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Title: The social burden of people with the migraine diagnosis in Japan: evidence from a population-based cross-sectional survey

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ABSTRACT (max. 300 words, current 291 words)

Objectives To quantify the social burden among Japanese migraine patients in the context of currently available migraine treatments, by comparison with non-migraine controls, and comparison of migraine patients currently taking prescription medication vs. not taking prescription medication.

Design Cross-sectional analysis.

Setting Data from the population-based online self-administered Japan National Health and Wellness Survey (NHWS) 2017.

Participants Respondents to the NHWS (N=30,001) were ≥18 years. Migraine patients were respondents with self-reported experience and physician diagnosis of migraine. Non-migraine controls reported no migraine experience. Migraine patients were sub-grouped into currently taking prescription medication for migraine (Rx) and currently not taking prescription medication (non-Rx).

Methods One-way ANOVA tests were performed to compare health-related quality of life (HRQoL), work productivity and activity impairment and healthcare resource utilization between migraine patients and matched non-migraine controls selected by 1:1 propensity score matching. Generalized linear models were used to compare outcomes and migraine related characteristics between Rx and non-Rx.

Results Compared to matched controls, migraine patients (N=1,265) had significantly lower HRQoL in terms of lower Physical Component Summary (48.36 vs. 51.29, p<0.001), Mental Component Summary (44.65 vs. 48.31, p<0.001), Role/Social Component Summary (41.78 vs. 46.18, p<0.001) and mean EuroQol 5-Dimension index (0.77 vs. 0.86, p<0.001) scores. Migraine patients experienced significantly higher absenteeism (6.95% vs. 3.07%, p<0.001), presenteeism (32.73% vs. 18.94%, p<0.001), work productivity loss (34.82% vs. 20.03%, p<0.001) and daily activity impairment (35.70% vs. 22.04%, p<0.001) and visited healthcare professionals more often (8.38 vs. 4.57, p<0.001) than controls. No significant differences in these outcomes were found when comparing Rx (N=587) and non-Rx (N=678) patients.

Conclusions There is an unmet need for improved HRQoL and work productivity in Japanese migraine patients despite the currently available prescription medications, which are important factors to consider for future development of migraine therapies.

STRENGTHS AND LIMITATIONS

- The recruitment of respondents to the Japan 2017 NHWS utilized a stratified random sampling procedure with strata by sex and age according to national census data, thereby ensuring that the demographic composition of the sample was representative of the adult population in Japan.

- This study used the validated instruments Short Form-12 version 2, EuroQol-5 Dimension, Work Productivity and Activity Impairment questionnaire to quantify the burden of migraine and Headache Impact Test for assessment of headache-related disability.

- The data from NHWS is cross-sectional and no causal relationships can be assumed.

- As all data are self-reported, no verification of patient reported outcomes was conducted, and data is subject to recall bias.

- Although NHWS is broadly representative of the Japanese adult population, it is unclear the extent to which the migraine patients and migraine patients taking Rx are representative of the larger population.

INTRODUCTION

Migraine is a common disabling headache disorder, known to impose a burden on both patients and societies worldwide[1,2]. Since 1990, migraine has been the second leading cause of years lived with disability (YLD) and the sixth most prevalent disease[3]. Globally the prevalence of migraine has been estimated to be 11.6%, and in Asia 10.1%[4]. In Japan, the prevalence has been estimated to be between 6.0 - 8.9%[5–7].

A recent study of European migraine patients showed that suffering from more than 3 monthly headache days (MHD) was associated with poorer health related quality of life (HRQoL), high healthcare resource utilizations (HCRU) and loss of work productivity compared to non-migraine controls[1]. In Japan, previous studies have also reported an incremental impact of migraine on patients' social life and work. In a nationwide survey from 1997, 30% of migraine patients reported a severe impairment of their daily activities where bed rest was frequently required. Furthermore, 32% of migraine patients reported moderate to severe impairment in social activities including cancellation of work and daily appointments[5]. Similarly, in the regional Daisen study from 1999, 20.3% of migraine patients reported that they had experienced time or days off from work and 27.3% reported being unable to do housework[6]. The general health perception was worse compared to non-headache subjects, as migraine patients more often reported their health as "poor" and half of the patients suffered from sleep disturbance[6]. Despite the disabling impact of migraine, both surveys revealed large populations of underdiagnosed and undertreated migraine patients. More than 60% of patients had never consulted a physician for headache, as few as 5%–7% of patients continuously consulted a physician for migraine[5,6], and only 11.6% of patients were aware that their headache was migraine[5,6]. Further studies have investigated the impact of migraine on the active Japanese workforce, which found that 22.4% of migraineurs had missed work due to headaches several times in the past year[7].

Additionally, migraine and headaches were the leading cause of absence from work (absenteeism) for employed women in their 50s (6.2 days of absence, 4 weeks recall period), and the leading cause of not being able to fully perform while at work (presenteeism) for employed men in their 20s with 49.5 hours lost in the last 4 weeks[8].

With these most recent studies of migraine burden performed in 2008[7] and 2013[8], there has been a paucity in research and there is a need for updated data to gain further insights and understand the current burden of migraine in Japan, in the context of currently available treatments. Therefore, the objective of this study was to quantify the migraine associated burden by comparison of HRQoL, work productivity and activity impairment (WPAI) and HCRU in migraine patients and people without migraine experience, and among the treated migraine population vs. non-treated migraine population.

METHODS

This research was a cross-sectional study using data from the National Health and Wellness Survey (NHWS) conducted in 2017. NHWS is an online self-administered survey and was granted exemption status upon review by Pearl International Review Board (Indianapolis, IN). All respondents provided informed consent prior to participating.

Study population

Respondents to the NHWS were aged 18 years or older and were recruited from web-based opt-in consumer panels. Respondents were already members of these panels, recruited through opt-in emails, co-registration with panel partners, newsletter campaigns, banner placements and had provided informed consent prior to participation. Recruitment of NHWS respondents utilized a stratified random sampling procedure, with strata by sex and age

according to census data from the US census database which sources from the Japan Ministry of Internal Affairs & Communications[9], which was implemented to ensure that the demographic composition of the sample was representative of the Japan adult population. Representation of NHWS data has been validated and weighted against reliable sources including government agencies' health statistics and unaffiliated third parties[10,11]. Respondents who self-reported a physician diagnosis of migraine were included in the migraine patient group. Those who self-reported no experience of migraine were the non-migraine controls. Respondents with self-reported physician diagnosis of migraine were further sub-grouped into patients who reported currently taking prescription medication for migraine (Rx) and patients currently not taking any prescription medication (non-Rx).

Patient involvement

Patients and respondents to NHWS were not involved in setting the research questions, outcomes measures nor the design of the study. The data used in this study were obtained from patients and respondents who provided self-reported information in the NHWS.

Measures

Covariates

The demographic and general health characteristics included: gender, age, marital status, number of children living in the household, household income, employment status, smoking status, alcohol use, exercise behaviour and Charlson Comorbidity Index (CCI)[12–14].

Measures

HRQoL was assessed by the Short Form-12 health survey version 2 (SF-12v2)[15], which consists of 12 questions with summary scores that was translated and validated for use in the Japanese population[16,17]. The mental component summary score (MCS), physical component summary score (PCS) and role/social component summary (RCS) were calculated based on survey responses. Each domain and summary score was calculated using a norm-based scoring algorithm which allows for all measures to be viewed together on the same graph and allows for scores to be interpreted relative to population means. Higher scores indicate better quality of life.

Health state utilities were quantified with the EuroQol 5-Dimension 5 Levels (EQ-5D 5L) instrument, which is a standardized measure of health status to provide a simple, generic measure of health[18]. EQ-5D index score is a single summary index derived from the EQ-5D 5L questions[19], scored by using the Japanese tariff. Higher scores indicate better health status. In addition, the EuroQol visual analogue scale (EQ VAS) was used which records the patient's self-rated health on a 100mm VAS, where the endpoints are labelled 'The best health you can imagine' (100) and 'The worst health you can imagine' (0). The VAS can be used as a quantitative measure of health outcome that reflect the patient's own judgement.

For work productivity assessment, the Work Productivity and Activity Impairment (WPAI) questionnaire[20] was used to measure the impact of health on both employment-related and daily activities. This six-item validated instrument consists of four metrics: absenteeism (the percentage of work time missed because of one's health in the past 7 days), presenteeism (the percentage of impairment experienced because of one's health while at work in the past 7 days), overall work productivity loss (an overall impairment estimate that is a combination of absenteeism and presenteeism), and daily activity impairment (the percentage of impairment in daily activities because of one's health in the past 7 days). These four subscales are

generated in the form of percentages, with higher values indicating greater impairment. Only respondents who reported being full-time, part-time, or self-employed provide data for absenteeism, presenteeism, and overall work impairment. All respondents provide data for activity impairment.

HCRU was considered in terms of the number of outpatient visits in the past 6 months to healthcare providers (practitioner/family practitioners, internists, and dentists as well as more specialized physicians), the emergency room (ER), and the hospitalization for the participant's own medical condition.

Respondents with migraine utilized the validated Headache Impact Test (HIT-6) scale for assessment of headache-related disability[21]. Scores from HIT-6 range from 36 to 78. A higher HIT-6 score indicates a greater impact of headache on the daily life of respondents.

Migraine-specific characteristics and treatment

All migraine patients were asked several questions in relation to their migraine including the symptoms experienced due to migraine, number of years experiencing migraine, diagnosing physician, number of migraines in the past 30 days and in the past 6 months, number of headache days in the past 30 days, experienced migraine related to menstrual cycle, days of missed work due to migraine in the past 6 months, days of missed household activities due to migraine in the past 6 months, current use of prescription medication (Rx) to treat or prevent migraine, and usage of over-the-counter (OTC) or herbal products to treat migraine.

Respondents specified the type of Rx which included the following drug classes: triptan, anticonvulsant, beta blocker, non-steroidal anti-inflammatory drugs (NSAIDs) and others.

The top 10 self-reported OTC and herbal products contained the following active ingredients: loxoprofen, aspirin, ibuprofen, acetaminophen, chondroitin, and ergotamine. In addition,

respondents with migraine answered the validated HIT-6 scale for assessment of headache-related disability[21].

Statistical analysis

Demographic factors and general health characteristics were compared between migraine patients and non-migraine controls to understand the baseline differences in the two groups. Demographic factors, general health characteristics, and migraine-specific variables were summarized descriptively among migraine patients. Age, CCI, gender, employment status, household income, smoking status, and alcohol use were used in the 1:1 propensity score matching using a greedy matching algorithm to form the matched non-migraine control group. Post-matching bivariate comparisons were conducted between migraine patients and matched non-migraine respondents to assess the balance of the matching. After propensity score matching, outcomes were compared between patients with migraine and matched non-migraine controls. One-way ANOVA tests were used for comparison of these continuous outcome variables.

Demographic factors, general health characteristics, migraine-specific variables (including migraine-related symptoms) were also compared between migraine patients currently taking Rx and not currently taking Rx, using chi-square test for categorical variables and one-way analyses of variance (ANOVA) for continuous variables. Generalized linear models (GLMs) were used to compare the outcomes between migraine patients currently taking Rx and migraine patients currently not taking Rx, accounting for demographic and clinical characteristics of the patients. Normal distribution with identity link were specified in the GLMs for normally distributed outcomes, such as HRQoL scores. Negative binomial distribution with log link were specified for outcomes with skewed distributions, such as WPAI and HCRU. Estimated adjusted means and p-values were reported for each health

outcome. All outcome variables were pre-determined before the analyses and the analyses were not of exploratory manner. No correction for multiple testing was conducted for this study. Complete data were available, and no imputation was carried out. For all analyses, statistical significance was assessed at a significance level of 0.05. All data analyses were performed using IBM SPSS Statistics Version 22[22] and R Version 3.4.4[23].

RESULTS

A total of 25,209 respondents without self-reported experience with migraine were included in the non-migraine group and 4,792 respondents self-reported experience with migraine (Figure 1). Among the 4,792 respondents who self-reported experience with migraine, 74% (n=3,527) had never been diagnosed by a physician. The 1,265 respondents with self-reported physician diagnosed migraine were included in the migraine patient group for the further analyses.

