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Review Articles

Sex-Related Differences in Epidemiological and Clinic-Based Headache Studies

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This manuscript discusses sex-related differences in headache prevalence, the symptoms and natural history of migraine, associated disability, and co-morbid disorders. The role of sex hormones is discussed with reference to the effects of hormonal events across the reproductive years and the specific effects of the menstrual cycle on migraine. Differences between the sexes were identified across all parameters reviewed. Future research should ensure that data are analyzed separately for men and women to ensure that differences between the sexes are identified.

Key words: epidemiology, headache, hormone, migraine, sex

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The higher prevalence of headache in women compared to men has been attributed to the effect of female sex hormones. Recent recognition of menstrual migraine as a specific entity has resulted in improved diagnosis and management of this condition. However, sex differences extend beyond the effects of menstrual cycle hormones. This paper reviews the evidence for differences between men and women on a broad range of parameters with a particular focus on migraine.

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EFFECT OF SEX ON INCIDENCE AND PREVALENCE OF HEADACHE AND MIGRAINE

A review of the global population-based data for the most common headache disorders identified that in adults with an active headache disorder, 46% experienced headache in general, 11% had migraine, 42% had tension-type headache, and 3% had chronic daily headache.[1] Overall, current headache was more

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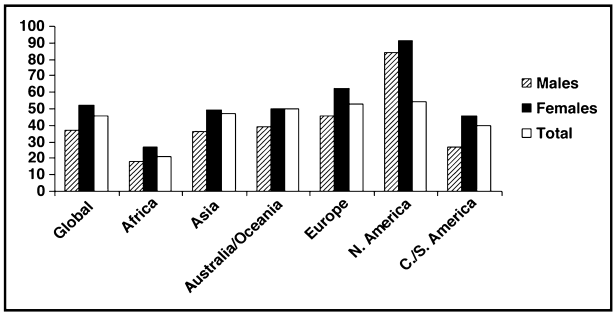

Fig 1.—Prevalence of current headache in adults for the different continents.[1]

prevalent in women than in men across all continents studied (Fig. 1). Of the individual headache types, migraine, tension-type and chronic headache were more prevalent in women, although the difference is less marked for tension-type headache (Table 1). Trigeminal autonomic cephalalgias are rare, affecting less than 0.001% of the population.[2] With the exception of paroxysmal hemicrania, which has a 2.1 to 2.4:1 female to male ratio, they are more prevalent in men (cluster headache 1:3.5 to 7; short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing [SUNCT] 1:1.2).[2]

Regarding migraine, a series of large national surveys have been undertaken in the USA. In 1989, 29,727 respondents from 20,000 households were surveyed as part of the American Migraine Study, with a follow-up study 10 years later.[3,4] The 2005 American Migraine Prevalence and Prevention (AMPP) Study was a 5-year longitudinal survey of 120,000 US households with 162,576 respondents.[5] These and other national studies consistently show higher prevalence of migraine in women, with a female to male ratio in the order of 2.3:1.[1] The ratio is not consistent across ages. There are few data on incidence and prevalence of migraine without and migraine with aura in childhood. In a population-based study in Uppsala, Sweden in 1955, 9059 children aged between 7 and 15 years were questioned about episodic headaches with at least 2 of nausea, visual aura, 1-sided pain and familial occurrence of similar headache in parents and siblings.[6] Among the 8993 respondents, migraine affected the same percentage of boys and girls aged 7-9 (2.5% boys, 2.4% girls) but in older age groups,

Table 1.—Mean (Range) Prevalence (%) of Different Headaches in Adults-Based Pooled Data[1]

	All Headache			Migraine			Tension-Type			Chronic Daily Headache		
	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total
Current	37 (3-84)	52 (7-91)	46 (1-87)	6 (1-20)	14 (2-25)	11 (1-25)	40 (16-81)	47 (19-90)	42 (20-87)	1.9 (1.0-5.2)	4.9 (2.3-9.3)	3.4 (1.7-7.3)
No. of studies	24	25	35	41	43	41	6	7	7	8	8	10
Lifetime	65 (6-93)	69 (10-99)	64 (8-96)	10 (2-22)	22 (4-33)	15 (3-28)	42 (11-69)	49 (12-88)	46 (12-78)	1.3 (0.9-1.3)	3.0 (4.2-3.0)	2.2 (1.4-3.0)
No. of studies	12	12	21	14	16	15	5	5	5	2	2	2

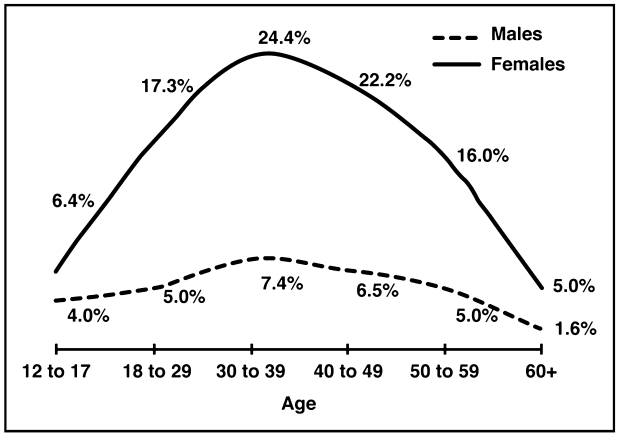

Fig 2.—One-year period prevalence of migraine by age and sex adjusted for demographics.[110]

more girls were affected than boys (age 10-12: 3.9% boys, 5.4% girls; age 13-15: 4.0% boys, 6.4% girls). At puberty, the incidence of migraine without aura rises in women, with 10% to 20% of women reporting their 1st migraine occurring during the same year as menarche.[3,7] From adolescence, migraine is more prevalent in girls than boys.[3,8] Migraine prevalence peaks in women during their 30s and 40s followed by a gradual decline, particularly following menopause. In men, the rise in prevalence is more gradual but the peak age and decline in adult men are similar to those in women (Fig. 2).

