



Associations Between Headache-Free Days and Patient-Reported Outcomes Among Migraine Patients: A Cross-Sectional Analysis of Survey Data in Europe

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ABSTRACT

Introduction: Migraine imposes a substantial burden on patients, society, and healthcare systems. This study aimed to assess the associations between the number of headache-free days (HFDs) and health-related quality of life (HRQoL), work productivity and activity impairment (WPAI), and healthcare resource utilization (HRU) in patients with migraine in the EU5 (France, Germany, Italy, Spain, and the United Kingdom).

Methods: This retrospective cross-sectional study collected survey responses from adults aged ≥ 18 years from the 2017 National Health and Wellness Survey ($N = 62,000$). Migraine patients with a physician's diagnosis of migraine and who had experienced at least 4 monthly headache days in the prior month were included ($N = 1569$). Number of HFDs was

compared with Short-Form 12-Item Survey Instrument, version 2 (SF-12v2) physical and mental component summary scores (PCS and MCS), Short-Form-6D (SF-6D) and EuroQoL-5D (EQ-5D) scores, WPAI, and HRU in migraine patients. Correlation analyses were conducted to test the bivariate associations, whereas generalized linear models were used for multivariable analyses.

Results: An increase of 1 HFD was associated with average increases of 0.171, 0.306, 0.003, and 0.008 points for MCS, PCS, SF-6D utility score, and EQ-5D index score, respectively ($p < 0.001$ for all). Extrapolating the results to a tenfold increase in monthly HFDs corresponded to clinically meaningful increases in PCS and EQ-5D scores. An increase of 1 HFD was associated with expected average decreases in absenteeism of 3.9% and presenteeism of 2.1%. Further, an increase of 1 HFD was associated with expected decreases in HCP visits and neurologist visits of 1.0% and 4.7%, respectively.

Conclusion: An increase in the number of HFDs was associated with better health-related outcomes in patients suffering from migraine. Further, the results demonstrate a need for more effective treatments that can reduce migraine frequency and thus improve HRQoL, increase work productivity, and reduce both activity impairment and HRU.

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INTRODUCTION

Headache disorders, one of the most common nervous system disorders characterized by recurrent headache, are broadly classified into primary and secondary headache disorders [1]. Primary headache disorders include migraines, tension-type headaches, and cluster headaches [2]. Secondary headache disorders include headaches attributed to: (1) trauma or injury to the head and/or neck, (2) cranial and/or cervical vascular disorder, (3) nonvascular intracranial disorder, (4) a substance or its withdrawal, (5) infection, (6) disorder of homeostasis, and (7) psychiatric disorder [3].

Migraine is a common neurological disorder that can be disabling, and is the most common form of primary headache disorder. The two major types of migraine are migraine with aura and migraine without aura. Based on the headache frequency, migraine can be divided into episodic migraine (headaches for < 15 days/month) and chronic migraine (headaches for ≥ 15 days/month for > 3 months) [3].

Per the Global Burden of Disease Study 2016, migraine affects nearly 1.04 billion people globally [4]. A recent study by Woldeamanuel et al. reported the prevalence of migraine at 11.6% globally and 11.4% in Europe [5]. Migraine is the second leading cause of years lived with disability (YLDs) in 2016, contributing 45.1 million YLDs globally [4]. Migraine is 2–3 times more common among women than men [6]. Furthermore, the prevalence of migraine is highest during the prime years of productivity, i.e., 30–39 years [7].

Previous studies have clearly established that migraine is associated with a decreased health-related quality of life (HRQoL) [8, 9]. Migraine also impacts the functional capacity of individuals, disrupting work and social activities [10]. In addition, migraine imposes an economic burden on both individuals and society [11, 12].

The increased frequency of headaches experienced by migraineurs has an additional impact on HRQoL, work productivity and activity impairment (WPAI), healthcare resource utilization (HRU), and associated costs [13–15]. Chronic migraine is more disabling than episodic migraine and is associated with greater impairment of HRQoL in addition to greater societal burden [12]. A recent study by Vo et al. in the EU5 (i.e., France, Germany, Italy, Spain, and the United Kingdom) demonstrated that migraine patients experiencing ≥ 4 monthly headache days (MHDs) experienced incremental burdens in HRQoL, WPAI, and HRU [16].