On average, migraine patients tend to be younger than non-migraine respondents (43.8 vs. 52.8 years, $p < 0.001$) and have a significantly higher CCI index (0.24 vs. 0.17, $p < 0.001$) (Supplementary Table 1). More migraine patients are female (66.6% vs. 47.1%, $p < 0.001$), currently employed (59.8% vs. 54.7%, $p < 0.001$) and have children in the household (27.7% vs. 18.6% $p < 0.001$). Compared to controls, fewer migraine patients are married/living with partner (53.1% vs. 62.5%, $p < 0.001$) and have completed university (42.5% vs. 49.2%, $p < 0.001$). Migraine patients have similar household income to non-migraine respondents. A slightly higher percentage of migraine patients currently smoke (44.0% vs. 41.2%, p=0.046) compared to non-migraine respondents, but slightly fewer migraine patients currently consume alcohol (63.2% vs. 66.2%, p=0.031). Detailed results are listed in Supplementary Table 1.

Comparison of outcomes in migraine patients vs. matched non-migraine controls

After 1:1 propensity score matching, the majority of demographic and clinical characteristics were balanced between migraine patients and matched non-migraine controls (Supplementary Table 1). Bivariate comparison between matched non-migraine controls and migraine patients were conducted to evaluate the burden of migraine in terms of HRQoL, WPAI and HCRU (Figure 2). We found that migraine patients had significantly lower PCS (48.36 vs. 51.29, p<0.001), MCS (44.65 vs. 48.31, p<0.001), and RCS (41.78 vs. 46.18, p<0.001) scores as well as significantly lower EQ-5D index (0.77 vs. 0.86, p<0.001) and EQ-5D VAS (64.41 vs. 73.49, p<0.001) scores. The differences in MCS and RCS between the two groups were more than 3 points, which is defined as a minimum clinically important difference (MCID)[24] (Figure 2A).

In terms of WPAI, migraine patients experienced significantly higher absenteeism (6.95% vs. 3.07%, p<0.001), presenteeism (32.73% vs. 18.94%, p<0.001), work productivity loss (34.82% vs. 20.03%, p<0.001) and daily activity impairment (35.70% vs. 22.04%, p<0.001) compared to matched controls (Figure 2B).

Compared to controls, migraine patients visited health care professionals (HCPs) almost twice as often (8.38 vs. 4.57, p<0.001) and visited the ER 4 times as often (0.12 vs. 0.03, p<0.001). There were no significant differences in the number of hospitalizations between the two groups (Figure 2C).

Migraine-related health characteristics among migraine patients

On average, patients received a migraine diagnosis 11.77 years ago (standard deviation (SD) 10.84), and the majority (58.3%) were diagnosed by a primary care physician/general practitioner (GP)/internist (Table 1). On average, patients experienced migraine 4.69 times

(SD 6.22) in the past 30 days and 23.36 times (SD 33.72) in the past 6 months. In the past 30 days, migraine patients had an average of 6.45 (SD 7.02) headache days. Among female migraine patients, 41.4% experienced menstrual-related migraine. An average of 1.62 days of work and 2.94 days of household activities were missed due to migraine in the past 6 months. Among all patients, the average HIT-6 score was 59.37 (SD 7.97) and more than half (57.2%) of patients were severely impacted (HIT-6 score ≥60)[21].

The most common migraine-related symptom was pulsating, throbbing, or pounding pain (66.9%), followed by "pain being worse on one side of your head or occurs on one side of your head only" (54.8%), moderate to severe pain (39.1%), nausea and/or vomiting (38.5%), bothered by or unusually sensitive to light (32.3%), bothered by or unusually sensitive to sound (27.9%), pain made worse by routine activities such as walking or climbing stairs (26.5%), migraine lasting for at least four hours but not more than 72 hours if untreated (23.0%), aura (19.1%), and seeing spots, flashing lights, or "heat waves" before or during the migraine (17.5%). 4.4% of patients experienced none of the above symptoms (Figure 3).

Table 1. Bivariate comparison of migraine-related health characteristics in diagnosed migraine patients and patients currently taking Rx vs. patients not currently taking Rx (non-Rx).

		Diagnosed migraine patients (N=1,265)		Non-Rx (N=678)		Rx (N=587)		p-value Non-Rx vs. Rx
		Mean or %	[SD] or (n)	Mean or %	[SD] or (n)	Mean or %	[SD] or (n)	
Time since migraine (years), mean [SD]*		11.27	[10.87]	11.14	[11.20]	11.44	[10.41]	.635
Diagnosing physician, % (n)*	Primary Care Physician/GP/Internist	58.3%	(686)	60.3%	(409)	55.5%	(277)	.181
	Neurologist	27.2%	(320)	25.2%	(171)	29.9%	(149)	
	Other	14.5%	(171)	14.5%	(98)	14.6%	(73)	
Number of migraine in the past 30 days, mean [SD]		4.69	[6.22]	3.61	[5.54]	5.95	[6.72]	< .001
Number of migraine in the past 6 months, mean [SD]		23.36	[33.72]	17.70	[29.13]	29.91	[37.31]	< .001
Days missed work due to migraine in the past 6 months, mean [SD]		1.62	[10.24]	1.39	[9.37]	1.89	[11.17]	.384
Days of household activities missed due to migraine in the past 6 months, mean [SD]		2.94	[12.67]	1.81	[5.70]	4.25	[17.48]	< .001
Number of headache days in the past 30 days, mean [SD]		6.45	[7.02]	5.12	[5.88]	7.70	[7.75]	< .001
Number of headache days in the past 30 days, % (n)	0-3 MHDs	49.4%	(365)	57.3%	(205)	42.0%	(160)	< .001
	4-14 MHDs	36.8%	(272)	33.8%	(121)	39.6%	(151)	
	≥15 MHDs	13.8%	(102)	8.9%	(32)	18.4%	(70)	
	Don't know	24.0%	(304)	24.4%	(161)	24.0%	(143)	
	Not asked	17.5%	(222)	10.7%	(159)	17.5%	(63)	
Menstrual-related migraine (N=female only), % (n)**		41.4%	(349)	38.0%	(167)	45.3%	(182)	.031
Use of OTC/Herbal products to treat migraine, % (n)		12.9%	(163)	14.6%	(99)	10.9%	(64)	.050
Currently using Rx to treat or prevent migraine, % (n)		46.4%	(587)	-	-	100%	(587)	-
Acute medication only, % (n)***		77.5%	(455)	-	-	77.5%	(455)	
Preventive medication only, % (n)***		14.3%	(84)	-	-	14.3%	(84)	
Both, % (n)***		8.2%	(48)	-	-	8.2%	(48)	
HIT-6 score, mean [SD]		59.37	[7.97]	57.76	[8.00]	61.23	[7.52]	< .001
HIT-6 impact grade, % (n)	Little to no impact	11.3%	(143)	14.9%	(101)	7.2%	(42)	< .001
	Moderate impact	16.3%	(206)	19.8%	(134)	12.3%	(72)	
	Substantial impact	15.3%	(193)	16.4%	(111)	14.0%	(82)	
	Severe impact	57.2%	(723)	49.0%	(332)	66.6%	(391)	

Abbreviations: Rx = prescription medication, SD = standard deviation, GP = General practitioner, MHD = monthly headache days, OTC = over-the-counter medication, HIT = Headache Impact Test.

*Sample size of diagnosed migraine patients who reported the time since diagnosis: N=1177, Non-Rx: N=678, Rx: N=499. **Sample size of diagnosed migraine patients: N=842, Non-Rx: N=440, Rx: N=402. ***Sample size of diagnosed migraine patients taking Rx: N=587.

Treatment use in migraine patients

Among all migraine patients, the majority (678; 53.6%) did not currently take any prescription medication (Rx) (Figure 1). 587 (46.4%) were currently taking prescription medication (Rx), whereof 77.5% currently used acute treatment, 14.3% used preventive treatments and 8.2% used both (Table 1). Of the 678 migraine patients not currently taking Rx, 384 (56.6%) had previously used a prescription medication and 294 (43.4%) had never used a prescription medication, and 50 (17.0%) of the 294 patients had been recommended a prescription medication by the physician before. Out of the total 1,265 migraine patients, only 163 patients (12.9%) had used OTC or herbal product to treat migraine and 142 patients recalled the name of the OTCs they used.

Comparison of outcomes in Rx patients vs. non-Rx patients

There were no differences in demographic characteristics between the Rx and non-Rx group, except for marital status. Significantly fewer patients taking Rx were married or living with partner (47.0% vs. 58.4%, p<0.001) (Table 2). In terms of migraine-related characteristics, migraine patients currently taking Rx experienced migraine significantly more often in the past 30 days (5.95 vs. 3.61, p<0.001) and in the past 6 months (29.91 vs. 17.70, p<0.001) compared to those not currently taking Rx (Table 1). More days of household activities (4.25 vs. 1.81, p<0.001) were missed due to migraine among patients currently taking Rx and a significantly higher percentage of patients had ≥15 MHD (18.4% vs. 8.9%, p<0.001) (Table 1). A significantly higher average HIT-6 score (61.23 vs. 57.76, p<0.001) was observed among migraine patients currently taking Rx and a higher percentage were determined to have severe impact (66.6% vs. 49.0%, p<0.001) (Table 1).

Without adjustment, the bivariate comparisons of outcomes in Rx vs. non-Rx showed that migraine patients currently taking Rx had a lower MCS, higher daily activity impairment and

increased number of visits to physicians in the past 6 months. No other differences in outcomes were observed (Supplementary Table 2).

After adjusting for potential confounding effects (age, CCI, gender, marital status, currently employed and number of migraines in the past 30 days), no significant differences in HRQoL, WPAI or HCRU were found between the two groups (Figure 2 D-F).

Table 2. Bivariate comparison of demographics and general health characteristics in diagnosed migraine patients and patients currently taking Rx vs. patients not currently taking Rx (non-Rx).

		Diagnosed migraine patients (N=1,265)		Non-Rx (N=678)		Rx (N=587)		p-value No Rx vs. Rx
		Mean or %	[SD] or (n)	Mean or %	[SD] or (n)	Mean or %	[SD] or (n)	
Age, mean [SD]		43.79	[14.27]	44.06	[14.82]	43.47	[13.61]	.463
Gender, % (n)	Female	66.6%	(842)	64.9%	(440)	68.5%	(402)	.177
Marital status, % (n)	Married or living with partner	53.1%	(672)	58.4%	(396)	47.0%	(276)	< .001
Having children <18 in the household, % (n)	Yes	27.7%	(351)	27.7%	(188)	27.8%	(163)	.987
Employment status, % (n)	Currently employed	59.8%	(756)	60.0%	(407)	59.5%	(349)	.835
Household income, % (n)	<¥3,000,000	18.7%	(237)	18.4%	(125)	19.1%	(112)	.318
	¥3,000,000 to <¥5,000,000	25.0%	(316)	24.2%	(164)	25.9%	(152)	
	¥5,000,000 to <¥8,000,000	24.6%	(311)	26.0%	(176)	23.0%	(135)	
	¥8,000,000 or more	17.0%	(215)	18.1%	(123)	15.7%	(92)	
	decline to answer	14.7%	(186)	13.3%	(90)	16.4%	(96)	
CCI, mean [SD]		0.24	[1.00]	0.19	[0.60]	0.29	[1.32]	.072
Currently smoking, % (n)	Yes	44.0%	(557)	43.8%	(297)	44.3%	(260)	.862
Currently use alcohol, % (n)	Yes	63.2%	(800)	64.9%	(440)	61.3%	(360)	.189
Currently exercise, % (n)	Yes	44.3%	(561)	43.4%	(294)	45.5%	(267)	.449

Abbreviations: CCI = Charlson Comorbidity Index, Rx = prescribed medication

DISCUSSION

In this study we found that migraine patients in Japan experience a significant burden of illness compared to matched controls without migraine in terms of lower HRQoL, higher WPAI and HCRU (Figure 2), and 88.8% of patients reported that migraine had a moderate to severe impact on their daily life (HIT-6 score) (Table 1). Compared to matched controls, migraine patients had 2.93 points decreased PCS ($p<0.001$) and more than 3 points decreased MCS (3.66 points, $p<0.001$) and RCS (4.40 points, $p<0.001$) (Figure 2), which indicates that migraine has a clinically significant impact on migraine patients' mental health and role/social functioning. In comparison, similarly lower MCS scores have been reported in Japanese patients with arthritis (-3.4 points) and ischemic heart disease (-4.1) compared to controls, and similarly lower PCS scores were reported in patients with diabetes (-3.0 point), chronic lung disease (-3.1 point) and ischemic heart disease (-2.6 points)[25].

