


RESEARCH SUBMISSIONS

Burden of migraine in Brazil: A cross-sectional real-world study

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Abstract

Objective: To assess the burden and consequences of migraine in Brazil in terms of health-related quality of life (HRQoL), work productivity and daily activities, and healthcare resource utilization (HRU).

Background: Despite existing data on how migraine affects populations worldwide, there are limited data on the burden of migraine in Latin America.

Methods: This cross-sectional study used patient-reported data from the 2018 Brazil National Health and Wellness Survey. HRQoL scores (EuroQol 5-dimension 5-level [EQ-5D-5L]; 36-item Short Form Health Survey, version 2 [SF-36v2]; and Short Form 6-dimension [SF-6D]), impairments to work productivity and daily activities (Work Productivity and Activity Impairment questionnaire), and all-cause HRU were compared between migraine respondents and matched non-migraine controls.

Results: Of the 12,000 total respondents in the survey database, 1643 self-reported a physician diagnosis of migraine and were propensity score matched 1:1 with controls without migraine. HRQoL was lower in patients with migraine versus non-migraine controls, with significantly lower SF-36v2 physical (mean [\pm SD] 50.3 [7.5] vs. 52.0 [7.6]) and mental component (mean [\pm SD] 42.9 [10.2] vs. 46.0 [9.9]) summary scores and SF-6D (mean [\pm SD] 0.7 [0.1] vs. 0.7 [0.1]) and EQ-5D-5L (mean [\pm SD] 0.7 [0.2] vs. 0.8 [0.2]) utility scores (all $p < 0.001$). Patients with migraine reported higher levels of work productivity loss (mean [\pm SD], 40.6% [31.4%] vs. 28.6% [30.9%], including absenteeism 12.8% [19.1%] vs. 8.4% [17.1%] and presenteeism 35.0% [28.7%] vs. 24.8% [28.0%]; all $p < 0.001$); activity impairment (mean [\pm SD] 36.0% [28.8%] vs. 25.5% [28.1%]; $p < 0.001$); and significantly higher HRU in the past 6 months (healthcare provider and emergency department visits [mean [\pm SD] 7.2 [9.5] vs. 4.5 [6.3] and 1.7 [3.8] vs. 0.9 [2.2]; both $p < 0.001$] and hospitalizations [mean [\pm SD] 0.4 [2.7] vs. 0.2 [1.1]; $p = 0.002$]) than controls.

Conclusion: Migraine is associated with poorer HRQoL, higher all-cause HRU, and greater activity impairment and work productivity loss versus non-migraine controls in Brazil.

KEYWORDS

burden, healthcare resource use, health-related quality of life, migraine, work impairment

Abbreviations: ANOVA, analysis of variance; CCI, Charlson Comorbidity Index; CM, chronic migraine; ED, emergency department; EM, episodic migraine; EQ-5D-5L, EuroQol 5-dimension 5-level; HCP, healthcare provider; HRQoL, health-related quality of life; HRU, healthcare resource utilization; MCS, mental component summary; MID, minimally important difference; NHWS, National Health and Wellness Survey; NSAID, non-steroidal anti-inflammatory drug; PCS, physical component summary; SD, standard deviation; SF-36v2, 36-item Short Form Health Survey, version 2; SF-6D, Short-Form 6-dimension.

[Correction added on the 8th of December 2022, after first online publication: The degree for Marcelo Calderaro was changed from "PhD" to "MD".]

INTRODUCTION

Migraine was ranked in the Global Burden of Disease study as the second leading cause worldwide of years lived with disability, ranking among the 10 most disabling disorders in each of the 21 study regions.¹ Migraine was the sixth most prevalent disease, with an estimated 1.04 billion (95% uncertainty interval, 1.00, 1.09) people living with migraine worldwide.¹ The prevalence was higher for women, but percentages of all years lived with disability were highest in the group aged 15–49 years for both sexes,¹ demonstrating a higher burden during work-productive years. In Brazil, migraine affects an estimated 15.8% of the population and is significantly more prevalent in women than in men (20.9% vs. 9.3%).² Approximately 23% of citizens have private health insurance to combat any bottlenecks that may arise within Brazil's decentralized, universal public system.³ Yet access to comprehensive tertiary headache centers or migraine specialists is often limited, as are migraine prevention and treatment resources provided by some private specialty clinics.⁴ About 30% of the patients with migraine who depend on public services (which assist non-paying patients) do not receive preventive treatments, while nearly 90% of the patients who seek treatment from private centers receive the prescription of preventive treatments, which are generally tricyclic antidepressants, neuromodulators, and/or beta blockers.⁴