Further, patients with episodic migraine can progress to episodic high-frequency or chronic migraine over time if treatment is not effective. Hence, treating episodic migraine patients with lifestyle management and prophylaxis and selecting and initiating the most appropriate treatment strategy can reduce pain, frequency, and severity of headache days [17, 18].

Globally, there is a need to understand the relationship between the number of headache-free days (HFDs) and the aforementioned parameters to reduce the burden of migraine patients, particularly of those suffering from the chronic form. However, there is a paucity of data on the associations of the number of HFDs with various patient-reported outcomes in migraine patients [19].

The objective of this study was therefore to assess the associations between the number of HFDs and various patient-reported outcomes (HRQoL, WPAI, and HRU) in patients suffering from migraine in the EU5.

METHODS

Sample

This retrospective cross-sectional study collected survey responses from adults aged 18 years or older from the 2017 National Health and Wellness Survey (NHWS; $N = 62,000$) in the EU5. All respondents consented to participate in the survey and could read and write in the primary language of their country of residence (i.e., French, German, Italian, Spanish, and

English for France, Germany, Italy, Spain, and the UK, respectively) at the time of the survey.

Potential respondents to this survey were members of MySurvey.com or its partners, which are opt-in survey panels. Recruitment of respondents was through opt-in e-mail, co-registration with MySurvey.com partners, e-newsletter campaigns, banner placements, and both internal and external affiliate networks. For respondents from countries with insufficient internet penetration among the elderly (i.e., Spain and Italy), telephone recruitment using quota sampling based on age and gender supplemented the online recruitment to provide an adequate sample of the elderly population. For those without internet access, a computer in a private center was provided to complete the survey. All respondents provided informed consent. All potential panelists for this survey registered with the panel through a unique e-mail address and password and completed an in-depth demographic registration profile. The protocol and questionnaire for the NHWS were reviewed by the Pearl Institutional Review Board and found to be exempt from review for the current study. All NHWS respondents provided informed consent prior to their participation.

From this general survey, migraine patients were defined as those who (1) reported a doctor's diagnosis of migraine, (2) experienced at least 1 migraine during the prior month, and (3) experienced at least 4 headache days during the prior month.

Measures

Sociodemographic Characteristics

Measures included gender, country of residence (i.e., France, Germany, Italy, Spain, and the UK), age, employment status (employed vs. unemployed), annual household income (low vs. medium vs. high vs. declined to answer), marital status (married or living with partner vs. single/divorced/widowed), level of education (completed university education vs. not completed university education), and labor force participation (currently in the labor force vs. not currently in the labor force).

General Health Characteristics

General health characteristics included body mass index (BMI) calculated from self-reported height and weight and categorized as underweight ($< 18.5 \text{ kg/m}^2$), normal weight (18.5 to $< 25.0 \text{ kg/m}^2$), overweight (25.0 to $< 30.0 \text{ kg/m}^2$), obese ($\geq 30.0 \text{ kg/m}^2$), or declined to answer. Other characteristics included cigarette smoking (current vs. former vs. nonsmokers), frequency of alcohol use (daily vs. less than daily vs. none), days of exercise in the past 30 days, and the Charlson Comorbidity Index (CCI) [20]. CCI weights the presence of the various conditions according to their severity and then sums the result; those conditions are human immunodeficiency virus infection/acquired immune deficiency syndrome (HIV/AIDS), metastatic tumor, lymphoma, leukemia, any tumor, moderate/severe renal disease, hemiplegia, diabetes, mild liver disease, ulcer disease, connective tissue disease, chronic pulmonary disease, dementia, cerebrovascular disease, peripheral vascular disease, myocardial infarction, congestive heart failure, and diabetes with end-organ damage. The greater the total index score, the greater the comorbid burden on the patient.

Health-Related Quality of Life

SF-12v2 The 2017 NHWS included the standard 4-week recall period of the revised Medical Outcomes Study 12-Item Short-Form Survey Instrument, version 2 (SF-12v2), which is a multipurpose, generic health status instrument comprising 12 questions [21] that are designed to report on 8 health concepts (i.e., physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health). Physical component summary (PCS) and mental component summary (MCS) scores were calculated from the SF-12v2. Higher scores indicate a better quality of life (QoL).

