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RESEARCH ARTICLE

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

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Key words: Migraine, sex differences, sex stratification, population-based study; burden; blood donors

Abbreviations: DaMP = Danish Migraine Population Cohort, DBDS = Danish Blood Donor Study, MA = migraine with aura, MAMO = migraine with and without aura, MO = migraine without aura, PPV = positive predictive value.

Abstract

Background

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

Methods

We performed a population-based study of 62,672 Danish blood donors (both present and previous donors), of whom 12,658 had migraine. All participants completed a 105-item diagnostic migraine questionnaire send via 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 9,184 females (mean age=45.1) and 3,434 males (mean age=48.0). The three-months prevalence of migraine without aura was 11% in females and 3.59% in males. The three-months prevalence of migraine with aura was 1.72% in females and 1.58% in males. In females, the age-related three-months prevalence of migraine without aura increased markedly during the childbearing age. In males, both migraine with- and without aura showed less age variation. Females had a higher frequency of migraine attacks (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%), while 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.

Background

Migraine is predominately 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) among females during the child-bearing 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 to examine migraine characteristic differences between females and males are even absent in European countries[2]. On a small scale, Steiner and colleagues found migraine characteristics to be significantly different in females and males (N=574). The exact numbers were, however, not reported[13]. 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 health care system differs significantly from that of

many European health care systems. There are two main sources for migraine epidemiological studies in US, which are internet-based, longitudinal studies of episodic and chronic migraine, using modified ICHD-2 migraine criteria: American Migraine Prevalence and Prevention[15] and Chronic Migraine Epidemiology and Outcomes[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. While definitions may vary, for the purpose of this paper, we will use the currently accepted definitions from the American Physiological Association guidelines on sexual orientation and gender diversity[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, we studied sex assigned at birth, 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 International Classification of Headache Disorders (ICHD-3).

Materials and methods

The Danish Blood Donor Study (DBDS)

The Danish Blood Donor Study (DBDS) started in 2010 and is an ongoing nationwide multicenter, epidemiological cohort and biobank. The demographics of the DBDS has been described in detail elsewhere[19]. We recontacted 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). 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, Codimagnyl, Codipar, Acetylsalicylic Acid, and Treo). Acute treatment effect was scaled from 0-10, and efficacy was defined as the interval from 50% pain relief to pain freedom, i.e., 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 (MAC and JO). 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 (Supplementary Figure 1). The questionnaire was in-cohort validated using a validated semi-structured telephone interview[20,21] performed by a specially trained neurology resident (MAC) 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 use analgesics of any form, thus, the risk of an overestimation of medication overuse among 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 details elsewhere[22,23] and is calculated by multiplying the migraine

frequency within the last three months (days per month) by the pain intensity (scaled from 0-10) and migraine attack duration (fraction of 24 hours). The MDB was calculated by multiplying the median MHIS by the three-months 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).

Data availability

Data are available from the corresponding authors upon reasonable request and require both a material transfer agreement and memorandum of understanding in order to obtain ethical and data protection agency approval.

Results

The Danish Migraine Population Cohort (DaMP) 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 x 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]. We 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, i.e., 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, we decided not to include probable migraine in the main analysis in the present study.

The three-months prevalence of migraine without aura among females was significantly age-dependent

Although we did not include probable migraine in the main analysis, we provided Table 1 with the prevalence of migraine and its subtypes for each sex for transparency and since such data have been lacking in the literature. Among all participants in DaMP, there were 9,184 females (72.8%) and 3,434 (27.2%) males. The female predominance was greater for migraine without aura (MO) than migraine with aura (MA), while 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 distribution of overall migraine and migraine subtypes, MA, MO and MAMO, among females and males are presented in Figures 1 and 2. It has been reported that assessment of three-months prevalence of migraine instead of one-year prevalence may reduce variability in data[28]. The three-months prevalence was defined as migraine during the three months prior to assessment. The three-months prevalence of overall migraine was markedly age-dependent among females and less age-dependent among males (Figure 1).

For the migraine subtypes, the three-months prevalence of MO in females was highly correlated with age and had two phases, the three-months prevalence was rapidly increasing and peaked at age of 40 with a rapid decrease after the age of 40. The three-months prevalence of MAMO was also age dependent for females, however, less pronounced compared with MO, while the prevalence of MA did not show any correlation with age. Among males, the three-months prevalence of MO was also age-dependent, however, less

markedly compared with females. After 40 years the three-months prevalence of MO and MAMO decreased for males, while 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 (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 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).

