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Title: Comorbidities in Patients with Migraine in Japan: A Cross-sectional Study Using Data from National Health and Wellness Survey

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ABSTRACT (250 WORDS)

Objectives – This study aims to examine the association between migraine and various psychiatric and somatic comorbidities in Japan.

Design – Cross-sectional study using existing data of the 2017 Japan National Health and Wellness Survey (NHWS).

Setting – Nationally representative sample of persons (in terms of age and gender) living in the general community aged 18 years or older in Japan.

Participants – Out of a sample of 30,001 NHWS respondents, 378 respondents were identified as migraine patients and 25,209 were identified as non-migraine patients. After propensity score (PS)-matching (1:4), 1,512 matched non-migraine respondents were identified.

Primary and secondary outcome measures – Prevalence and PS-matched prevalence odds-ratio (POR) were assessed for each psychiatric and somatic comorbidity among migraine patients and matched non-migraine respondents (including migraine patients with less than 15 monthly headache days [MHDs] and migraine patients with more than 15 MHDs).

Results – Migraine patients were predominately female and had significantly higher prevalence than matched non-migraine respondents to have psychiatric and somatic comorbidities. Psychiatric comorbidities with >5% prevalence among migraine patients included depression, posttraumatic stress disorder, and anxiety disorders, while gastrointestinal disorders were the most prevalent somatic comorbidity category. Other somatic comorbidities included allergies, insomnia, pre-menstrual syndrome, and anemia. Migraine patients with more than 15 MHDs tended to have higher point estimates for POR.

Conclusion – Psychiatric and somatic conditions were more prevalent in migraine patients than matched non-migraine respondents, some being novel associations not previously reported in

Japan. This study provided insights on comorbidities which could complicate care, clinical practice, and outcomes among migraine patients.

Keywords - Comorbidities; Migraine; Prevalence Odds-ratio; Health Survey

Trial registration – Not applicable

ARTICLE SUMMARY

Strengths and limitations

- An age-and-gender-stratified sampling frame was imposed during the recruitment to ensure and reflection of the general adult population of Japan in terms of age and gender.
- The study identified potential psychiatric and somatic comorbidities from self-reported medical history of migraine patients as well as several covariates including sociodemographic factors, general health characteristics and migraine-specific covariates
- This study uses an online survey and thus respondents without internet access were not included in the study
- This study assessed respondents' self-declaration of migraine manifestation and comorbidities which may bias the prevalence odds-ratio and the causal relationship between migraine and comorbidities cannot be concluded

INTRODUCTION

Migraine is a common debilitating neurological disorder that is highly prevalent globally.[1] In Japan, the estimated prevalence of migraine among the general population was 6% in 2004,[2] and more recently, 9% among working, socially active individuals in the Tokyo metropolitan area.[3]

Previous reports demonstrated that approximately 90% of chronic migraine patients have at least one comorbidity.[4] The previously reported comorbidities of migraine include various psychiatric[5–7] and somatic conditions such as cardiovascular disorders,[8–10] gastrointestinal disorders,[10–13] allergy-related disorders,[10,14,15] sleep disorders,[10,16,17] and gynecological disorders.[18] A nationwide population-based study in the United States reported an association between migraine comorbidities and the intensity of headache pain and frequency.[10]

In Japan, there is an evidence gap on the comorbidities of migraine. Although there were a few studies investigating the comorbidities of migraine in Japan, previous studies primarily focused on one disease or one category of diseases.[19,20] To our knowledge, no studies have been published that assess for a range of comorbidities of migraine referencing non-migraine individuals in Japan.

Therefore, the objective of this study was to examine the association between migraine and a range of psychiatric and somatic comorbidities in Japan by assessing the prevalence odds ratio (POR) between migraine and these comorbidities, with referencing to non-migraine individuals. The findings from this study may provide insights to the etiology of migraine and help physicians and patients with effective migraine management and treatment.

METHODS

This study utilized existing data collected from a cross-sectional online survey, the 2017 Japan National Health and Wellness Survey (NHWS). Individuals aged 18 years or older were recruited to the NHWS through an existing, general-purpose (i.e., not healthcare-specific) web-based consumer panel. All panelists explicitly agreed to join the panel and receive periodic invitations to participate in online surveys. An age-and-gender-stratified sampling frame, based on Japan governmental census data, was imposed during the recruitment from the panelists. This was to ensure representativeness of panelists who completed the NHWS to reflect the general adult population of Japan in terms of age and gender.

The NHWS was granted exemption status upon review by the Pearl Pathways Institutional Review Board (IN, US). All NHWS respondents provided informed consent prior to participation. This analysis was granted exemption by the Public Health Research Foundation Ethical Review Committee (Tokyo, Japan).

Study Population

Migraine patients in this study were defined by ICHD-3 (International Classification of Headache Disorders, 3rd Edition)-like criteria which was detailed in a previous publication using the same data,[21] among respondents who self-reported migraine in the past 12 months and self-reported having at least 4 monthly headache days (MHDs) (Figure 1). The ICHD-3 like criteria was based on the diagnostic criteria from ICHD-3 but modified for the variables available in the existing NHWS data.[21] Respondents having migraine without aura or migraine with aura, as per the ICHD-3 like criteria, and having at least 4 MHDs, were identified as migraine patients in this study. Respondents who did not self-report migraine were classified as non-migraine respondents.

Patient and Public Involvement

Respondents and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Covariate and Outcome Assessment

Sociodemographic and general health characteristics variables measured in this study included age, gender, marital status, level of education, household income, region, insurance type, employment status, Charlson comorbidity index (CCI),[22] body mass index (BMI), smoking status, alcohol use, and exercise behavior. Migraine-specific covariates were assessed using the Headache Impact Test-6 (HIT-6). The HIT-6 measures the impact of headaches on the respondents' ability to function in social situations including home and work. Higher HIT-6 depicts greater functional impairment.[23]

A list of potential psychiatric and somatic comorbidities was created from the self-reported medical history of the NHWS respondents (refer to full list in Figure 2 and Figure 3). The list includes diseases for which the associations with migraine have been reported; diseases for which the association may be explained from the pathophysiology; and other conditions of special interest related to treatment choices. All respondents answered the questions "Have you ever experienced …" or "Have you experienced … in the past 12 months" depending on the condition in NHWS.

Statistical Analysis

Sociodemographic and health characteristics were summarized using counts and percentages for categorical variables and means and standard deviations (SDs) for continuous variables for migraine patients and non-migraine respondents.

Propensity score (PS) matching with 1:4 ratio of migraine patients to non-migraine respondents, using a greedy matching algorithm was conducted to create a matched comparison group of non-migraine respondents. Sociodemographic (age, gender, marital status, education, household income, region, insurance, and employment status) and general health characteristics (BMI, smoking status, alcohol use and exercise behavior) were used in the matching. Balance of matching were assessed using standardized mean differences (SMDs) between migraine patients and matched non-migraine respondents. Standardized mean differences greater than 0.1 were considered unbalanced after matching.

Prevalence of the selected psychiatric and somatic comorbidities among migraine patients and matched non-migraine respondents were calculated. Then, PS-matched prevalence odds-ratio (POR) and its 95% confidence intervals (CI) for each comorbidity were calculated to evaluate the potential associations of these conditions with migraine.

A post-hoc subgroup analysis was conducted among migraine patients with less than 15 MHDs (episodic migraine) and their respective matched non-migraine respondents, as well as among migraine patients with at least 15 MHDs (chronic migraine) and their respective matched non-migraine respondents.

All statistical analyses were performed using IBM SPSS version 25 and R3.5.1. No correction for multiple testing was conducted as the study was out of exploratory nature and no formal hypothesis testing was planned. P-values were provided as an indication of the difference between migraine patients and non-migraine respondents.

RESULTS

Participant demographics and health characteristics

A total of 30,001 respondents aged 18 years and older provided informed consent and participated in the 2017 Japan NHWS. Among these respondents, 378 respondents were identified as migraine patients and 25,209 respondents were identified as non-migraine respondents (Figure 1).

After PS matching, a total of 1,512 non-migraine respondents were identified and matching was found to be balanced between matched non-migraine respondents and migraine patients, with all SMDs less than 0.1 (Table 1).

Sociodemographic and general health characteristics of migraine patients and matched non-migraine respondents are described in Table 1.

Migraine patients (N=378) had an average age of 41.6 and were predominantly females (79.9%). The majority (83.6%) of migraine patients in this study had severe impact (HIT-6 score: 60-78). The CCI, which was not part of the PS matching, was higher in migraine patients than matched non-migraine respondents (mean: 0.24 vs. 0.08).

Table 1. Sociodemographic and general health characteristics among migraine patients and matched non-migraine respondents

	Migraine patients (N=378)		Matched non-migraine respondents (N=1,512)		SMD
	%	Count	%	Count	
Age [Mean (SD)]	41.6 (12.7)		41.2 (15.2)		0.026

Gender	*Male*	20.1%	76	20.0%	303	0.002
	Female	79.9%	302	80.0%	1,209	
Marital status	*Married or living with partner*	48.9%	185	49.0%	741	0.001
	Divorced/ Separated/ Widowed/ Decline to answer	51.1%	193	51.0%	771	
Level of education	*Completed university education*	41.3%	156	43.2%	653	0.042
	Not completed	46.6%	176	44.6%	674	
	Decline to answer	12.2%	46	12.2%	185	
Household income	*<¥3,000,000*	19.6%	74	18.9%	286	0.029
	¥3,000,000 to <¥5,000,000	27.0%	102	27.6%	417	
	¥5,000,000 to <¥8,000,000	24.6%	93	23.9%	361	
	¥8,000,000 or more	14.8%	56	15.4%	233	
	Decline to answer	14.0%	53	14.2%	215	
Region	*Hokkaido*	3.2%	12	2.9%	44	0.063
	Tohoku	6.6%	25	7.1%	107	
	Kanto	39.4%	149	40.7%	615	
	Chubu	14.6%	55	14.6%	221	
	Kansai/Kinki	18.8%	71	16.9%	255	
	Chugoku	4.2%	16	4.4%	67	
	Shikoku	3.2%	12	3.7%	56	
	Kyushu/Okinawa	10.1%	38	9.7%	147	
Insurance type	*National health insurance*	52.1%	197	50.8%	768	0.034
	Social insurance	44.7%	169	46.1%	697	
	Other (Late-stage elderly insurance / Other / None of the above)	3.2%	12	3.1%	47	
Employment status	*Currently not employed*	39.9%	151	40.6%	614	0.013
	Currently employed	60.1%	227	59.4%	898	
BMI	*Underweight (BMI<18.5)*	18.3%	69	18.5%	280	0.045
	Normal weight (18.5≤BMI<25)	62.4%	236	59.7%	903	
	Pre-obese (25≤BMI<30)	14.8%	56	13.6%	205	
	Obese (BMI≥30)	4.5%	17	4.0%	61	
	Decline to answer	4.2%	16	4.2%	63	
Smoking status	*Never smoker*	55.8%	211	56.7%	858	0.045
	Former smoker	20.9%	79	19.1%	289	
	Current smoker	23.3%	88	24.1%	365	
Alcohol use	*Abstain*	40.5%	153	40.8%	617	0.007
	Currently consume alcohol	59.5%	225	59.2%	895	
Vigorous exercise in past 30 days	*No*	58.2%	220	60.0%	907	0.036
	Yes	41.8%	158	40.0%	605	
CCI* [Mean (SD)]		0.24 (0.86)		0.08 (0.33)		0.242
HIT-6 impact grades*	*Little-to-no impact (HIT-6 score: 36-49)*	1.1%	4	-	-	-
	Moderate impact (HIT-6 score: 50-55)	6.6%	25	-	-	
	Substantial impact (HIT-6 score: 56-59)	8.7%	33	-	-	
	Severe impact (HIT-6 score: 60-78)	83.6%	316	-	-	

BMI, body mass index; CCI, Charlson comorbidity index; SMD, standardized mean difference.