Data from 40,892 men, women, and children with a self-reported physician diagnosis of migraine who participated in the 2003 US National Health Interview Survey were analyzed.[9] These showed a bimodal distribution of migraine prevalence for both sexes, with the first peak in the late teens and 20s and a second peak around 50 years of age. For women, the peak periods for migraine risk were at a mean ± SD age of 25 ± 8.6 years and 50 ± 15.8 years. For men, the peak risk periods (18.7 ± 7.4 years and 47.6 ± 16.8 years) were earlier than in women, and both peaks were approximately of the same magnitude. The rate of acceleration of the prevalence rate was highest during the teenage years in both boys and girls.

Few studies have assessed incidence of headache. Of 549 participants in a population-based 12-year longitudinal study in Denmark, the incidence of frequent tension-type headache was 14.2 per 1000 person-years (male to female ratio, 1:3) and the incidence of migraine was 8.1 per 1000 person-years (male to female ratio, 1:6). Both rates decreased with age.[10] In the AMPP study, cumulative incidence of migraine was 43% in women and 18% in men.[11] Migraine incidence peaked between the ages of 20 and 24 years in women (18.2 per 1000 person-years) and the ages of 15 and 19 years in men (6.2 per 1000 person-years); 75% had migraine before age 35 years.

Subtypes of Migraine.—In both men and women, migraine without aura is more common than migraine with aura. In a Danish population-based study of 1000 people, lifetime prevalence of migraine with aura was 5%, male to female ratio 1:2. Lifetime prevalence of without aura was 8%, male to female ratio 1:7.[12]

In a recent population-based study of migraine in Germany, 1-year prevalence of all migraine was 10.6% and migraine with visual aura was 3.6%. Of these, 1-year migraine prevalence in women was 15.6% and migraine with visual aura was 5.6%; prevalence of migraine in men was 5.3% and migraine with visual aura was 1.5%.[13]

In a US study, age- and sex-specific incidence rates for the onset of migraine headache with and without preceding visual aura were estimated from a population-based telephone interview survey of 10,169 randomly selected residents of Washington County, Maryland, between the ages of 12 and 29 years.[7] A total of 392 men and 1018 women were identified as having a history of migraine. Of these, 27% of men and 28% of women were defined as having migraine with visual aura. Among both men and women, the incidence rate for migraine with visual aura appears to have peaked as much as 3-5 years earlier than the age peak for migraine without aura. For men, the age-specific incidence for migraine with visual aura peaked on or before 5 years of age. In contrast, the highest incidence for migraine without aura occurred between 10 and 11 years of age. For women, the highest incidence of migraine with aura occurred between 12 and 13 years of age; the highest incidence for migraine without aura occurred between 14 and 17 years of age.

EFFECT OF SEX ON NATURAL HISTORY OF MIGRAINE

There are few data on the effect of sex on the progression of migraine. In a 40-year prospective investigation of 73 schoolchildren with migraine in Sweden, it was noted that in puberty and as young adults, 23% of the cohort were free of migraine.[14] Within this group, more boys were migraine-free than girls (34% vs 15%). Boys were also more likely to remain migraine-free compared to girls (chi-square 3.92, $P < .05$). By the 40-year follow-up, when the cohort had reached around 50 years of age, 46% were migraine-free, and no sex differences were observed at that point.

Respite from migraine may also be affected by sex. A Danish study noted cessation of migraine with aura was more likely among men than women.[15]

Whether or not female sex is also a risk factor for the development from episodic migraine to daily headache (including "transformed migraine," "chronic migraine," "chronic daily headache") is unclear. Analysis of data from the AMPP study found that risk of transition from episodic to chronic migraine was greater in women than in men (OR = 2.9, 95% CI = 1.2-6.9), even after controlling for triptan use and headache frequency.[16] In the adjusted analyses, risk of incident "transformed migraine" associated with use of opioids was higher in men (OR = 2.76, 95% CI = 1.20-6.38) compared with women (OR = 1.28, 95% CI = 0.81-1.97). In contrast, use of barbiturate compounds was associated with a higher risk in women (OR = 1.97, 95% CI = 1.21-3.23) compared to men (OR = 1.29, 95% CI = 0.38-4.37). However, a later analysis of the same AMPP database suggests that women are at no greater risk of developing incident daily headache as 5.4% of men initially diagnosed with episodic migraine had developed "transformed migraine" within 1 year, compared to 4.4% of women.[17] A longitudinal study followed 1134 cases with chronic daily headache and 798 controls with episodic headache (including migraine) over 11 months.[18] In this study, chronic daily headache was more common in women (OR = 1.65, 95% CI = 1.3-2.0) but there was no sex difference for incident chronic daily headache in women compared to men (OR = 0.99, 95% CI = 0.4-2.4) or for remission (OR = 0.80, 95% CI = 0.5-1.2).

A population-based study conducted in Taipei recruited 3377 participants of whom 108 had a headache frequency >15 days/month with a duration of >4 hour/day.[19] The prevalence was higher in women (4.3%) than men (1.9%). A higher female to male ratio was noted in subjects with transformed migraine, ie, with a history of migraine or current features of migraine (5.6:1), compared to chronic tension-type headache (1.5:1).