In addition to generating profile and summary PCS and MCS scores, the SF-12v2 can also be used to generate health state utilities. This is achieved through application of the Short-Form Six-Dimension (SF-6D), which takes 6 items from the survey. The SF-6D is a preference-based single index measure for health using the values

for the UK general population [22]. The SF-6D index has interval scoring properties and yields summary scores on a theoretical 0–1 scale. Higher scores indicate a better QoL.

EQ-5D-5L index score

The EuroQoL-5D (EQ-5D) index score is a preference-based measure of health on a theoretical scale of 0–1 with 1 equal to full health and 0 being equal (in terms of preference) to death. It is derived from responses to the EQ-5D-5L, a widely used survey instrument that measures health in five dimensions. The most recent version with a 5-point rating scale for each dimension was included in the questionnaire for this study [23]. The index score for the UK was calculated per the standard value set for the UK, and the index values for France, Germany, Italy, and Spain were calculated using the crosswalk from the EQ-5D-3L, as the value set for the 5L version has not been published yet. The EQ-5D-5L also provided additional measures of HRQoL beyond the index. This included the visual analog scale (VAS) [23], which is a single item that allows the respondents to rate their health from 0 to 100, with 0 representing the worst possible health state and 100 representing the best possible health state.

Work Productivity and Activity Impairment

Work productivity impairment was assessed using the General Health version of the Work Productivity and Activity Impairment (WPAI-GH) questionnaire [24], a 6-item validated instrument that consists of 4 metrics: absenteeism (the percentage of work time missed because of one's health in the past 7 days), presenteeism (the percentage of impairment experienced while at work in the past 7 days because of one's health), overall work productivity loss (an overall impairment estimate that is a combination of absenteeism and presenteeism), and activity impairment (the percentage of impairment in daily activities because of one's health in the past 7 days).

Only respondents who reported being full-time, part-time, or self-employed provided data for absenteeism, presenteeism, and overall work impairment. All respondents completed the activity impairment questionnaire.

Healthcare Resource Utilization

Healthcare use was defined by visits to different medical providers during the prior 6 months. For traditional healthcare providers (HCPs), such as physicians and nurses, the visits were summarized and analyzed for each type of provider in the prior 6 months as well as the number of visits during that time. Reported data included overall visits to a HCP, primary care provider, neurologist, psychiatrist, psychologist, emergency room (ER), and hospitalization in the past 6 months.

Statistical Methods

All data management and analyses were performed in SPSS 23.0 and/or SAS 9.4. The overall sample was characterized based on the variables using descriptive statistics, including frequencies and percentages for categorical variables and means and standard deviations for continuous variables. Correlation analyses were conducted to test the bivariate associations between the number of HFDs and various outcomes using Pearson and Spearman correlation tests to examine parametric and non-parametric associations, respectively. Demographic and health characteristics that were found to significantly correlate with the number of HFDs were included as covariates in the multivariable analysis.

For multivariable analyses, generalized linear models (GLMs) were used to estimate the associations of the number of HFDs with various health outcomes after controlling for covariates. GLMs specifying a normal distribution and identity function were used with normally distributed outcomes (such as HRQoL) [25], whereas GLMs specifying a negative binomial distribution and log-link function were used for count data (e.g., WPAI [26] and HRU [27]).

The rate ratio (RR) was calculated as follows: If $RR < 1$, a 1-unit (i.e., 1-day) increase in the number of HFDs is associated with a $(1 - RR) \times 100\%$ decrease in the outcome. If $RR > 1$, a 1-unit (i.e., 1-day) increase in the number of HFDs is associated with a $(1 + RR) \times 100\%$ increase in the outcome.

RESULTS

Of the 62,000 respondents in total, approximately 13,063 indicated experiencing migraine, and 6181 respondents indicated a physician's diagnosis of migraine, completed the migraine module, and provided the frequency of migraines. Out of these 6181 respondents, 4612 either reported that they had not experienced any migraines in the past month or they did not know the number of MHDs experienced in the prior month or they provided a migraine frequency corresponding to rare migraine (≤ 3 MHDs); those respondents were excluded from this study. Migraine patients who had a physician's diagnosis of migraine and had experienced at least 4 MHDs in the prior month were included in this analysis ($N = 1569$). The number of HFDs in migraine patients was defined as: 30 days – number of headache days in the past 30 days (Fig. 1).