* CCI and HIT-6 impact grades are not included in the propensity score matching.

Psychiatric comorbidities in migraine patients vs. matched non-migraine respondents (Figure 2)

The psychiatric comorbidities with prevalence higher than 5.0% in migraine patients were depression (22.2%), post-traumatic stress disorder (PTSD) (7.7%), anxiety disorders (6.1% for phobias to 14.6% for anxiety), and obsessive-compulsive disorder (OCD) (5.0%).

Among the comorbidities with relatively high prevalence (5.0% or higher) in migraine patients, migraine patients had a significantly higher odds than matched non-migraine respondents for PTSD (PS-matched POR [95% CI]: 11.3 [5.4, 25.4]), various anxiety disorders (generalized anxiety disorder (GAD): 9.9 [5.1, 20.3] to social anxiety disorder (4.9 [3.0, 7.8]), OCD (5.3 [2.5, 11.3]), and depression (2.9 [2.1, 3.9]).

Somatic comorbidities in migraine patients vs. matched non-migraine respondents (Figure 3)

Gastrointestinal comorbidities

Most of the gastrointestinal comorbidities assessed in this study showed the prevalence higher than 5.0% in migraine patients: heartburn (42.6%), chronic constipation (28.8%), frequent diarrhea (26.2%), gastroesophageal reflux disease (GERD) (20.6%), irritable bowel syndrome (19.8%), and ulcers (11.4%).

Among the gastrointestinal comorbidities with relatively high prevalence, compared with matched non-migraine respondents, migraine patients had a significantly higher odds for irritable bowel syndrome (PS-matched POR [95% CI]: 3.8 [2.7, 5.4]), heartburn (3.6 [2.8, 4.7]),

GERD (3.5 [2.5, 4.8]), ulcers (3.1 [2.0, 4.8]), frequent diarrhea (3.1 [2.3, 4.1]) and chronic constipation (2.5 [1.9, 3.3]).

Allergy-related comorbidities

All the allergy-related comorbidities assessed in this study have a prevalence higher than 5.0% in migraine patients: allergies (43.1%), hay fever (44.2%), atopic dermatitis (19.6%), and asthma (17.5%).

Compared with matched non-migraine respondents, migraine patients had a significantly higher odds for allergies (PS-matched POR [95% CI]: 3.0 [2.3, 3.8]), hay fever (2.9 [2.2, 3.6]), asthma (2.2 [1.6, 3.1]), and atopic dermatitis (2.0 [1.5, 2.7]).

Sleep comorbidities

The following sleep disorders presented in migraine patients with a prevalence higher than 5.0% included insomnia (35.4%) and sleep difficulties (12.7%). Migraine patients had a significantly higher odds for insomnia (PS-matched POR [95% CI]: 4.3 [3.3, 5.7]) and sleep difficulties (4.1 [2.7, 6.3]), compared to matched non-migraine respondents.

Gynecological comorbidities

The gynecological disorders assessed in this study with a prevalence higher than 5.0% among migraine patients were pre-menstrual syndrome (32.1%), pre-menstrual dysphoric disorder (19.9%), fibroid (13.0%), and endometriosis (9.5%). Compared with matched non-migraine respondents, migraine patients had a significantly higher odds for pre-menstrual dysphoric disorder (PS-matched POR [95% CI]: 5.5 [3.6, 8.4]), pre-menstrual syndrome (5.3 [3.8, 7.4]), endometriosis (2.4 [1.5, 3.7]), and fibroids (1.8 [1.2, 2.6]).

Cardiovascular comorbidities

The cardiovascular disorders assessed in this study showed a lower than 5.0% prevalence among migraine patients except for high blood pressure (hypertension) (7.4%). Compared with

matched non-migraine respondents, the odds of having hypertension, heart attack, stroke, or mini-stroke/transient ischemic attack (TIA) were not significantly different in migraine patients.

Other comorbidities

Most other disorders assessed in this study showed the prevalence lower than 5.0% among migraine patients except for anemia (23.3%), thyroid condition (5.8%), and restless leg syndrome (5.8%). Compared with matched non-migraine respondents, migraine patients had a significantly higher odds for restless leg syndrome (PS-matched POR [95% CI]: 2.9 [1. 6, 5.1]), thyroid condition (2.9 [1. 6, 5.1]) and anemia (2.3 [1.7, 3.1]). Compared with matched non-migraine respondents, migraine patients had a significantly higher odds for fibromyalgia (prevalence among migraine patients: 1.6%; POR [95% CI]: 12.2 [2.2, 123.7]). For all other disorders assessed in this study (rheumatoid arthritis, lupus, Parkinson's disease, epilepsy, genital herpes, genital warts, and breast cancer), the odds among migraine patients were not different from matched non-migraine respondents.

Post-hoc subgroup analysis by MHDs

Majority of the baseline characteristics remained balanced at the subgroup level (results not shown). Post-hoc analysis demonstrated consistent results in both subgroups of the migraine patients MHDs<15 and MHDs≥15 with the overall analysis. The most prevalent psychiatric and somatic comorbidities were similar in both migraine patients with MHDs<15 and migraine patients with MHDs≥15 (Supplementary Tables 1 and 2).

Migraine patients with MHDs≥15 tended to have higher point estimates for POR although formal statistical testing was not performed to assess the interaction for the association between comorbidities and migraine by MHD.

DISCUSSION

This study showed that patients with migraine have a significantly higher prevalence for various psychiatric and somatic comorbidities, compared with matched non-migraine respondents. Our study is the first to report the broad range of comorbidities associated with migraine as a population-based study in Japan.

Potential pathological mechanisms for comorbidities were proposed – for example, uni- or bi-directional causality or shared environmental or genetic risk factors. Although various explanations for the association between migraines and psychiatric conditions have been proposed, exact causal relationships and mechanisms for the associations are yet to be elucidated.

Psychiatric comorbidities

Psychiatric disorders that our study found associated with migraine such as PTSD, anxiety disorders, OCD and depression have been described in previous literature.[5–7] Associations between migraines and psychiatric conditions have been hypothesized for neurotransmitters, such as serotonin, and ovarian hormonal influences, which might lead to serotonergic processing dysfunction and hypothalamic-pituitary-adrenal (HPA) axis dysregulation.[24] A genome-wide association study with over 1 million individuals found significantly overlapped genetic risks of migraine with psychiatric conditions such as attention-deficit/hyperactivity disorder (ADHD) or depression.[25]

Somatic comorbidities

Gastrointestinal comorbidities

We found that bowel movement dysregulations such as constipation, diarrhea, and irritable bowel syndrome, are more prevalent in migraine patients than matched non-migraine respondents, which was consistent with previous literature.[11–13] Autonomic nervous system dysfunction and other mechanisms such as dysregulation of neuroendocrine, immunological factors, the brain-gut axis, or intestinal microbiota[12] were thought as potential mechanisms to alter visceral sensitivity and common pathology with migraine.

Both GERD[13] and gastric ulcer[10,13] were shown to have higher prevalence in migraine patients than matched non-migraine respondents in this study. Association of migraine with *Helicobacter pylori* infection has been shown in a meta-analysis of observational studies,[26] and this may explain the high prevalence of GERD and gastric ulcer in migraine patients[12] Other possible explanations for the association between migraine and gastrointestinal disorders includes analgesics use in migraine patients.[12,15]

Allergy-related comorbidities

In this study, migraine patients were more likely to have allergy-related comorbidities, which are consistent with previous research.[10,14,15] The association between migraine and allergy-related comorbidities could in part be due to common pathophysiology of inflammatory, immune, and genetic factors.[14]

Sleep comorbidities

Migraine patients in this study had a significantly increased prevalence for sleep disorders including insomnia and sleep difficulties, compared to non-migraine respondents, consistent with previous studies.[10,16,17] The association between migraine and sleep disorders is thought to be bidirectional: headache was shown to be a risk factor for insomnia, while

insomnia could be a contributing factor of migraine attacks. A large population-based study reported that those with comorbid migraine and poor sleep showed significantly poorer anxiety and depression scores.[17]

Gynecological comorbidities

Headache has been known to be a common symptom for perimenstrual syndrome.[27] Furthermore, the association between endometriosis and migraine was previously reported.[18] The findings from the present study were consistent with the previous research. The association between migraines and gynecological comorbidities could be due to hormonal changes in women throughout the menstrual cycle or during menopause which may cause migraine through estrogen-mediated pathways including the association of estrogen receptor markers from genetic studies.[28]

Cardiovascular comorbidities

Previous studies pointed out the association between migraine and cardiovascular conditions such as hypertension,[10] myocardial infarction[9,10] and stroke,[8–10] and the association specifically on migraine with aura[8,9] or other risk factors such as age, smoking habit, and use of oral contraceptives.[8] However, no association was observed between migraine and cardiovascular conditions such as hypertension, probably due to the younger age of migraine patients in this study or small numbers of high-risk migraine patients for cardiovascular conditions.

Other comorbidities

As found in our study, anemia,[29] and thyroid dysfunction[30] have been described as comorbidities of migraine. Similarly, restless leg syndrome[19] has been shown for the association, although the association may be controversial.[31]

The observation on the relationship between migraine and fibromyalgia in this study is consistent with previous studies.[32] Fibromyalgia may share a pathological pathway with migraine through chronic hypothalamic neuroendocrine dysfunction, resulting in abnormal central nervous system sensory processing.[33]

Clinical Implications

Although some of the associations are not solidly established with potential pathological explanation, the findings from this study appear to have clinical importance. Various comorbidities are at high prevalence among migraine patients. Migraine patients may experience impairment for daily life and loss of productivity not only because of the migraine but also its comorbidities. In the treatment of migraine, comorbidities may influence therapeutic choices in two ways. First, by taking comorbidities into consideration, medication can be selected both for migraine and comorbidities. Second, therapeutic options for migraine may be limited if there are comorbidities as contraindications to migraine medications.[34] Therefore, accounting for comorbidities in clinical practice is warranted when therapeutic options are considered.[34,35] Additionally, comorbidities may provide insights to the physiopathology of migraine which could facilitate effective management and treatment of migraine.