Females carried 79% of the migraine disease burden

The Migraine Headache Index Score (MHIS) was calculated by multiplying the migraine frequency by the intensity of pain and the migraine attack duration for attacks within the last three months, stratified by migraine subtype. For females with MO, the median MHIS (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). We calculated the median migraine disease burden (MDB), stratified by migraine subtype and sex, by multiplying the median MHIS by the three-months prevalence of MO for females (11%) and males (3.59%), and the three-months prevalence of MA for females (1.72%) and males (1.58%). For females with MO, the MDB (IQR) was 2,652 (4,243) 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 3,439 (2,652+688+55+44), thus, females carried 79% of the total MDB ((55+2,652)/3,439). Females with MO alone carried 77% (2,652/3,439) of the total MDB. Males carried 20% (688/3,439) of the total MDB. Females with MA carried 1.6% (55/3,439) of the total MDB, which was similar to males with MA, who carried 1.3% (44/3,439) of the total MDB.

Sex differences in drug treatment

Males (n=1,509, 59.0%) had a better effect of over-the-counter simple analgesics than females (n=4,095, 54.0%) (OR=0.86, 95%CI [0.76–0.91], P<0.001), while there was no difference in the treatment effect of migraine specific treatment by triptans between males (n=309, 73.4%) and females (n=1,565, 76.4%) (OR=1.15, 95%CI [0.87–1.51], P=0.33). Regarding prophylactic treatment, 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 among all females and males with migraine. At time of the study, 212 females and 44 males were active users of prophylactic drugs. Efficacy of prophylactic treatment was defined as at least 50% reduction in the frequency of days with migraine. Among 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

We report the largest European-based migraine population with the primary aim to assess the differences between females and males concerning migraine characteristics. We have applied precise migraine diagnoses as per International Headache Society guidelines and provide an in-cohort validation showing high sensitivity and specificity of the diagnoses. We found that the three-months prevalence of MO was 11% in females and 3.59% in males. The three-months 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 and pulsatile pain, more exacerbation by physical activity, and more nausea, vomiting, photophobia, phonophobia, osmophobia, and allodynia than males. Overall, females had a higher Migraine Headache Index Score than males. The female predominance was greater for migraine without aura (MO) than migraine with aura (MA), while 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 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 among active users of prophylactic drugs, proportionally more females reported a better effect of their prophylactic treatment. However, results were not significant, and we conclude 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 three-months prevalence of MO, MA and MAMO has not previously been reported, hence, we can only compare with overall results. We found that the age-related three-months 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 neither females nor males, although there was a slight increase after 40 years among 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, we sub-classified migraine into validated MO, MA and MAMO diagnoses, which is unique for large population-based cohorts of migraine. In the US-based AMPP study[29], Lipton and colleagues described the one-year period prevalence of migraine by age and sex adjusted for demographics. The one-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 and colleagues assessed the age- and sex-specific one-year

period prevalence of self-reported migraine in a US population among individuals who participated in the 2003 National Health Interview Survey[30]. 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. We do not find a bimodal distribution for the migraine subtypes.

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[31]. 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 were the Eurolight study[32] and the HUNT study[33]. 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 among other questions have answered 13 headache questions. Based on literature search, the only previous high quality European study evaluating sex differences regarding migraine characteristics, in a smaller scale than the present study, was the study by Lebedeva et al, who found that accompanying symptoms including photo- and/or phonophobia, nausea, and vomiting occurred more often in females using face-to-face interviews[34]. The Eurolight project reported a 1-year prevalence of migraine of 35% after sex adjustment[32], which is significantly higher than the US-based 12-13%[29]. Applying a three-months prevalence of migraine with less variation[28], we find that 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[35–39].

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, e.g. 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, however, 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[40].

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, i.e. associated symptoms, are less common and results have been inconsistent[7,41,42]. 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]. In a smaller scale (n=833), a French nationwide survey of migraine reported no sex differences with regards to frequency and duration of attacks nor length of disease, while we find the opposite. Other clinical characteristics were not reported[43]. 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[44]. 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[7,45]. Females more often reported severe headache associated with nausea, vomiting, unilateral head pain, pulsing or throbbing pain, photophobia, phonophobia, blurred vision, and visual aura[7,44].

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 we show that the migraine disease burden is dependent on migraine subtype and sex. The disease burden was almost exclusively carried by MO in females (77%), while males with MO carried 20% of the total migraine disease burden. The migraine disease burden 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[46], and our data support this.

Strengths and limitations

The strengths of our study include a carefully validated migraine questionnaire with a positive predictive value (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 not possible with high numbers needed in this study. However, we emphasize that the in-cohort validation we 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. We expect 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[47,48]. 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 among 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 migraine disease burden. Moreover, there is a striking difference in the age-related three-months prevalences of MO, MA and MAMO between sexes. The findings suggest that preventive strategies should be offered earlier to females with migraine without aura, while probable migraine should be recognized in males to avoid under-diagnosis and under-treatment.