In addition to lower HRQoL, we observed that migraine patients who were currently employed had higher levels of work productivity loss compared to matched non-migraine controls, with 2.2-fold higher absenteeism ($p<0.001$), 1.7-fold higher presenteeism ($p<0.001$) and 1.7-fold higher work productivity loss ($p<0.001$) (Figure 2). The actual work loss that Japanese migraine patients experience was thereby quantified based on the validated WPAI tool[20], and supports the previous findings that migraine can cause a substantial loss of work productivity[5–8].

The finding in this current study that 74% of surveyed participants who reported ever having experienced migraine had not received a physician diagnosis of migraine indicates a large population of underdiagnosed migraine patients in Japan. This is supported by other studies showing that large proportions of migraine sufferers never consulted a physician[5,6].

Additionally, in this study we found that more than half of the diagnosed migraine patients (53.6%) were currently not receiving treatment with prescribed medication (non-Rx) (Figure

1). However, 56.6% of non-Rx had previously received treatment which indicates a high treatment discontinuation rate which is supported by the previous study by Meyers et al. where 62.2% discontinued prophylactic treatment after an average of 61.2 days[26]. Also, 43.4% of non-Rx patients have not previously received prescription medication which reflects an unmet need for treatment. Other studies have similarly described that 30 – 60% of migraine patients had never received prescription of preventive therapy[27], and that lack of efficacy and side effects were the most common reasons for discontinuation of both acute and preventive therapy[27–30]. A recent study reported that among Japanese migraine patients who visited HCPs, lack of efficacy with both preventive (anticonvulsants and calcium antagonist) and acute treatment (triptans and NSAIDs) was reported by half and a third of the patients, respectively[27].

Migraine patients currently taking prescribed medication (Rx) had significantly worse migraine-related characteristics compared to migraine patients currently not taking any Rx (Table 1, Figure 3). This indicates that those taking Rx suffer from more severe migraine. Interestingly, migraine patients receiving Rx suffer similar impairment of HRQoL and work productivity as non-Rx patients (Figure 2). This indicates that despite currently available preventive and acute treatments for migraine, there is an unmet need for improved HRQoL and work productivity among migraine patients, implying that current treatments have limited effects on these outcomes for patients. Additionally, only 14.3% of patients currently taking Rx received preventive treatments for migraine, indicating a lack of prescription of preventive therapy. These are important factors to consider for future treatment development.

The limitations of the study should be recognized. The data from NHWS is cross-sectional and no causal relationships can be assumed. As all data are self-reported, no verification of patient reported outcomes was conducted, and data is subject to recall bias. Although NHWS is broadly representative of the Japanese adult population, it is unclear the extent to which the

migraine patients and migraine patients taking Rx are representative of the larger population. Due to the design of the survey, the reasons for not taking Rx or for discontinuation of Rx (e.g. less migraine episodes or lack of efficacy) were not reported and could not be concluded. Also, NWHS primarily relied upon respondents with Internet access and these patients could potentially be different from the broader population (e.g., more knowledgeable or engaged in their healthcare).

CONCLUSION

Migraine patients in Japan experience a significant burden of illness with decreased HRQoL, around 2-fold increased work productivity loss and twice as many visits to HCPs compared to non-migraine controls. There is a large proportion of both underdiagnosed and undertreated migraine patients. The migraine patients not receiving prescribed medication for treatment of their disease suffer similarly decreased HRQoL and high levels of work productivity loss as patients currently receiving prescribed medication. These results indicate an unmet need for improved HRQoL and work productivity in Japanese migraine patients despite the currently available prescription medications, which are important factors to consider for future development of migraine therapies.

AUTHOR CONTRIBUTIONS

HI, KU and TN conceptualized the study and analysed and interpreted the data. SJ, ZC and YC designed the analysis plan, conducted the analyses and interpreted the data. All authors revised the manuscript drafts for intellectual content and edited the manuscript. All authors reviewed and approved the final draft.

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PATIENT CONSENT FOR PUBLICATION

Not required

ETHIS APPROVAL

NHWS was granted exemption status upon review by Pearl International Review Board (Indianapolis, IN).

DATA SHARING STATEMENT

Data are available upon reasonable request.

REFERENCES

1 Vo P, Fang J, Bilitou A, *et al.* Patients' perspective on the burden of migraine in Europe: a cross-sectional analysis of survey data in France, Germany, Italy, Spain, and the United Kingdom. *J Headache Pain* 2018;**19**:82. doi:10.1186/s10194-018-0907-6

2 Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. *Cephalalgia Int J Headache* 2018;**38**:1–211. doi:10.1177/0333102417738202

3 GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Lond Engl* 2017;**390**:1211–59. doi:10.1016/S0140-6736(17)32154-2

4 Woldeamanuel YW, Cowan RP. Migraine affects 1 in 10 people worldwide featuring recent rise: A systematic review and meta-analysis of community-based studies involving 6 million participants. *J Neurol Sci* 2017;**372**:307–15. doi:10.1016/j.jns.2016.11.071

5 Sakai F, Igarashi H. Prevalence of migraine in Japan: a nationwide survey. *Cephalalgia Int J Headache* 1997;**17**:15–22. doi:10.1046/j.1468-2982.1997.1701015.x

6 Takeshima T, Ishizaki K, Fukuhara Y, *et al.* Population-based door-to-door survey of migraine in Japan: the Daisen study. *Headache* 2004;**44**:8–19. doi:10.1111/j.1526-4610.2004.04004.x

7 Suzuki N, Ishikawa Y, Gomi S, *et al.* Prevalence and characteristics of headaches in a socially active population working in the Tokyo metropolitan area -surveillance by an industrial health consortium. *Intern Med* 2014;**53**:683–9. doi:10.2169/internalmedicine.53.1700

8 Wada K, Arakida M, Watanabe R, *et al.* The Economic Impact of Loss of Performance Due to Absenteeism and Presenteeism Caused by Depressive Symptoms and Comorbid Health Conditions among Japanese Workers. *Ind Health* 2013;**51**:482–9. doi:10.2486/indhealth.2013-0016

9 United States Census Bureau. International Data Base. https://www.census.gov/data-tools/demo/idb/informationGateway.php

10 Bolge SC, Doan JF, Kannan H, *et al.* Association of insomnia with quality of life, work productivity, and activity impairment. *Qual Life Res Int J Qual Life Asp Treat Care Rehabil* 2009;**18**:415–22. doi:10.1007/s11136-009-9462-6

11 DiBonaventura MD, Wagner J-S, Yuan Y, *et al.* Humanistic and economic impacts of hepatitis C infection in the United States. *J Med Econ* 2010;**13**:709–18. doi:10.3111/13696998.2010.535576

12 Charlson ME, Pompei P, Ales KL, *et al.* A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;**40**:373–83.

13 Charlson ME, Charlson RE, Peterson JC, *et al.* The Charlson comorbidity index is adapted to predict costs of chronic disease in primary care patients. *J Clin Epidemiol* 2008;**61**:1234–40. doi:10.1016/j.jclinepi.2008.01.006

14 Quan H, Li B, Couris CM, *et al.* Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol* 2011;**173**:676–82. doi:10.1093/aje/kwq433

15 Brazier JE, Roberts J. The Estimation of a Preference-Based Measure of Health From the SF-12: *Med Care* 2004;**42**:851–9. doi:10.1097/01.mlr.0000135827.18610.0d

16 Fukuhara S, Bito S, Green J, *et al.* Translation, adaptation, and validation of the SF-36 Health Survey for use in Japan. *J Clin Epidemiol* 1998;**51**:1037–44. doi:10.1016/s0895-4356(98)00095-x

17 Fukuhara S, Ware JE, Kosinski M, *et al.* Psychometric and clinical tests of validity of the Japanese SF-36 Health Survey. *J Clin Epidemiol* 1998;**51**:1045–53. doi:10.1016/s0895-4356(98)00096-1

18 EuroQol - a new facility for the measurement of health-related quality of life. *Health Policy* 1990;**16**:199–208. doi:10.1016/0168-8510(90)90421-9

19 Shiroiwa T, Fukuda T, Ikeda S, *et al.* Japanese population norms for preference-based measures: EQ-5D-3L, EQ-5D-5L, and SF-6D. *Qual Life Res* 2016;**25**:707–19. doi:10.1007/s11136-015-1108-2

20 Reilly MC, Gooch KL, Wong RL, *et al.* Validity, reliability and responsiveness of the Work Productivity and Activity Impairment Questionnaire in ankylosing spondylitis. *Rheumatol Oxf Engl* 2010;**49**:812–9. doi:10.1093/rheumatology/kep457

21 Kosinski M, Bayliss MS, Bjorner JB, *et al.* A six-item short-form survey for measuring headache impact: the HIT-6. *Qual Life Res Int J Qual Life Asp Treat Care Rehabil* 2003;**12**:963–74. doi:10.1023/a:1026119331193

22 *IBM SPSS Statistics for Windows, Version 22.0*. IBM Corp 2013.

23 R Core Team. *R: A language and environment for statistical computing*. Vienna, Austria: : R Foundation for Statistical Computing 2018. https://www.R-project.org/

24 Maruish ME. *User's Manual for the SF-36v2 Health Survey*. 3rd ed. Quality Metric Incorporated 2011.

25 Alonso J, Ferrer M, Gandek B, *et al.* Health-related quality of life associated with chronic conditions in eight countries: Results from the International Quality of Life Assessment (IQOLA) Project. *Qual Life Res* 2004;**13**:283–98. doi:10.1023/B:QURE.0000018472.46236.05

26 Meyers JL, Davis KL, Lenz RA, *et al.* Treatment patterns and characteristics of patients with migraine in Japan: A retrospective analysis of health insurance claims data. *Cephalalgia* 2019;**39**:1518–34. doi:10.1177/0333102419851855

27 Ueda K, Ye W, Lombard L, *et al.* Real-world treatment patterns and patient-reported outcomes in episodic and chronic migraine in Japan: analysis of data from the Adelphi migraine disease specific programme. *J Headache Pain* 2019;**20**:68. doi:10.1186/s10194-019-1012-1

28 Lipton RB, Hutchinson S, Ailani J, *et al.* Discontinuation of Acute Prescription Medication for Migraine: Results From the Chronic Migraine Epidemiology and Outcomes (CaMEO) Study. *Headache J Head Face Pain* 2019;**59**:1762–72. doi:10.1111/head.13642

29 Wells RE, Markowitz SY, Baron EP, *et al.* Identifying the Factors Underlying Discontinuation of Triptans. *Headache* 2014;**54**:278–89. doi:10.1111/head.12198

30 Blumenfeld AM, Bloudek LM, Becker WJ, *et al.* Patterns of Use and Reasons for Discontinuation of Prophylactic Medications for Episodic Migraine and Chronic Migraine: Results From the Second International Burden of Migraine Study (IBMS-II). *Headache J Head Face Pain* 2013;**53**:644–55. doi:10.1111/head.12055

FIGURE LEGENDS

Figure 1. Respondent flow chart

Abbreviations: NHWS = National Health and Wellness Survey, Rx = prescription medication

Figure 2. Comparison of health outcomes between migraine patients and matched non-migraine respondents (A-C), and between migraine patients currently taking Rx and not currently taking Rx (D-F)

A-C: Migraine patients and matched non-migraine respondents: *Bivariate analysis for comparison of health outcomes between migraine patients and matched non-migraine respondents.* ***D-F: Migraine patients currently taking prescription medication (Rx) and migraine patients not currently taking Rx:*** *Adjusted means from GLM analysis for comparison of health outcomes between migraine patients currently taking prescription medication (Rx) and migraine patients not currently taking Rx.*

Abbreviations: Rx = prescription medication, HRQoL = Health-related quality of life, PCS = physical component summary score, MCS = mental component summary score, RCS = role/social component summary score, EQ-5D = EuroQol-5 Dimension, WPAI = Work Productivity and Activity Impairment, HCRU = healthcare resource utilization, ER = emergency room.

