


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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ABSTRACT

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), 1512 matched non-migraine respondents were identified.

Primary and secondary outcome measures Prevalence and PS-matched prevalence ORs (PORs) 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, post-traumatic stress disorder and anxiety disorders, while gastrointestinal disorders were the most prevalent somatic comorbidity category. Other somatic comorbidities included allergies, insomnia, premenstrual syndrome and anaemia. 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.

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,

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ 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 OR and the causal relationship between migraine and comorbidities cannot be concluded.

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 USA 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,^{6 12 13} gastrointestinal disorders,^{6 14–16} allergy-related disorders,^{6 17 18} sleep disorders^{6 19 20} and gynaecological 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 metabolic-endocrine (eg, 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 recognised 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 OR (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 aetiology of migraine and help physicians and patients with effective migraine management and treatment.

METHODS

This study used 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 (ie, not healthcare-specific) web-based consumer panel. All panellists explicitly agreed to join the panel and receive periodic invitations to participate in online surveys. An age-stratified and gender-stratified sampling frame, based on Japan governmental census data, was imposed during the recruitment from the panellists. This was to ensure representativeness of panellists who completed the NHWS to reflect the general adult population of Japan in terms of age and gender.

Study population

Migraine patients in this study were defined by ICHD-3 (International Classification of Headache Disorders, third Edition)-like criteria which were 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 were 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 define 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 4 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

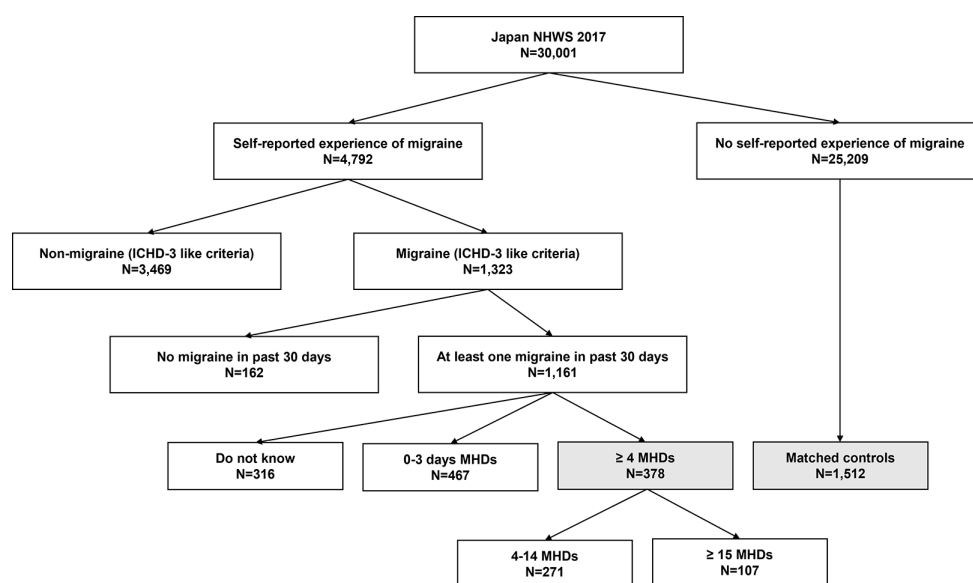


Figure 1 Respondent flow chart. Note: Shaded squares indicate the study populations—migraine patients (≥ 4 MHDs; $N=378$) and matched non-migraine respondents (matched controls, $N=1512$). ICHD-3, International Classification of Headache Disorder, third edition; MHDs, Monthly Headache Days; NHWS, National Health and Wellness Survey.