EFFECT OF SEX ON MIGRAINE SYMPTOMS

Frequency, Severity and Duration.—Most studies support the findings that women experience more frequent, longer-lasting and more painful headaches compared with men. In a US population survey of migraineurs, the mean number of days with a headache in the 3 months prior was higher in women (7.6) than in men (7.0).[4]

A population-based study in the UK reported mean un-medicated headache duration of 28.4 hours in men vs 36.7 hours in women ($P = .01$).[20] Attack frequency and pain intensity were not significantly different between sexes.

A questionnaire survey of members of the Finnish Migraine Association found that migraine attacks of less than 6 hours' duration were almost twice as common in men as in women (RR = 1.8, 95% CI = 1.4-2.3). Attacks lasting 24-72 hours affected women almost 3 times more often than men (RR = 2.9, 95% CI = 1.8-4.8). The differences between age groups were prominent in women, attacks of short duration occurring most frequently in women under 20 years of age and long-lasting attacks (24-72 hours) most frequently in women aged 40 to 70 years.[21]

A cross-sectional general population survey in the UK found that women are more likely to experience light sensitivity (74% vs 82%), sound sensitivity (70% vs 77%), and nausea (65% vs 75%) with their headaches compared to men.[22]

Similar findings were seen among the respondents in a US Washington County population-based survey, which assessed headaches in the 4 weeks prior

to the survey. Compared to men, women with headache reported significantly more nausea, scalp soreness, headache waking the respondent from sleep, and visual scotoma prior to headache onset ($P < .01$).[23] Subjective pain severity associated with each subject's headache and the duration of the attacks were systematically greater for women than men.

Response to Treatment and Relapse of Headache.—Given that women are more likely than men to consult for headache,[24,25] it is not surprising that most studies of acute and prophylactic treatment include women as a majority. However, treatment outcomes generally include pooled data from men and women and there is a paucity of published data regarding treatment outcomes stratified by sex.

Regarding relapse, a 6-month observational study assessing headache return during migraine treated with triptans, found that female patients had a greater risk than male patients of experiencing headache return following pain-free response (25.2% vs 13.0%,OR 1.17, chi-square 4.8, $P = .028$).[26]

In a study of risk factors for headache recurrence after oral and subcutaneous sumatriptan, recurrence following oral sumatriptan was more frequent in female patients.[27] Both men and women with headache recurrence used significantly more doses of sumatriptan per attack and per month and more often reported the sensation of a subclinically ongoing migraine attack, despite being headache-free after sumatriptan.

Use of Medication.—Analysis of data from the AMPP study showed that compared to men with migraine, women are more likely to receive prescription acute medication (OR = 1.54, 95% CI = 1.43-1.65) and to use preventive medication (OR = 1.37, 95% CI = 1.27-1.48).[5] The reasons for this are unclear but may reflect that women are more likely than men to consult a physician about their migraine and that their attacks are more disabling.

EFFECT OF SEX ON HEADACHE-ASSOCIATED DISABILITY AND QUALITY OF LIFE

The World Health Organization recognizes migraine as the 12th leading cause of years lived with disability for women vs the 19th leading cause for both sexes combined.[28] A global internet-based study identified that patient-reported moderate or severe migraine-related disability was approximately 2-fold more frequent among women vs men (30% vs 17%).[29]

Women in a German population-based prevalence study reported more often severe and frequent headaches reported significantly, more disability, and rated their health worse compared to men (all differences $P < .001$)[13]

In the American Migraine Study, a similar proportion of men and women reported severe disability. Duration of migraine-associated activity restriction was greater among women than men with 30.5% of women experiencing 1-2 days of activity restriction during a migraine vs 22.9% of men.[4] In a US Washington County study, women were significantly more likely to report recent headache-related disability and to seek healthcare services for their headaches, even after adjusting for headache severity.[23]

In an analysis of work-related disability data from the American Migraine Study, 51.1% of women and 38.1% of male migraineurs experienced 6 or more lost workday equivalents (LWDE) per year. This subgroup of migraineurs accounted for about 90% of the total LWDE experienced by all respondents. Among women, headache duration of 24 hours or more was the strongest predictor of LWDE whereas in men, only pain level was significantly associated with LWDE.[30] The median number of missed workdays per year from the most severe attack was 1 day among men and 2 days among women. However, the average number of missed workdays was 3.8 among men and 8.3 among women, indicating a highly skewed distribution. There were no sex differences in frequency or pain levels but fewer men than women missed at least 1 day of work per year because of migraine (56.4% vs 73.6%). A total of 30.1% women and 17.1% men missed 6 or more workdays per year although there were no sex differences in number of days at work with a headache.

Disability estimates of 3.8 bed rest days per year for male migraineurs and 5.6 days for women result in a total of 112 million bedridden days each year across the USA.[31] Severity of migraine attacks, as measured by the proportion of attacks that require bed rest,

tends to decrease with increasing age. The length of bed rest in women aged 50 to 64 years was nearly twice that of those aged 20 to 29 years. Although the same proportion of men and women required bed rest, women required longer stays in bed in all age groups.