Figure 3. Migraine-related symptoms

Abbreviations: Rx = patients currently taking prescription medication, non-Rx = patients currently not taking prescription medication

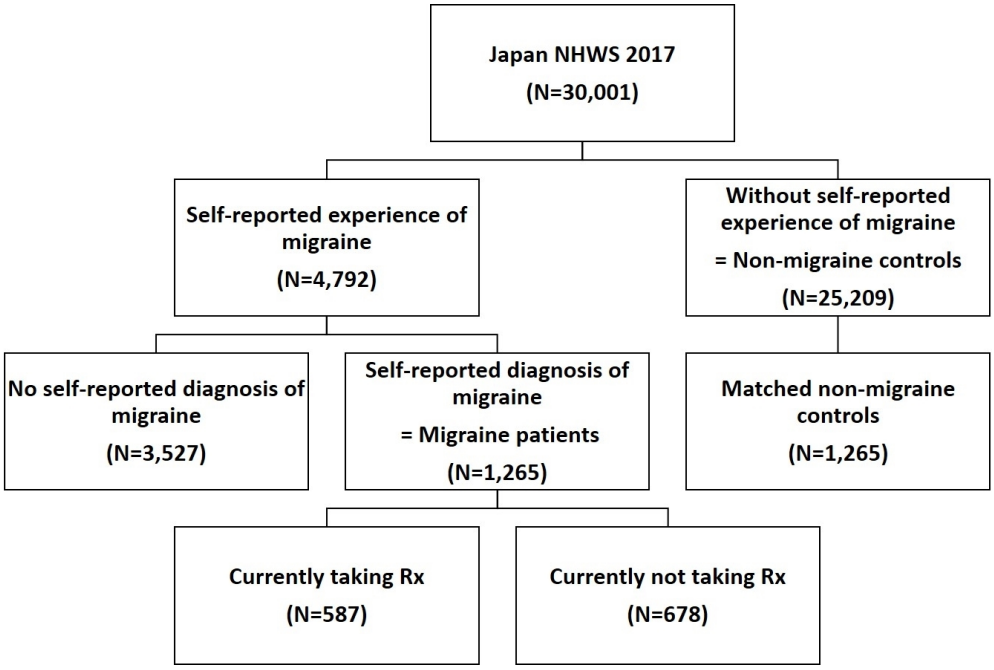

Figure 1. Respondent flow chart
Legend: Abbreviations: NHWS = National Health and Wellness Survey, Rx = prescription medication

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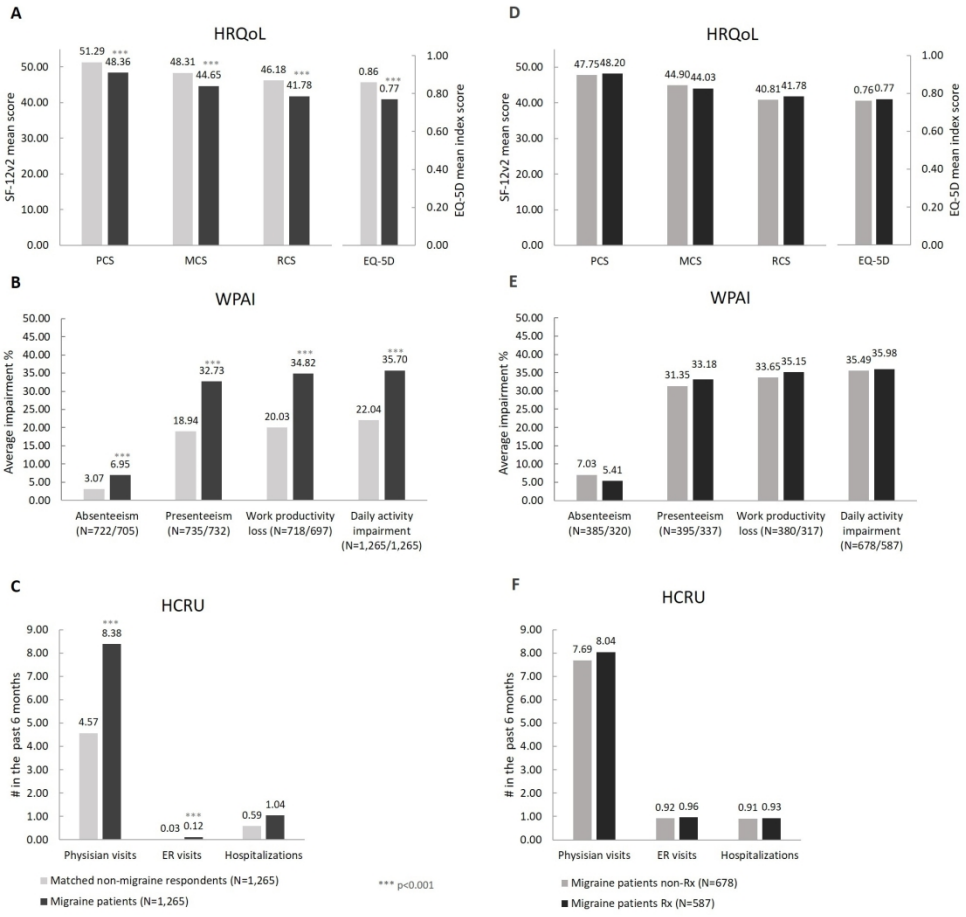

Figure 2. Comparison of health outcomes between migraine patients and matched non-migraine respondents (A-C), and between migraine patients currently taking Rx and not currently taking Rx (D-F)
Legend: A-C: Migraine patients and matched non-migraine respondents: Bivariate analysis for comparison of health outcomes between migraine patients and matched non-migraine respondents. D-F: Migraine patients currently taking prescription medication (Rx) and migraine patients not currently taking Rx: Adjusted means from GLM analysis for comparison of health outcomes between migraine patients currently taking prescription medication (Rx) and migraine patients not currently taking Rx.Abbreviations: Rx = prescription medication, HRQoL = Health-related quality of life, PCS = physical component summary score, MCS = mental component summary score, RCS = role/social component summary score, EQ-5D = EuroQol-5 Dimension, WPAI = Work Productivity and Activity Impairment, HCRU = healthcare resource utilization, ER = emergency room.

349x331mm (150 x 150 DPI)

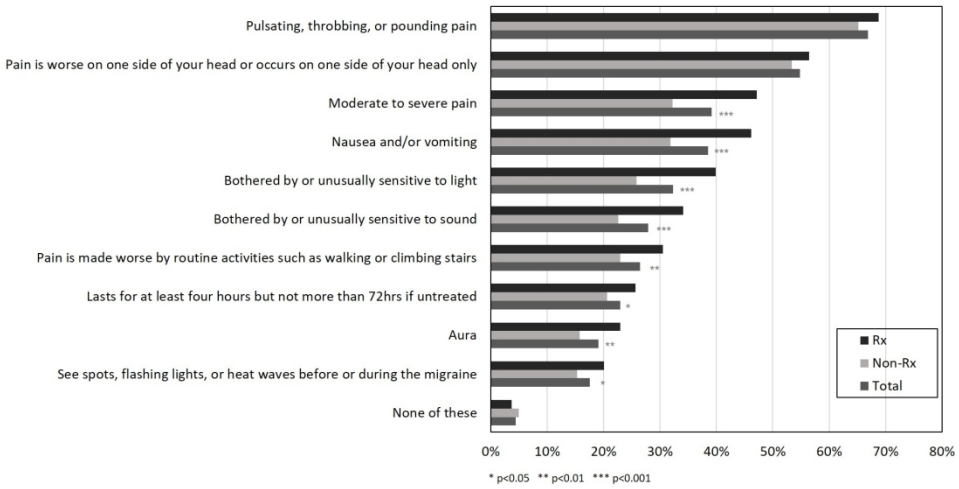

Figure 3. Migraine-related symptoms

Legend: Abbreviations: Rx = patients currently taking prescription medication, non-Rx = patients currently not taking prescription medication

333x170mm (150 x 150 DPI)

Supplementary Table 1. Bivariate comparison of demographic and health characteristics between respondents with no experience of migraine (non-migraine), patients diagnosed with migraine and matched non-migraine respondents.

		Non-migraine (N=25,209)		Matched Non-migraine (N=1,265)		Diagnosed migraine (N=1,265)		p-value	p-value
		Mean or %	[SD] or (n)	Mean or %	[SD] or (n)	Mean or %	[SD] or (n)	Non-migraine vs. Diagnosed	Matched vs. Diagnosed
Age, mean [SD]		52.80	[16.53]	43.45	[14.59]	43.79	[14.27]	< .001	.559
CCI, mean [SD]		0.17	[0.53]	0.18	[1.05]	0.24	[1.00]	< .001	.117
Gender, % (n)	Female	47.1%	(11,861)	67.4%	(852)	66.6%	(842)	< .001	.673
Employment status, % (n)	Currently employed	54.7%	(13,801)	60.1%	(760)	59.8%	(756)	< .001	.871
Household income, % (n)	<¥3,000,000	18.3%	(4623)	17.9%	(227)	18.7%	(237)	.683	.948
	¥3,000,000 to <¥5,000,000	24.4%	(6154)	24.5%	(310)	25.0%	(316)		
	¥5,000,000 to <¥8,000,000	23.9%	(6027)	25.9%	(328)	24.6%	(311)		
	¥8,000,000 or more	18.7%	(4704)	16.9%	(214)	17.0%	(215)		
	decline to answer	14.7%	(3701)	14.7%	(186)	14.7%	(186)		
Currently smoking, % (n)	Yes	41.2%	(10,385)	44.3%	(561)	44.0%	(557)	.046	.873
Currently use alcohol, % (n)	Yes	66.2%	(16,685)	63.0%	(797)	63.2%	(800)	.031	.902

Abbreviations: CCI = Charlson Comorbidity Index

Supplementary Table 2. Unadjusted bivariate comparison of health outcomes between migraine patients currently taking Rx and migraine patients not currently taking Rx

Outcomes	Non-Rx (N=678)		Rx (N=587)		p-values
	Mean	SD	Mean	SD	
HRQoL					
SF-12v2: PCS	48.70	12.42	47.96	12.16	.290
SF-12v2: MCS	45.26	10.13	43.95	10.24	.022
SF-12v2: RCS	41.93	14.40	41.61	15.40	.703
EQ-5D index score	.77	.16	.76	.16	.255
EQ-5D VAS	65.33	23.11	63.35	23.95	.134
WPAI					
Absenteeism %*	7.10	17.71	6.76	16.98	.795
Presenteeism %**	31.01	26.60	34.75	27.52	.063
Work Productivity Loss %***	33.27	28.78	36.68	28.84	.119
Daily Activity Impairment %	34.07	27.52	37.58	28.28	.026
HCRU					
Number of physician visits in the past 6 months	7.52	10.05	9.37	16.16	.013
Number of ER visits in the past 6 months	.13	.62	.10	.71	.515
Number of times hospitalized in the past 6 months	.98	4.71	1.11	8.85	.738

Abbreviations: Rx = prescription medication, SD = standard deviation, HRQoL = Health-related quality of life, SF-12v2 = Short Form 12 health survey version 2, PCS = physical component summary score, MCS = mental component summary score, RCS = role/social component summary score, EQ-5D = EuroQol 5-Dimension, WPAI = Work Productivity and Activity Impairment, HCRU = healthcare resource utilization, ER = emergency room

*Sample size of Non-Rx: N=385, Rx: N=320. **Sample size of Non-Rx: N=395, Rx: N=337. ***Sample size of Non-Rx: N=380 Rx: N=317.

pSTROBE 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	Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 5
Methods			
Study design	4	Present key elements of study design early in the paper	Page 5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	Page 5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 6-8
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	Page 6-8
Bias	9	Describe any efforts to address potential sources of bias	Not applicable
Study size	10	Explain how the study size was arrived at	Not applicable
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 6-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 8-9
		(*b*) Describe any methods used to examine subgroups and interactions	Page 9
		(*c*) Explain how missing data were addressed	Not applicable
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	Not applicable
		(*e*) Describe any sensitivity analyses	Not applicable
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	Page 10
		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	Page 10
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page 10
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
Outcome data	15*	Report numbers of outcome events or summary measures	
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	Supplementary table 1, and page 8-9
		(*b*) Report category boundaries when continuous variables were categorized	Not applicable
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Page 11-16
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 18
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	Page 19-20
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 18-19
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 20
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	Page 21

*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.

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The social burden of people with the migraine diagnosis in Japan: evidence from a population-based cross-sectional survey

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Title: The social burden of people with the migraine diagnosis in Japan: evidence from a population-based cross-sectional survey

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ABSTRACT (max. 300 words, current 292 words)

Objectives To quantify the social burden among Japanese migraine patients in the context of currently available migraine treatments, by comparison with non-migraine controls, and comparison of migraine patients currently taking prescription medication vs. not taking prescription medication.

Design Cross-sectional analysis.

Setting Data from the population-based online self-administered Japan National Health and Wellness Survey (NHWS) 2017.

Participants Respondents to the NHWS (N=30,001) were ≥18 years. Migraine patients were respondents with self-reported experience and physician diagnosis of migraine. Non-migraine controls reported no migraine experience. Migraine patients were sub-grouped into currently taking prescription medication for migraine (Rx) and currently not taking prescription medication (non-Rx).