The demographic characteristics of respondents diagnosed with migraine who reported HFDs are presented in Table 1. Among the respondents diagnosed with migraine, 21.9% were from France, 26.1% from Germany, 23.9% from the UK, 20.0% from Italy, and 8.1% from Spain. Additionally, 77.8% of them were female and had a mean age of 43.27 years, 60.7% were married or living with a partner, and 27.9%, 36.8%, and 28.9% belonged to the low-,

medium-, and high-income groups, respectively. Furthermore, 36.8% completed a university education, and 59.8% reported being currently employed. Based on health characteristics, 48.8% were overweight or obese, 29.7% were smokers, 71.8% drank alcohol, and 60.2% mentioned that they have done some sort of exercise in the past 30 days.

The mean MCS, PCS, SF-6D, and EQ-5D scores of migraine patients who reported HFDs were 39.73, 46.61, 0.62, and 0.71, respectively. Among employed respondents, mean absenteeism, presenteeism, and total work productivity impairment were 13.39, 34.70, and 37.73, respectively. The mean activity impairment in the migraine respondents was 43.31. Among migraine respondents who reported HFDs, the mean number of HCP visits in the past 6 months was 8.38, the mean number of hospitalizations was 0.22, the mean number of ER visits was 0.47, and the mean number of neurologist visits was 0.28 (Table 2).

Bivariate Analyses

Correlational Analyses Among Migraine Patients in the EU5

There were weak, positive, and significant correlations among EU respondents between the number of HFDs and each of the following characteristics: employment status, marital status, household income, and level of education (all $p < 0.05$; see Fig. 2). These results indicate that employed respondents had a greater number of HFDs than unemployed respondents, married respondents had a greater number of HFDs than respondents who were not married, and respondents with a university education had a greater number of HFDs than respondents who did not complete university education. Similarly, there were weak, positive, and significant correlations between the number of HFDs and CCI, BMI, alcohol use, and exercise in the past month (all $p < 0.05$). These results indicate that respondents with more severe CCI and higher BMI had fewer HFDs than respondents with less severe CCI and respondents with lower BMI, respectively (data not shown).

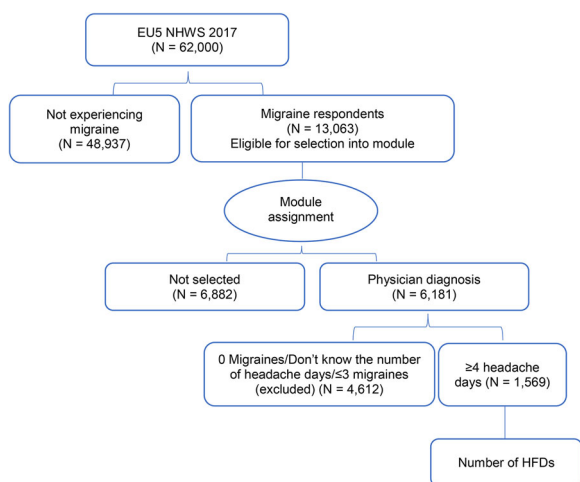


Fig. 1 Selection of the study population. *HFDs* headache-free days, *NHWS* National Health and Wellness Survey

Table 1 Demographic characteristics of migraine patients with HFDs ($N = 1569$)

Parameters	<i>n</i> (%)
Gender	
Male	349 (22.2)
Female	1220 (77.8)
Country	
France	344 (21.9)
Germany	409 (26.1)
United Kingdom	375 (23.9)
Italy	314 (20.0)
Spain	127 (8.1)
Age group	
18–29	309 (19.7)
30–39	343 (21.9)
40–49	393 (25.0)
50–64	389 (24.8)
65+	135 (8.6)
Marital status	
Married or living with partner	953 (60.7)
Household income	
Low	437 (27.9)
Medium	577 (36.8)
High	454 (28.9)
Declined to answer	101 (6.4)
Level of education	
Completed university education	577 (36.8)
Employment status	
Yes	938 (59.8)
No	631 (40.2)
CCI categories	
0	1136 (72.4)
1	252 (16.1)
2+	181 (11.5)