In a UK population-based study, women (34%) were more likely than men (25%) to miss time at work or school more than rarely. Almost half (>45%) of men and women who rarely or never missed work or school required bed rest with a median duration of 2 hours.[20]

In a study of over 1000 women referred to Italian headache centers, 84% of women with menstrual migraine engaged in fewer social activities, 81% had difficulty performing household chores, 58% had to limit family activities, 55% could not engage in sports, and 45% had work-related disability.[32] Work-related disability is more often reported for premenstrual migraines than for non-menstrual attacks ($P = .006$).[33] Similarly, time spent at less that 50% productivity is greater for menstrual than non-menstrual attacks ($P = .01$).[34]

EFFECT OF SEX ON MIGRAINE CO-MORBIDITIES

Medical Conditions.—Migraine is co-morbid with a number of medical disorders, including arterial disease, hypothyroidism, asthma, and endometriosis, as well as depression, anxiety and somatic conditions such as irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, and interstitial cystitis.[35-40] A population-based study assessing co-morbidity of migraine with somatic disease in Danish twins noted that women with migraine had more co-morbid diseases than men (11 vs 5; Fig. 3). In particular, stroke, non-coronary thrombosis, scoliosis, fibromyalgia, psoriasis, thyroid disease, asthma, Ménière's disease, and epilepsy were highly associated with migraine with aura in women (Table 2).[41]

Cluster analysis of 223 migraineurs attending a university headache clinic in the USA identified 3 distinct co-morbid constellations.[42] Group 1 was defined by physical co-morbidities of hypertension, hyperlipidemia, diabetes mellitus, and hypothyroidism; group 2 was defined by somatic co-morbidities of depression, anxiety, and fibromyalgia; group 3 had no defining co-morbidities. Sex differences were notable, with more men in group 1 vs group 2 suggesting that men with migraine are more likely to have physical co-morbid diseases whereas women are more likely to have psychiatric and somatic co-morbid conditions.

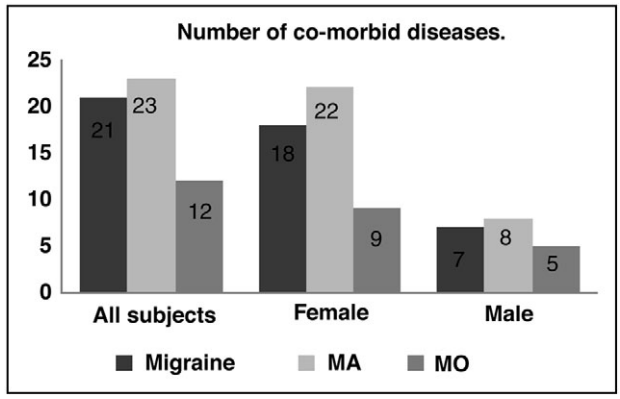

Fig 3.—Number of diseases co-morbid with migraine, migraine with aura (MA) and migraine without aura (MO).[41]

These findings might be anticipated given that many of the co-morbid conditions are more prevalent in women. Similarly, multiple sclerosis is a condition that women are more susceptible to than men.[43] However, compared to population controls, a study of patients with multiple sclerosis showed a 3-fold increased relative frequency of migraine that was independent of sex (55.7% vs 17.1%, prevalence ratio [PR] = 3.26, $P < .001$ for women; 18.4% vs 5.6%, PR = 3.29, $P < .001$ for men).[44]

Arterial Disease.—Population-based studies and meta-analyses have established migraine with aura as a risk factor for arterial disease, including subclinical brain infarcts, ischemic stroke, ischemic heart disease, claudication, and cardiovascular mortality.[45-48] Migraineurs are more likely than controls to have risk factors for cardiovascular disease, particularly diabetes, hypertension, and high cholesterol.[45] Data from the US Physicians' Health Study, a prospective cohort study of 20,084 men, found that overall migraine was associated with increased risk of major cardiovascular disease compared to controls (hazard ratio [HR] = 1.24, 95% CI = 1.06-1.46, $P = .008$), driven particularly by increased risk of myocardial infarction (HR = 1.42, 95% CI = 1.15-1.77, $P < .001$).[49] In women, migraine with aura has a more significant

Table 2.—Prevalence of Somatic Medical Diseases (%) in Women and Men With Self-Reported Migraine With Significance Level $P < .001$ vs No Migraine[41]

	Women			Men		
	Migraine	No Migraine	OR (99.9% CI)	Migraine	No Migraine	OR (99.9% CI)
Any cardiovascular disease	14.3	9.6	1.57 (1.33-1.84)	14.4	10.4	1.46 (1.18-1.80)
Hypertension treated with prescription medicine	12.6	8.5	1.55 (1.30-1.85)	12.1	8.4	1.51 (1.20-1.91)
Stroke	1.7 (migraine with aura)*	0.8	2.34 (1.25-4.39)	1.3	1.1	NS
Non-coronary thrombosis	2.5 (migraine with aura)*	1.0	2.52 (1.46-4.36)	1.9	1.1	NS
Any musculoskeletal disorder	81.7	66.4	2.25 (1.98-2.57)	77.4	63.3	1.98 (1.67-2.35)
Low back trouble	70.6	56.6	1.85 (1.64-2.08)	67.2	56.1	1.60 (1.37-1.88)
Neck trouble	66.1	43.7	2.51 (2.24-2.82)	51.2	32.6	2.16 (1.85-2.53)
Whiplash in the neck	9.0	4.4	2.15 (1.73-2.67)	8.0	4.0	2.11 (1.58-2.82)
Osteoarthritis	12.1	7.9	1.60 (1.34-1.92)	8.1	6.6	NS
Scheuermann's disease	3.1 (migraine with aura)*	1.9	1.68 (1.06-2.68)	5.9 (migraine with aura)*	3.3	1.80 (1.07-3.03)
Scoliosis	2.7 (migraine with aura)*	1.5	1.90 (1.15-3.13)	1.0	0.8	NS
Fibromyalgia	2.8 (migraine with aura)*	0.6	4.91 (2.70-8.91)	0.2	0.1	NS
Any autoimmune disorder	9.9	6.8	1.50 (1.24-1.82)	8.3	6.4	1.34 (1.02-1.76)
Psoriasis	5.1	3.7	1.40 (1.08-1.81)	5.1	3.8	NS
Rheumatoid arthritis	2.0 (migraine with aura)*	0.9	2.17 (1.19-3.95)	1.9 (migraine with aura)*	0.6	3.35 (1.30-8.64)
Hyperthyroidism	3.6 (migraine with aura)*	2.0	1.86 (1.20-2.89)	0.7	0.5	NS
Hypothyroidism	2.8	1.7	1.72 (1.20-2.48)	0.3	0.4	NS
Asthma	13.7 (migraine with aura)*	8.7	1.67 (1.33-2.10)	8.4	7.4	NS
Dust/pollen/animal allergy	24.3 (migraine with aura)*	17.7	1.49 (1.24-1.79)	22.3 (migraine with aura)*	16.9	1.41 (1.06-1.89)
Ménière's disease	1.3 (migraine with aura)*	0.4	3.25 (1.47-7.21)	0.6	0.4	NS
Tinnitus	7.7	4.8	1.66 (1.33-2.06)	15.8 (migraine with aura)*	9.7	1.75 (1.25-2.44)
Epilepsy	2.7 (migraine with aura)*	1.5	1.77 (1.07-2.94)	2.3	1.5	NS
Kidney stone	3.7	2.3	1.68 (1.22-2.30)	5.8 (migraine without aura)**	3.8	1.55 (1.06-2.29)