Migraine is associated with substantial personal, occupational, and social burdens, as well as increased healthcare resource utilization (HRU). In the recent My Migraine Voice disease burden study, 87% of patients with migraine for whom previous preventive treatments had failed reported negative consequences of migraine on their private, social, or professional lives; patients missed an average of 4.6 workdays due to migraine in the prior month.⁵ In a separate study of disease burden, patients with ≥ 4 migraine days reported significantly lower health-related quality of life (HRQoL) across multiple outcomes compared with non-migraine controls, as well as significantly higher work and productivity impairment (all $p < 0.001$). Additionally, patients with migraine had higher HRU compared with non-migraine controls based on healthcare provider (HCP) visits (8.5 vs. 5.1 visits over 6 months; $p < 0.001$) and emergency department (ED) visits (0.46 vs. 0.21 visits over 6 months; $p = 0.011$).⁶

Despite the growing body of evidence around the impact of migraine worldwide, there is a paucity of data in Latin America. Although some observational studies investigating epidemiology, patients' journeys, and treatments have been performed in tertiary hospitals,^{4,7–9} migraine has not been included in major national surveys,¹⁰ preventing comprehensive assessment of the disease impact on Latin American populations.^{3,4} Therefore, this study aimed to assess the burden of illness and consequences of migraine for Brazilian patients and the health system. We hypothesized that patients with migraine have lower HRQoL, greater work productivity loss and activity impairment, and higher HRU compared with individuals without migraine. The primary objective of this study was to evaluate the impact of migraine via HRQoL, work productivity and activity impairment, and HRU by comparing patients with migraine with individuals without migraine. The secondary objective was to examine current treatments used by patients with migraine.

METHODS

Data source

This cross-sectional observational study, a secondary analysis of previously collected data, included patient-reported data from the 2018 Brazil National Health and Wellness Survey (NHWS), which had a total of 12,000 respondents.^{11–14} The NHWS is a proprietary database of self-reported, real-world patient-level information. All respondents were aged ≥ 18 years, provided their informed consent online prior to participating in the web-based survey, and were known only by a unique identifier. The 2018 NHWS was granted exemption from review by the Pearl Institutional Review Board (Indianapolis, IN, USA).

Respondents to the NHWS were recruited through an existing, general-purpose, web-based consumer panel. Recruitment was through opt-in emails, co-registration with panel partners, e-newsletter campaigns, banner placements, and affiliate networks. All potential panelists registered with the panel through a unique email address and completed an in-depth demographic registration profile. To ensure the representativeness of findings in the Brazilian adult population, a stratified sampling strategy was used during the recruitment of panel members. Relative proportions of age, sex, and socioeconomic groups in Brazil were based on data from the International Database of the US Census Bureau and mimicked during recruitment, ensuring the final NHWS sample matched Brazilian demographic proportions.

Sample and eligibility criteria

This study is focused on individuals who self-reported a diagnosis of migraine by a physician. A propensity score-matching method, using sociodemographic characteristics and health history variables, was utilized to create a matched control group (among individuals who did not report migraine diagnosis) for the group of patients with self-reported migraine diagnosis in a 1:1 proportion.

In addition, subgroups of patients were identified based on migraine classification (episodic migraine [EM] or chronic migraine [CM]), with EM defined as having 4–14 self-reported headache days in the past 30 days and CM defined as having ≥ 15 headache days in the past 30 days.

Measures

Sociodemographic and health characteristics

The demographic characteristics collected included age, sex, ethnicity, marital status, level of education, monthly household income, and insurance type.

The health history information collected included body mass index, smoking status, alcohol use, exercise behavior, and the

Charlson Comorbidity Index (CCI). The CCI weighs the presence of several conditions and sums the result. The greater the total index score, the greater the comorbid burden on the patient.

Comorbidity information also was captured by self-reported physician diagnoses. Their inclusion was based on the most frequently occurring comorbidities among patients with migraine in the sample (e.g., depression or pain) and those identified to be of clinical significance. The number of comorbidities was treated as both a continuous variable and a categorical variable (e.g., 0, 1–2, ≥ 3).

Additional details on study methods are presented in the [Supplementary Methods](#).

Migraine-related variables

Disease-specific variables included migraine symptoms, the number of migraine attacks in the past 30 days and in the past 6 months, the number of headache days in the past 30 days, the number of work days missed due to migraine, the number of household activity days missed due to migraine, the number of years lived with migraine after diagnosis, the current treatment used for migraine attacks, and whether patients were treated with acute or preventive therapies.