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Author contribution

Study concept and design: Chalmer, Olesen and Hansen. Analysis and interpretation of data: Chalmer and Hansen. Drafting of the manuscript: Chalmer. Critical revision of the manuscript for important intellectual content: All authors.

Competing interests

The authors report no competing interests.

References

1. Stewart WF, Wood C, Reed ML, Roy J, Lipton RB. Cumulative lifetime migraine incidence in women and men. *Cephalalgia*. 2008;28(11):1170-1178. doi:10.1111/j.1468-2982.2008.01666.x

2. Vetvik KG, MacGregor EA. Sex differences in the epidemiology, clinical features, and pathophysiology of migraine. *Lancet Neurol*. 2017;16(1):76. doi:10.1016/S1474-4422(16)30293-9

3. Vos T, Lim SS, Abbafati C, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet*. 2020;396(10258):1204-1222. doi:10.1016/S0140-6736(20)30925-9

4. Steiner TJ, Stovner LJ, Jensen R, Uluduz D, Katsarava Z. Migraine remains second among the world's causes of disability, and first among young women: findings from GBD2019. *J Headache Pain*. 2020;21(1):4-7. doi:10.1186/s10194-020-01208-0

5. Buse DC, Fanning KM, Reed ML, et al. Life With Migraine: Effects on Relationships, Career, and Finances From the Chronic Migraine Epidemiology and Outcomes (CaMEO) Study. *Headache*. 2019;59(8):1286-1299. doi:10.1111/head.13613

6. Brusa P, Allais G, Rolando S, et al. Migraine attacks in the pharmacy: a gender subanalysis on treatment preferences. *Neurol Sci*. 2015;36:93-95. doi:10.1007/s10072-015-2156-7

7. Buse DC, Loder EW, Gorman JA, et al. Sex differences in the prevalence, symptoms, and associated features of migraine, probable migraine and other severe headache: Results of the American Migraine prevalence and prevention (AMPP) study. *Headache*. 2013;53(8):1278-1299. doi:10.1111/head.12150

8. Boardman HF, Thomas E, Croft PR, Millson DS. Epidemiology of headache in an English district. *Cephalalgia*. 2003;23(2):129-137. doi:10.1046/j.1468-2982.2003.00468.x

9. Celentano DD, Linet MS, Stewart WF. Gender differences in the experience of headache. *Soc Sci Med*. 1990;30(12):1289-1295. doi:10.1016/0277-9536(90)90309-G

10. RUSSELL MB, RASMUSSEN BK, THORVALDSEN P, OLESEN J. Prevalence and Sex-Ratio of the Subtypes of Migraine. *Int J Epidemiol*. 1995;24(3):612-618. doi:10.1093/ije/24.3.612

11. Stovner LJ, Hagen K, Jensen R, et al. The global burden of headache: A documentation of headache prevalence and disability worldwide. *Cephalalgia*. 2007;27(3):193-210. doi:10.1111/j.1468-2982.2007.01288.x

12. Delaruelle Z, Ivanova TA, Khan S, et al. Male and female sex hormones in primary headaches. *J Headache Pain*. 2018;19(1):1-12. doi:10.1186/s10194-018-0922-7

13. Steiner TJ, Scher AI, Stewart WF, Kolodner K, Liberman J, Lipton RB. The prevalence and disability burden of adult migraine in England and their relationships to age, gender and ethnicity. *Cephalalgia*. 2003;23(7):519-527. doi:10.1046/j.1468-2982.2003.00568.x

14. Bolay H, Ozge A, Saginc P, et al. Gender influences headache characteristics with increasing age in migraine patients. *Cephalalgia*. 2015;35(9):792-800. doi:10.1177/0333102414559735

15. Silberstein S, Loder E, Diamond S, Reed M, Bigal M, Lipton R. Probable Migraine in the United States: Results Of The American Migraine Prevalence and Prevention (AMPP) Study. *Cephalalgia*. 2007;27(3):220-229. doi:10.1111/j.1468-2982.2006.01275.x

16. Adams AM, Serrano D, Buse DC, et al. The impact of chronic migraine: The Chronic Migraine Epidemiology and Outcomes (CaMEO) Study methods and baseline results. *Cephalalgia*. 2015;35(7):563-578. doi:10.1177/0333102414552532

17. Schroeder RA, Brandes J, Buse DC, et al. Sex and Gender Differences in Migraine—Evaluating Knowledge Gaps. *J Women's Heal*. 2018;27(8):965-973. doi:10.1089/jwh.2018.7274

18. Guidelines for psychological practice with lesbian, gay, and bisexual clients. *Am Psychol*. 2012;67(1):10-42. doi:10.1037/a0024659