Limitations

There are a few limitations to be mentioned for this study. NHWS is cross-sectional and causal relationship between migraine and comorbidities cannot be concluded, i.e., if the comorbidities were induced by migraine or treatment for migraine or vice versa. In addition, respondents self-reported their migraine symptoms as well as comorbidities, which may lead to potential recall

bias. Although ICHD-3 like criteria were created for this study using available self-reported data, discrepancies between the criteria used in this study and the formal ICHD-3 criteria still exist. Lastly, NHWS is an online survey and thus respondents without internet access were not included in the study.

CONCLUSION

Our study found that migraine patients are more likely to have psychiatric and somatic comorbidities compared with matched non-migraine respondents, some of which are novel ones previously unreported in Japan. This study showed that migraine patients in Japan face an additional comorbid burden and provides insights on comorbidities of migraine they may suffer. It is hoped that identifying and treating migraine along with their comorbidities, which usually complicate care, will help in good clinical practice and improve outcomes among migraine patients.

Ethics approval and consent to participate

The 2017 Japan NHWS survey was approved with exemption status upon review by Pearl Institutional Review Board (Indianapolis, IN, IRB Study Number: 17-KANT-150). All NHWS respondents provided informed online consent prior to participating. Study participants or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Patient consent form: Not required

Consent for publication

Not applicable.

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Competing interests

SK and TT received consultation fee for this study. YC is an employee at Cerner Enviza, Singapore. Cerner Enviza received funding from Amgen K.K. for conduction of the analysis and manuscript development. MH and KI are employees at Amgen K.K., and KA is a former employee at Amgen K.K. and is currently an employee of IQVIA Solutions Japan, K.K. MH holds, and KA held stocks of Amgen Inc.

Author contributions

SK, YC, KI, MH, KA, and TT conceptualized and designed the study. YC analyzed the data. SK, YC, KI, MH, KA, and TT interpreted the results and contributed to the original draft of the manuscript. All authors read and approve the final manuscript.

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Data sharing statement

Study data to support our findings are available from Cerner Enviza, but availability of the data is restricted and was used under license for this study and are not publicly available. Data are, however, available from the authors upon reasonable request and with the permission of Cerner Enviza.

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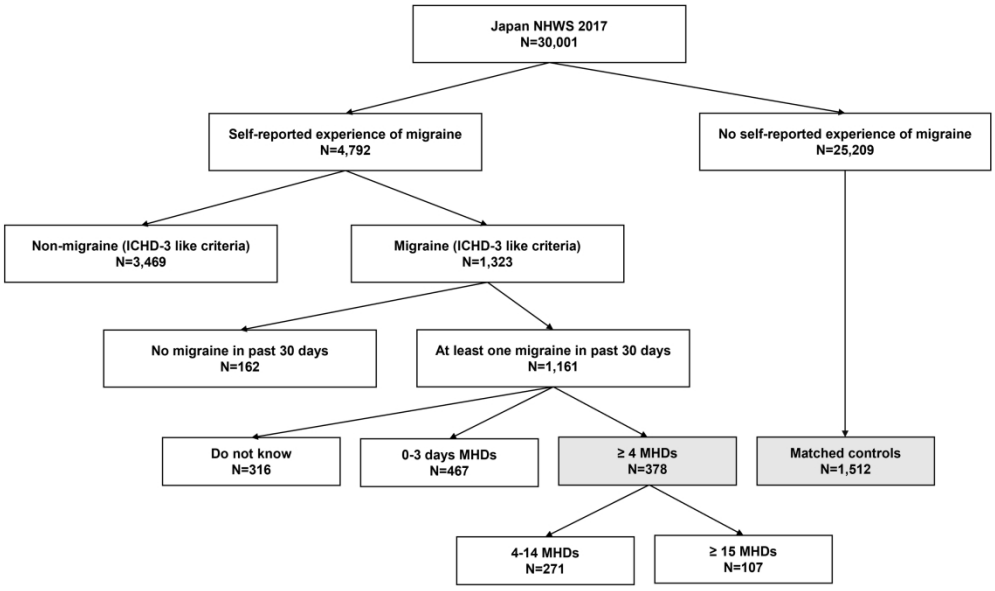
Figure legends

Figure 1. Respondent flow chart

Figure 2. Propensity score-matched prevalence odds ratio for psychiatric comorbidities

Figure 3. Propensity score-matched prevalence odds ratio for somatic comorbidities

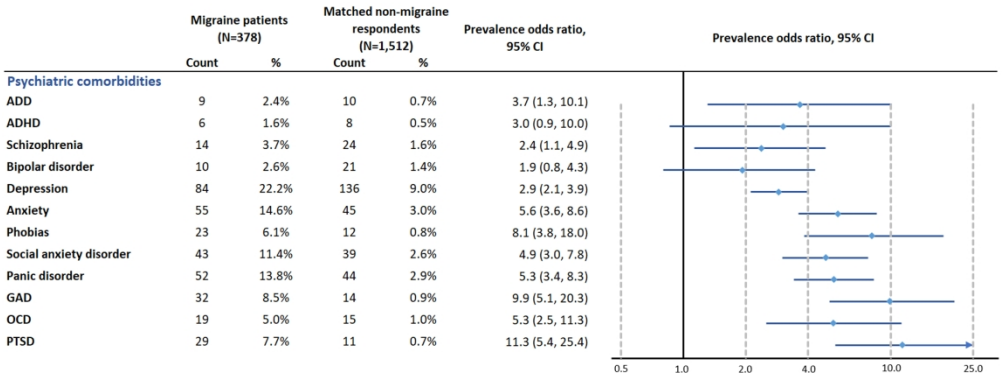


ICHD-3, International Classification of Headache Disorder, 3rd Edition; MHDs, Monthly Headache Days.

Note: Shaded squares indicate the study populations – migraine patients (≥ 4MHDs; N=378) and matched non-migraine respondents (Matched controls, N=1,512).

Figure 1. Respondent flow chart

130x86mm (600 x 600 DPI)

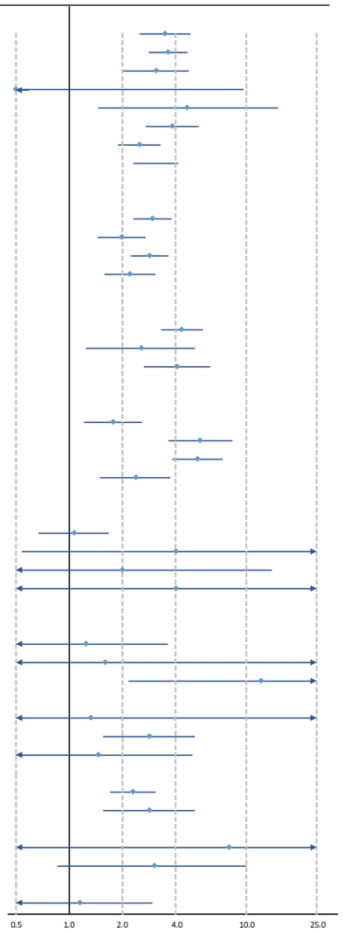


ADD, attention-deficit disorder; ADHD, attention-deficit/hyperactivity disorder; GAD, generalized anxiety disorder; OCD, obsessive-compulsive disorder; PTSD, posttraumatic stress disorder.
Note: Comorbidities with prevalence between 5% to 10% among migraine patients: phobias, GAD, OCD, and PTSD. Comorbidities with more than 10% prevalence among migraine patients: depression, anxiety, social anxiety disorder, and panic disorder.

Figure 2. Propensity score-matched prevalence odds ratio for psychiatric comorbidities

139x67mm (600 x 600 DPI)

	Migraine patients (N=378)		Matched non-migraine respondents (N=1,512)		Prevalence odds ratio, 95% CI
	Count	%	Count	%	
(A) Gastrointestinal disorders					
GERD	78	20.6%	105	6.9%	3.5 (2.5, 4.8)
Heartburn	161	42.6%	257	17.0%	3.6 (2.8, 4.7)
Ulcers	43	11.4%	60	4.0%	3.1 (2.0, 4.8)
Crohn's disease	0	0.0%	3	0.2%	0.0 (0.0, 9.7)
Ulcerative colitis	8	2.1%	7	0.5%	4.7 (1.5, 15.2)
Irritable bowel Syndrome	75	19.8%	92	6.1%	3.8 (2.7, 5.4)
Chronic constipation (12m)	109	28.8%	211	14.0%	2.5 (1.9, 3.3)
Frequent diarrhea (12m)	99	26.2%	156	10.3%	3.1 (2.3, 4.1)
(B) Allergic-related disorders					
Allergies (12m)	163	43.1%	308	20.4%	3.0 (2.3, 3.8)
Atopic dermatitis	74	19.6%	165	10.9%	2.0 (1.5, 2.7)
Hay fever	167	44.2%	328	21.7%	2.9 (2.2, 3.6)
Asthma	66	17.5%	132	8.7%	2.2 (1.6, 3.1)
(C) Sleep disorders					
Insomnia	134	35.4%	170	11.2%	4.3 (3.3, 5.7)
Sleep apnea	15	4.0%	24	1.6%	2.6 (1.2, 5.1)
Sleep difficulties	48	12.7%	52	3.4%	4.1 (2.7, 6.3)
(D) Gynecological disorders					
Fibroids	49	13.0%	119	7.9%	1.8 (1.2, 2.6)
Pre-menstrual dysphoric disorder (12m)	60	19.9%	52	4.3%	5.5 (3.6, 8.4)
Pre-menstrual syndrome (12m)	97	32.1%	99	8.2%	5.3 (3.8, 7.4)
Endometriosis	36	9.5%	65	4.3%	2.4 (1.5, 3.7)
(E) Cardiovascular disorders					
High blood pressure (hypertension)	28	7.4%	105	6.9%	1.1 (0.7, 1.7)
Heart attack	3	0.8%	3	0.2%	4.0 (0.5, 30.1)
Mini-stroke/TIA	2	0.5%	4	0.3%	2.0 (0.2, 14.1)
Stroke	2	0.5%	2	0.1%	4.0 (0.3, 55.5)
(F) Others					
Rheumatoid arthritis	5	1.3%	16	1.1%	1.3 (0.4, 3.6)
Lupus	2	0.5%	5	0.3%	1.6 (0.2, 9.8)
Fibromyalgia (12m)	6	1.6%	2	0.1%	12.2 (2.2, 123.7)
Parkinson's disease	1	0.3%	3	0.2%	1.3 (0.0, 16.7)
Restless leg syndrom (12m)	22	5.8%	32	2.1%	2.9 (1.6, 5.1)
Epilepsy	4	1.1%	11	0.7%	1.5 (0.3, 5.0)
Anemia (12m)	88	23.3%	177	11.7%	2.3 (1.7, 3.1)
Thyroid condition	22	5.8%	32	2.1%	2.9 (1.6, 5.1)
Genital warts	2	0.5%	1	0.1%	8.0 (0.4, 473.0)
Genital herpes	6	1.6%	8	0.5%	3.0 (0.9, 10.0)
Breast cancer	6	1.6%	21	1.4%	1.2 (0.4, 3.0)



GERD, gastroesophageal reflux disease; TIA, transient ischemia attack.
Note: Comorbidities with prevalence between 5% to 10% among migraine patients: endometriosis, high blood pressure, restless leg syndrome, and thyroid condition. Comorbidities with more than 10% prevalence among migraine patients: irritable bowel syndrome, heartburn, GERD, ulcers, frequent diarrhea, chronic constipation, allergies, hay fever, asthma, atopic dermatitis, insomnia, sleep difficulties, pre-menstrual dysphoric disorder, pre-menstrual syndrome, fibroids, and anemia.

