteria of migraine with CAS [29].

[a]Only participants with migraine with aura.

[b]Defined by the proposed diagnostic criteria for migraine with cranial autonomic symptoms (doi:10.1177/03331024221094548).

significantly more females had tried any prophylactic drug (*n* = 838, 9.12%) compared with males (*n* = 239, 6.96%) (OR = 1.37, 95% CI [1.18–1.59], *p* < 0.001). Table 3 gives an overview of the distribution of the different migraine prophylactic treatments amongst all females and males with migraine. At the time of the study, 212 females and 44 males were active users of prophylactic drugs. The efficacy of prophylactic treatment was defined as at least a 50% reduction in the frequency of days with migraine. Amongst active users, proportionally more females reported efficacy of any prophylactic treatment (*n* = 143, 67.5%) compared with males (*n* = 25, 56.8%); however, the results may be inconclusive given the lack of statistical power (OR = 1.40, 95% CI [0.69–2.79], *p* = 0.339).

DISCUSSION

The largest European-based migraine population is reported with the primary aim of assessing the differences between females and males concerning migraine characteristics. Precise migraine diagnoses as per International Headache Society guidelines were applied and an in-cohort validation is provided showing high sensitivity and specificity of the diagnoses. It was found that the 3-month prevalence of MO was 11% in females and 3.59% in males. The 3-month prevalence of MA was 1.72% in females and 1.58% in males. Females had a significantly higher migraine attack frequency, a greater intensity of pain, longer duration of migraine attacks, more unilateral

TABLE 3 Current or previous use of prophylactic treatment amongst all participants with migraine

	Females (*N* = 9184)		Males (*N* = 3435)				
Variables	***N* tried**	**Effect %**	***N***	**%**	**OR**	**95% CI**	***p* value**
Migraine prophylactic treatment							
Angiotensin-converting enzyme	21	0.229	5	0.146	1.58	0.64–4.74	0.362
Angiotensin II receptor blocker	75	0.817	16	0.466	1.72	1.03–3.07	0.004
Beta blockers	213	2.32	35	1.02	2.32	1.64–3.38	<0.001
Calcium channel blockers	19	0.207	4	0.116	1.83	0.69–6.34	0.272
Antidepressants	54	0.588	11	0.320	1.82	0.99–3.68	0.007
Anticonvulsants	51	0.555	10	0.291	1.87	0.99–3.91	0.007
Botulinum toxin	45	0.490	7	0.204	2.34	1.13–5.70	0.003
Calcitonin gene-related peptide therapy	8	0.087	2	0.058	1.48	0.37–9.85	0.619

Note: Males were used as reference in the adjusted logistic regression analysis. Results are presented as numbers (*n*), percentages (%) and odds ratios (OR) with corresponding 95% confidence intervals (CI).