19. Erikstrup C, Sørensen E, Nielsen KR, et al. Cohort Profile: The Danish Blood Donor Study. *Int J Epidemiol*. Published online October 4, 2022. doi:10.1093/ije/dyac194

20. Rasmussen BK, Jensen R, Olesen J. Questionnaire Versus Clinical Interview in the Diagnosis of Headache. *Headache J Head Face Pain*. 1991;31(5):290-295. doi:10.1111/j.1526-4610.1991.hed3105290.x

21. Gervil M, Ulrich V, Olesen J, Russell MB. Screening for migraine in the general population: validation of a simple questionnaire. *Cephalalgia*. 1998;18(6):342-348. doi:10.1046/j.1468-2982.1998.1806342.x

22. Chepla KJ, Oh E, Guyuron B. Clinical outcomes following supraorbital foraminotomy for treatment of frontal migraine headache. *Plast Reconstr Surg*. 2012;129(4):656-662. doi:10.1097/PRS.0b013e3182450b64

23. Kelishadi MR, Naeini AA, Khorvash F, Askari G, Heidari Z. The beneficial effect of Alpha-lipoic acid supplementation as a potential adjunct treatment in episodic migraines. *Sci Rep*. 2022;12(1):1-12. doi:10.1038/s41598-021-04397-z

24. Rigas AS, Skytthe A, Erikstrup C, et al. The healthy donor effect impacts self-reported physical and mental health – results from the Danish Blood Donor Study (DBDS). *Transfus Med*. 2019;29(S1):65-69. doi:10.1111/tme.12478

25. Burgdorf KS, Simonsen J, Sundby A, et al. Socio-demographic characteristics of Danish blood donors. *PLoS One*. 2017;12(2):1-11. doi:10.1371/journal.pone.0169112

26. Davidsson OB, Olofsson IA, Kogelman LJ, et al. Twenty-five years of triptans - a nationwide population study. *Cephalalgia*. Published online February 14, 2021:333102421991809. doi:10.1177/0333102421991809

27. Chalmer MA, Hansen TF, Lebedeva ER, Dodick DW, Lipton RB, Olesen J. Proposed new diagnostic criteria for chronic migraine. *Cephalalgia*. 2019;40(4):399-406. doi:10.1177/0333102419877171

28. Serrano D, Lipton RB, Scher AI, et al. Fluctuations in episodic and chronic migraine status over the course of 1 year: implications for diagnosis, treatment and clinical trial design. *J Headache Pain*. 2017;18(1):101. doi:10.1186/s10194-017-0787-1

29. Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML. Migraine prevalence , disease burden , and the need for preventive therapy. *Neurology*. 2007;68(5):343-349.

30. Victor T, Hu X, Campbell J, Buse D, Lipton R. Migraine prevalence by age and sex in the United States: A life-span study. *Cephalalgia*. 2010;30(9):1065-1072. doi:10.1177/0333102409355601

31. Stovner LJ, Hagen K, Linde M, Steiner TJ. The global prevalence of headache: an update, with analysis of the influences of methodological factors on prevalence estimates. *J Headache Pain*. 2022;23(1):1-17. doi:10.1186/s10194-022-01402-2

32. Steiner TJ, Stovner LJ, Katsarava Z, et al. The impact of headache in Europe: principal results of the Eurolight project. *J Headache Pain*. 2014;15(1):1-11. doi:10.1186/1129-2377-15-31

33. Hagen K, Zwart JA, Vatten L, Stovner LJ, Bovim G. Prevalence of migraine and non-migrainous headache--head-HUNT, a large population-based study. *Cephalalgia*. 2000;20(10):900-906. doi:10.1046/j.1468-2982.2000.00145.x

34. Lebedeva ER, Kobzeva NR, Gilev D, Olesen J. Prevalence of primary headache disorders diagnosed according to ICHD-3 beta in three different social groups. *Cephalalgia*. 2016;36(6):579-588. doi:10.1177/0333102415596442

35. Linde M, Gustavsson A, Stovner LJ, et al. The cost of headache disorders in Europe: The Eurolight project. *Eur J Neurol*. 2012;19(5):703-711. doi:10.1111/j.1468-1331.2011.03612.x

36. Hawkins K, Wang S, Rupnow M. Direct Cost Burden Among Insured US Employees With Migraine. *Headache J Head Face Pain*. 2008;48(4):553-563. doi:10.1111/j.1526-4610.2007.00990.x

37. Hawkins K, Wang S, Rupnow MFT. Indirect Cost Burden of Migraine in the United States. *J Occup Environ Med*. 2007;49(4):368-374. doi:10.1097/JOM.0b013e31803b9510

38. Hu XH, Markson LE, Lipton RB, Stewart WF, Berger ML. Burden of Migraine in the United States. *Arch Intern Med*. 1999;159(8):813. doi:10.1001/archinte.159.8.813