Figure 3. Propensity score-matched prevalence odds ratio for somatic comorbidities

86x94mm (600 x 600 DPI)

Supplementary Table 1. Propensity score-matched prevalence odds ratio for psychiatric comorbidities among patients with migraine with <15 monthly headache days vs. ≥15 monthly headache days

	Migraine patients MHDs<15 (N=271)		Matched non-migraine respondents (N=1,084)		Prevalence odds ratio, 95% CI MHDs<15	Prevalence odds ratio, 95% CI MHDs≥15	Migraine patients MHDs≥15 (N=107)		Matched non-migraine respondents (N=428)	
	Count	%	Count	%			Count	%	Count	%
ADD	9	2.4%	10	0.7%	3.7 (1.3, 10.1)	6.1 (0.7, 73.9)	3	2.8%	2	0.5%
ADHD	6	1.6%	8	0.5%	3.0 (0.9, 10.0)	12.3 (1.0, 645.5)	3	2.8%	1	0.2%
Schizophrenia	14	3.7%	24	1.6%	2.4 (1.1, 4.9)	5.0 (1.3, 21.2)	6	5.6%	5	1.2%
Bipolar disorder	10	2.6%	21	1.4%	1.9 (0.8, 4.3)	3.0 (0.7, 11.0)	5	4.7%	7	1.6%
Depression	84	22.2%	136	9.0%	2.9 (2.1, 3.9)	6.5 (3.6, 11.6)	36	33.6%	31	7.2%
Anxiety	55	14.6%	45	3.0%	5.6 (3.6, 8.6)	9.5 (4.5, 20.5)	26	24.3%	14	3.3%
Phobias	23	6.1%	12	0.8%	8.1 (3.8, 18.0)	17.2 (3.3, 167.4)	8	7.5%	2	0.5%
Social anxiety disorder	43	11.4%	39	2.6%	4.9 (3.0, 7.8)	6.7 (2.8, 16.4)	16	15.0%	11	2.6%
Panic disorder	52	13.8%	44	2.9%	5.3 (3.4, 8.3)	12.1 (5.3, 29.2)	24	22.4%	10	2.3%
GAD	32	8.5%	14	0.9%	9.9 (5.1, 20.3)	18.6 (5.8, 77.8)	16	15.0%	4	0.9%
OCD	19	5.0%	15	1.0%	5.3 (2.5, 11.3)	11.5 (2.7, 67.6)	8	7.5%	3	0.7%
PTSD	29	7.7%	11	0.7%	11.3 (5.4, 25.4)	22.0 (4.5, 207.0)	10	9.3%	2	0.5%

ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; GAD, generalized anxiety disorder; OCD, obsessive compulsive disorder; PTSD, post-traumatic stress disorder.

Supplementary Table 2. Propensity score-matched prevalence odds ratio for somatic comorbidities among patients with migraine with <15 monthly headache days vs. ≥15 monthly headache days

	Migraine patients MHDs<15 (N=271)		Matched non-migraine respondents (N=1,084)		Prevalence odds ratio, 95% CI MHDs<15	Prevalence odds ratio, 95% CI MHDs≥15	Migraine patients MHDs≥15 (N=107)		Matched non-migraine respondents (N=428)	
	Count	%	Count	%			Count	%	Count	%
Gastrointestinal disorders										
GERD	43	15.9%	74	6.8%	2.6 (1.7, 3.9)	6.2 (3.5, 11.1)	35	32.7%	31	7.2%
Heartburn	104	38.4%	180	16.6%	3.1 (2.3, 4.2)	5.1 (3.2, 8.2)	57	53.3%	78	18.2%
Ulcers	28	10.3%	45	4.2%	2.7 (1. 6, 4.5)	4.5 (2.0, 10.2)	15	14.0%	15	3.5%
Crohn's disease	0	0.0%	2	0.2%	0.0 (0.0, 21.3)	0.0 (0.0, 155.6)	0	0.0%	1	0.2%
Ulcerative colitis	4	1.5%	6	0.6%	2.7 (0.6, 11.4)	16.6 (1.6, 814.6)	4	3.7%	1	0.2%
Irritable bowel Syndrome	45	16.6%	71	6.5%	2.8 (1.9, 4.3)	7.6 (3.9, 14.6)	30	28.0%	21	4.9%
Chronic constipation (12m)	74	27.3%	141	13.0%	2.5 (1.8, 3.5)	2.5 (1.5, 4.2)	35	32.7%	69	16.1%
Frequent diarrhea (12m)	64	23.6%	118	10.9%	2.53 (1.8, 3.6)	4.9 (2.8, 8.4)	35	32.7%	39	9.1%
Allergic-related disorders										
Allergies (12m)	115	42.4%	202	18.6%	3.2 (2.4, 4.3)	2.4 (1.5, 3.9)	48	44.9%	107	25.0%
Atopic dermatitis	53	19.6%	121	11.2%	1.9 (1.3, 2.8)	2.2 (1.2, 4.0)	21	19.6%	43	10.0%
Hay fever	117	43.2%	217	20.0%	3.0 (2.3, 4.1)	2.5 (1.6, 3.9)	50	46.7%	112	26.2%
Asthma	42	15.5%	88	8.1%	2.1 (1.4, 3.1)	2.5 (1.4, 4.5)	24	22.4%	44	10.3%
Sleep disorders										
Insomnia	83	30.6%	119	11.0%	3.6 (2. 6, 5.0)	6.7 (4.0, 11.2)	51	47.7%	51	11.9%
Sleep apnea	13	4.8%	21	1.9%	2.6 (1.2, 5.4)	2.7 (0.2, 23.8)	2	1.9%	3	0.7%
Sleep difficulties	31	11.4%	37	3.4%	3.7 (2.1, 6.2)	5.2 (2.3, 11.6)	17	15.9%	15	3.5%
Gynecological disorders										

Fibroids	34	12.5%	91	8.4%	1.6 (1.0, 2.4)	1.8 (1.2, 2.6)	15	14.0%	28	6.5%
Pre-menstrual dysphoric disorder (12m)	38	14.0%	40	3.7%	4.4 (2.6, 7.2)	5.5 (3.6, 8.4)	22	20.6%	12	2.8%
Pre-menstrual syndrome (12m)	64	23.6%	64	5.9%	5.2 (3.5, 7.8)	5.3 (3.8, 7.4)	33	30.8%	34	7.9%
Endometriosis	22	8.1%	47	4.3%	2.0 (1.1, 3.4)	2.4 (1.5, 3.7)	14	13.1%	18	4.2%
Cardiovascular disorders										
High blood pressure (hypertension)	24	8.9%	76	7.0%	1.3 (0.8, 2.1)	0.5 (0.1, 1.6)	4	3.7%	29	6.8%
Heart attack	3	1.1%	3	0.3%	4.0 (0.5, 30.3)	NA	0	0.0%	0	0.0%
Mini-stroke/TIA	1	0.4%	4	0.4%	1.0 (0.02, 10.2)	Inf (0.1, Inf)	1	0.9%	0	0.0%
Stroke	2	0.7%	2	0.2%	4.0 (0.3, 55.6)	NA	0	0.0%	0	0.0%
Others										
Rheumatoid arthritis	4	1.5%	13	1.2%	1.2 (0.3, 4.0)	1.3 (0.03, 16.8)	1	0.9%	3	0.7%
Lupus	2	0.7%	2	0.2%	4.0 (0.3, 10.2)	0.0 (0.0, 9.7)	0	0.0%	3	0.7%
Fibromyalgia (12m)	3	1.1%	2	0.2%	6.1 (0.7, 72.6)	Inf (1.7, Inf)	3	2.8%	0	0.0%
Parkinson's disease	1	0.4%	3	0.3%	1.3 (0.03, 16.7)	NA	0	0.0%	0	0.0%
Restless leg syndrome (12m)	14	5.2%	25	2.3%	2.3 (1.1, 4.7)	4.9 (1.5, 16.1)	8	7.5%	7	1.6%
Epilepsy	2	0.7%	6	0.6%	1.3 (0.1, 7.5)	1.6 (0.2, 10.0)	2	1.9%	5	1.2%
Anemia (12m)	58	21.4%	121	11.2%	2.2 (1.5, 3.1)	2.6 (1.5, 4.4)	30	28.0%	56	13.1%
Thyroid condition	14	5.2%	23	2.1%	2.5 (1.2, 5.2)	3.8 (1.2, 11.3)	8	7.5%	9	2.1%
Genital warts	2	0.7%	1	0.1%	8.1 (0.4, 474.0)	NA	0	0.0%	0	0.0%
Genital herpes	5	1.8%	6	0.6%	3.4 (0.8, 13.4)	2.0 (0.03, 38.8)	1	0.9%	2	0.5%
Breast cancer	3	1.1%	18	1.7%	0.7 (0.1, 2.3)	6.1 (0.7, 73.9)	3	2.8%	2	0.5%

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1 & 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			5-7
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
8-9		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	7
		(*e*) Describe any sensitivity analyses	NA
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	8 (Figure 1)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-9 (Table 1)
		(b) Indicate number of participants with missing data for each variable of interest	NA
Outcome data	15*	Report numbers of outcome events or summary measures	8-12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-12
		(*b*) Report category boundaries when continuous variables were categorized	8-12
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12
Discussion			13-17
Key results	18	Summarise key results with reference to study objectives	13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16-17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	16-17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Comorbidities in Patients with Migraine in Japan: A Cross-sectional Study Using Data from National Health and Wellness Survey

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Manuscript ID	bmjopen-2022-065787.R1
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Title: Comorbidities in Patients with Migraine in Japan: A Cross-sectional Study Using Data from National Health and Wellness Survey

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ABSTRACT (250 WORDS)

Objectives – This study aims to examine the association between migraine and various psychiatric and somatic comorbidities in Japan.

Design – Cross-sectional study using existing data of the 2017 Japan National Health and Wellness Survey (NHWS).

Setting – Nationally representative sample of persons (in terms of age and gender) living in the general community aged 18 years or older in Japan.

Participants – Out of a sample of 30,001 NHWS respondents, 378 respondents were identified as migraine patients and 25,209 were identified as non-migraine patients. After propensity score (PS)-matching (1:4), 1,512 matched non-migraine respondents were identified.

Primary and secondary outcome measures – Prevalence and PS-matched prevalence odds-ratio (POR) were assessed for each psychiatric and somatic comorbidity among migraine patients and matched non-migraine respondents (including migraine patients with less than 15 monthly headache days [MHDs] and migraine patients with more than 15 MHDs).