*Not significant for migraine without aura.
**Not significant for migraine with aura.

association with cardiovascular disease than migraine without aura. Data from the US Women's Health Study, a prospective cohort of 27,840 women, associated migraine with aura but not migraine without aura, with significant increased risk of major cardiovascular disease, myocardial infarction, ischemic stroke, death due to ischemic cardiovascular disease, coronary revascularization, and angina compared to controls.[50]

A prospective cohort study in Iceland studied the association of migraine with overall and cause-specific mortality in 9044 men and 9681 women, with an average age of 52.8 (range 33-81) years at study entry, for a median of 25.9 (0.1-40.2) years.[51] Migraine was diagnosed in 6% of men and 15% of women (migraine without aura in 1% men and 5% women; migraine with aura in 5% men and 10% women). People with migraine with aura were at increased risk of all cause mortality (adjusted HR = 1.21, 95% CI = 1.12-1.30) and mortality from cardiovascular disease (adjusted HR = 1.27, 95% CI = 1.13-1.43) compared to people with no headache; those with migraine without aura and non-migraine headache were at no increased risk. Men with migraine with aura were at increased risk of mortality from stroke (multivariate adjusted hazard ratio for men: HR = 1.76, 95% CI = 1.22-2.54; women: HR = 1.26, 95% CI = 0.92 to 1.73, $P = .15$) and coronary heart disease (adjusted hazard ratio for men: HR = 1.43, 95% CI = 1.18-1.74; women: HR = 1.17, 95% CI = 0.93 to 1.47, $P = .12$). Women were at increased risk of mortality from causes other than cardiovascular disease or cancer (adjusted hazard ratio for men: HR = 1.08, 95% CI = 0.84-1.40; women HR = 1.33, 95% CI = 1.13 to 1.57, $P = .001$). However, the authors note that prevalence of aura was higher than has been reported in other population studies suggesting some misclassification. Notably, diagnosis of aura was less specific than the IHS criteria and included visual disturbance during or preceding headache, and unilateral numbness preceding headache.[52] The result of this misclassification is likely to attenuate the relationship between migraine with aura and mortality.

Frequency of migraine aura may be particularly relevant for increased risk of ischemic stroke in healthy young women.[53] Use of estrogen-containing oral contraceptives is an additional risk factor as even low estrogen dose pills (<50 mcg ethinylestradiol) are associated with a 2-fold increased risk of ischemic stroke in current users (RR = 1.93, 95% CI = 1.35-2.74).[54] Risk is particularly increased for women with migraine with aura who smoke and use oral contraceptives. The population-based case–control Stroke Prevention Young Women Study found that risk of ischemic stroke was 7.0-fold higher (95% CI = 1.4-22.8) in women who had migraine with visual aura who smoked and used oral contraceptives compared with women who had migraine with visual aura who were non-smokers and non-oral contraceptives users and 10.0-fold higher (95% CI = 1.4-73.7) compared with women with no migraine history who were non-smokers and non-oral contraceptives users.[55] Data from the Dutch population-based case–control MRI CAMERA study found that female migraineurs were at increased risk of high-deep-white-matter T2-weighted hyperintensity load independent of migraine subtype and cardiovascular risk factors (OR = 2.0, 95% CI = 1.0-4.2).[46]

Psychiatric Disorders.—Systematic reviews confirm that women have a higher rate than men of major depressive disorders, dysthymia, and anxiety but that men and women are equally affected by bipolar 1 disorder.[56,57] Several studies have shown that migraine is co-morbid with major depressive disorders.[58,59] In a Canadian study, the prevalence of migraine in the total sample (n = 36,984) was 15.2% for women and 6.1% for men. The 12-month and lifetime prevalence of mental disorders was more than twice as high in those with migraine than those without. The 12-month prevalence was 8.6% (95% CI = 7.3-9.8) in migraineurs vs 3.4% (95% CI = 3.1-3.7) in non-migraineurs, and the lifetime prevalence of major depressive disorder was 18.8% (95% CI = 17.0-20.5) in migraineurs vs 9.8% (95% CI = 9.3-10.3) in non-migraineurs. A similar trend was noted for bipolar disorder, panic disorder (and agoraphobia with panic symptoms), and social phobia, all occurring more than twice as often in those with migraine compared with those without migraine. There were no differences in the sex-specific prevalence of major depressive disorder between men and women with