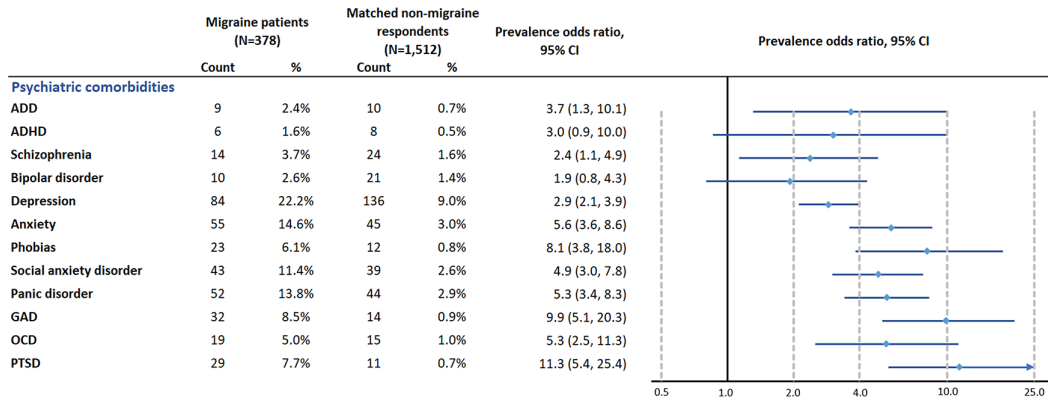


Figure 2 Propensity score-matched prevalence OR for psychiatric comorbidities. Comorbidities with prevalence between 5% and 10% among migraine patients: phobias, GAD, OCD and PTSD. Comorbidities with more than 10% prevalence among migraine patients: depression, anxiety, social anxiety disorder and panic disorder. ADD, attention-deficit disorder; ADHD, attention-deficit/hyperactivity disorder; GAD, Generalised Anxiety Disorder; OCD, obsessive-compulsive disorder; PTSD, post-traumatic stress disorder.

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 behaviour. 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 figures 2 and 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 summarised using counts and percentages for categorical variables and means and SDs for continuous variables for migraine patients and non-migraine respondents.

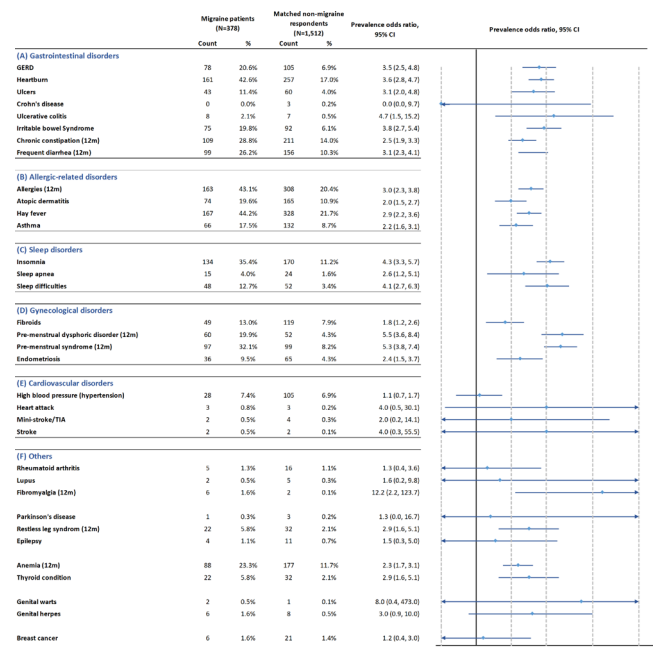


Figure 3 Propensity score-matched prevalence OR for somatic comorbidities. Comorbidities with prevalence between 5% and 10% among migraine patients: endometriosis, high blood pressure, restless leg syndrome and thyroid condition. Comorbidities with more than 10% prevalence among migraine patients: irritable bowel syndrome, heartburn, GERD, ulcers, frequent diarrhoea, chronic constipation, allergies, hay fever, asthma, atopic dermatitis, insomnia, sleep difficulties, premenstrual dysphoric disorder, premenstrual syndrome, fibroids and anaemia. GERD, gastro-oesophageal reflux disease; TIA, transient ischaemia attack.

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 behaviour) were used in the matching. Balance of matching was assessed using standardised mean differences (SMDs) between migraine patients and matched non-migraine respondents. SMDs 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 POR and its 95% CIs 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 V.25 and R V.3.5.1. 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 30001 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 25209 respondents were identified as non-migraine respondents (figure 1).

After PS matching, a total of 1512 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

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).