Table 1 continued

Parameters	<i>n</i> (%)
BMI	
Underweight (< 18.5 kg/m ²)	67 (4.3)
Normal weight (18.5 to < 25.0 kg/m ²)	668 (42.6)
Overweight (25.0 to < 30.0 kg/m ²)	406 (25.9)
Obese (30.0 kg/m ² and above)	360 (22.9)
Declined to answer	68 (4.3)
Smoking status	
Current	466 (29.7)
Former	413 (26.3)
Never	690 (44.0)
Use of alcohol	
Daily	52 (3.3)
Less than daily	1074 (68.5)
No	443 (28.2)
Exercise in past 30 days	
Yes	945 (60.2)
No	624 (39.8)
Age in years [mean ± SD]	43.27 ± 13.81
CCI [mean ± SD]	0.50 ± 1.16

BMI body mass index, *CCI* Charlson Comorbidity Index, *HFDs* headache-free days, *SD* standard deviation

Multivariable Analyses

Regression Analyses Among Migraine Patients in the EU5

Multivariable analyses were performed to examine the adjusted associations between the number of HFDs and outcomes after adjusting for the following covariates: sex, country, employment status, marital status, household income, education, BMI, alcohol use, exercise, age in years, and CCI. Based on multivariable GLMs, an increase of 1 HFD was associated with average increases of 0.171 points for MCS, 0.306 points for PCS, 0.003

Table 2 Health outcomes, WPAI, and HRU of migraine patients with HFDs

Outcomes	Mean \pm SD (<i>N</i> = 1569)
HRQoL	
MCS	39.73 \pm 10.90
PCS	46.61 \pm 9.90
SF-6D utility score	0.62 \pm 0.12
EQ-5D index	0.71 \pm 0.26
Health status, EQ VAS	62.96 \pm 23.68
WPAI	
Absenteeism ^a	13.39 \pm 26.05
Presenteeism ^a	34.70 \pm 27.84
Total work productivity impairment ^a	37.73 \pm 30.17
Activity impairment	43.31 \pm 29.36
HRU (in the past 6 months)	
Total number of HCP visits	8.38 \pm 9.29
Total number of hospitalizations	0.22 \pm 0.79
Total number of ER visits	0.47 \pm 1.25
Total number of general practitioner/family practitioner visits	3.02 \pm 3.65
Total number of neurologist visits	0.28 \pm 0.87
Total number of psychiatrist visits	0.36 \pm 1.79
Total number of psychologist/therapist visits	0.87 \pm 3.65

ER emergency room, EQ-5D EuroQoL-5D, EQ VAS EuroQol visual analog scale, HCP healthcare provider, HFDs headache-free days, HRQoL health-related quality of life, HRU healthcare resource utilization, MCS mental component summary, PCS physical component summary, SD standard deviation, SF-6D Short-Form Six-Dimension, WPAI work productivity and activity impairment

^a Includes employed respondents only; absenteeism (*n* = 877), presenteeism (*n* = 839), and total work productivity impairment (*n* = 832)

points for SF-6D utility score, and 0.008 points for EQ-5D index score (all *p* < 0.001). An increase of 5 HFDs would result in average

increases of 0.855 points for MCS, 1.530 points for PCS, 0.015 points for SF-6D utility score, and 0.040 points for EQ-5D index score (Table 3).

An increase of 1 HFD was associated with expected decreases in absenteeism of 3.9%, presenteeism and total work impairment of 2.1%, and activity impairment of 1.8%. An increase of 5 HFDs would result in expected decreases in absenteeism of 18.2%, presenteeism of 10.3%, total work impairment of 10.1%, and activity impairment of 8.7% (Table 4).

Also, a greater number of HFDs was associated with fewer visits to different HCPs. An increase of 1 HFD was associated with expected decreases in HCP visits of 1.0% and neurologist visits of 4.7%. Similarly, an increase of 5 HFDs would result in expected decreases in HCP visits of 4.7% and neurologist visits of 21.0%, respectively (Table 5).

DISCUSSION

Previous studies have reported the relationship between migraine burden and patient-reported outcomes by comparing migraineurs with non-migraine controls [16] or episodic with chronic migraineurs [12]. The present study adds to the existing knowledge by reporting, for the first time, associations between the number of HFDs and patient-reported outcomes in terms of HRQoL, WPAI, and HRU among migraine patients experiencing ≥ 4 MHDs in the EU5.