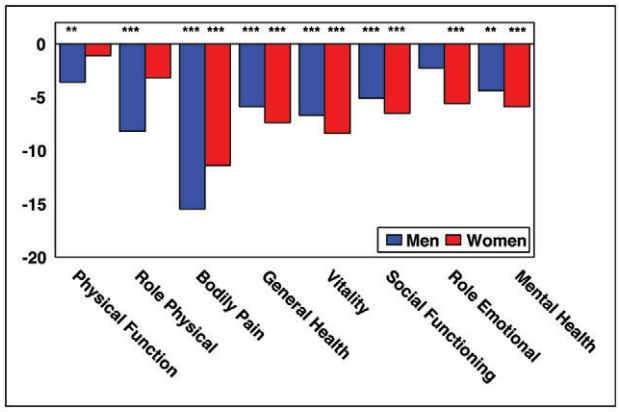

Fig 4.—The association between headache and dimensions of health-related quality of life (SF-36) for men and women aged 20-64 years controlled for age, other pain conditions, psychiatric problems, and somatic problems (*$P < .05$, **$P < .01$, ***$P < .001$).[62]

migraine, although there was a trend for women to have a higher prevalence. No sex differences in migraineurs with bipolar or anxiety disorders (panic disorder and social phobia) were noted.[60] In the population-based US National Health Interview Survey of 30,852 adults, migraine risk was increased in both women (OR 1.93) and men (OR 2.42) with self-reported depressive symptoms ($P < .001$), but men with self-reported anxious symptoms had a higher migraine risk compared with women with self-reported anxious symptoms ($P < .001$).[61]

Pain.—A cross-sectional survey from Sweden analyzed 4506 people aged 20-64 years. The prevalence of pain conditions, especially headache, was higher among women (17.6% vs 6.7%). Women reported more severe pain. Co-morbidity between pain conditions and psychiatric and somatic problems was higher among women (OR = 1.37, 95% CI = 1.19-1.58). Health-related quality of life (SF-36) differed by sex and type of pain condition. The physical dimensions of health-related quality of life were more affected by headache among men; psychological dimensions were more affected among women (Fig. 4). Among both men and women, pain conditions were associated with poorer socio-economic conditions and lifestyle factors but there were sex differences. Education and unemployment were important only among men while financial difficulties, part-time work, and being married were associated with pain among women. Obesity, early disability retirement, long-time sick leave, and lack of exercise were associated with pain conditions generally.[62]

Obesity.—There are conflicting data regarding the association between migraine and obesity, which may reflect differences in measurement of obesity (self-reported vs measured), population selection (inclusion of pre- and post-reproductive age vs age-stratified), and migraine diagnosis (self-reported vs use of IHS diagnostic criteria). Recent research in women of reproductive age suggests a clear association between obesity and both episodic and chronic migraine.[63-66]

Two studies to date have evaluated the association specifically in women of reproductive age. The first included 21,783 participants (10,623 men and 11,160 women) participating in a general population survey in the USA. Self-report of migraine/severe headaches and measured body mass indices (BMIs), including height, weight, and waist circumference were analyzed.[67] Between 20 and 55 years of age, migraine prevalence was higher in both men and women with total body obesity, as estimated by BMI, compared with those without ($P \leq .001$). Migraine was also more prevalent in those with abdominal obesity (waist circumference ≥88 cm for women and ≥102 cm for men) compared with those without abdominal obesity (men: 20.1% vs 15.9%, $P < .001$; women: 36.9% vs 28.8.2%, $P < .001$). Furthermore, the increased risk of migraine in reproductive-aged women with abdominal obesity remained significant even after adjusting for BMI. After 55 years of age, the odds of migraine were not increased in either women or men with either total body or abdominal obesity.

The second study included 3733 reproductive-aged women participating in the Omega study, a prospective cohort study designed to examine risk factors of adverse pregnancy outcome.[66] Self-reported physician diagnosis of migraine, measured BMIs at presentation, and self-reported weight at age 18 were evaluated. After adjusting for confounders, relative to women of normal BMI (18.5-24.9 kg/m^2), obese women (BMI 30-34.9 kg/m^2) had a 1.48-fold increased odds of migraine (OR = 1.48, 95% CI 1.12-1.96), as did severely obese (BMI 35-39.9 kg/m^2,

OR = 2.07, 95% CI = 1.27-3.39) and morbidly obese (BMI $\geq$ 40 kg/m^2, OR = 2.75, 95% CI = 1.60-4.70). Additionally, women with a history of migraine diagnosed under age 18 years had a 1.67-fold higher odds of gaining at least 10 kg above their weight at age 18 compared with non-migraineurs (OR = 1.67, 95% CI = 1.13-2.47).

In a cross-sectional study of 5847 adolescents aged 13-18 living in Norway, being overweight (BMI $\geq$ 25 kg/m^2) was associated with increased risk of recurrent headache in both girls (OR = 1.4, 95% CI 1.2-1.8, $P < .0001$) and boys (OR = 1.4, 95% CI 1.1-1.8, $P < .01$).[64] The association between overweight and migraine (adjusted for age, gender, smoking, and physical activity) was 1.6 (95% CI 1.4-2.2, $P < .0001$), for tension-type headache 1.4 (95% CI 1.1-1.6, $P < .0001$), and for non-classifiable headache 1.4 (95% CI 1.0-1.9, $P < .06$).

However, it is important that studies consider all lifestyle factors associated with obesity in their analyses. Age-adjusted data from 63,467 participants in the population-based Women's Health Study showed that increasing BMI was associated with a significant increased risk migraine. Compared with women without migraine and a BMI < 23 kg/m^2, women with a BMI between 30.0 and 34.9 kg/m^2 had an OR of any migraine history of 1.11 (95% CI = 1.04-1.19) that further increased to an OR of 1.21 (95% CI = 1.12-1.32) for women with a BMI $\geq$ 35.0 kg/m^2. The effect estimates were very similar for active migraine and prior migraine. After controlling for smoking, exercise, alcohol consumption, history of hypertension, postmenopausal status, postmenopausal hormone intake, and history of elevated cholesterol levels, the association between BMI and migraine disappeared entirely (OR = 1.03, 95% CI = 0.95-1.12).[68]

SEX OR SEX HORMONES?