Results – Migraine patients were predominately female and had significantly higher prevalence than matched non-migraine respondents to have psychiatric and somatic comorbidities. Psychiatric comorbidities with >5% prevalence among migraine patients included depression, posttraumatic stress disorder, and anxiety disorders, while gastrointestinal disorders were the most prevalent somatic comorbidity category. Other somatic comorbidities included allergies, insomnia, pre-menstrual syndrome, and anemia. Migraine patients with more than 15 MHDs tended to have higher point estimates for POR.

Conclusion – Psychiatric and somatic conditions were more prevalent in migraine patients than matched non-migraine respondents, some being novel associations not previously reported in

Japan. This study provided insights on comorbidities which could complicate care, clinical practice, and outcomes among migraine patients.

Keywords - Comorbidities; Migraine; Prevalence Odds-ratio; Health Survey

Trial registration – Not applicable

ARTICLE SUMMARY

Strengths and limitations

- An age-and-gender-stratified sampling frame was imposed during the recruitment to ensure and reflection of the general adult population of Japan in terms of age and gender.
- The study identified potential psychiatric and somatic comorbidities from self-reported medical history of migraine patients as well as several covariates including sociodemographic factors, general health characteristics and migraine-specific covariates
- This study uses an online survey and thus respondents without internet access were not included in the study
- This study assessed respondents' self-declaration of migraine manifestation and comorbidities which may bias the prevalence odds-ratio and the causal relationship between migraine and comorbidities cannot be concluded

INTRODUCTION

Migraine is a common debilitating neurological disorder that is highly prevalent globally.[1] The global prevalence of migraine was approximately 14.0%, with annual prevalence estimates increasing over the years.[2] In Japan, the estimated prevalence of migraine among the general population was 6% in 2004,[3] and more recently, 9% among working, socially active individuals in the Tokyo metropolitan area.[4]

Previous reports demonstrated that approximately 90% of chronic migraine patients have at least one comorbidity.[5] A nationwide population-based study in the United States reported an association between migraine comorbidities and the intensity of headache pain and frequency.[6] It is important to take into consideration the comorbidities of migraine from diagnosis through to treatment.[7] The previously reported comorbidities of migraine include various psychiatric[8–11] and somatic conditions such as cardiovascular disorders,[12,13,6] gastrointestinal disorders,[6,14–16] allergy-related disorders,[6,17,18] sleep disorders,[6,19,20] and gynecological disorders.[21] A meta-analysis showed that the most frequently addressed comorbidities among migraine patients in clinical and population studies were depressive disorders, hypertension, and anxiety disorders.[22]

Studies have shown a strong bidirectional association between migraine and psychiatric conditions such as depression, anxiety, suicide risks,[9,10] and may have shared neuropathic mechanisms.[11,23] Similarly, somatic comorbidities such as those of cerebrovascular and metaboloendocrine (e.g., stroke, insulin sensitivity, hypothyroidism, endometriosis) also reportedly have bidirectional association with migraine.[23]

In Japan, there is an evidence gap on the comorbidities of migraine. Comorbidities such as hypertension, heart diseases, cerebrovascular diseases, depression, bipolar disorder, anxiety disorder, epilepsy, asthma, allergic diseases, and autoimmune diseases had been recognized as

common migraine comorbidities in the Clinical Practice Guideline for Chronic Headache.[24]. Although there were a few studies investigating the comorbidities of migraine in Japan, previous studies primarily focused on one disease or one category of diseases.[25,26] However, to our knowledge, no studies have been published that assessed a range of comorbidities associated with migraine referencing non-migraine individuals in Japan.

Therefore, the objectives of this study were to identify a list of potential psychiatric and somatic comorbidities experienced by migraine patient as well as examine the association between migraine and these psychiatric and somatic comorbidities in Japan by assessing the prevalence odds ratio (POR) between migraine and these comorbidities, with reference to non-migraine individuals. The initial findings from this study on the potential comorbidities of migraine may provide insights to learning the etiology of migraine and help physicians and patients with effective migraine management and treatment.

METHODS

This study utilized existing data collected from a cross-sectional online survey, the 2017 Japan National Health and Wellness Survey (NHWS). Individuals aged 18 years or older were recruited to the NHWS through an existing, general-purpose (i.e., not healthcare-specific) web-based consumer panel. All panelists explicitly agreed to join the panel and receive periodic invitations to participate in online surveys. An age-and-gender-stratified sampling frame, based on Japan governmental census data, was imposed during the recruitment from the panelists. This was to ensure representativeness of panelists who completed the NHWS to reflect the general adult population of Japan in terms of age and gender.

The NHWS was granted exemption status upon review by the Pearl Pathways Institutional Review Board (IN, US). All NHWS respondents provided informed consent prior to participation. This analysis was granted exemption by the Public Health Research Foundation Ethical Review Committee (Tokyo, Japan).

Study Population

Migraine patients in this study were defined by ICHD-3 (International Classification of Headache Disorders, 3rd Edition)-like criteria which was detailed in a previous publication using the same data,[27] among respondents who self-reported migraine in the past 12 months and self-reported having at least 4 monthly headache days (MHDs) (Figure 1). The ICHD-3 like criteria was based on the diagnostic criteria from ICHD-3 but modified for the variables available in the existing NHWS data.[27] The ICHD-3 like inclusion criteria also defines migraine respondents without aura as having at least five migraines in the past 6 months or self-reported physician diagnosis of migraine, migraine lasting for at least four hours but not more than 72 hours if untreated, experienced at least two migraine pain symptoms (pain on one side of head; pulsating, throbbing or pounding pain; moderate-to-severe pain; or pain made worse by routine), and experienced at least in one migraine-related symptom (nausea and/or vomiting; light hypersensitivity; or sound hypersensitivity). Migraine with aura was defined as respondents having at least two migraines in the past 6 months or self-reported physician diagnosis of migraine, and experience migraine-related symptom (see spots, flashing lights; or heat waves) before or during the migraine. Respondents having migraine without aura or migraine with aura were also included as migraine patients in this study. Respondents who did not self-report migraine were classified as non-migraine respondents. There were no exclusion criteria.

Patient and Public Involvement

Respondents and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Covariate and Outcome Assessment

Sociodemographic and general health characteristics variables measured in this study included age, gender, marital status, level of education, household income, region, insurance type, employment status, Charlson comorbidity index (CCI),[28] body mass index (BMI), smoking status, alcohol use, and exercise behavior. Migraine-specific covariates were assessed using the Headache Impact Test-6 (HIT-6). The HIT-6 measures the impact of headaches on the respondents' ability to function in social situations including home and work. Higher HIT-6 depicts greater functional impairment.[29]

A list of potential psychiatric and somatic comorbidities was created from the self-reported medical history of the NHWS respondents (refer to full list in Figure 2 and Figure 3). The list includes diseases for which the associations with migraine have been reported; diseases for which the association may be explained from the pathophysiology; and other conditions of special interest related to treatment choices. All respondents answered the questions "Have you ever experienced …" or "Have you experienced … in the past 12 months" depending on the condition in NHWS.

Statistical Analysis

Sociodemographic and health characteristics were summarized using counts and percentages for categorical variables and means and standard deviations (SDs) for continuous variables for migraine patients and non-migraine respondents.

Propensity score (PS) matching with 1:4 ratio of migraine patients to non-migraine respondents, using a greedy matching algorithm was conducted to create a matched comparison group of non-migraine respondents. Sociodemographic (age, gender, marital status, education, household income, region, insurance, and employment status) and general health characteristics (BMI, smoking status, alcohol use and exercise behavior) were used in the matching. Balance of matching were assessed using standardized mean differences (SMDs) between migraine patients and matched non-migraine respondents. Standardized mean differences greater than 0.1 were considered unbalanced after matching.

Prevalence of the selected psychiatric and somatic comorbidities among migraine patients and matched non-migraine respondents were calculated. Then, PS-matched prevalence odds-ratio (POR) and its 95% confidence intervals (CI) for each comorbidity were calculated to evaluate the potential associations of these conditions with migraine.

A post-hoc subgroup analysis was conducted among migraine patients with less than 15 MHDs (episodic migraine) and their respective matched non-migraine respondents, as well as among migraine patients with at least 15 MHDs (chronic migraine) and their respective matched non-migraine respondents.

All statistical analyses were performed using IBM SPSS version 25 and R3.5.1. No correction for multiple testing was conducted as the study was out of exploratory nature and no formal hypothesis testing was planned. P-values were provided as an indication of the difference between migraine patients and non-migraine respondents.

RESULTS

Participant demographics and health characteristics

A total of 30,001 respondents aged 18 years and older provided informed consent and participated in the 2017 Japan NHWS. Among these respondents, 378 respondents were identified as migraine patients and 25,209 respondents were identified as non-migraine respondents (Figure 1).

After PS matching, a total of 1,512 non-migraine respondents were identified and matching was found to be balanced between matched non-migraine respondents and migraine patients, with all SMDs less than 0.1 (Table 1).

Sociodemographic and general health characteristics of migraine patients and matched non-migraine respondents are described in Table 1.

Migraine patients (N=378) had an average age of 41.6 and were predominantly females (79.9%). The majority (83.6%) of migraine patients in this study had severe impact (HIT-6 score: 60-78). The CCI, which was not part of the PS matching, was higher in migraine patients than matched non-migraine respondents (mean: 0.24 vs. 0.08).

Table 1. Sociodemographic and general health characteristics among migraine patients and matched non-migraine respondents

	Migraine patients (N=378)		Matched non-migraine respondents (N=1,512)		SMD
	%	Count	%	Count	
Age [Mean (SD)]	41.6 (12.7)		41.2 (15.2)		0.026

Gender	*Male*	20.1%	76	20.0%	303	0.002
	Female	79.9%	302	80.0%	1,209	
Marital status	*Married or living with partner*	48.9%	185	49.0%	741	0.001
	Divorced/ Separated/ Widowed/ Decline to answer	51.1%	193	51.0%	771	
Level of education	*Completed university education*	41.3%	156	43.2%	653	0.042
	Not completed	46.6%	176	44.6%	674	
	Decline to answer	12.2%	46	12.2%	185	
Household income	*<¥3,000,000*	19.6%	74	18.9%	286	0.029
	¥3,000,000 to <¥5,000,000	27.0%	102	27.6%	417	
	¥5,000,000 to <¥8,000,000	24.6%	93	23.9%	361	
	¥8,000,000 or more	14.8%	56	15.4%	233	
	Decline to answer	14.0%	53	14.2%	215	
Region	*Hokkaido*	3.2%	12	2.9%	44	0.063
	Tohoku	6.6%	25	7.1%	107	
	Kanto	39.4%	149	40.7%	615	
	Chubu	14.6%	55	14.6%	221	
	Kansai/Kinki	18.8%	71	16.9%	255	
	Chugoku	4.2%	16	4.4%	67	
	Shikoku	3.2%	12	3.7%	56	
	Kyushu/Okinawa	10.1%	38	9.7%	147	
Insurance type	*National health insurance*	52.1%	197	50.8%	768	0.034
	Social insurance	44.7%	169	46.1%	697	
	Other (Late-stage elderly insurance / Other / None of the above)	3.2%	12	3.1%	47	
Employment status	*Currently not employed*	39.9%	151	40.6%	614	0.013
	Currently employed	60.1%	227	59.4%	898	
BMI	*Underweight (BMI<18.5)*	18.3%	69	18.5%	280	0.045
	Normal weight (18.5≤BMI<25)	62.4%	236	59.7%	903	
	Pre-obese (25≤BMI<30)	14.8%	56	13.6%	205	
	Obese (BMI≥30)	4.5%	17	4.0%	61	
	Decline to answer	4.2%	16	4.2%	63	
Smoking status	*Never smoker*	55.8%	211	56.7%	858	0.045
	Former smoker	20.9%	79	19.1%	289	
	Current smoker	23.3%	88	24.1%	365	
Alcohol use	*Abstain*	40.5%	153	40.8%	617	0.007
	Currently consume alcohol	59.5%	225	59.2%	895	
Vigorous exercise in past 30 days	*No*	58.2%	220	60.0%	907	0.036
	Yes	41.8%	158	40.0%	605	
CCI* [Mean (SD)]		0.24 (0.86)		0.08 (0.33)		0.242
HIT-6 impact grades*	*Little-to-no impact (HIT-6 score: 36-49)*	1.1%	4	-	-	-
	Moderate impact (HIT-6 score: 50-55)	6.6%	25	-	-	
	Substantial impact (HIT-6 score: 56-59)	8.7%	33	-	-	
	Severe impact (HIT-6 score: 60-78)	83.6%	316	-	-	

BMI, body mass index; CCI, Charlson comorbidity index; SMD, standardized mean difference.