Methods One-way ANOVA tests were performed to compare health-related quality of life (HRQoL), work productivity and activity impairment and healthcare resource utilization between migraine patients and matched non-migraine controls selected by 1:1 propensity score matching. Generalized linear models were used to compare outcomes and migraine related characteristics between Rx and non-Rx.

Results Compared to matched controls, migraine patients (N=1,265) had significantly lower HRQoL in terms of lower Physical Component Summary (48.36 vs. 51.29, p<0.001), Mental Component Summary (44.65 vs. 48.31, p<0.001), Role/Social Component Summary (41.78 vs. 46.18, p<0.001) and mean EuroQol 5-Dimension index (0.77 vs. 0.86, p<0.001) scores. Migraine patients experienced significantly higher absenteeism (6.95% vs. 3.07%, p<0.001), presenteeism (32.73% vs. 18.94%, p<0.001), work productivity loss (34.82% vs. 20.03%, p<0.001) and daily activity impairment (35.70% vs. 22.04%, p<0.001) and visited health care professionals more often (8.38 vs. 4.57, p<0.001) than controls. No significant differences in these outcomes were found when comparing Rx (N=587) and non-Rx (N=678) patients.

Conclusions There is an unmet need for improved HRQoL and work productivity in Japanese migraine patients despite the currently available prescription medications, which are important factors to consider for future development of migraine therapies.

STRENGTHS AND LIMITATIONS

- The recruitment of respondents to the Japan 2017 NHWS utilized a stratified random sampling procedure with strata by sex and age according to national census data, thereby ensuring that the demographic composition of the sample was representative of the adult population in Japan.

- This study used the validated instruments Short Form-12 version 2, EuroQol-5 Dimension, Work Productivity and Activity Impairment questionnaire to quantify the burden of migraine and Headache Impact Test for assessment of headache-related disability.

- The data from NHWS is cross-sectional and no causal relationships can be assumed.

- As all data are self-reported, no verification of patient reported outcomes was conducted, and data is subject to recall bias.

- Although NHWS is broadly representative of the Japanese adult population, it is unclear the extent to which the migraine patients and migraine patients taking Rx are representative of the larger population.

INTRODUCTION

Migraine is a common disabling headache disorder, known to impose a burden on both patients and societies worldwide[1–3]. Since 1990, migraine has been the second leading cause of years lived with disability (YLD) and the sixth most prevalent disease[4]. Globally the prevalence of migraine has been estimated to be 11.6%, and in Asia 10.1%[5]. The 1-year prevalence of migraine among adults in East Asia ranged from 6.0% to 14.3%[6]. In Japan, the prevalence has been estimated to be between 6.0 - 8.9%, with the 1-year prevalence among non-elderly adults reported at 6.0%[6–9].

A recent study of European migraine patients showed that suffering from at least 4 monthly headache days (MHDs) was associated with poorer health related quality of life (HRQoL), high healthcare resource utilizations (HCRU) and loss of work productivity compared to non-migraine controls[1]. In another study among migraine patients with at least 4 MHDs and had failed at least one preventive migraine treatment, impact of migraine on professional, private, and social domains were reported by 70%, 64% and 78% of the respondents, respectively[10]. Migraine was also reported to be associated with a high economic burden, with annual direct cost of chronic migraine substantially higher than that of episodic migraine[11]. In Japan, previous studies have also reported an incremental impact of migraine on patients' social life and work. In a nationwide survey from 1997, 30% of migraine patients reported a severe impairment of their daily activities where bed rest was frequently required. Furthermore, 32% of migraine patients reported moderate to severe impairment in social activities including cancellation of work and daily appointments[7]. Similarly, in the regional Daisen study from 1999, 20.3% of migraine patients reported that they had experienced time or days off from work and 27.3% reported being unable to do housework[8]. The general health perception was worse compared to non-headache subjects, as migraine patients more often reported their health as "poor" and half of the patients

suffered from sleep disturbance[8]. Despite the disabling impact of migraine, both surveys revealed large populations of underdiagnosed and undertreated migraine patients. More than 60% of patients had never consulted a physician for headache, as few as 5%–7% of patients continuously consulted a physician for migraine[7,8], and only 11.6% of patients were aware that their headache was migraine[7,8]. Further studies have investigated the impact of migraine on the active Japanese workforce, which found that 22.4% of migraineurs had missed work due to headaches several times in the past year[9]. Additionally, migraine and headaches were the leading cause of absence from work (absenteeism) for employed women in their 50s (6.2 days of absence, 4 weeks recall period), and the leading cause of not being able to fully perform while at work (presenteeism) for employed men in their 20s with 49.5 hours lost in the last 4 weeks[12].

With these most recent studies of migraine burden performed in 2008[9] and 2013[12], there has been a paucity in research and there is a need for updated data to gain further insights and understand the current burden of migraine in Japan, in the context of currently available treatments. Therefore, the objective of this study was to quantify the migraine associated burden by comparison of HRQoL, work productivity and activity impairment (WPAI) and HCRU in migraine patients and people without migraine experience, and among the treated migraine population vs. non-treated migraine population.

METHODS

This research was a cross-sectional study using data from the National Health and Wellness Survey (NHWS) conducted in 2017. NHWS is an online self-administered survey and was granted exemption status upon review by Pearl International Review Board (Indianapolis, IN). All respondents provided informed consent prior to participating.

Study population

Respondents to the NHWS were aged 18 years or older and were recruited from web-based opt-in consumer panels. Respondents were already members of these panels, recruited through opt-in emails, co-registration with panel partners, newsletter campaigns, banner placements and had provided informed consent prior to participation. Recruitment of NHWS respondents utilized a stratified random sampling procedure, with strata by sex and age according to census data from the US census database which sources from the Japan Ministry of Internal Affairs & Communications[13], which was implemented to ensure that the demographic composition of the sample was representative of the Japan adult population. Representation of NHWS data has been validated and weighted against reliable sources including government agencies' health statistics and unaffiliated third parties[14,15]. Respondents who self-reported a physician diagnosis of migraine were included in the migraine patient group. Those who self-reported no experience of migraine were the non-migraine controls. Respondents with self-reported physician diagnosis of migraine were further sub-grouped into patients who reported currently taking prescription medication for migraine (Rx) and patients currently not taking any prescription medication (non-Rx).

Patient involvement

Patients and respondents to NHWS were not involved in setting the research questions, outcomes measures nor the design of the study. The data used in this study were obtained from patients and respondents who provided self-reported information in the NHWS.

Measures

Covariates

The demographic and general health characteristics included: gender, age, marital status, number of children living in the household, household income, employment status, smoking status, alcohol use, exercise behaviour and Charlson Comorbidity Index (CCI)[16–18].

Measures

HRQoL was assessed by the Short Form-12 health survey version 2 (SF-12v2)[19], which consists of 12 questions with summary scores that was translated and validated for use in the Japanese population[20,21]. The mental component summary score (MCS), physical component summary score (PCS) and role/social component summary (RCS) were calculated based on survey responses. Each domain and summary score was calculated using a norm-based scoring algorithm which allows for all measures to be viewed together on the same graph and allows for scores to be interpreted relative to population means. Higher scores indicate better quality of life.

Health state utilities were quantified with the EuroQol 5-Dimension 5 Levels (EQ-5D 5L) instrument, which is a standardized measure of health status to provide a simple, generic measure of health[22]. EQ-5D index score is a single summary index derived from the EQ-5D 5L questions[23], scored by using the Japanese tariff. Higher scores indicate better health status. In addition, the EuroQol visual analogue scale (EQ VAS) was used which records the patient's self-rated health on a 100mm VAS, where the endpoints are labelled 'The best health you can imagine' (100) and 'The worst health you can imagine' (0). The VAS can be used as a quantitative measure of health outcome that reflect the patient's own judgement.

For work productivity assessment, the Work Productivity and Activity Impairment (WPAI) questionnaire[24] was used to measure the impact of health on both employment-related and daily activities. This six-item validated instrument consists of four metrics: absenteeism (the percentage of work time missed because of one's health in the past 7 days), presenteeism (the

percentage of impairment experienced because of one's health while at work in the past 7 days), overall work productivity loss (an overall impairment estimate that is a combination of absenteeism and presenteeism), and daily activity impairment (the percentage of impairment in daily activities because of one's health in the past 7 days). These four subscales are generated in the form of percentages, with higher values indicating greater impairment. Only respondents who reported being full-time, part-time, or self-employed provide data for absenteeism, presenteeism, and overall work impairment. All respondents provide data for activity impairment.

HCRU was considered in terms of the number of outpatient visits in the past 6 months to healthcare providers (practitioner/family practitioners, internists, and dentists as well as more specialized physicians), the emergency room (ER), and the hospitalization for the participant's own medical condition.

Respondents with migraine utilized the validated Headache Impact Test (HIT-6) scale for assessment of headache-related disability[25]. Scores from HIT-6 range from 36 to 78. A higher HIT-6 score indicates a greater impact of headache on the daily life of respondents.

Migraine-specific characteristics and treatment

All migraine patients were asked several questions in relation to their migraine including the symptoms experienced due to migraine, number of years experiencing migraine, diagnosing physician, number of migraines in the past 30 days and in the past 6 months, number of headache days in the past 30 days, experienced migraine related to menstrual cycle, days of missed work due to migraine in the past 6 months, days of missed household activities due to migraine in the past 6 months, current use of prescription medication (Rx) to treat or prevent migraine, and usage of over-the-counter (OTC) or herbal products to treat migraine.

Respondents specified the type of Rx which included the following drug classes: triptan,

anticonvulsant, beta blocker, non-steroidal anti-inflammatory drugs (NSAIDs) and others. The top 10 self-reported OTC and herbal products contained the following active ingredients: loxoprofen, aspirin, ibuprofen, acetaminophen, chondroitin, and ergotamine. In addition, respondents with migraine answered the validated HIT-6 scale for assessment of headache-related disability[25].

Statistical analysis

Demographic factors and general health characteristics were compared between migraine patients and non-migraine controls to understand the baseline differences in the two groups. Demographic factors, general health characteristics, and migraine-specific variables were summarized descriptively among migraine patients. Age, CCI, gender, employment status, household income, smoking status, and alcohol use were used in the 1:1 propensity score matching using a greedy matching algorithm to form the matched non-migraine control group. Post-matching bivariate comparisons were conducted between migraine patients and matched non-migraine respondents to assess the balance of the matching. After propensity score matching, outcomes were compared between patients with migraine and matched non-migraine controls. One-way ANOVA tests were used for comparison of these continuous outcome variables.

Demographic factors, general health characteristics, migraine-specific variables (including migraine-related symptoms) were also compared between migraine patients currently taking Rx and not currently taking Rx, using chi-square test for categorical variables and one-way analyses of variance (ANOVA) for continuous variables. Generalized linear models (GLMs) were used to compare the outcomes between migraine patients currently taking Rx and migraine patients currently not taking Rx, accounting for demographic and clinical characteristics of the patients. Normal distribution with identity link were specified in the

GLMs for normally distributed outcomes, such as HRQoL scores. Negative binomial distribution with log link were specified for outcomes with skewed distributions, such as WPAI and HCRU. Estimated adjusted means and p-values were reported for each health outcome. All outcome variables were pre-determined before the analyses and the analyses were not of exploratory manner. No correction for multiple testing was conducted for this study. Complete data were available, and no imputation was carried out. For all analyses, statistical significance was assessed at a significance level of 0.05. All data analyses were performed using IBM SPSS Statistics Version 22[26] and R Version 3.4.4[27].

RESULTS

A total of 25,209 respondents without self-reported experience with migraine were included in the non-migraine group and 4,792 respondents self-reported experience with migraine (Figure 1). Among the 4,792 respondents who self-reported experience with migraine, 74% (n=3,527) had never been diagnosed by a physician. The 1,265 respondents with self-reported physician diagnosed migraine were included in the migraine patient group for the further analyses.

On average, migraine patients tend to be younger than non-migraine respondents (43.8 vs. 52.8 years, $p < 0.001$) and have a significantly higher CCI index (0.24 vs. 0.17, $p < 0.001$) (Supplementary Table 1). More migraine patients are female (66.6% vs. 47.1%, $p < 0.001$), currently employed (59.8% vs. 54.7%, $p < 0.001$) and have children in the household (27.7% vs. 18.6% $p < 0.001$). Compared to controls, fewer migraine patients are married/living with partner (53.1% vs. 62.5%, $p < 0.001$) and have completed university (42.5% vs. 49.2%, $p < 0.001$). Migraine patients have similar household income to non-migraine respondents. A slightly higher percentage of migraine patients currently smoke (44.0% vs. 41.2%, p=0.046) compared to non-migraine respondents, but slightly fewer migraine patients currently

consume alcohol (63.2% vs. 66.2%, p=0.031). Detailed results are listed in Supplementary Table 1.