The Role of Genes.—Analysis of data from a controlled family study included 260 probands and their 1232 first-degree adult relatives found that although the risk of migraine was 3 times greater among the relatives of probands with migraine compared with controls, there was no differential risk of migraine among the relatives of male vs female probands with migraine. Taking these data together with other family studies, the authors concluded that the increased risk of migraine in women is likely to result from increased exposure to non-familial endogenous or exogenous risk factors for migraine that lower the threshold for expression of migraine in women.[69]

The Role of Female Sex Hormones in Migraine.—Female sex hormones are the most likely candidates to explain differences in migraine between men and women. This hypothesis was studied in a group of Dutch transsexuals who were using antiandrogens to suppress male sex characteristics and estrogens to induce female sex characteristics.[70] The male to female transsexuals experienced a migraine prevalence of 26%. This was higher the expected male prevalence of 7.5% and no different than expected prevalence of 25% for genetic women. This highlights differences between sex and gender, suggesting that hormonal changes, exogenous as well as endogenous, may be more important than genetic differences between men and women.

Throughout the reproductive years, menstruation is one of the most significant risk factors for attacks of migraine without aura.[71,72] Migraine is most likely to occur on the days directly before and after the first day of menstruation.[73-76] In a population-based study in the USA, there was a 2-fold increased risk of migraine without aura on the first 2 days of menstruation compared to all other times of the cycle (OR = 2.04, 95% CI = 1.49-2.81).[75] The lowest risk for headache was around the expected time of ovulation (OR = 0.44, 95% CI = 0.27-0.72).

In a clinic-based study in the UK, women were 25% (RR = 1.25) more likely to have migraine in the 5 days leading up to menstruation increasing to 71% (RR = 1.71, 95% CI = 1.45-2.01, $P < .0001$) in the 2 days before menstruation.[76] The risk of migraine was highest on the first day of menstruation and the following 2 days (RR = 2.50, 95% CI = 2.24-2.77, $P < .0001$). Similarly, in a population-based study in Austria, the highest risk of migraine was on the first 3 days of menses (HR = 1.96, $P < .00001$).

This association between migraine and menstruation is apparent from puberty. A retrospective analysis of 896 adolescent girls identified 331 (50.3%) who reported headaches with menstruation of whom 63.6% reported migraine on or between day –2 to +3

of menstruation.[77] Of note is that a monthly pattern was apparent in 160 girls even before their first menstrual period.

The development of criteria for pure menstrual migraine and menstrually related migraine has facilitated research comparing menstrual vs non-menstrual attacks.[52,78] A consistent finding using within-woman analyses is that, compared with migraine at other times of the cycle, menstrual attacks last longer, are more severe, are more likely to relapse, are less responsive to treatment, and are associated with greater disability.[21,29,32-34,73,74,77-80]

Studies using drugs that suppress the natural ovarian cycle and induce amenorrhea suggest a beneficial effect on migraine.[79] Continuous combined hormonal contraceptives induce amenorrhea in 80% to 100% of women by 10 to 12 months of treatment.[80] The menstrual cycle can also be suppressed using gonadotropin releasing hormone (GnRH) analogs.[81-83]

Natural hormonal events, such as pregnancy and post menopause, associated with stable high- or low-hormone states, are also accompanied by respite from migraine without aura. Although there is little improvement in the first trimester of pregnancy, during the second and third trimesters up to 80% of women with migraine will experience fewer attacks compared to pre-pregnancy.[71,84,85] Improvement is more likely with a history of menstrual or menstrually related migraine.[71,85,86] In the week immediately post partum, headache affects around 30% to 40% of women.[85,87,88] In a longitudinal study of 404 women enrolled in the Penn Ovarian Aging Study, the percentage of women reporting moderate to severe headache fell from 34% during premenopause to 24% postmenopause ($P = .003$).[89] A study of 1436 women showed a migraine prevalence of 10.5% in spontaneous menopausal women compared with 16.7% in premenopausal and perimenopausal women (OR = 0.6, 95% CI = 0.4-0.9, $P = .03$).[90] Time since menopause is associated with improvement.[89,91]

The type of menopause has a substantial effect on migraine. Natural menopause is associated with a lower prevalence of migraine compared to surgical menopause. In a retrospective questionnaire of 47 postmenopausal women with migraine, 8 women (17%) reported new onset of migraine with menopause.[92] Of those women who had had a physiological menopause, 67% reported improvement or complete remission of migraine postmenopause, 24% reported no change, and 9% reported worsening migraine. Regarding surgical menopause, 33% reported improvement following the procedure, and in 67% migraine was worse. Similarly, a retrospective study of 164 postmenopausal women with migraine without aura attending specialist headache centers in Italy compared surgical and natural menopause.[93] Surgical menopause was associated with worsening of migraine ($P < .01$); natural menopause was associated with improvement ($P < .01$).