* CCI and HIT-6 impact grades are not included in the propensity score matching.

Psychiatric comorbidities in migraine patients vs. matched non-migraine respondents (Figure 2)

The psychiatric comorbidities with prevalence higher than 5.0% in migraine patients were depression (22.2%), post-traumatic stress disorder (PTSD) (7.7%), anxiety disorders (6.1% for phobias to 14.6% for anxiety), and obsessive-compulsive disorder (OCD) (5.0%).

Among the comorbidities with relatively high prevalence (5.0% or higher) in migraine patients, migraine patients had a significantly higher odds than matched non-migraine respondents for PTSD (PS-matched POR [95% CI]: 11.3 [5.4, 25.4]), various anxiety disorders (generalized anxiety disorder (GAD): 9.9 [5.1, 20.3] to social anxiety disorder (4.9 [3.0, 7.8]), OCD (5.3 [2.5, 11.3]), and depression (2.9 [2.1, 3.9]).

Somatic comorbidities in migraine patients vs. matched non-migraine respondents (Figure 3)

Gastrointestinal comorbidities

Most of the gastrointestinal comorbidities assessed in this study showed the prevalence higher than 5.0% in migraine patients: heartburn (42.6%), chronic constipation (28.8%), frequent diarrhea (26.2%), gastroesophageal reflux disease (GERD) (20.6%), irritable bowel syndrome (19.8%), and ulcers (11.4%).

Among the gastrointestinal comorbidities with relatively high prevalence, compared with matched non-migraine respondents, migraine patients had a significantly higher odds for irritable bowel syndrome (PS-matched POR [95% CI]: 3.8 [2.7, 5.4]), heartburn (3.6 [2.8, 4.7]),

GERD (3.5 [2.5, 4.8]), ulcers (3.1 [2.0, 4.8]), frequent diarrhea (3.1 [2.3, 4.1]) and chronic constipation (2.5 [1.9, 3.3]).

Allergy-related comorbidities

All the allergy-related comorbidities assessed in this study have a prevalence higher than 5.0% in migraine patients: allergies (43.1%), hay fever (44.2%), atopic dermatitis (19.6%), and asthma (17.5%).

Compared with matched non-migraine respondents, migraine patients had a significantly higher odds for allergies (PS-matched POR [95% CI]: 3.0 [2.3, 3.8]), hay fever (2.9 [2.2, 3.6]), asthma (2.2 [1.6, 3.1]), and atopic dermatitis (2.0 [1.5, 2.7]).

Sleep comorbidities

The following sleep disorders presented in migraine patients with a prevalence higher than 5.0% included insomnia (35.4%) and sleep difficulties (12.7%). Migraine patients had a significantly higher odds for insomnia (PS-matched POR [95% CI]: 4.3 [3.3, 5.7]) and sleep difficulties (4.1 [2.7, 6.3]), compared to matched non-migraine respondents.

Gynecological comorbidities

The gynecological disorders assessed in this study with a prevalence higher than 5.0% among migraine patients were pre-menstrual syndrome (32.1%), pre-menstrual dysphoric disorder (19.9%), fibroid (13.0%), and endometriosis (9.5%). Compared with matched non-migraine respondents, migraine patients had a significantly higher odds for pre-menstrual dysphoric disorder (PS-matched POR [95% CI]: 5.5 [3.6, 8.4]), pre-menstrual syndrome (5.3 [3.8, 7.4]), endometriosis (2.4 [1.5, 3.7]), and fibroids (1.8 [1.2, 2.6]).

Cardiovascular comorbidities

The cardiovascular disorders assessed in this study showed a lower than 5.0% prevalence among migraine patients except for high blood pressure (hypertension) (7.4%). Compared with

matched non-migraine respondents, the odds of having hypertension, heart attack, stroke, or mini-stroke/transient ischemic attack (TIA) were not significantly different in migraine patients.

Other comorbidities

Most other disorders assessed in this study showed the prevalence lower than 5.0% among migraine patients except for anemia (23.3%), thyroid condition (5.8%), and restless leg syndrome (5.8%). Compared with matched non-migraine respondents, migraine patients had a significantly higher odds for restless leg syndrome (PS-matched POR [95% CI]: 2.9 [1. 6, 5.1]), thyroid condition (2.9 [1. 6, 5.1]) and anemia (2.3 [1.7, 3.1]). Compared with matched non-migraine respondents, migraine patients had a significantly higher odds for fibromyalgia (prevalence among migraine patients: 1.6%; POR [95% CI]: 12.2 [2.2, 123.7]). For all other disorders assessed in this study (rheumatoid arthritis, lupus, Parkinson's disease, epilepsy, genital herpes, genital warts, and breast cancer), the odds among migraine patients were not different from matched non-migraine respondents.

Post-hoc subgroup analysis by MHDs

Majority of the baseline characteristics remained balanced at the subgroup level (results not shown). Post-hoc analysis demonstrated consistent results in both subgroups of the migraine patients MHDs<15 and MHDs≥15 with the overall analysis. The most prevalent psychiatric and somatic comorbidities were similar in both migraine patients with MHDs<15 and migraine patients with MHDs≥15 (Supplementary Tables 1 and 2).

Migraine patients with MHDs≥15 tended to have higher point estimates for POR although formal statistical testing was not performed to assess the interaction for the association between comorbidities and migraine by MHD.

DISCUSSION

This study showed that patients with migraine have a significantly higher prevalence for various psychiatric and somatic comorbidities, compared with matched non-migraine respondents. Our study is the first to report the broad range of comorbidities associated with migraine as a population-based study in Japan.

Potential pathological mechanisms for comorbidities were proposed – for example, uni- or bi-directional causality or shared environmental or genetic risk factors.[23] Although various explanations for the association between migraines and psychiatric conditions have been proposed, exact causal relationships and mechanisms for the associations are yet to be elucidated in this study.

Psychiatric comorbidities

Psychiatric disorders that our study found associated with migraine such as PTSD, anxiety disorders, OCD and depression have been described in previous literature.[8–11] Various neurotransmitter systems and brain regions implicated in psychiatric disorders have been postulated to overlap with that in migraine.[7,11,23] Neurotransmitters such as serotonin and other monoamines, and ovarian hormonal influences, might lead to serotonergic processing dysfunction and hypothalamic-pituitary-adrenal (HPA) axis dysregulation which underlie most psychiatric disorders.[23] For instance, migraine patients exhibit ictal or interictal alterations in neurotransmitters blood levels which share common pathophysiology to depression, stress, and bipolar disorder.[7,23] Genetic factors could also potentially influence the association between migraine and psychiatric disorders. A genome-wide association study with over 1

million individuals found significantly overlapped genetic risks of migraine with psychiatric conditions such as attention-deficit/hyperactivity disorder (ADHD) or depression.[30] Emerging functional neuroimaging hint at that possibility of long-term chronic migraine could alter brain activity and increase disease burden,[7,11] implying a need to understand the shared pathophysiology of psychiatric comorbidities and migraine to facilitate better management of both conditions among patients.

Somatic comorbidities

Gastrointestinal comorbidities

We found that bowel movement dysregulations such as constipation, diarrhea, and irritable bowel syndrome, are more prevalent in migraine patients than matched non-migraine respondents, which was consistent with previous literature.[14–16] Autonomic nervous system dysfunction and other mechanisms such as dysregulation of neuroendocrine, immunological factors, the brain-gut axis, or intestinal microbiota[15] were thought as potential mechanisms to alter visceral sensitivity and common pathology with migraine.

Both GERD[16] and gastric ulcer[6,16] were shown to have higher prevalence in migraine patients than matched non-migraine respondents in this study. Association of migraine with *Helicobacter pylori* infection has been shown in a meta-analysis of observational studies,[31] and this may explain the high prevalence of GERD and gastric ulcer in migraine patients[15] Other possible explanations for the association between migraine and gastrointestinal disorders includes analgesics use in migraine patients.[15,18]

Allergy-related comorbidities

In this study, migraine patients were more likely to have allergy-related comorbidities, which are consistent with previous research.[6,17,18] The association between migraine and allergy-

related comorbidities could in part be due to common pathophysiology of inflammatory (including neuroinflammation), immune, and genetic factors.[17,23]

Sleep comorbidities

Migraine patients in this study had a significantly increased prevalence for sleep disorders including insomnia and sleep difficulties, compared to non-migraine respondents, consistent with previous studies.[6,19,20] A large population-based study reported that those with comorbid migraine and poor sleep showed significantly poorer anxiety and depression scores.[20] The association between migraine and sleep disorders is thought to be bidirectional: headache was shown to be a risk factor for insomnia, while insomnia (and oversleeping) had been reportedly to be a contributing factor of migraine attacks.[11,32] It was suggested that aminergic neurotransmitter systems such as those involved in the sleep-wake cycle could underlie the association between migraine and sleep disorders.[11,23,32]

Gynecological comorbidities

Headache has been known to be a common symptom for perimenstrual syndrome.[33] Furthermore, the association between endometriosis and migraine was previously reported,[21,23] wherein the occurrence of endometriosis was more frequent among women with migraines than women without.[23] The findings from the present study were consistent with the previous research. The association between migraines and gynecological comorbidities could be due to hormonal changes in women throughout the menstrual cycle or during menopause which may cause migraine through estrogen-mediated pathways including the association of estrogen receptor markers from genetic studies.[34]

Cardiovascular comorbidities

Previous studies pointed out the association between migraine and cardiovascular conditions such as hypertension,[6] myocardial infarction[6,13] and stroke,[6,12,13] and the association

specifically on migraine with aura[12,13] or other risk factors such as age, smoking habit, and use of oral contraceptives.[12] However, no association was observed between migraine and cardiovascular conditions such as hypertension, probably due to the younger age of migraine patients in this study or small numbers of high-risk migraine patients for cardiovascular conditions.