39. Allais G, Chiarle G, Sinigaglia S, Airola G, Schiapparelli P, Benedetto C. Gender-related differences in migraine. *Neurol Sci*. 2020;41(S2):429-436. doi:10.1007/s10072-020-04643-8

40. Stovner LJ, Al Jumah M, Birbeck GL, et al. The methodology of population surveys of headache prevalence, burden and cost: Principles and recommendations from the Global Campaign against Headache. *J Headache Pain*. 2014;15(1):1-30. doi:10.1186/1129-2377-15-5

41. Franconi F, Finocchi C, Allais G, et al. Gender and triptan efficacy: A pooled analysis of three double-blind, randomized, crossover, multicenter, Italian studies comparing frovatriptan vs. other triptans. *Neurol Sci*. 2014;35(SUPPL. 1):99-105. doi:10.1007/s10072-014-1750-4

42. Kallela M, Wessman M, Färkkilä M, et al. Clinical Characteristics of Migraine in A Population-Based Twin Sample: Similarities and Differences Between Migraine with and Without Aura. *Cephalalgia*. 1999;19(3):151-158. doi:10.1046/j.1468-2982.1999.1903151.x

43. Henry P, Michel P, Brochet B, et al. A nationwide survey of migraine in france: Prevalence and clinical features in adults. *Cephalalgia*. 1992;12(4):229-237. doi:10.1046/j.1468-2982.1992.1204229.x

44. Lipton RB, Munjal S, Alam A, et al. Migraine in America Symptoms and Treatment (MAST) Study: Baseline Study Methods, Treatment Patterns, and Gender Differences. *Headache*. 2018;58(9):1408-1426. doi:10.1111/head.13407

45. 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(8):1280-1289. doi:10.1111/head.12878

46. Lebedeva ER. *Sex and Age Differences in Migraine Treatment and Management Strategies*. Vol 164. 1st ed. Elsevier Inc.; 2022. doi:10.1016/bs.irn.2022.07.003

47. Buse DC, Manack AN, Fanning KM, et al. Chronic migraine prevalence, disability, and sociodemographic factors: Results from the American migraine prevalence and prevention study. *Headache*. 2012;52(10):1456-1470. doi:10.1111/j.1526-4610.2012.02223.x

48. Bigal ME, Serrano D, Buse D, Scher A, Stewart WF, Lipton RB. Acute migraine medications and evolution from episodic to chronic migraine: A longitudinal population-based study. *Headache*. 2008;48(8):1157-1168. doi:10.1111/j.1526-4610.2008.01217.x

49. Christensen CG, Techlo TR, Kogelman LJ, et al. Population-based prevalence of cranial autonomic symptoms in migraine and proposed diagnostic appendix criteria. *Cephalalgia*. Published online May 29, 2022:033310242210945. doi:10.1177/03331024221094548

Figure Legends

Figure 1: Sex and age-related three-months prevalence of overall migraine. Three-months prevalence of migraine stratified by sex within the DBDS-cohort (n=62,672) in 15 age groups. Each age group consists of equal number of participants. Red=Females, blue=males.

Figure 2: Sex and age-related three-months prevalence of migraine subtypes. Three-months 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 equal number of participants. Red=$MO_{females}$, green=$MA_{females}$, blue=MO_{males}, purple=MA_{males}.

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

Table Legends

Table 1: Prevalence of migraine subtypes. Migraine with aura (MA), migraine without aura (MO), both (MAMO), probable migraine with and without aura (pMA and pMO). Males were used as reference (ref) in the adjusted logistic regression analysis. Results are presented as numbers (n), percentages (%) and odds ratios (OR) with corresponding 95% confidence intervals (CI).

Table 2: Clinical migraine characteristics among females and males with migraine. Males were used as reference (ref) in the adjusted logistic regression analysis. Results are presented as numbers (n), percentages (%) and odds ratios (OR) with corresponding 95% confidence intervals (CI). OTC analgesics: over-the-counter analgesics. Migraine with CAS was defined by the proposed diagnostic criteria of migraine with CAS[49].

Table 3: Current or previous use of migraine prophylactic treatment. Males were used as reference (ref) in the adjusted logistic regression analysis. Results are presented as numbers (n), percentages (%) and odds ratios (OR) with corresponding 95% confidence intervals (CI).