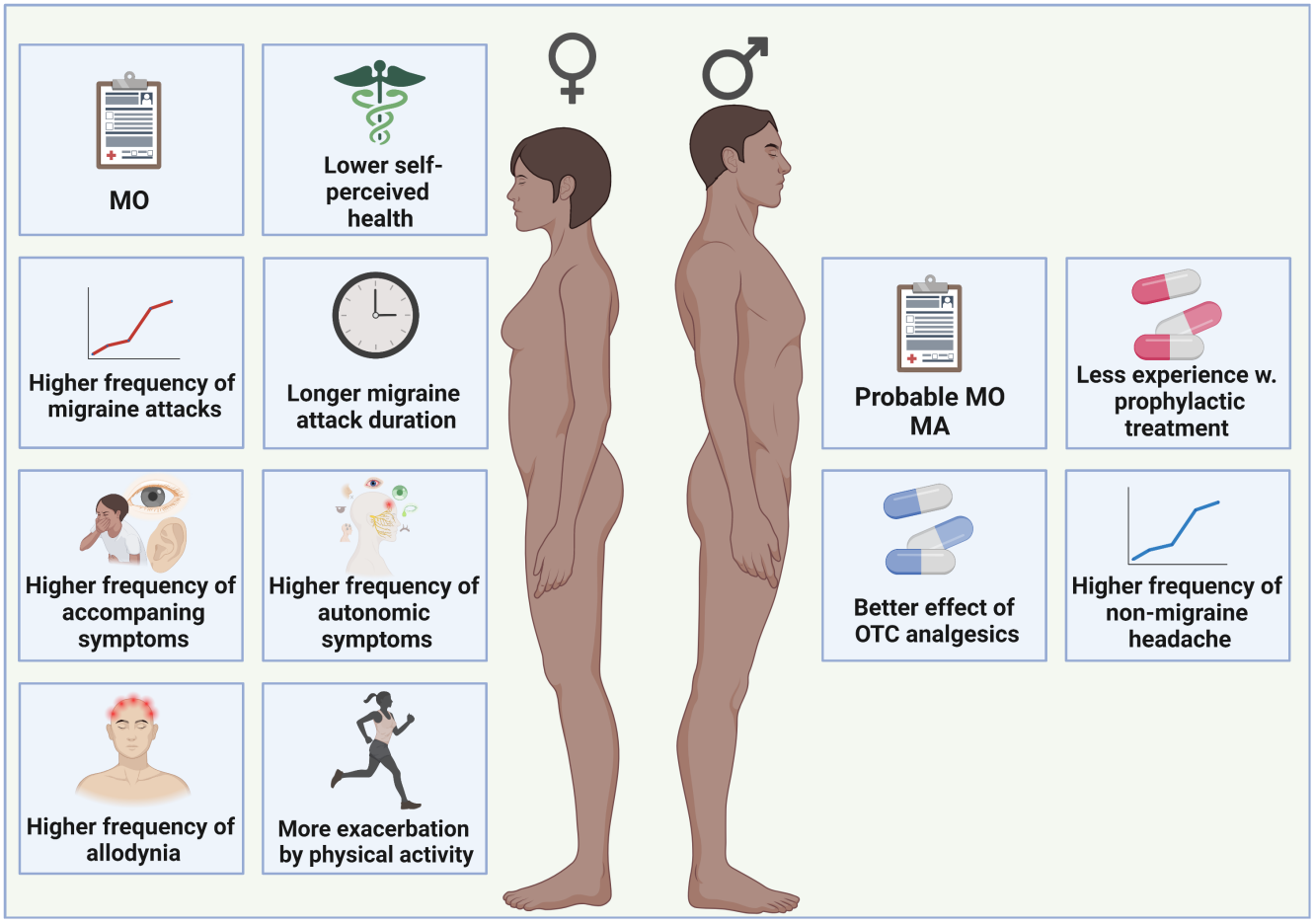

FIGURE 3 Overview of sex differences in migraine. MA, migraine with aura; MO, migraine without aura; OTC analgesics, over-the-counter analgesics. Figure created with BioRender.com.

and pulsatile pain, more exacerbation by physical activity, and more nausea, vomiting, photophobia, phonophobia, osmophobia and allodynia than males. Overall, females had a higher MHIS than males. The female predominance was greater for MO than MA, whilst the proportion of probable MO and MA was greater for males (Figure 3 shows an overview of the sex differences detected in the study). There was no major difference in the treatment effect of triptans between females and males, but males had a better effect of over-the-counter simple analgesics than females. Effect sizes were generally large enough to be clinically relevant. In correspondence with previous reports based on US populations [7] males had less experience with prophylactic drugs compared with females and, amongst active users of prophylactic drugs, proportionally more females reported a better effect of their prophylactic treatment. However, results were not significant, and the conclusion is made with caution as the number of participants who had tried migraine prophylactics was small.

The prevalence of migraine without aura is markedly age dependent in females which is not true for migraine with aura

Assessment of the sex-specific, age-related 3-month prevalence of MO, MA and MAMO has not previously been reported; hence, only overall results can be compared. It was found that the age-related 3-month prevalence of MO, MA and MAMO was significantly different between females and males. The prevalence of MO for both sexes was bell-shaped with the highest peak in the reproductive years. The prevalence of MA was not age dependent for females or males, although there was a slight increase after 40 years amongst males. Correct case definition according to the International Headache Society criteria is important, and validation of diagnoses is crucial for prevalence studies. In contrast to previous studies, migraine was sub-classified into validated MO, MA and MAMO diagnoses, which is unique for large population-based cohorts of migraine. In the US-based AMPP study [30], Lipton et al. described the 1-year period prevalence of migraine by age and sex adjusted for demographics. The 1-year prevalence of migraine was higher in females than in males across the life span in the ages examined; however, stratification on MO and MA was absent. Victor et al. [31] assessed the age- and sex-specific 1-year period prevalence of self-reported migraine in a US population amongst individuals who participated in the 2003 National Health Interview Survey. They showed that females had a higher prevalence of migraine than males, and the prevalence had a bimodal distribution in both sexes. Here, the phenotyping (answering yes to 'a doctor has diagnosed migraine within the past 90 days') did not allow for stratification on migraine subtypes. No bimodal distribution for the migraine subtypes was found.

