

## Sex Differences of Migraine: Results of a Nationwide Home-based Study in Turkey

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### ABSTRACT

**Introduction:** The prevalence of migraine was found to be more than three-fold higher in women as compared with men, and in addition to differences in prevalence rates, the characteristics and associated features might also differ between the sexes. The aim of this study was to compare sex-specific features of migraine and demographic parameters in a nationwide population-based study in Turkey.

**Methods:** Among 5323 subjects, a total of 871 patients who were diagnosed as having definite migraine according to the diagnostic criteria of the International Classification of Headache Disorders-III (ICHD-III) were included in our study. The demographic characteristics, associated features, and triggers of migraine were examined with regard to sex.

**Results:** The study group comprised 640 women (73.5%) and 231 men (26.5%), with a female to male ratio of 2.8:1. Attack duration, mean migraine disability assessment scores (MIDAS), frequencies of nausea, vomiting, osmophobia, vertigo/dizziness, and allodynia were found significantly different between women and men. When we compared

these parameters between men and postmenopausal women, all these parameters were still significant except nausea. Odor was statistically more frequent as a reported trigger in women, whereas excessive sleep was a statistically more frequent triggering factor in men. The rates of depression and allergy were significantly higher in women when compared with men.

**Conclusion:** Longer attack duration, higher MIDAS scores, and the frequencies of nausea, vomiting, osmophobia, vertigo/dizziness, and allodynia were more significant in women and this variance in sex persisted after menopause. Also, some trigger factors and comorbidities differed between the sexes. These findings might result from complex genetic factors besides sociocultural influences, biologic, and sociocultural roles. Future studies should continue to explore biologic and genetic factors with respect to sex in migraine.

**Keywords:** Migraine; sex differences; postmenopausal women

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### INTRODUCTION

Migraine is a common and disabling disorder, constituting a major health problem for individuals and society. Studies of migraineurs in the general population have consistently demonstrated that migraine is more prevalent in women as compared with men (1, 2). The prevalence of migraine was found to be more than three-fold higher in women and, in addition to differences in prevalence rates, the characteristics and associated features might also differ between two sexes (1-3). Many factors could account for these differences including fluctuations in sex hormones, receptor binding, genetic predisposition, environmental factors, and pain perception, as well as differences in brain function and structure (4-6).

Although it is well-established that migraine is highly prevalent, especially in younger women, the differences of symptomatology, associations, and disability between men and women are poorly understood (1, 2). Moreover, several unresolved questions remain because there are only a

handful of population-based studies comparing migraineurs in relation to sex (3). Therefore, in the current study, we aimed to compare sex-specific features of migraine and demographic parameters in a nationwide population-based study in Turkey.

### METHODS

In 2008, we designed a nationwide, community-based prevalence study in subjects aged 18-65 years conducted through face-to-face interviews with 33 trained general physicians. Twenty-one cities from seven geographic regions of Turkey representing the characteristics of households were selected based on the ratio of their population to the total population of Turkey (7).

The evaluation of households was made by using a structured electronic questionnaire. The comprehensive interview form included questions

for diagnoses of migraine according to the diagnostic criteria of the International Classification of Headache Disorders (ICHD)-II. The recently published ICHD-III diagnostic criteria were examined and the evaluations of the forms were made according to ICHD-III (8). In addition to the characteristics and associated features of headaches, we also assessed the demographic and socioeconomic status of the subjects, comorbidities, hormonal changes, and disability using the validated Turkish version of the Migraine Disability Assessment (MIDAS) questionnaire (9).

To prevent any genetic effect, only one subject was interviewed and a Kish sampling grid was used to select the subject. From 6000 households, a total of 5323 subjects were investigated after excluding households that were surveyed but not interviewed because of various reasons. As a result, statistical analyses were performed with a standard error of  $\pm 1.3\%$  and the results are presented with 95% confidence intervals.

The postmenopausal period was defined as the point of time when menstruation ceased after 12 months of amenorrhea.

For this study, we evaluated migraineurs in relation to sex and compared the demographic characteristics, associated features, and trigger factors. Significant parameters were also evaluated between men and postmenopausal women.

Descriptive statistics were applied for the investigated parameters and the Chi-square test and t-test were performed for categorical variables where appropriate. For group comparisons, the Shapiro-Wilk test was used to determine whether the data were normally distributed. Binary logistic regression tests were performed to explore the differentiating variables between female and male migraineurs. The Statistical Package for the Social Sciences (IBM SPSS Statistics, New York, USA) 21.0 software was used for statistical evaluations, and  $p \leq 0.05$  was accepted as the limit of significance.

Ethics Committee approved this study and written informed consent was obtained from all participants.