The current study results are consistent with a recent study of migraine patients experiencing ≥ 4 HFDs in the US, wherein 1 HFD was correlated with a 0.15-point reduction in the Headache Impact Test (HIT)-6 score. Moreover, each 10-day increase in HFDs was associated with a 1.34-point reduction in HIT-6 score on average [19]. A corollary to Bell et al.'s study [19] was provided by a study by Vo et al. [16] wherein migraineurs suffering from ≥ 4 MHDs reported a decreased QoL along with a reduced mean PCS, MCS, SF-6D health state utility score, and EQ-5D score compared to non-migraine controls in the EU5. Extrapolating the current study results to a tenfold increase in HFDs per month correlates with established minimally

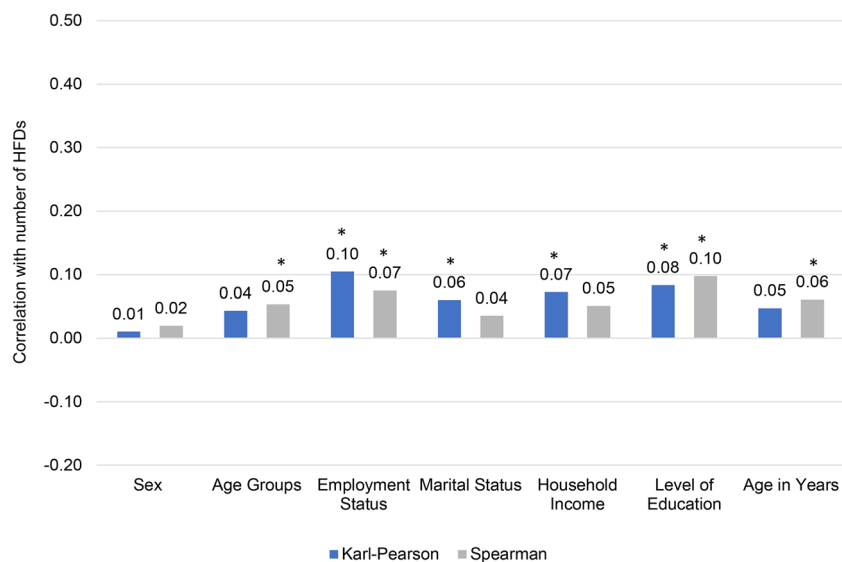


Fig. 2 Correlations between demographics and number of HFDs. HFDs headache-free days. * $p < 0.05$. Variables are defined as: sex (male = 1, female = 0); age groups: (18–29 = 1, 30–39 = 2, 40–49 = 3, 50–64 = 4, 65+ = 5); employment status (yes = 1, no = 0); marital

status (married or living with partner = 1, not married or living with partner = 0); household income (low = 1, medium = 2, high = 3); level of education (completed university education = 1, not completed university education = 0)

important differences (MID) (for both MCS and PCS—3 points [21], SF-6D—0.041 points, and EQ-5D—0.074 points [28]), which would result in clinically meaningful increases in PCS and EQ-5D scores, thus increasing the QoL in migraine patients.

A systematic review of the literature identified physical functioning as one of the most important psychosocial difficulties encountered by migraine patients [29]. Existing evidence suggests an improvement in physical health with a consequent decrease in the frequency of headache days in migraine patients [30, 31]. EQ-5D provides a broader assessment of patients' health status [28], and the increased EQ-5D scores among migraine patients in our study could be related to the overall improved health status.

Previous studies have shown that increased migraine days result in greater work productivity loss, with higher levels of absenteeism and presenteeism, thereby imposing a greater economic burden on the individual, employer, and society [16, 32]. Migraineurs with 8 migraine days per month were predicted to have 0.95 absenteeism days and 2.34 presenteeism days

per month [33]. A study by Stewart et al. [34] reported that the mean lost productive time (the total of absenteeism and presenteeism) due to headaches was 4.7 h per week. In the present study, an increased number of HFDs was associated with less impairment of work activities among employed respondents after adjusting for covariates. The observed results are consistent with a previous study which showed that decreased levels of absenteeism and presenteeism in migraine patients were due to an increased number of HFDs [19].