Comparison of outcomes in migraine patients vs. matched non-migraine controls

After 1:1 propensity score matching, the majority of demographic and clinical characteristics were balanced between migraine patients and matched non-migraine controls (Supplementary Table 1). Bivariate comparison between matched non-migraine controls and migraine patients were conducted to evaluate the burden of migraine in terms of HRQoL, WPAI and HCRU (Figure 2). We found that migraine patients had significantly lower PCS (48.36 vs. 51.29, p<0.001), MCS (44.65 vs. 48.31, p<0.001), and RCS (41.78 vs. 46.18, p<0.001) scores as well as significantly lower EQ-5D index (0.77 vs. 0.86, p<0.001) and EQ-5D VAS (64.41 vs. 73.49, p<0.001) scores. The differences in MCS and RCS between the two groups were more than 3 points, which is defined as a minimum clinically important difference (MCID)[28] (Figure 2A).

In terms of WPAI, migraine patients experienced significantly higher absenteeism (6.95% vs. 3.07%, p<0.001), presenteeism (32.73% vs. 18.94%, p<0.001), work productivity loss (34.82% vs. 20.03%, p<0.001) and daily activity impairment (35.70% vs. 22.04%, p<0.001) compared to matched controls (Figure 2B).

Compared to controls, migraine patients visited health care professionals (HCPs) almost twice as often (8.38 vs. 4.57, p<0.001) and visited the ER 4 times as often (0.12 vs. 0.03, p<0.001). There were no significant differences in the number of hospitalizations between the two groups (Figure 2C).

Migraine-related health characteristics among migraine patients

On average, patients received a migraine diagnosis 11.77 years ago (standard deviation (SD) 10.84), and the majority (58.3%) were diagnosed by a primary care physician/general practitioner (GP)/internist (Table 1). On average, patients experienced migraine 4.69 times (SD 6.22) in the past 30 days and 23.36 times (SD 33.72) in the past 6 months. In the past 30 days, migraine patients had an average of 6.45 (SD 7.02) headache days. Among female migraine patients, 41.4% experienced menstrual-related migraine. An average of 1.62 days of work and 2.94 days of household activities were missed due to migraine in the past 6 months. Among all patients, the average HIT-6 score was 59.37 (SD 7.97) and more than half (57.2%) of patients were severely impacted (HIT-6 score ≥60)[25].

The most common migraine-related symptom was pulsating, throbbing, or pounding pain (66.9%), followed by "pain being worse on one side of your head or occurs on one side of your head only" (54.8%), moderate to severe pain (39.1%), nausea and/or vomiting (38.5%), bothered by or unusually sensitive to light (32.3%), bothered by or unusually sensitive to sound (27.9%), pain made worse by routine activities such as walking or climbing stairs (26.5%), migraine lasting for at least four hours but not more than 72 hours if untreated (23.0%), aura (19.1%), and seeing spots, flashing lights, or "heat waves" before or during the migraine (17.5%). 4.4% of patients experienced none of the above symptoms (Figure 3).

Table 1. Bivariate comparison of migraine-related health characteristics in diagnosed migraine patients and patients currently taking Rx vs. patients not currently taking Rx (non-Rx).

		Diagnosed migraine patients (N=1,265)		Non-Rx (N=678)		Rx (N=587)		p-value Non-Rx vs. Rx
		Mean or %	[SD] or (n)	Mean or %	[SD] or (n)	Mean or %	[SD] or (n)	
Time since migraine (years), mean [SD]*		11.27	[10.87]	11.14	[11.20]	11.44	[10.41]	.635
Diagnosing physician, % (n)*	Primary Care Physician/GP/Internist	58.3%	(686)	60.3%	(409)	55.5%	(277)	.181
	Neurologist	27.2%	(320)	25.2%	(171)	29.9%	(149)	
	Other	14.5%	(171)	14.5%	(98)	14.6%	(73)	
Number of migraine in the past 30 days, mean [SD]		4.69	[6.22]	3.61	[5.54]	5.95	[6.72]	< .001
Number of migraine in the past 6 months, mean [SD]		23.36	[33.72]	17.70	[29.13]	29.91	[37.31]	< .001
Days missed work due to migraine in the past 6 months, mean [SD]		1.62	[10.24]	1.39	[9.37]	1.89	[11.17]	.384
Days of household activities missed due to migraine in the past 6 months, mean [SD]		2.94	[12.67]	1.81	[5.70]	4.25	[17.48]	< .001
Number of headache days in the past 30 days, mean [SD]		6.45	[7.02]	5.12	[5.88]	7.70	[7.75]	< .001
Number of headache days in the past 30 days, % (n)	0-3 MHDs	49.4%	(365)	57.3%	(205)	42.0%	(160)	< .001
	4-14 MHDs	36.8%	(272)	33.8%	(121)	39.6%	(151)	
	≥15 MHDs	13.8%	(102)	8.9%	(32)	18.4%	(70)	
	Don't know	24.0%	(304)	24.4%	(161)	24.0%	(143)	
	Not asked	17.5%	(222)	10.7%	(159)	17.5%	(63)	
Menstrual-related migraine (N=female only), % (n)**		41.4%	(349)	38.0%	(167)	45.3%	(182)	.031
Use of OTC/Herbal products to treat migraine, % (n)		12.9%	(163)	14.6%	(99)	10.9%	(64)	.050
Currently using Rx to treat or prevent migraine, % (n)		46.4%	(587)	-	-	100%	(587)	-
Acute medication only, % (n)***		77.5%	(455)	-	-	77.5%	(455)	
Preventive medication only, % (n)***		14.3%	(84)	-	-	14.3%	(84)	
Both, % (n)***		8.2%	(48)	-	-	8.2%	(48)	
HIT-6 score, mean [SD]		59.37	[7.97]	57.76	[8.00]	61.23	[7.52]	< .001
HIT-6 impact grade, % (n)	Little to no impact	11.3%	(143)	14.9%	(101)	7.2%	(42)	< .001
	Moderate impact	16.3%	(206)	19.8%	(134)	12.3%	(72)	
	Substantial impact	15.3%	(193)	16.4%	(111)	14.0%	(82)	
	Severe impact	57.2%	(723)	49.0%	(332)	66.6%	(391)	

Abbreviations: Rx = prescription medication, SD = standard deviation, GP = General practitioner, MHD = monthly headache day, OTC = over-the-counter medication, HIT = Headache Impact Test.

*Sample size of diagnosed migraine patients who reported the time since diagnosis: N=1177, Non-Rx: N=678, Rx: N=499. **Sample size of diagnosed migraine patients: N=842, Non-Rx: N=440, Rx: N=402. ***Sample size of diagnosed migraine patients taking Rx: N=587.

Treatment use in migraine patients

Among all migraine patients, the majority (678; 53.6%) were not currently taking any prescription medication (Rx) (Figure 1). 587 (46.4%) were currently taking prescription medication (Rx), whereof 77.5% currently used acute treatment, 14.3% used preventive treatments and 8.2% used both (Table 1). Of the 678 migraine patients not currently taking Rx, 384 (56.6%) had previously used a prescription medication and 294 (43.4%) had never used a prescription medication, and 50 (17.0%) of the 294 patients had been recommended a prescription medication by the physician before. Of the migraine patients not currently taking Rx, 99 (14.6%) had used OTC or herbal product to treat migraine. Out of the total 1,265 migraine patients, only 163 patients (12.9%) had used OTC or herbal product to treat migraine and 142 patients recalled the name of the OTCs they used.

Comparison of outcomes in Rx patients vs. non-Rx patients

There were no differences in demographic characteristics between the Rx and non-Rx group, except for marital status. Significantly fewer patients taking Rx were married or living with partner (47.0% vs. 58.4%, $p<0.001$) (Table 2). In terms of migraine-related characteristics, migraine patients currently taking Rx experienced migraine significantly more often in the past 30 days (5.95 vs. 3.61, $p<0.001$) and in the past 6 months (29.91 vs. 17.70, $p<0.001$) compared to those not currently taking Rx (Table 1). More days of household activities (4.25 vs. 1.81, $p<0.001$) were missed due to migraine among patients currently taking Rx and a significantly higher percentage of patients had ≥15 MHDs (18.4% vs. 8.9%, $p<0.001$) (Table 1). A significantly higher average HIT-6 score (61.23 vs. 57.76, $p<0.001$) was observed among migraine patients currently taking Rx and a higher percentage were determined to have severe impact (66.6% vs. 49.0%, $p<0.001$) (Table 1).

Without adjustment, the bivariate comparisons of outcomes in Rx vs. non-Rx showed that migraine patients currently taking Rx had a lower MCS, higher daily activity impairment and increased number of visits to physicians in the past 6 months. No other differences in outcomes were observed (Supplementary Table 2).

After adjusting for potential confounding effects (age, CCI, gender, marital status, currently employed and number of migraines in the past 30 days), no significant differences in HRQoL, WPAI or HCRU were found between the two groups (Figure 2 D-F).

Table 2. Bivariate comparison of demographics and general health characteristics in diagnosed migraine patients and patients currently taking Rx vs. patients not currently taking Rx (non-Rx).

		Diagnosed migraine patients (N=1,265)		Non-Rx (N=678)		Rx (N=587)		p-value No Rx vs. Rx
		Mean or %	[SD] or (n)	Mean or %	[SD] or (n)	Mean or %	[SD] or (n)	
Age, mean [SD]		43.79	[14.27]	44.06	[14.82]	43.47	[13.61]	.463
Gender, % (n)	Female	66.6%	(842)	64.9%	(440)	68.5%	(402)	.177
Marital status, % (n)	Married or living with partner	53.1%	(672)	58.4%	(396)	47.0%	(276)	< .001
Having children <18 in the household, % (n)	Yes	27.7%	(351)	27.7%	(188)	27.8%	(163)	.987
Employment status, % (n)	Currently employed	59.8%	(756)	60.0%	(407)	59.5%	(349)	.835
Household income, % (n)	<¥3,000,000	18.7%	(237)	18.4%	(125)	19.1%	(112)	.318
	¥3,000,000 to <¥5,000,000	25.0%	(316)	24.2%	(164)	25.9%	(152)	
	¥5,000,000 to <¥8,000,000	24.6%	(311)	26.0%	(176)	23.0%	(135)	
	¥8,000,000 or more	17.0%	(215)	18.1%	(123)	15.7%	(92)	
	decline to answer	14.7%	(186)	13.3%	(90)	16.4%	(96)	
CCI, mean [SD]		0.24	[1.00]	0.19	[0.60]	0.29	[1.32]	.072
Currently smoking, % (n)	Yes	44.0%	(557)	43.8%	(297)	44.3%	(260)	.862
Currently use alcohol, % (n)	Yes	63.2%	(800)	64.9%	(440)	61.3%	(360)	.189
Currently exercise, % (n)	Yes	44.3%	(561)	43.4%	(294)	45.5%	(267)	.449

Abbreviations: CCI = Charlson Comorbidity Index, Rx = prescribed medication

DISCUSSION

In this study we found that migraine patients in Japan experience a significant burden of illness compared to matched controls without migraine in terms of lower HRQoL, higher WPAI and HCRU (Figure 2), and 88.8% of patients reported that migraine had a moderate to severe impact on their daily life (HIT-6 score) (Table 1). Compared to matched controls, migraine patients had 2.93 points decreased PCS ($p<0.001$) and more than 3 points decreased MCS (3.66 points, $p<0.001$) and RCS (4.40 points, $p<0.001$) (Figure 2), which indicates that migraine has a clinically significant impact on migraine patients' mental health and role/social functioning. In comparison, similarly lower MCS scores have been reported in Japanese patients with arthritis (-3.4 points) and ischemic heart disease (-4.1) compared to controls, and similarly lower PCS scores were reported in patients with diabetes (-3.0 point), chronic lung disease (-3.1 point) and ischemic heart disease (-2.6 points)[29].