Necessity of different population-based estimates

A recent review by Stovner et al. summarized global prevalence estimates of all headache including migraine and showed that geographical differences influenced prevalence estimates and that migraine prevalence increased over time [32]. The authors also underlined methodological problems with headache epidemiology. Understanding the prevalence of migraine in a sex-specific manner helps decision makers prioritize resources. The largest European-based migraine or headache studies are the Eurolight study [33] and the HUNT study [34]. The former is a large data-gathering exercise primarily to inform health policy in the European Union about the cost of migraine and headache. Data vary from population- to clinic-based, and some surveys were from national headache patients' organizations. The HUNT study is a large population-based health study in Norway, where participants amongst other questions have answered 13 headache questions. Based on a literature search, the only previous high quality European study evaluating sex differences regarding migraine characteristics, on a smaller scale than the present study, was the study by Lebedeva et al. who found that accompanying symptoms including photophobia and/or phonophobia, nausea and vomiting occurred more often in females using face-to-face interviews [35]. The Eurolight project reported a 1-year prevalence of migraine of 35% after sex adjustment [33], which is significantly higher than the US-based 12%–13% [30]. Applying a 3-month prevalence of migraine with less variation [28], it was found that the prevalence of migraine should not only be stratified by sex but also by migraine subtype in migraine epidemiology studies. In addition to prevalence differences, there are health economic differences which further reflect differences in disease severity [36–40].

The burden of migraine in the two sexes

It is well established that the prevalence of migraine is higher in females than in males [1, 8–11]. However, results from population-based studies comparing migraine characteristics in females and males are less common [2], and the largest population-based studies are US based. However, these studies have several shortcomings: (a) diagnoses are not strictly based on ICHD definitions but on modified criteria, (b) no in-cohort diagnostic validation has been done and (c) the definition of sex or gender is absent; for example, the CaMEO studies refer to gender but the methodology suggests that sex was elicited [16]; in the AMPP study gender is the prevailing term used, but sex is also used [15]. The methods and quality of published headache epidemiology studies are very variable. This variability has led to published recommendations for headache epidemiological studies, aiming to improve the quality of studies of headache prevalence and burden [41].

Most available data regarding migraine characteristics are from clinic-based studies, and the most common finding is that females report longer duration of headache attacks than males [13, 14]. Reports about the frequency, pain intensity and the presence of non-headache symptoms, that is, associated symptoms, are less common and results have been inconsistent [7, 42, 43]. One challenge is that in most studies prevalence is the primary objective, and

attack frequency, pain intensity and other migraine characteristics are secondary findings [2]. On a smaller scale ($n = 833$), a French nationwide survey of migraine reported no sex differences with regard to frequency and duration of attacks nor length of disease, whilst the opposite was found here. Other clinical characteristics were not reported [44]. Disregarding the shortcomings, the US-based population studies showed results similar to ours with headache-related disability being greater in females than males for both episodic and chronic migraine [45]. Females utilized prescription and non-prescription headache medication more often than males, and there was no sex difference in the use of prescription preventive headache medication [7, 46]. Females more often reported severe headache associated with nausea, vomiting, unilateral head pain, pulsing or throbbing pain, photophobia, phonophobia, blurred vision and visual aura [7, 45].

It has been very difficult to arrive at one simple figure for the total burden of migraine in females and males, but our data show that females are more bothered than males, because they have a higher migraine attack frequency, longer migraine attack duration, more severe migraine attacks and more migraine-associated symptoms than males. Our data provide evidence that females carry 79% of the total burden of migraine, and it is shown that the MDB is dependent on migraine subtype and sex. The disease burden was almost exclusively carried by MO in females (77%), whilst males with MO carried 20% of the total MDB. The MDB of MA was small compared with MO and with no sex difference, 1.6% was carried by females and 1.3% was carried by males. According to a previous comprehensive review, future guidelines of migraine management and treatment should also include sex differences [47], and our data support this.

Strengths and limitations

The strengths of our study include a carefully validated migraine questionnaire with a PPV of 97% for any migraine as well as for the migraine subtypes MA (PPV = 97%) and MO (PPV = 95%). Our large sample size allowed for accurate statistical estimates. Face-to-face interview is the gold standard but is not possible with the high numbers needed in this study. However, it is emphasized that the in-cohort validation performed provided a clear and precise estimate of diagnostic specificity and sensitivity, which were both high. Our population-based cohort of blood donors had fewer participants with severe comorbidities and fewer participants with ≥8 migraine days per month than the population. It is expected that the burden of migraine in females may be even more pronounced as the transition from episodic migraine to chronic migraine occurs more often in females than in males [48, 49]. The response rate was 49% but responders were comparable to non-responders regarding migraine treatment based on data from the Danish health registers. Our study did not allow for assessment of medication overuse, but the risk of overuse amongst blood donors is very small, given the automated quarantine period if participants use analgesics of any form.

CONCLUSION

Migraine characteristics differ significantly between females and males, with females generally having more severe disease outcome. Our data show that females carry 79% of the total MDB. Moreover, there is a striking difference in the age-related 3-month prevalences of MO, MA and MAMO between sexes. The findings suggest that preventive strategies should be offered earlier to females with MO, whilst probable migraine should be recognized in males to avoid under-diagnosis and under-treatment.

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CONFLICT OF INTEREST STATEMENT

The authors report no competing interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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