Migraine imposes additional healthcare costs on the sufferers due to their increased use of healthcare resources [16, 35–37]. Previous research has shown that migraine patients make more visits to HCPs than non-migraine controls do [16, 38]. Further, chronic migraineurs reported more visits to primary care physicians, neurologists, nurse practitioners, and other healthcare professionals than episodic migraineurs [16, 39]. In the current study, an increase in the number of HFDs was associated with fewer visits to different HCPs.

Based on the results of the current study, it is evident that an increased number of HFDs is

Table 3 Associations between HRQoL and HFDs according to regression analyses

Outcomes	<i>B</i>	95% confidence interval	<i>p</i> value	Estimated increase associated with 5 HFDs
MCS	0.171	0.095–0.247	< 0.001	0.855
PCS	0.306	0.244–0.368	< 0.001	1.530
SF-6D utility score	0.003	0.003–0.004	< 0.001	0.015
EQ-5D index	0.008	0.006–0.009	< 0.001	0.040
Health status, EQ VAS	0.758	0.601–0.915	< 0.001	3.790

Generalized linear regression models with a normal distribution were used to adjust for covariates. Covariates = sex (female = reference), country (UK = reference), BMI (normal weight = reference), employment status (employed = reference), marital status (not married = reference), household income (low = reference), education (not completed university = reference), alcohol (none = reference), exercise (no = reference), age (years), and CCI

EQ-5D EuroQoL-5D, *EQ VAS* EuroQol visual analog scale, *HFDs* headache-free days, *HRQoL* health-related quality of life, *MCS* mental component summary, *PCS* physical component summary, *SF-6D* Short-Form Six-Dimension

associated with increased work productivity and reduced HRU, which are in turn expected to result in lower indirect and direct costs. A study of migraine patients in the US showed that increasing the number of HFDs from 0–10 to 21–26 per month had a greater impact on indirect costs than on direct costs [19]. Therefore, increasing the number of HFDs may reduce

annual costs for patients suffering from migraine.

The aim of any prophylactic treatment is to reduce disability and to restore functional ability by decreasing the frequency and severity of migraine [7, 40]. Studies on preventive pharmacologic treatment in migraine patients have shown that decreasing the frequency of migraine and the number of headache days significantly improves measures of migraine disability, impact of migraine, HRQoL [41], absenteeism and presenteeism [42], HRU, and costs [43]. In a study by Santoro et al. [44], medications significantly reduced MHDs compared to baseline and also reduced the intensity from Migraine Disability Assessment Scale (MIDAS) grade IV from the sixth month of treatment in patients with chronic migraine. Recent studies have reported clinically relevant improvements in patient-reported outcomes after treatment with erenumab in chronic migraine patients [41, 42]. Based on the results available, we propose that decreasing the frequency of migraine is an important determinant of improvements in QoL and other measures; hence, physicians treating migraine patients should consider reducing MHDs or increasing the number of HFDs. Future studies targeting an increase in the frequency of HFDs with appropriate therapeutic regimens that may translate to improved QoL or potential cost savings are necessary.

Limitations

This study has a few limitations. The NHWS is a panel-based survey, and though the panel administrators attempted to have the panel mirror the population as closely as possible (i.e., age and gender quotas for NHWS sampling), there could be a bias in the estimates whereby there are differences between the population in each country and the panel population. This would be most likely among segments of the population that do not have ready access to the

Table 4 Associations between WPAI and HFDs according to regression analyses

Outcomes	<i>B</i>	95% confidence interval	<i>p</i> value	Rate ratio (RR)	95% Wald confidence interval for RR		% decrease ^a	Estimated reduction associated with 5 HFDs
					Lower	Upper		
Absenteeism	− 0.040	− 0.051 to − 0.029	< 0.001	0.961	0.950	0.971	3.94	0.182
Presenteeism	− 0.022	− 0.033 to − 0.010	< 0.001	0.979	0.968	0.990	2.14	0.103
Total work productivity	− 0.021	− 0.033 to − 0.010	< 0.001	0.979	0.968	0.990	2.10	0.101
Activity impairment	− 0.018	− 0.026 to − 0.011	< 0.001	0.982	0.975	0.989	1.79	0.087