In addition to lower HRQoL, we observed that migraine patients who were currently employed had higher levels of work productivity loss compared to matched non-migraine controls, with 2.2-fold higher absenteeism ($p<0.001$), 1.7-fold higher presenteeism ($p<0.001$) and 1.7-fold higher work productivity loss ($p<0.001$) (Figure 2). The actual work loss that Japanese migraine patients experience was thereby quantified based on the validated WPAI tool[24], and supports the previous findings that migraine can cause a substantial loss of work productivity[7–9,12].

The finding in this current study that 74% of surveyed participants who reported ever having experienced migraine had not received a physician diagnosis of migraine indicates a large population of underdiagnosed migraine patients in Japan. This is supported by other studies showing that large proportions of migraine sufferers never consulted a physician[7,8].

Additionally, in this study we found that more than half of the diagnosed migraine patients (53.6%) were currently not receiving treatment with prescribed medication (non-Rx) (Figure

1). However, 56.6% of non-Rx had previously received treatment which indicates a high treatment discontinuation rate which is supported by the previous study by Meyers et al. where 62.2% discontinued prophylactic treatment after an average of 61.2 days[30]. Also, 43.4% of non-Rx patients have not previously received prescription medication which reflects an unmet need for treatment. Other studies have similarly described that 30 – 60% of migraine patients had never received prescription of preventive therapy[31], and that lack of efficacy and side effects were the most common reasons for discontinuation of both acute and preventive therapy[31–34]. A recent study reported that among Japanese migraine patients who visited HCPs, lack of efficacy with both preventive (anticonvulsants and calcium antagonist) and acute treatment (triptans and NSAIDs) was experienced by half and a third of the patients, respectively[31].

Migraine patients currently taking prescribed medication (Rx) had significantly worse migraine-related characteristics compared to migraine patients currently not taking any Rx (Table 1, Figure 3). This indicates that those taking Rx suffer from more severe migraine. Interestingly, migraine patients receiving Rx suffer similar impairment of HRQoL and work productivity as non-Rx patients (Figure 2). This indicates that despite currently available preventive and acute treatments for migraine[6,10], there is an unmet need for improved HRQoL and work productivity among migraine patients, implying that current treatments have limited effects on these outcomes for patients. Additionally, only 14.3% of patients currently taking Rx received preventive treatments for migraine, indicating a lack of prescription of preventive therapy. These are important factors to consider for future treatment development.

The limitations of the study should be recognized. The data from NHWS is cross-sectional and no causal relationships can be assumed. As all data are self-reported, no verification of migraine diagnosis or patient reported outcomes was conducted, and data is subject to recall

bias. Although NHWS is broadly representative of the Japanese adult population, it is unclear the extent to which the migraine patients and migraine patients taking Rx are representative of the larger population. Due to the design of the survey, the reasons for not taking Rx or for discontinuation of Rx (e.g. less migraine episodes or lack of efficacy) were not reported and could not be concluded. Also, NWHS primarily relied upon respondents with Internet access and these patients could potentially be different from the broader population (e.g., more knowledgeable or engaged in their healthcare).

CONCLUSION

Migraine patients in Japan experience a significant burden of illness with decreased HRQoL, around 2-fold increased work productivity loss and twice as many visits to HCPs compared to non-migraine controls. There is a large proportion of both underdiagnosed and undertreated migraine patients. The migraine patients not receiving prescribed medication for treatment of their disease suffer similarly decreased HRQoL and high levels of work productivity loss as patients currently receiving prescribed medication. These results indicate an unmet need for improved HRQoL and work productivity in Japanese migraine patients despite the currently available prescription medications, which are important factors to consider for future development of migraine therapies.

AUTHOR CONTRIBUTIONS

HI, KU and TN conceptualized the study and analysed and interpreted the data. SJ, ZC and YC designed the analysis plan, conducted the analyses and interpreted the data. All authors revised the manuscript drafts for intellectual content and edited the manuscript. All authors reviewed and approved the final draft.

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PATIENT CONSENT FOR PUBLICATION

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ETHIS APPROVAL

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DATA SHARING STATEMENT

Data are available upon reasonable request.

REFERENCES

1 Vo P, Fang J, Bilitou A, *et al.* Patients' perspective on the burden of migraine in Europe: a cross-sectional analysis of survey data in France, Germany, Italy, Spain, and the United Kingdom. *J Headache Pain* 2018;**19**:82. doi:10.1186/s10194-018-0907-6

2 Yao C, Wang Y, Wang L, *et al.* Burden of headache disorders in China, 1990-2017: findings from the Global Burden of Disease Study 2017. *J Headache Pain* 2019;**20**:102. doi:10.1186/s10194-019-1048-2

3 Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. *Cephalalgia Int J Headache* 2018;**38**:1–211. doi:10.1177/0333102417738202

4 GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Lond Engl* 2017;**390**:1211–59. doi:10.1016/S0140-6736(17)32154-2

5 Woldeamanuel YW, Cowan RP. Migraine affects 1 in 10 people worldwide featuring recent rise: A systematic review and meta-analysis of community-based studies involving 6 million participants. *J Neurol Sci* 2017;**372**:307–15. doi:10.1016/j.jns.2016.11.071

6 Takeshima T, Wan Q, Zhang Y, *et al.* Prevalence, burden, and clinical management of migraine in China, Japan, and South Korea: a comprehensive review of the literature. *J Headache Pain* 2019;**20**:111. doi:10.1186/s10194-019-1062-4

7 Sakai F, Igarashi H. Prevalence of migraine in Japan: a nationwide survey. *Cephalalgia Int J Headache* 1997;**17**:15–22. doi:10.1046/j.1468-2982.1997.1701015.x

8 Takeshima T, Ishizaki K, Fukuhara Y, *et al.* Population-based door-to-door survey of migraine in Japan: the Daisen study. *Headache* 2004;**44**:8–19. doi:10.1111/j.1526-4610.2004.04004.x

9 Suzuki N, Ishikawa Y, Gomi S, *et al.* Prevalence and characteristics of headaches in a socially active population working in the Tokyo metropolitan area -surveillance by an industrial health consortium. *Intern Med* 2014;**53**:683–9. doi:10.2169/internalmedicine.53.1700

10 Martelletti P, Schwedt TJ, Lanteri-Minet M, *et al.* My Migraine Voice survey: a global study of disease burden among individuals with migraine for whom preventive treatments have failed. *J Headache Pain* 2018;**19**:115. doi:10.1186/s10194-018-0946-z

11 Negro A, Sciattella P, Rossi D, *et al.* Cost of chronic and episodic migraine patients in continuous treatment for two years in a tertiary level headache Centre. *J Headache Pain* 2019;**20**:120. doi:10.1186/s10194-019-1068-y

12 WADA K, ARAKIDA M, WATANABE R, *et al.* The Economic Impact of Loss of Performance Due to Absenteeism and Presenteeism Caused by Depressive Symptoms

and Comorbid Health Conditions among Japanese Workers. *Ind Health* 2013;**51**:482–9. doi:10.2486/indhealth.2013-0016

13 United States Census Bureau. International Data Base. https://www.census.gov/data-tools/demo/idb/informationGateway.php

14 Bolge SC, Doan JF, Kannan H, *et al.* Association of insomnia with quality of life, work productivity, and activity impairment. *Qual Life Res Int J Qual Life Asp Treat Care Rehabil* 2009;**18**:415–22. doi:10.1007/s11136-009-9462-6

15 DiBonaventura MD, Wagner J-S, Yuan Y, *et al.* Humanistic and economic impacts of hepatitis C infection in the United States. *J Med Econ* 2010;**13**:709–18. doi:10.3111/13696998.2010.535576

16 Charlson ME, Pompei P, Ales KL, *et al.* A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;**40**:373–83.

17 Charlson ME, Charlson RE, Peterson JC, *et al.* The Charlson comorbidity index is adapted to predict costs of chronic disease in primary care patients. *J Clin Epidemiol* 2008;**61**:1234–40. doi:10.1016/j.jclinepi.2008.01.006

18 Quan H, Li B, Couris CM, *et al.* Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol* 2011;**173**:676–82. doi:10.1093/aje/kwq433

19 Brazier JE, Roberts J. The Estimation of a Preference-Based Measure of Health From the SF-12: *Med Care* 2004;**42**:851–9. doi:10.1097/01.mlr.0000135827.18610.0d

20 Fukuhara S, Bito S, Green J, *et al.* Translation, adaptation, and validation of the SF-36 Health Survey for use in Japan. *J Clin Epidemiol* 1998;**51**:1037–44. doi:10.1016/s0895-4356(98)00095-x

21 Fukuhara S, Ware JE, Kosinski M, *et al.* Psychometric and clinical tests of validity of the Japanese SF-36 Health Survey. *J Clin Epidemiol* 1998;**51**:1045–53. doi:10.1016/s0895-4356(98)00096-1

22 EuroQol - a new facility for the measurement of health-related quality of life. *Health Policy* 1990;**16**:199–208. doi:10.1016/0168-8510(90)90421-9

23 Shiroiwa T, Fukuda T, Ikeda S, *et al.* Japanese population norms for preference-based measures: EQ-5D-3L, EQ-5D-5L, and SF-6D. *Qual Life Res* 2016;**25**:707–19. doi:10.1007/s11136-015-1108-2

24 Reilly MC, Gooch KL, Wong RL, *et al.* Validity, reliability and responsiveness of the Work Productivity and Activity Impairment Questionnaire in ankylosing spondylitis. *Rheumatol Oxf Engl* 2010;**49**:812–9. doi:10.1093/rheumatology/kep457

25 Kosinski M, Bayliss MS, Bjorner JB, *et al.* A six-item short-form survey for measuring headache impact: the HIT-6. *Qual Life Res Int J Qual Life Asp Treat Care Rehabil* 2003;**12**:963–74. doi:10.1023/a:1026119331193

26 *IBM SPSS Statistics for Windows, Version 22.0*. IBM Corp 2013.

27 R Core Team. *R: A language and environment for statistical computing*. Vienna, Austria: : R Foundation for Statistical Computing 2018. https://www.R-project.org/

28 Maruish ME. *User's Manual for the SF-36v2 Health Survey*. 3rd ed. Quality Metric Incorporated 2011.

29 Alonso J, Ferrer M, Gandek B, *et al.* Health-related quality of life associated with chronic conditions in eight countries: Results from the International Quality of Life Assessment (IQOLA) Project. *Qual Life Res* 2004;**13**:283–98. doi:10.1023/B:QURE.0000018472.46236.05

30 Meyers JL, Davis KL, Lenz RA, *et al.* Treatment patterns and characteristics of patients with migraine in Japan: A retrospective analysis of health insurance claims data. *Cephalalgia* 2019;**39**:1518–34. doi:10.1177/0333102419851855

31 Ueda K, Ye W, Lombard L, *et al.* Real-world treatment patterns and patient-reported outcomes in episodic and chronic migraine in Japan: analysis of data from the Adelphi migraine disease specific programme. *J Headache Pain* 2019;**20**:68. doi:10.1186/s10194-019-1012-1

32 Lipton RB, Hutchinson S, Ailani J, *et al.* Discontinuation of Acute Prescription Medication for Migraine: Results From the Chronic Migraine Epidemiology and Outcomes (CaMEO) Study. *Headache J Head Face Pain* 2019;**59**:1762–72. doi:10.1111/head.13642

33 Wells RE, Markowitz SY, Baron EP, *et al.* Identifying the Factors Underlying Discontinuation of Triptans. *Headache* 2014;**54**:278–89. doi:10.1111/head.12198

34 Blumenfeld AM, Bloudek LM, Becker WJ, *et al.* Patterns of Use and Reasons for Discontinuation of Prophylactic Medications for Episodic Migraine and Chronic Migraine: Results From the Second International Burden of Migraine Study (IBMS-II). *Headache J Head Face Pain* 2013;**53**:644–55. doi:10.1111/head.12055

FIGURE LEGENDS

Figure 1. Respondent flow chart

Abbreviations: NHWS = National Health and Wellness Survey, Rx = prescription medication

Figure 2. Comparison of health outcomes between migraine patients and matched non-migraine respondents (A-C), and between migraine patients currently taking Rx and not currently taking Rx (D-F)

A-C: Migraine patients and matched non-migraine respondents: *Bivariate analysis for comparison of health outcomes between migraine patients and matched non-migraine respondents.* ***D-F: Migraine patients currently taking prescription medication (Rx) and migraine patients not currently taking Rx:*** *Adjusted means from GLM analysis for comparison of health outcomes between migraine patients currently taking prescription medication (Rx) and migraine patients not currently taking Rx.*

Abbreviations: Rx = prescription medication, HRQoL = Health-related quality of life, PCS = physical component summary score, MCS = mental component summary score, RCS = role/social component summary score, EQ-5D = EuroQol-5 Dimension, WPAI = Work Productivity and Activity Impairment, HCRU = healthcare resource utilization, ER = emergency room.