Psychiatric comorbidities in migraine patients versus matched non-migraine respondents

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 to 25.4)), various anxiety disorders (generalised anxiety disorder: 9.9 (95% CI 5.1 to 20.3) to social anxiety disorder (4.9 (95% CI 3.0 to 7.8)), OCD (5.3 (95% CI 2.5 to 11.3)) and depression (2.9 (95% CI 2.1 to 3.9)) (figure 2).

Somatic comorbidities in migraine patients versus matched non-migraine respondents

Figure 3 describes the somatic comorbidities of migraine patients compared to non-migraine respondents.

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 diarrhoea (26.2%), gastro-oesophageal 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 to 5.4)), heartburn (3.6 (95% CI 2.8 to 4.7)), GERD (3.5 (2.5, 4.8)), ulcers (3.1 (95% CI 2.0 to 4.8)), frequent diarrhoea (3.1 (95% CI 2.3 to 4.1)) and chronic constipation (2.5 (95% CI 1.9 to 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 to 3.8)), hay fever (2.9 (95% CI 2.2 to 3.6)), asthma (2.2 (95% CI 1.6 to 3.1)) and atopic dermatitis (2.0 (95% CI 1.5 to 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 (95% CI 3.3 to 5.7)) and sleep difficulties (4.1 (95% CI 2.7 to 6.3)), compared with matched non-migraine respondents.

Gynaecological comorbidities

The gynaecological disorders assessed in this study with a prevalence higher than 5.0% among migraine patients were premenstrual syndrome (32.1%), premenstrual dysphoric disorder (19.9%), fibroid (13.0%) and

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

| | Migraine patients (N=378) | | Matched non-migraine respondents (N=1512) | | 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 | 1209 | |
| 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 kg/m ²) | 18.3 | 69 | 18.5 | 280 | 0.045 |
| Normal weight (18.5≤BMI<25 kg/m ²) | 62.4 | 236 | 59.7 | 903 | |
| Preobese (25≤BMI<30 kg/m ²) | 14.8 | 56 | 13.6 | 205 | |
| Obese (BMI ≥30 kg/m ²) | 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 |

Continued

**Table 1** Continued

| | Migraine patients (N=378) | | Matched non-migraine respondents (N=1512) | | SMD |
|--|------------------------------|-------|--|-------|-------|
| | % | Count | % | Count | |
| 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 | – | – | |

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

BMI, body mass index; CCI, Charlson Comorbidity Index; HIT-6, Headache Impact Test-6; SMD, standardised mean difference.

endometriosis (9.5%). Compared with matched non-migraine respondents, migraine patients had a significantly higher odds for premenstrual dysphoric disorder (PS-matched POR (95% CI): 5.5 (3.6 to 8.4)), premenstrual syndrome (5.3 (95% CI 3.8 to 7.4)), endometriosis (2.4 (95% CI 1.5 to 3.7)) and fibroids (1.8 (95% CI 1.2 to 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 ministroke/transient ischaemic attack 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 anaemia (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 to 5.1)), thyroid condition (2.9 (95% CI 1.6 to 5.1)) and anaemia (2.3 (95% CI 1.7 to 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 to 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 (online supplemental 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, unidirectional or bidirectional 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 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 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, diarrhoea 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 microbiota¹⁵ were thought as potential mechanisms to alter visceral sensitivity and common pathology with migraine.

Both GERD¹⁶ 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 with 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}

Gynaecological 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} in which the occurrence of endometriosis was more frequent among women with migraines than women without.²³ The findings from this study were consistent with the previous research. The association between migraines and gynaecological 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 oestrogen 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, anaemia³⁵ and thyroid dysfunction³⁶ have been described as comorbidities of migraine. Similarly, restless leg syndrome²⁵ 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} In addition, 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, that is, 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 minimise misclassification, discrepancies between the criteria used in this study and the formal ICHD-3-like 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. In addition, 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 that 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 (eg, OCD, gastrointestinal comorbidities, sleep comorbidities, gynaecological 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.

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Contributors TT led and all authors (SK, YC, KI, MH, KA, and TT) conceptualised 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 approved the final manuscript.

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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.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

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