Other comorbidities

As found in our study, anemia,[35] and thyroid dysfunction[36] have been described as comorbidities of migraine. Similarly, restless leg syndrome[25] has been shown for the association, although the association may be controversial.[37]

The observation on the relationship between migraine and fibromyalgia in this study is consistent with previous studies.[38] Fibromyalgia may share a pathological pathway with migraine through chronic hypothalamic neuroendocrine dysfunction, resulting in abnormal central nervous system sensory processing.[39]

Clinical Implications

Although some of the associations are not solidly established with potential pathological explanation, the findings from this study appear to have clinical importance. Various comorbidities are at high prevalence among migraine patients. Migraine patients may experience impairment for daily life and loss of productivity not only because of the migraine but also its comorbidities. In the treatment of migraine, comorbidities may influence therapeutic choices in two ways. First, by taking comorbidities into consideration, medication regimens could be selected to treat for both migraine and comorbidities simultaneously. Second, therapeutic options for migraine may be limited if there are comorbidities as contraindications to migraine medications.[40] Therefore, accounting for comorbidities which

could complicate care in clinical practice is warranted when considering appropriate therapeutic options for migraine management.[24,40] Additionally, with the growing migraine prevalence,[2] elucidating the associated comorbidities may provide insights to the shared physiopathology with migraine which could facilitate effective management and treatment of migraine.[7]

Limitations

There are a few limitations to be mentioned for this study. NHWS is cross-sectional and causal relationship between migraine and comorbidities cannot be concluded, i.e., if the comorbidities were induced by migraine or treatment for migraine or vice versa. In addition, respondents self-reported their migraine symptoms as well as comorbidities, which may lead to potential recall bias. Although ICHD-3 like criteria were created for this study using available self-reported data as objective classification criteria and to minimize misclassification, discrepancies between the criteria used in this study and the formal ICHD-3 criteria still exist. As such, the interpretation of the findings in this study would only be valid in comparison with the groups defined within this study. Additionally, NHWS is an online survey and thus respondents without access to internet or internet-related technology (such as those with more severe comorbidities or older respondents) were not included in the study and may not be well-represented in this study. Lastly, patient demographics such as gender and lifestyle could potentially influence the association of migraine with psychiatric and/or somatic comorbidities which was not explored and warrants further investigation.

CONCLUSION

Our study found that migraine patients are more likely to have psychiatric and somatic comorbidities compared with matched non-migraine respondents, some of which are novel ones previously unreported (e.g., OCD, gastrointestinal comorbidities, sleep comorbidities, gynecological comorbidities) in Japan. This study showed that migraine patients in Japan face an additional comorbid burden and provided insights to types of comorbidities that patients with migraine may suffer. As such, accounting for comorbidities, which could usually complicate care, when treating migraine would help in good clinical practice and improve outcomes among migraine patients.

Ethics approval and consent to participate

The 2017 Japan NHWS survey was approved with exemption status upon review by Pearl Institutional Review Board (Indianapolis, IN, IRB Study Number: 17-KANT-150). All NHWS respondents provided informed online consent prior to participating. Study participants or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research. This database study was also granted exemption by the Public Health Research Foundation (https://www.phrf.jp/), Japan.

Patient consent form: Not required

Consent for publication

Not applicable.

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Competing interests

SK and TT received consultation fee for this study. YC is an employee at Cerner Enviza, Singapore. Cerner Enviza received funding from Amgen K.K. for conduction of the analysis and manuscript development. MH and KI are employees at Amgen K.K., and KA is a former employee at Amgen K.K. and is currently an employee of IQVIA Solutions Japan, K.K. MH holds, and KA held stocks of Amgen Inc.

Author contributions

SK, YC, KI, MH, KA, and TT conceptualized and designed the study. YC analyzed the data. SK, YC, KI, MH, KA, and TT interpreted the results and contributed to the original draft of the manuscript. All authors read and approve the final manuscript.

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Data sharing statement

Study data to support our findings are available from Cerner Enviza, but availability of the data is restricted and was used under license for this study and are not publicly available. Data are,

however, available from the authors upon reasonable request and with the permission of Cerner Enviza.

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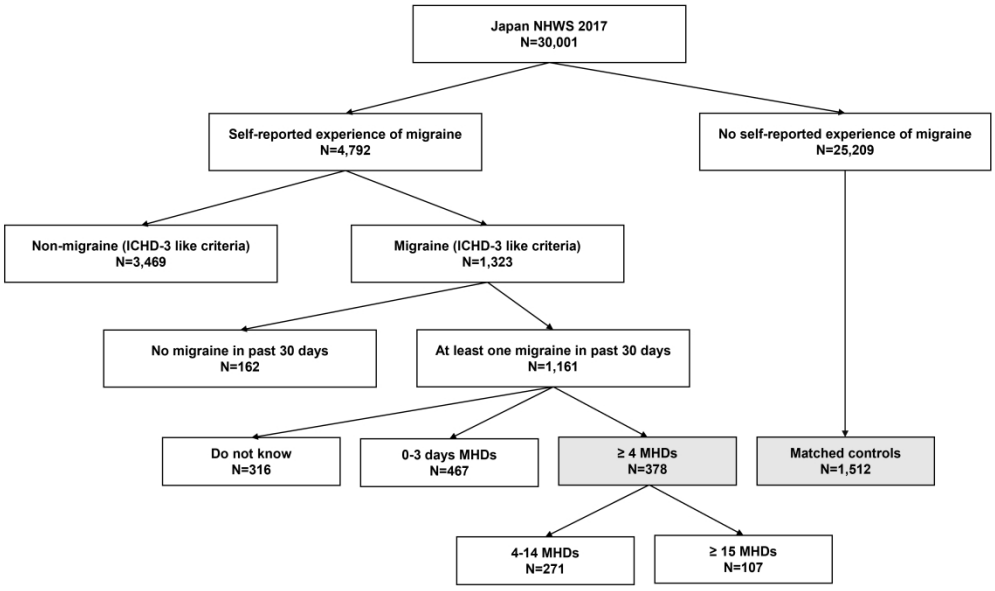
Figure legends

Figure 1. Respondent flow chart

Figure 2. Propensity score-matched prevalence odds ratio for psychiatric comorbidities

Figure 3. Propensity score-matched prevalence odds ratio for somatic comorbidities



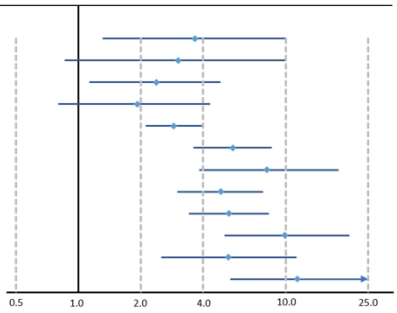
ICHD-3, International Classification of Headache Disorder, 3rd Edition; MHDs, Monthly Headache Days.

Note: Shaded squares indicate the study populations – migraine patients (≥ 4MHDs; N=378) and matched non-migraine respondents (Matched controls, N=1,512).

Figure 1. Respondent flow chart

130x86mm (800 x 800 DPI)

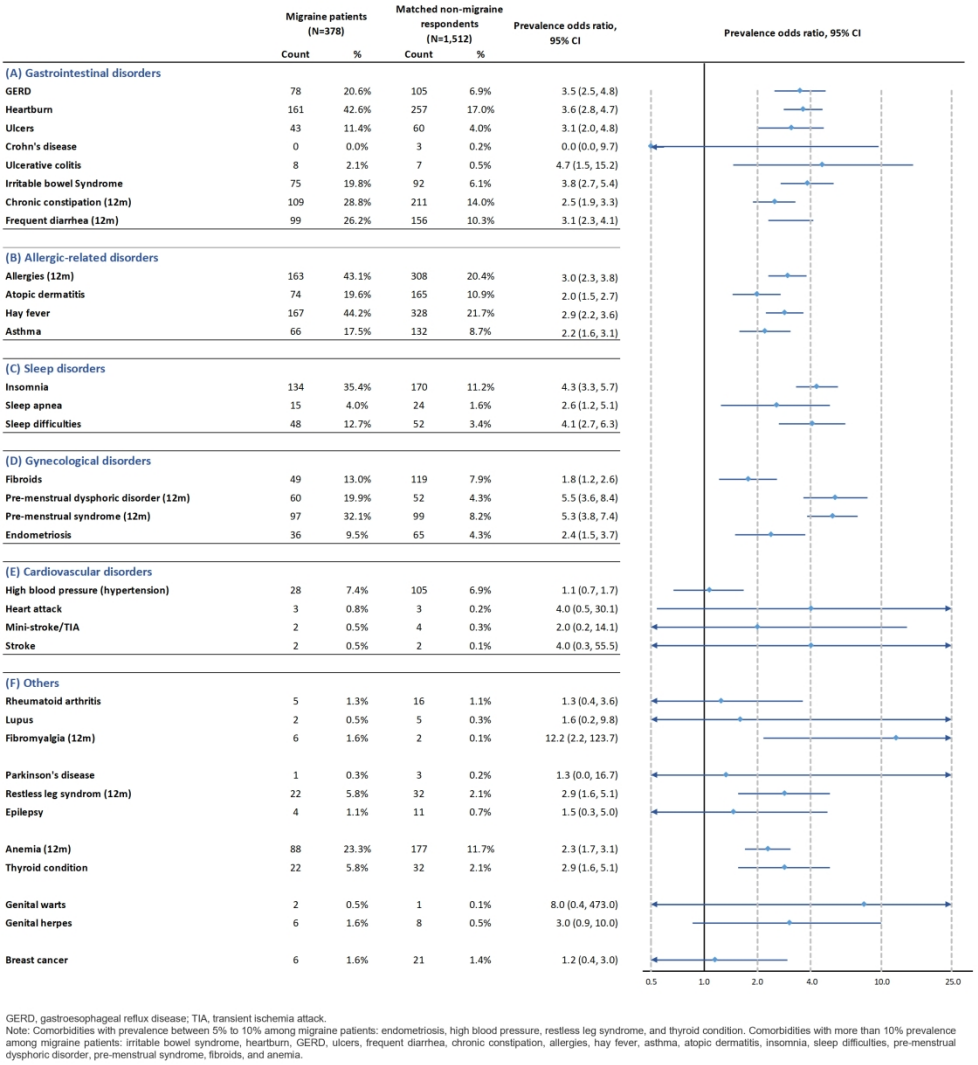
	Migraine patients (N=378)		Matched non-migraine respondents (N=1,512)		Prevalence odds ratio, 95% CI
	Count	%	Count	%	
Psychiatric comorbidities					
ADD	9	2.4%	10	0.7%	3.7 (1.3, 10.1)
ADHD	6	1.6%	8	0.5%	3.0 (0.9, 10.0)
Schizophrenia	14	3.7%	24	1.6%	2.4 (1.1, 4.9)
Bipolar disorder	10	2.6%	21	1.4%	1.9 (0.8, 4.3)
Depression	84	22.2%	136	9.0%	2.9 (2.1, 3.9)
Anxiety	55	14.6%	45	3.0%	5.6 (3.6, 8.6)
Phobias	23	6.1%	12	0.8%	8.1 (3.8, 18.0)
Social anxiety disorder	43	11.4%	39	2.6%	4.9 (3.0, 7.8)
Panic disorder	52	13.8%	44	2.9%	5.3 (3.4, 8.3)
GAD	32	8.5%	14	0.9%	9.9 (5.1, 20.3)
OCD	19	5.0%	15	1.0%	5.3 (2.5, 11.3)
PTSD	29	7.7%	11	0.7%	11.3 (5.4, 25.4)



ADD, attention-deficit disorder; ADHD, attention-deficit/hyperactivity disorder; GAD, generalized anxiety disorder; OCD, obsessive-compulsive disorder; PTSD, posttraumatic stress disorder.
Note: Comorbidities with prevalence between 5% to 10% among migraine patients: phobias, GAD, OCD, and PTSD. Comorbidities with more than 10% prevalence among migraine patients: depression, anxiety, social anxiety disorder, and panic disorder.