Figure 3. Migraine-related symptoms

Abbreviations: Rx = patients currently taking prescription medication, non-Rx = patients currently not taking prescription medication

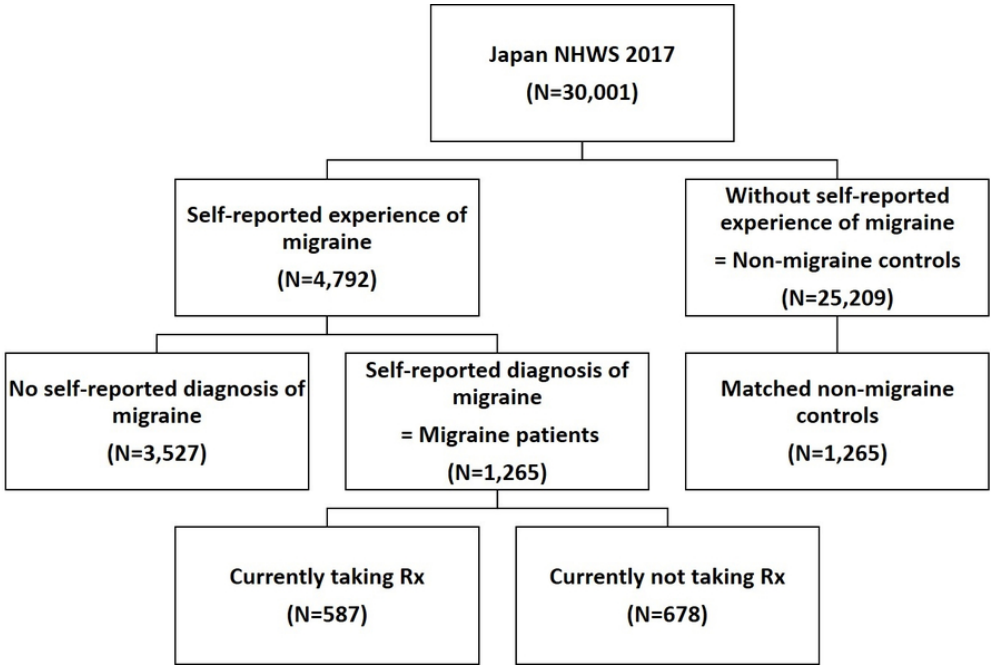

Figure 1. Respondent flow chart
Abbreviations: NHWS = National Health and Wellness Survey, Rx = prescription medication

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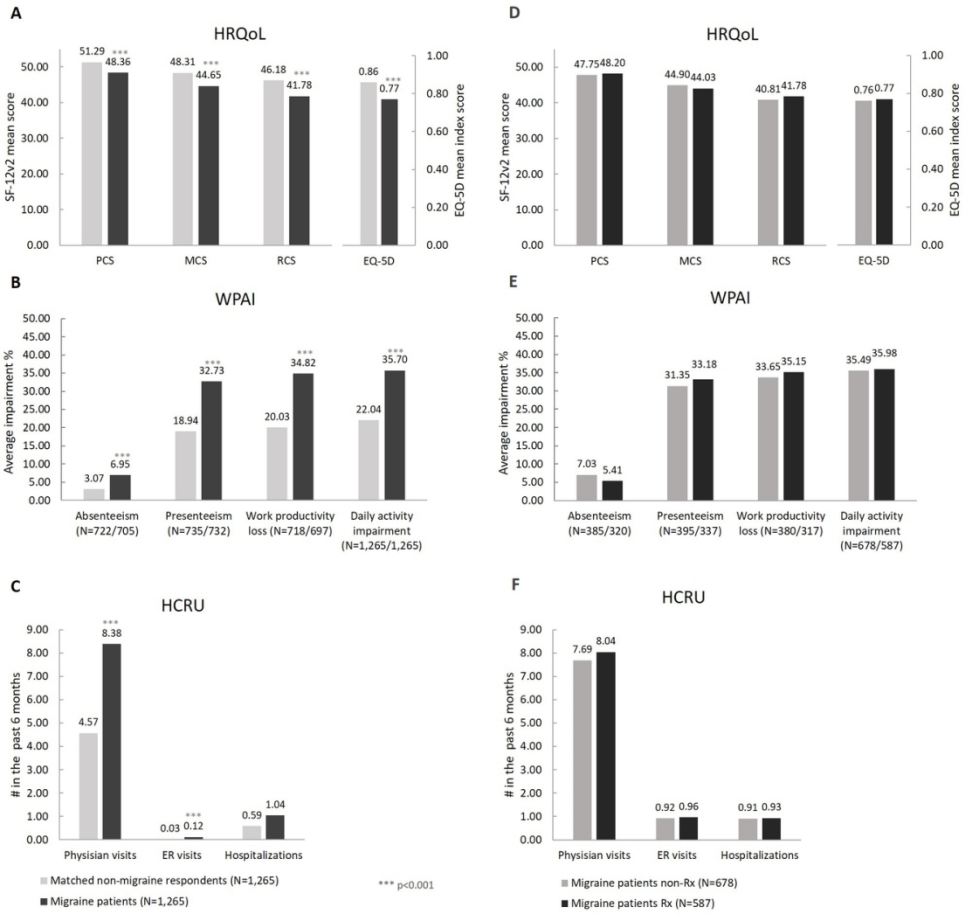

Figure 2. Comparison of health outcomes between migraine patients and matched non-migraine respondents (A-C), and between migraine patients currently taking Rx and not currently taking Rx (D-F)
A-C: Migraine patients and matched non-migraine respondents: Bivariate analysis for comparison of health outcomes between migraine patients and matched non-migraine respondents. D-F: Migraine patients currently taking prescription medication (Rx) and migraine patients not currently taking Rx: Adjusted means from GLM analysis for comparison of health outcomes between migraine patients currently taking prescription medication (Rx) and migraine patients not currently taking Rx.
Abbreviations: Rx = prescription medication, HRQoL = Health-related quality of life, PCS = physical component summary score, MCS = mental component summary score, RCS = role/social component summary score, EQ-5D = EuroQol-5 Dimension, WPAI = Work Productivity and Activity Impairment, HCRU = healthcare resource utilization, ER = emergency room.

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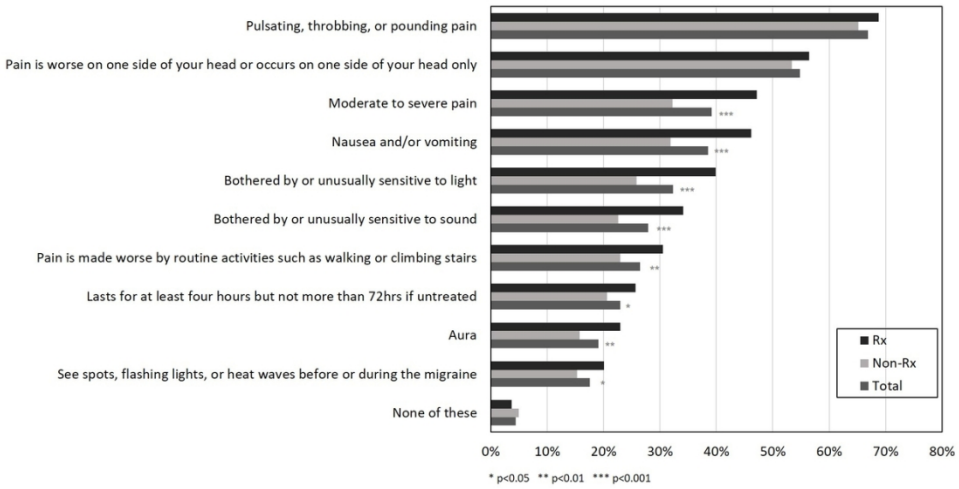

Figure 3. Migraine-related symptoms
Abbreviations: Rx = patients currently taking prescription medication, non-Rx = patients currently not taking prescription medication

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Supplementary Table 1. Bivariate comparison of demographic and health characteristics between respondents with no experience of migraine (non-migraine), patients diagnosed with migraine and matched non-migraine respondents.

		Non-migraine (N=25,209)		Matched Non-migraine (N=1,265)		Diagnosed migraine (N=1,265)		p-value	p-value
		Mean or %	[SD] or (n)	Mean or %	[SD] or (n)	Mean or %	[SD] or (n)	Non-migraine vs. Diagnosed	Matched vs. Diagnosed
Age, mean [SD]		52.80	[16.53]	43.45	[14.59]	43.79	[14.27]	< .001	.559
CCI, mean [SD]		0.17	[0.53]	0.18	[1.05]	0.24	[1.00]	< .001	.117
Gender, % (n)	Female	47.1%	(11,861)	67.4%	(852)	66.6%	(842)	< .001	.673
Employment status, % (n)	Currently employed	54.7%	(13,801)	60.1%	(760)	59.8%	(756)	< .001	.871
Household income, % (n)	<¥3,000,000	18.3%	(4623)	17.9%	(227)	18.7%	(237)	.683	.948
	¥3,000,000 to <¥5,000,000	24.4%	(6154)	24.5%	(310)	25.0%	(316)		
	¥5,000,000 to <¥8,000,000	23.9%	(6027)	25.9%	(328)	24.6%	(311)		
	¥8,000,000 or more	18.7%	(4704)	16.9%	(214)	17.0%	(215)		
	decline to answer	14.7%	(3701)	14.7%	(186)	14.7%	(186)		
Currently smoking, % (n)	Yes	41.2%	(10,385)	44.3%	(561)	44.0%	(557)	.046	.873
Currently use alcohol, % (n)	Yes	66.2%	(16,685)	63.0%	(797)	63.2%	(800)	.031	.902

Abbreviations: CCI = Charlson Comorbidity Index

Supplementary Table 2. Unadjusted bivariate comparison of health outcomes between migraine patients currently taking Rx and migraine patients not currently taking Rx

Outcomes	Non-Rx (N=678)		Rx (N=587)		p-values
	Mean	SD	Mean	SD	
HRQoL					
SF-12v2: PCS	48.70	12.42	47.96	12.16	.290
SF-12v2: MCS	45.26	10.13	43.95	10.24	.022
SF-12v2: RCS	41.93	14.40	41.61	15.40	.703
EQ-5D index score	.77	.16	.76	.16	.255
EQ-5D VAS	65.33	23.11	63.35	23.95	.134
WPAI					
Absenteeism %*	7.10	17.71	6.76	16.98	.795
Presenteeism %**	31.01	26.60	34.75	27.52	.063
Work Productivity Loss %***	33.27	28.78	36.68	28.84	.119
Daily Activity Impairment %	34.07	27.52	37.58	28.28	.026
HCRU					
Number of physician visits in the past 6 months	7.52	10.05	9.37	16.16	.013
Number of ER visits in the past 6 months	.13	.62	.10	.71	.515
Number of times hospitalized in the past 6 months	.98	4.71	1.11	8.85	.738

Abbreviations: Rx = prescription medication, SD = standard deviation, HRQoL = Health-related quality of life, SF-12v2 = Short Form 12 health survey version 2, PCS = physical component summary score, MCS = mental component summary score, RCS = role/social component summary score, EQ-5D = EuroQol 5-Dimension, WPAI = Work Productivity and Activity Impairment, HCRU = healthcare resource utilization, ER = emergency room

*Sample size of Non-Rx: N=385, Rx: N=320. **Sample size of Non-Rx: N=395, Rx: N=337. ***Sample size of Non-Rx: N=380 Rx: N=317.

pSTROBE 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	Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 5
Methods			
Study design	4	Present key elements of study design early in the paper	Page 5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 5-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	Page 5-6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 6-8
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	Page 6-8
Bias	9	Describe any efforts to address potential sources of bias	Not applicable
Study size	10	Explain how the study size was arrived at	Not applicable
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 6-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 8-9
		(*b*) Describe any methods used to examine subgroups and interactions	Page 9
		(*c*) Explain how missing data were addressed	Not applicable
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	Not applicable
		(*e*) Describe any sensitivity analyses	Not applicable
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	Page 10
		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	Page 10
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page 10
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
Outcome data	15*	Report numbers of outcome events or summary measures	
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	Supplementary table 1, and page 8-9
		(*b*) Report category boundaries when continuous variables were categorized	Not applicable
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Page 11-16
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 18
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	Page 19-20
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 18-19
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 20
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	Page 21

*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.