Generalized linear regression models with a negative binomial distribution were used to adjust for covariates. Employed $N = 938$. Absenteeism, presenteeism, and total work productivity among employed respondents only. Covariates = sex (female = reference), country (UK = reference), BMI (normal weight = reference), employment status (employed = reference; only for activity impairment), marital status (not married = reference), household income (low = reference), education (not completed university = reference), alcohol (none = reference), exercise (no = reference), age (years), and CCI

HFDs headache-free days, WPAI work productivity and activity impairment

^a $RR < 1$ is associated with a $(1 - RR) \times 100\%$ decrease in WPAI outcomes per increase of 1 HFD. $RR > 1$ is associated with a $(1 + RR) \times 100\%$ increase in WPAI outcomes per increase of 1 HFD

internet (e.g., elderly people, institutionalized patients, and those with severe comorbidities and disabilities).

Another limitation is the use of self-reported data, since the diagnosis of migraine and other relevant diagnoses (e.g., those used to calculate the CCI) cannot be confirmed; nor can reports of healthcare visits.

The magnitude of the impact of migraine is likely affected by the frequency, severity, and duration of migraine. Moderate or severe pain is one of the diagnostic criteria for migraine, and available data on measures of severity are likely to be too coarse to be useful given this range restriction, so severity is not considered here. Duration is not captured in the NHWS, except for an item to confirm the 4-h to 72-h duration

included in the diagnostic criteria, and so duration may be an important unmeasured variable in this study.

CONCLUSION

Previous studies have shown worsened HRQoL and greater work productivity loss and HRU in migraine patients. This study provides the first evidence that an increase in the number of HFDs is associated with improved HRQoL, decreased work productivity loss and activity impairment, and HRU among patients with migraine in the EU5. Thus, increasing the frequency of HFDs using appropriate medications may lessen the burden of migraine and

Table 5 Associations between HRU and HFDs according to regression analyses

Outcomes	<i>B</i>	95% confidence interval	<i>p</i> value	Rate ratio (RR)	95% Wald confidence interval for RR		% decrease ^a	Estimated reduction associated with 5 HFDs
					Lower	Upper		
Total number of HCP visits in the past 6 months	− 0.010	− 0.017 to − 0.002	0.015	0.990	0.983	0.998	0.96	0.047
Total number of hospitalizations in the past 6 months	− 0.023	− 0.039 to − 0.007	0.005	0.978	0.962	0.993	2.24	0.107
Total number of ER visits in the past 6 months	− 0.020	− 0.033 to − 0.007	0.002	0.980	0.968	0.993	1.99	0.096
Total number of general practitioner/family practitioner visits in the past 6 months	− 0.014	− 0.023 to − 0.006	0.001	0.986	0.977	0.994	1.43	0.069
Total number of neurologist visits in the past 6 months	− 0.047	− 0.062 to − 0.032	< 0.001	0.954	0.940	0.968	4.70	0.210
Total number of psychiatrist visits in the past 6 months	− 0.010	− 0.025 to 0.005	0.204	0.990	0.976	1.005	0.96	0.047
Total number of psychologist/therapist visits in the past 6 months	− 0.007	− 0.019 to 0.004	0.213	0.993	0.981	1.004	0.73	0.036

Generalized linear regression models with a negative binomial distribution were used to adjust for covariates. Covariates = sex (female = reference), country (UK = reference), BMI (normal weight = reference), employment status (employed = reference), marital status (not married = reference), household income (low = reference), education (not completed university = reference), alcohol (none = reference), exercise (no = reference), age (years), and CCI

ER emergency room, *HCP* healthcare provider, *HFDs* headache-free days, *HRU* healthcare resource utilization

^a RR < 1 is associated with a $(1 - \text{RR}) \times 100\%$ decrease of HRU outcomes per increase of 1 HFD. RR > 1 is associated with $(1 + \text{RR}) \times 100\%$ increase of HRU outcomes per increase of 1 HFD

provide incremental benefits to individuals and society.

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Data Availability. The NHWS data used in this study are available for noncommercial research and validation purposes upon request. Interested individuals may access these data for the purposes above in the same manner as the authors did without any additional restrictions. Interested parties should contact the corresponding author on reasonable request.

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