## RESULTS

Among 5323 subjects, a total of 871 were diagnosed as having definite migraine. The study group comprised 640 women (73.5%) and 231 men (26.5%), corresponding to a female to male ratio of 2.8:1. The ages of the subjects ranged between 18 and 65 years. The mean ages of the women and men were  $37.02 \pm 11.4$  years and  $36.74 \pm 10.8$  years, respectively.

The general characteristics of the patients in relation to sex are shown in Table 1.

Table 2 shows a comparison of the associated features of migraine in relation to sex. Among the investigated parameters, longer attack duration and higher MIDAS scores, and the frequencies of nausea, vomiting, osmophobia, vertigo/dizziness and allodynia were found significantly different between women and men. The significant parameters between women and men were also compared between men and postmenopausal women, which are also shown in Table 2 as  $p'$ . All these parameters were still significant except nausea.

As seen in Table 3, stress (68.5%), wind (54.4%), hunger (54.2%), and sleeplessness (53.0%) were common trigger factors across the entire group and there was no significant difference between women and men. Odor was reported to be a trigger in women statistically more frequently than in men, whereas excessive sleep was statistically more frequently reported as a trigger in men.

Binary logistic regression analyses were performed with important clinical variables. P values, odds ratios (ORs) and lower-upper 95% CI values according to the binary logistic analyses were as follows; allodynia ( $P=0.171$ , OR: 0.797, 95% CI: 0.576–1.103), osmophobia ( $P=0.044$ , OR:

**Table 1.** Demographic characteristics of women and men with migraine

	Women (n: 640) n (%)	Men (n: 231) n (%)	Total (n: 871) n (%)	p
Age	18–29 y	191 (29.8)	70 (30.3)	261 (30)
	30–39 y	186 (29.1)	71 (30.7)	257 (29.5)
	40–49 y	157 (24.5)	52 (22.5)	209 (24)
	50–65 y	106 (16.6)	38 (16.5)	144 (16.5)
Married or living together	449 (70.2)	160 (69.3)	609 (69.9)	NS
Education				
No education or primary school	258 (40.3)	55 (23.8)	313 (35.9)	<0.001*
High school or university	382 (59.7)	176 (76.2)	558 (64.1)	
Income				
Low (<1300 US\$)	484 (75.6)	173 (74.9)	657 (75.4)	NS
High ( $\geq 1300$ US\$)	156 (24.4)	58 (25.1)	214 (24.6)	
Living area				
Metropolitans	459 (71.7)	151 (65.4)	610 (70)	NS
Smaller cities or areas	181 (28.3)	80 (34.6)	261 (30)	
Current smoker	217 (33.9)	133 (57.6)	350 (40.2)	<0.001*
Alcohol consumption	90 (14.1)	75 (32.5)	165 (18.9)	<0.001*
Depression	209 (33.3)	34 (14.8)	243 (28.3) <sup>†</sup>	<0.001*
Epilepsy	8 (1.3)	1 (0.4)	9 (1)	NS
Olfactory hypersensitivity	528 (82.5)	167 (72.3)	695 (79.8)	0.001
Intolerance to odors (sick of smell)	533 (83.3)	165 (71.4)	698 (80.1)	<0.001*
Allergy	208 (32.5)	58 (25.1)	266 (30.5)	0.037*
Allergic asthma	55 (8.6)	13 (5.6)	68 (7.8)	NS
Hypertension	97 (15.2)	26 (11.3)	123 (14.1)	NS
Physician consult for headache	467 (73)	148 (64.1)	615 (70.6)	0.011*
Neurologist consult for headache	229 (35.8)	59 (25.5)	288 (33.1)	0.005*

\*Chi-square.

NS, not significant.

<sup>†</sup>13 subjects did not answer this question, evaluated from 858 subjects.