Supplementary material

Supplementary Figure 1: Flow diagram of recruitment. DBDS=Danish Blood Donor Study. ICHD-3=International Classification of Headache Disorders third edition. DaMP=Danish Migraine Population

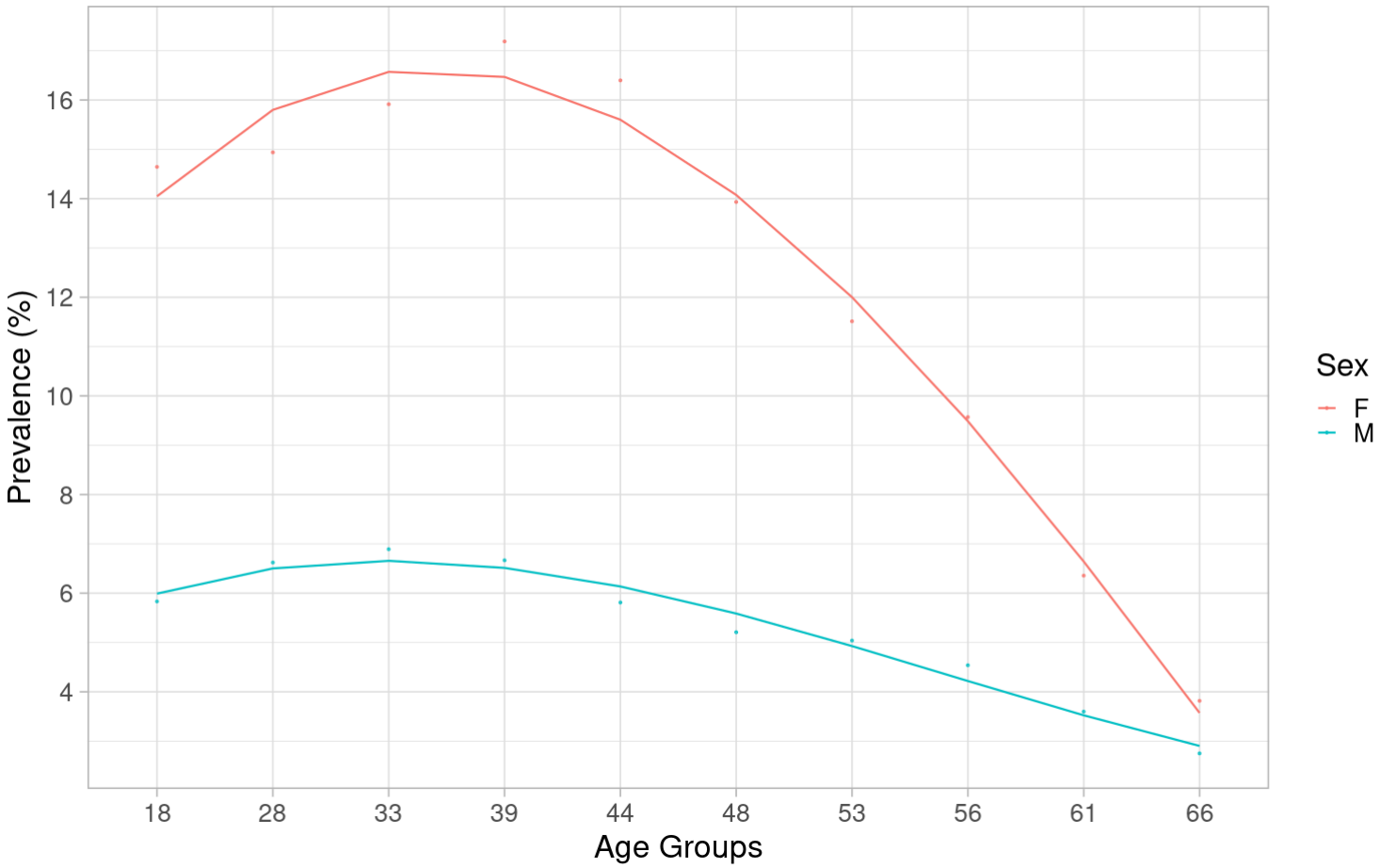
Table 1: Prevalence of migraine subtypes

	Females		Males				
Variables	**n**	**%**	**n**	**%**	**OR**	**95% CI**	**P-value**
Migraine subtypes							
MA	1,764	17.0	1,236	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	2,739	26.4	711	16.1	1.83	[1.65–2.02]	<0.001
MO	4,681	45.2	1,487	33.7	1.62	[1.50–1.74]	<0.001
pMO	1,100	10.6	902	20.5	0.47	[0.43–0.52]	<0.001