Figure 2. Propensity score-matched prevalence odds ratio for psychiatric comorbidities

139x67mm (800 x 800 DPI)



GERD, gastroesophageal reflux disease; TIA, transient ischemia attack.
Note: Comorbidities with prevalence between 5% to 10% among migraine patients: endometriosis, high blood pressure, restless leg syndrome, and thyroid condition. Comorbidities with more than 10% prevalence among migraine patients: irritable bowel syndrome, heartburn, GERD, ulcers, frequent diarrhea, chronic constipation, allergies, hay fever, asthma, atopic dermatitis, insomnia, sleep difficulties, pre-menstrual dysphoric disorder, pre-menstrual syndrome, fibroids, and anemia.

Figure 3. Propensity score-matched prevalence odds ratio for somatic comorbidities

86x94mm (800 x 800 DPI)

Supplementary Table 1. Propensity score-matched prevalence odds ratio for psychiatric comorbidities among patients with migraine with <15 monthly headache days vs. ≥15 monthly headache days

	Migraine patients MHDs<15 (N=271)		Matched non-migraine respondents (N=1,084)		Prevalence odds ratio, 95% CI MHDs<15	Prevalence odds ratio, 95% CI MHDs≥15	Migraine patients MHDs≥15 (N=107)		Matched non-migraine respondents (N=428)	
	Count	%	Count	%			Count	%	Count	%
ADD	9	2.4%	10	0.7%	3.7 (1.3, 10.1)	6.1 (0.7, 73.9)	3	2.8%	2	0.5%
ADHD	6	1.6%	8	0.5%	3.0 (0.9, 10.0)	12.3 (1.0, 645.5)	3	2.8%	1	0.2%
Schizophrenia	14	3.7%	24	1.6%	2.4 (1.1, 4.9)	5.0 (1.3, 21.2)	6	5.6%	5	1.2%
Bipolar disorder	10	2.6%	21	1.4%	1.9 (0.8, 4.3)	3.0 (0.7, 11.0)	5	4.7%	7	1.6%
Depression	84	22.2%	136	9.0%	2.9 (2.1, 3.9)	6.5 (3.6, 11.6)	36	33.6%	31	7.2%
Anxiety	55	14.6%	45	3.0%	5.6 (3.6, 8.6)	9.5 (4.5, 20.5)	26	24.3%	14	3.3%
Phobias	23	6.1%	12	0.8%	8.1 (3.8, 18.0)	17.2 (3.3, 167.4)	8	7.5%	2	0.5%
Social anxiety disorder	43	11.4%	39	2.6%	4.9 (3.0, 7.8)	6.7 (2.8, 16.4)	16	15.0%	11	2.6%
Panic disorder	52	13.8%	44	2.9%	5.3 (3.4, 8.3)	12.1 (5.3, 29.2)	24	22.4%	10	2.3%
GAD	32	8.5%	14	0.9%	9.9 (5.1, 20.3)	18.6 (5.8, 77.8)	16	15.0%	4	0.9%
OCD	19	5.0%	15	1.0%	5.3 (2.5, 11.3)	11.5 (2.7, 67.6)	8	7.5%	3	0.7%
PTSD	29	7.7%	11	0.7%	11.3 (5.4, 25.4)	22.0 (4.5, 207.0)	10	9.3%	2	0.5%

ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; GAD, generalized anxiety disorder; OCD, obsessive compulsive disorder; PTSD, post-traumatic stress disorder.

Supplementary Table 2. Propensity score-matched prevalence odds ratio for somatic comorbidities among patients with migraine with <15 monthly headache days vs. ≥15 monthly headache days

	Migraine patients MHDs<15 (N=271)		Matched non-migraine respondents (N=1,084)		Prevalence odds ratio, 95% CI MHDs<15	Prevalence odds ratio, 95% CI MHDs≥15	Migraine patients MHDs≥15 (N=107)		Matched non-migraine respondents (N=428)	
	Count	%	Count	%			Count	%	Count	%
Gastrointestinal disorders										
GERD	43	15.9%	74	6.8%	2.6 (1.7, 3.9)	6.2 (3.5, 11.1)	35	32.7%	31	7.2%
Heartburn	104	38.4%	180	16.6%	3.1 (2.3, 4.2)	5.1 (3.2, 8.2)	57	53.3%	78	18.2%
Ulcers	28	10.3%	45	4.2%	2.7 (1. 6, 4.5)	4.5 (2.0, 10.2)	15	14.0%	15	3.5%
Crohn's disease	0	0.0%	2	0.2%	0.0 (0.0, 21.3)	0.0 (0.0, 155.6)	0	0.0%	1	0.2%
Ulcerative colitis	4	1.5%	6	0.6%	2.7 (0.6, 11.4)	16.6 (1.6, 814.6)	4	3.7%	1	0.2%
Irritable bowel Syndrome	45	16.6%	71	6.5%	2.8 (1.9, 4.3)	7.6 (3.9, 14.6)	30	28.0%	21	4.9%
Chronic constipation (12m)	74	27.3%	141	13.0%	2.5 (1.8, 3.5)	2.5 (1.5, 4.2)	35	32.7%	69	16.1%
Frequent diarrhea (12m)	64	23.6%	118	10.9%	2.53 (1.8, 3.6)	4.9 (2.8, 8.4)	35	32.7%	39	9.1%
Allergic-related disorders										
Allergies (12m)	115	42.4%	202	18.6%	3.2 (2.4, 4.3)	2.4 (1.5, 3.9)	48	44.9%	107	25.0%
Atopic dermatitis	53	19.6%	121	11.2%	1.9 (1.3, 2.8)	2.2 (1.2, 4.0)	21	19.6%	43	10.0%
Hay fever	117	43.2%	217	20.0%	3.0 (2.3, 4.1)	2.5 (1.6, 3.9)	50	46.7%	112	26.2%
Asthma	42	15.5%	88	8.1%	2.1 (1.4, 3.1)	2.5 (1.4, 4.5)	24	22.4%	44	10.3%
Sleep disorders										
Insomnia	83	30.6%	119	11.0%	3.6 (2. 6, 5.0)	6.7 (4.0, 11.2)	51	47.7%	51	11.9%
Sleep apnea	13	4.8%	21	1.9%	2.6 (1.2, 5.4)	2.7 (0.2, 23.8)	2	1.9%	3	0.7%
Sleep difficulties	31	11.4%	37	3.4%	3.7 (2.1, 6.2)	5.2 (2.3, 11.6)	17	15.9%	15	3.5%
Gynecological disorders										

Fibroids	34	12.5%	91	8.4%	1.6 (1.0, 2.4)	1.8 (1.2, 2.6)	15	14.0%	28	6.5%
Pre-menstrual dysphoric disorder (12m)	38	14.0%	40	3.7%	4.4 (2.6, 7.2)	5.5 (3.6, 8.4)	22	20.6%	12	2.8%
Pre-menstrual syndrome (12m)	64	23.6%	64	5.9%	5.2 (3.5, 7.8)	5.3 (3.8, 7.4)	33	30.8%	34	7.9%
Endometriosis	22	8.1%	47	4.3%	2.0 (1.1, 3.4)	2.4 (1.5, 3.7)	14	13.1%	18	4.2%
Cardiovascular disorders										
High blood pressure (hypertension)	24	8.9%	76	7.0%	1.3 (0.8, 2.1)	0.5 (0.1, 1.6)	4	3.7%	29	6.8%
Heart attack	3	1.1%	3	0.3%	4.0 (0.5, 30.3)	NA	0	0.0%	0	0.0%
Mini-stroke/TIA	1	0.4%	4	0.4%	1.0 (0.02, 10.2)	Inf (0.1, Inf)	1	0.9%	0	0.0%
Stroke	2	0.7%	2	0.2%	4.0 (0.3, 55.6)	NA	0	0.0%	0	0.0%
Others										
Rheumatoid arthritis	4	1.5%	13	1.2%	1.2 (0.3, 4.0)	1.3 (0.03, 16.8)	1	0.9%	3	0.7%
Lupus	2	0.7%	2	0.2%	4.0 (0.3, 10.2)	0.0 (0.0, 9.7)	0	0.0%	3	0.7%
Fibromyalgia (12m)	3	1.1%	2	0.2%	6.1 (0.7, 72.6)	Inf (1.7, Inf)	3	2.8%	0	0.0%
Parkinson's disease	1	0.4%	3	0.3%	1.3 (0.03, 16.7)	NA	0	0.0%	0	0.0%
Restless leg syndrome (12m)	14	5.2%	25	2.3%	2.3 (1.1, 4.7)	4.9 (1.5, 16.1)	8	7.5%	7	1.6%
Epilepsy	2	0.7%	6	0.6%	1.3 (0.1, 7.5)	1.6 (0.2, 10.0)	2	1.9%	5	1.2%
Anemia (12m)	58	21.4%	121	11.2%	2.2 (1.5, 3.1)	2.6 (1.5, 4.4)	30	28.0%	56	13.1%
Thyroid condition	14	5.2%	23	2.1%	2.5 (1.2, 5.2)	3.8 (1.2, 11.3)	8	7.5%	9	2.1%
Genital warts	2	0.7%	1	0.1%	8.1 (0.4, 474.0)	NA	0	0.0%	0	0.0%
Genital herpes	5	1.8%	6	0.6%	3.4 (0.8, 13.4)	2.0 (0.03, 38.8)	1	0.9%	2	0.5%
Breast cancer	3	1.1%	18	1.7%	0.7 (0.1, 2.3)	6.1 (0.7, 73.9)	3	2.8%	2	0.5%

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1 & 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			5-7
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
8-9		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	7
		(*e*) Describe any sensitivity analyses	NA
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	8 (Figure 1)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8-9 (Table 1)
		(b) Indicate number of participants with missing data for each variable of interest	NA
Outcome data	15*	Report numbers of outcome events or summary measures	8-12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-12
		(*b*) Report category boundaries when continuous variables were categorized	8-12
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12
Discussion			13-17
Key results	18	Summarise key results with reference to study objectives	13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16-17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	16-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	16-17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.