**Table 2.** Associated features with migraine in relation to sex

		Women (n: 640) /postmenopausal women ‡ (n: 87)	Men (n: 231)	Total (n: 871)	<sup>P</sup> (women-men)/ <sup>P'</sup> (postmenopausal women-men)
Number of attacks per month mean ± SD		6.0±6	5.7±6	5.9±6	NS
Attack duration (hours) mean ± SD		39.1±78/47.7±94.1	24.0±49	35.1±72	0.006#/<0.001#
Number of days with headache per month mean ± SD		6.3±6	6.0±6	6.2±6	NS
≥15 headache days per month		73 (11.4)	22 (9.5)	95 (10.9)	NS
		n (%)/n (%)	n (%)	n (%)	
Headache Severity	Mild	37 (5.8)	22 (9.5)	59 (6.8)	NS
	Moderate	255 (39.8)	85 (36.8)	340 (39.0)	
	Severe	348 (54.4)	124 (53.7)	472 (54.2)	
Nausea		536 (83.8)/69 (79.3)	163 (70.6)	699 (80.3)	0.001*/NS
Vomiting		242 (37.8)/32 (36.8)	56 (24.2)	298 (34.2)	0.001*/0.002*
Photophobia		529 (82.7)	190 (82.3)	719 (82.5)	NS
Phonophobia		549 (85.8)	193 (83.5)	742 (85.2)	NS
Osmophobia		301 (47)/42 (48.3)	78 (33.8)	379 (43.5)	0.001*/0.01*
Vertigo/dizziness		431 (67.3)/61 (70.1)	103 (44.6)	534 (61.3)	<0.001*/<0.001*
Aggravation with movement		601 (93.9)	213 (92.2)	814 (93.5)	NS
Headache Side					
Only one sided headache		282 (44.1)	116 (50.2)	398 (45.7)	NS
Only or predominant in one side headache		421 (65.8)	152 (65.8)	573 (65.8)	NS
Only both sided headache		175 (27.3)	60 (26.4)	235 (27.1)	NS
Throbbing headache		534 (83.4)	177 (76.6)	711 (81.6)	NS
Pressure headache		172 (26.9)	65 (28.1)	237 (27.2)	NS
Prodrom of migraine		423 (66.1)	164 (71)	587 (67.4)	NS
Aura present		135 (21.1)	52 (22.5)	187 (21.5)	NS
Allodynia		410 (64.1)/60 (69)	122 (52.8)	532 (61.1)	0.003*/0.008*
MIDAS	1	322 (50.3)	156 (67.5)	478 (54.9)	
	2	122 (19.1)	50 (21.6)	172 (19.7)	
	3	125 (19.5)	13 (5.6)	138 (15.8)	
	4	71 (11.1)	12 (5.2)	83 (9.5)	
	Mean score ± SD	9.36±14.4/9.4±13.2	4.87±7.4	8.17±13.07	<0.001#/0.01#

\*chi-square

#2-tailed t test

NS, not significant

P, p value of women and men

p', p value of postmenopausal women and men

‡, 60 subjects did not answer

**Table 3.** Potential trigger factors of migraine in relation to sex

	Women n: 640/(%)	Men n: 231/(%)	Total n: 871/(%)	p
Wind	349 (54.5)	125 (54.1)	474 (54.4)	NS
Bright light	253 (39.5)	89 (38.5)	342 (39.3)	NS
Smoke	224 (35)	67 (29)	291 (33.4)	NS
Odor	183 (28.6)	49 (21.2)	232 (26.6)	0.03*
Food	70 (10.9)	29 (12.6)	99 (11.4)	NS
Hunger	345 (53.9)	127 (55)	472 (54.2)	NS
Sleeplessness	335 (52.3)	127 (55)	462 (53.0)	NS
Excessive sleep	130 (20.3)	70 (30.3)	200 (23.0)	0.002*
Stress	442 (69.1)	155 (67.1)	597 (68.5)	NS
Menstruation	251 (39.2)	-	-	-

\* chi-square.

NS, not significant.

1.414, 95% CI: 1.01–1.981), depression ( $P<0.001$ , OR: 2.564, 95% CI: 1.696–3.875), vertigo ( $P<0.001$ , OR: 0.503, 95% CI: 0.364–0.695), nausea ( $P=0.007$ , OR: 1.681, 95% CI: 1.152–2.453) and attack duration (>24 hours) ( $P=0.003$ , OR: 1.759, 95% CI: 1.206–2.566). Only allodynia lost its significance after binary logistic regression analysis.

## DISCUSSION

Our results showed that women had longer migraine attacks with more associated symptoms such as nausea, vomiting, osmophobia, vertigo/

dizziness, and allodynia, which causes more disability. Contrary to our hypothesis, these associated features were still significant when we compared postmenopausal women with men, except for nausea.

Several studies focused on the role of sex hormones in the pathophysiology of migraine (10, 11). Migraine frequency is lower and does not differ between the sexes before puberty. In women, its frequency increases during menstruation and lowers after physiologic menopause. The high migraine prevalence among women is attributed to fluctuating levels of gonadal hormones (12, 13). There is a complex relationship between

estrogen and migraine. For example, menstrual migraine is related with falling levels of estrogen, and oral contraceptive use results in aggravation in patients who have migraine with aura (14). It was also emphasized that the hormonal system modulates cortical, subcortical, and brainstem functions, and these modulations at cellular and functional levels might lead to some of the associated features related with migraine (15, 16). In addition, estrogen has a direct effect on the trigeminovascular system. Accordingly, migraine attacks may be accompanied by a variety of autonomic symptoms (e.g., nausea, vomiting, rhinorrhea, and ptosis), affective disorders and symptoms (e.g., depression and irritability), cognitive symptoms (e.g., difficulty in finding words, transient amnesia), and sensory symptoms (e.g., photophobia, phonophobia, osmophobia, and cutaneous allodynia) (15, 16). Our results showed that women had longer migraine attacks with more associated symptoms such as nausea, vomiting, osmophobia, vertigo/dizziness, and allodynia. When we compared these parameters between men and postmenopausal women, all these parameters were still significant except nausea. Although we do not have a single answer, we think a simple correlation between gonadal hormones and migraine does not seem to be sufficient for such a discrepancy between women and men.