Table 2: Clinical characteristics

	Females (N = 9,184)		Males (N = 3,435)				
Variables	**N**	**%**	**N**	**%**	**OR**	**95% CI**	**P-value**
Migraine frequency							
No migraine attacks the last three months	4,865	53.3	1,903	55.8	Ref	-	-
1-3 days/month	3,531	38.7	1,278	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[1]	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	2,291	25.2	720	21.3	0.59	[0.46–0.75]	< 0.001
≥1 day/year	4,632	51.0	1,602	47.4	0.55	[0.43–0.70]	< 0.001
≥1 day/month	1,233	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 hours[2]	1,245	13.7	929	27.5	0.53	[0.48-0.59]	< 0.001
4-24 hours	5,547	61.2	2,099	62.2	Ref	-	-
25-72 hours	2,213	24.4	336	9.95	2.56	[2.26-2.91]	< 0.001
>72 hours[2]	64	0.71	12	0.35	2.09	[1.17-4.08]	0.002
Characteristics							
Unilateral pain	3,535	39.5	1,142	34.5	1.22	[1.12–1.33]	< 0.001
Pulsatile pain	7,628	84.3	2,540	75.3	1.66	[1.50–1.83]	< 0.001
Routine activities exacerbate pain	6,836	76.3	2,138	63.8	1.73	[1.59–1.89]	< 0.001
Accompanying symptoms							
Nausea	6,574	72.6	1,730	51.5	2.45	[2.25–2.66]	< 0.001
Vomiting	4,410	48.8	1,199	35.7	1.74	[1.61–1.89]	< 0.001
Photophobia	8,138	89.7	2,833	83.9	1.59	[1.42–1.78]	< 0.001
Phonophobia	7,266	80.2	2,211	65.7	2.06	[1.88–2.25]	< 0.001
Photophobia and phonophobia	6,916	76.4	2,085	62.0	1.93	[1.77–2.10]	< 0.001
Osmophobia	3,164	35.1	502	15.0	3.10	[2.80–3.45]	< 0.001
Allodynia	1,834	20.4	393	11.6	1.89	[1.68–2.12]	< 0.001
Cranial autonomic symptoms[3]	2,614	30.6	1,049	32.2	0.90	[0.83–0.99]	0.002

Table 3: Current or previous use of prophylactic treatment among all participants with migraine							
	Females (N = 9,184)		Males (N = 3,435)				
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



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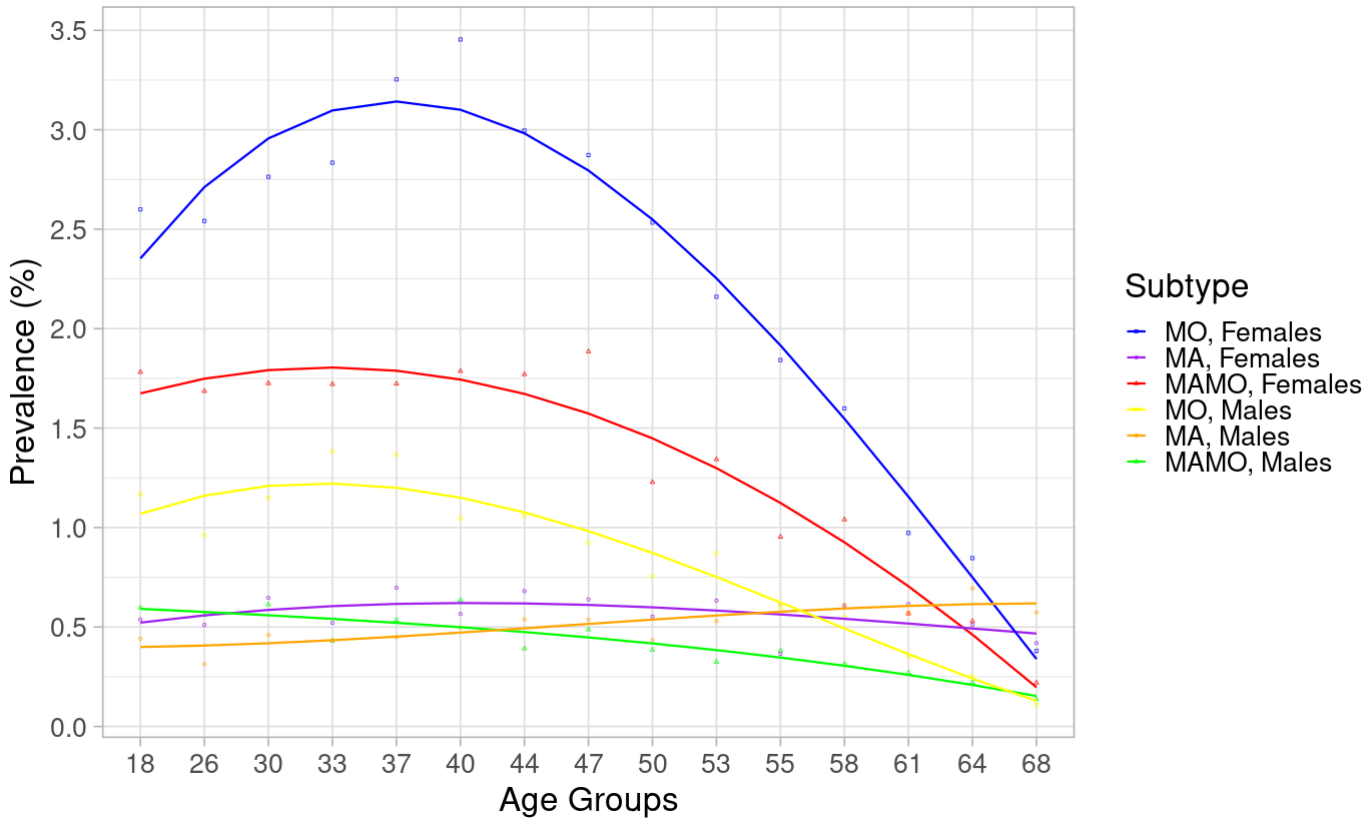