Migraine is also affected by whether the ovaries are retained or removed during hysterectomy. In a cross-sectional survey 15.1% of 986 hysterectomized women with 1 or both ovaries present reported moderate to severe migraine, compared with 8.8% of 5636 non-hysterectomized women with both ovaries present ($P < .001$).[94] In a separate study, migraine prevalence was lowest in those with hysterectomy and bilateral oophorectomy, although not to a statistically significant level (hysterectomy only, 28.6%; hysterectomy with unilateral oophorectomy, 36.4%; hysterectomy with bilateral oophorectomy, 15.8%; $P = .3$).[90]

Data on the effect of hormone replacement therapy (HRT) on migraine are conflicting.[95,96] In the population-based Women's Health Study, 6588 of 21,788 postmenopausal women (30.2%) had never used HRT and 10,519 (48.3%) were current users.[97] IHS migraine during the year preceding baseline was identified in 1396 (8.2%) never or current HRT users. Multivariate analyses controlled for age, race, smoking, alcohol use, ever use of contraception, age at menopause, and menopause type. Current use of HRT was associated with a 42% increased risk of migraine headache (OR = 1.42, 95% CI = 1.24-1.62) compared to never users. Compared to never users estrogen only HRT was associated with a 39% increased risk of migraine (OR = 1.39, 95% CI = 1.14-1.69) with a similar 41% increased risk in women using estrogen and progestogen (OR = 1.41, 95% CI = 1.22-1.63). There were no significant differences in risk of migraine headache in users of cyclic vs continuous progestogens.

High-estrogen states are associated with increased risk of migraine with aura. Higher levels of estrogen have been reported for migraine with aura during the normal menstrual cycle compared with migraine without aura: mean estradiol levels in women with migraine with aura during the normal menstrual cycle (94.4 ± 28.3 pg/mL) were double those of the control group (50.6 ± 8.9 pg/mL) and women with migraine without aura (41.6 ± 7.1 pg/mL).[98] High-estrogen states are also associated with the development of migraine aura in women who have not previously had migraine or who had attacks only of migraine without aura. This occurs in women starting combined oral contraceptives, HRT, and during pregnancy.[99-102] Resolution of aura typically occurs following a return to lower-estrogen states.[103]

EFFECT OF SEX ON ECONOMIC COSTS

Migraine is associated with a high economic burden, with a substantially greater contribution by women, who access healthcare resources significantly more than men.[13,104,105] The annual cost of treatment of a diagnosed male migraineur has been calculated to be USD 85.87 vs USD 100.36 for a female. Direct costs in the USA have been estimated at over 1 billion healthcare dollars in annual treatment, with women accounting for about 80% of the costs.[31] However, direct costs underestimate the true financial burden of migraine. Annual economic loss attributable to migraine-related absenteeism and reduced productivity, ie, indirect costs, are estimated to be around USD 13 billion. Once again, women consistently incurred higher costs in both workday loss and reduced function at work and accounted for about 80% of total labor costs due to migraine.

UNANSWERED QUESTIONS

Our review of the literature highlights a number of unanswered questions that merit further research. Of particular note is the lack of data regarding sex differences in response to acute and prophylactic drugs, which may have implications for pharmacotherapy.[106,107] Important attempts to review sex differences in co-morbidities with migraine have been undertaken but data are lacking, particularly for men.

Co-morbidities provide potential to identify common pathophysiology but for many disorders co-morbid with migraine it is unclear whether the associations are unidirectional or bidirectional. As with migraine, many of the co-morbid disorder are more common in women than in men but few studies control for female sex. Study of the genetic basis of these conditions could provide more insight into these associations.

Studies suggesting that puberty is associated with increased risk of migraine in girls have been based on age, whereas pubertal development may be a more relevant parameter. A US study of 3101 boys and girls aged 11-17 years assessed undertaken to test the hypothesis that prevalence of all pain conditions would increase as puberty progressed in girls but not boys.[108] For both sexes, pubertal development was a better predictor of pain than was age. During pubertal development prevalence of back pain, headache and temporomandibular dysfunction increased significantly in girls whereas boys experienced a significant increased prevalence of back pain and facial pain. Girls also experienced increasing rates of somatization, depression, and multiple pain conditions. In this study, pubertal development had little effect on headache prevalence.

The obvious effects of the menstrual cycle enable specific studies of the role of female sex hormones on migraine in women. Estrogen "withdrawal" is an established association with increased risk of migraine attacks in women but no studies have addressed the potential association between sex hormones and migraine in men. It is notable that migraine prevalence follows similar patterns increasing in rate during the teenage years in both boys and girls with a second transient increase in both sexes during their 40s.[9] Whether or not sex hormones play an equal part in these prevalence peaks in both men and women is not known. The second prevalence peak in women can perhaps be explained by hormonal fluctuations of the perimenopause and it has been suggested that age-related hormonal changes in men, such as reduction in free estradiol levels in middle life, might play a similar contributory role.[9,109] Yet, even post menopause the prevalence of migraine remains higher in women than in men.[4]

Future studies should address the mechanism for the differential effect of estrogen on migraine mentioned above, with high levels associated with increased risk of aura and falling levels associated with migraine without aura. Further work could also confirm or refute effects of sex hormones on other primary headaches.

CONCLUSIONS

Data from population-based studies of migraine provide evidence of sex differences for nearly all parameters studied. The changing endogenous and exogenous hormonal environment in women during the reproductive years affects the frequency, severity, and type of migraine with greater consequent disability and healthcare costs compared to men. As the menstrual cycle is established at puberty, risk of migraine increases. Situations resulting in estrogen "withdrawal" such as menstruation, the hormone-free interval of combined hormonal contraceptives, and immediately post partum, are associated with increased risk of migraine without aura. Postmenopause marks a time of improvement that is generally attributed to the absence of variations in sex hormone levels. Type of migraine is also affected by the hormonal environment. High-estrogen states during pregnancy and with use of combined hormonal contraceptives or estrogen replacement therapy increase risk of migraine with aura. The data on co-morbidity with migraine suggest a significant increased association in women compared to men but this may partly reflect the greater female prevalence of these conditions. We recommend that all migraine research should include data analyzed separately by sex.

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