Several studies may further support our thesis that some genetic risk factors influence the liability to migraine and its characteristics in relation with sex. Complex genetic factors are involved in migraine in up to 60% of cases (17, 18). Genetic factors, including ion-channel function, appear to set the individual threshold; internal and environmental factors including hormonal fluctuations may modulate this genetic predisposition (18). In addition, many years of hormonal fluctuations during the fertile period might result in irreversible changes in cortical, subcortical, and brainstem cells and circuits.

In our study, the rates of nausea and vomiting were significantly higher in women when compared with men. In the postmenopausal period, vomiting was still significantly high in women. Higher vagal tone in women as well as the well-known effects of gonadal hormones are reported to be associated with nausea and vomiting in women (19). Mitochondrial DNA sequence variations in migraine and cyclic vomiting syndrome support the genetic predisposition of vomiting in migraine patients (20). Our findings confirm the genetic effect of vomiting in female migraineurs, which starts in puberty and persists after menopause, is not solely an effect of sex hormones.

Allodynia is a marker of central sensitization in migraine patients. According to our findings, allodynia was more commonly seen in women even in the postmenopausal period. However, allodynia lost its statistical significance when binary logistic regression was performed to explore the differentiating variables between women and men. This might be as a result of associations of allodynia with longer duration of attacks, nausea, and vomiting, which have been shown in previous studies (21, 22).

Vertigo is two or three times more commonly reported as an associated symptom in migraine patients when compared with headache-free controls. Consistent with our results, previous studies have also reported a marked female predominance in vertiginous migraine (23).

Typical triggers such as stress, wind, hunger, and sleeplessness were common trigger factors across the entire group and they did not differ between women and men, concordant with previous studies (24, 25). Odor was a statistically more frequent trigger factor in women, whereas excessive sleep was a statistically more frequent trigger factor in men.

Odor is of importance in migraine in several ways besides being a trigger factor. As a trigger factor for migraine attacks, and in osmophobia during attacks, intolerance to odors and olfactory hypersensitivity are commonly reported. According to our study, all these factors associated with odor

were significantly higher in women when compared with men. Although most studies supported our findings, Kelman reported no significant difference between women and men in respect to odor triggers (26). In a population-based study in Sweden, odor intolerance was found to be two-fold higher in women (27). The mechanism of female predominance is not well understood but it is remarkable that osmophobia has a strong relationship with women. According to the diagnostic criteria of the Canadian Headache Society, osmophobia was included as a specific feature of migraine, also, the diagnostic and therapeutic guidelines of the Italian Society for the Study of Headaches recommended osmophobia among the additional supporting criteria for the diagnosis of migraine (28, 29). ICHD-III does not include osmophobia in the diagnostic criteria although these classifications recommended osmophobia as a specific feature of migraine. Our data support that osmophobia cannot be considered a peculiar symptom of migraine because of the high discrepancy in sex.

Excessive sleep was found to be a statistically more frequent trigger factor in men when compared with women. The exact explanation for this association between men and excessive sleep is not clear but it might be due to women's sleep patterns. Taking care of an infant or elderly relatives, which disturbs sleep, and different responsibilities and rights of women might condition them to require less sleep (30).

Migraine is co-morbid with various medical conditions, and there are more co-morbid diseases in migraine women compared with men. In our population, the rates of depression and allergy were significantly higher in women, in concordance with previous studies (5).

As a conclusion, this population-based study showed that longer attack duration, higher MIDAS scores, and the frequencies of nausea, vomiting, osmophobia, vertigo/dizziness, and allodynia were more significant in women, and this variance in sex persisted after menopause. Also, some trigger factors and co-morbidities differed between the sexes. This finding seems to result from complex genetic factors as well as sex hormones and receptor binding and psychosocial effects. We suggest that future studies should continue to explore biologic and genetic factors with respect to sex in migraine. As more is learned about the biology and genetics of migraine and about the differences between the sexes, we will be able to diagnose, treat, and estimate outcomes for both sexes more accurately.

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**Ethics Committee Approval:** Ethics committee approved this study.

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