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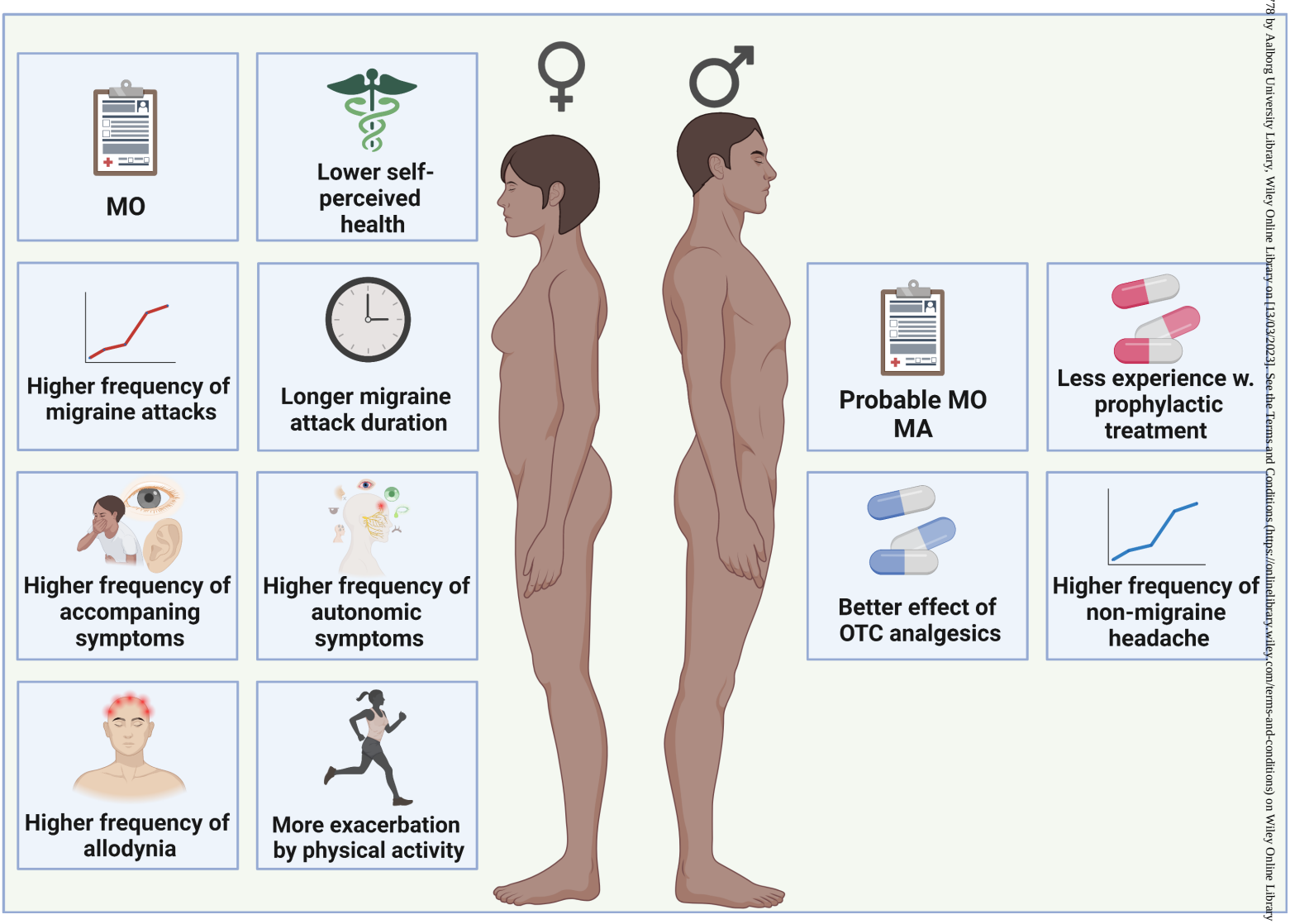

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