Health-related quality of life and work productivity and activity impairment

The Brazil 2018 NHWS is an international and standardized questionnaire in which individuals answer questions about their health status in several domains and therapeutic areas. The questionnaire uses generic instrument surveys to assess HRQoL indicators; these instruments allow for benchmarking against an established set of values and facilitate comparisons against other conditions. The NHWS included two measures of HRQoL: (i) the EuroQol 5-dimension 5-level (EQ-5D-5L)¹⁵ and (ii) the 36-item Short Form Health Survey, version 2 (SF-36v2).¹⁶ For the EQ-5D-5L, the minimally important difference (MID) is ~0.07 points,¹⁷ while for the SF-36v2, the MID is 5 points for domain scores, 3 points for the two summary scores (physical component summary [PCS] and mental component summary [MCS]),¹⁸ and 0.041 points for the Short Form 6-dimension (SF-6D) classification of health utilities (derived using the SF-6D classification system).¹⁷

Loss of productivity at work and activity impairment were assessed using the Work Productivity and Activity Impairment questionnaire, a six-item validated instrument that consists of four metrics: absenteeism, presenteeism, overall work productivity loss, and activity impairment.¹⁹

Healthcare resource utilization

HRU comprised the number of visits to HCPs and to the ED and the number of hospitalizations in the 6 months before survey participation due to any medical condition.

Statistical analyses

A priori statistical power calculation was not performed before the analysis, because the data were already collected, and we were using the full sample of individuals with migraine that was available. We had anticipated that there would be an adequate sample size for individuals with migraine, as migraine is not a low-prevalence condition and the NHWS is representative of the general population. Version 23.0 of the IBM Statistical Package for the Social Sciences software (IBM Corp., Armonk, NY, USA) was used to conduct statistical analyses.

Descriptive analyses

Descriptive statistics were reported for all study measures. Categorical variables were reported using frequencies and percentages, and continuous variables were reported using means and standard deviations.

Propensity score matching

As the objective of this study was to evaluate the burden of illness by comparing patients with migraine with individuals without migraine (controls), a propensity score-matching methodology was used to identify a group without migraine that closely resembled those with migraine, minimizing sample-size imbalances.²⁰ The two groups were matched for age, sex, marital status, income, education, smoking status, body mass index category, and CCI. Given that there were 1643 individuals who reported a physician diagnosis of migraine, a 1:1 match would produce an adequate sample size for statistical comparisons while having a balanced sample size between groups.

Bivariate analyses

Differences between matched groups (migraine vs. control) and unmatched groups (EM vs. CM) were examined. For continuous variables, a one-way analysis of variance (ANOVA) was used. Due to the large sample size for our data ($n = 1643$ per group), the use of parametric tests, such as ANOVA, is justified even for non-normally distributed outcomes.^{21,22} Additionally, due to the equal sample size in our groups, ANOVA is robust against any violations of equal variances. For categorical variables, chi-square tests were used to determine significant differences. Differences between groups regarding migraine-specific variables and outcomes also were analyzed to assess unadjusted differences using one-way ANOVA. A two-tailed $p < 0.05$ was considered statistically significant.

RESULTS

Of the total 12,000 respondents of the Brazil 2018 NHWS, the sample for the primary study objective included data from 1643

respondents who self-reported a physician diagnosis of migraine and 10,357 respondents who did not self-report a migraine diagnosis. After the propensity score-matching process, a matched control group among individuals without migraine was created for patients with migraine in a 1:1 proportion (Figure 1).

Among the 1643 respondents who self-reported a migraine diagnosis, the mean age was 36.3 years, 74.6% were female, and 60.5% were White. After the propensity score-matching procedure, demographic and health characteristic comparisons across diagnosed migraine versus matched control groups resulted in standardized differences of <0.10 , demonstrating balance between groups (Table 1). Of the patients who reported their number of headache days over a 30-day period ($n = 475$), 393 (82.7%) were classified as having EM and 82 (17.3%) as having CM. For patients with EM and CM, respectively, the mean age was 36.6 and 34.5 years, 75.8% and 78.0% were female, and 61.1% and 56.1% were White (Table S1).

Comparisons of migraine versus non-migraine matched controls

Health-related quality of life

Bivariate comparison of matched groups demonstrated that patients with migraine reported statistically significantly lower HRQoL scores than individuals without migraine in both the PCS and MCS components measured by the SF-36v2. The mean PCS was significantly lower in patients with migraine than in non-migraine matched controls, as was the mean MCS (both $p < 0.001$), suggesting worse

health status in patients with migraine (Table 2). Additionally, the incremental difference of 3.09 in the MCS reached the previously reported MID of 3 points.¹⁸ In addition, mean PCS and MCS scores for patients with EM were comparable to those for patients with CM (Table S2).

Patients with migraine also reported statistically significantly lower SF-6D and EQ-5D-5L (both $p < 0.001$) health utility scores than matched non-migraine controls (Table 2). These changes represent incremental differences of 0.05 and 0.09 in the SF-6D and EQ-5D-5L utility scores, respectively, reaching the MIDs previously reported for these scores (0.04 for SF-6D; 0.07 for EQ-5D-5L).¹⁷

Work productivity impairment and activity impairment

At the time of the survey, 1223 (74.4%) respondents with migraine were employed while 5724 (65.7%) unmatched control and 1143 (69.6%) matched control respondents were employed. Only respondents who reported being employed full-time or part-time provided data for absenteeism, presenteeism, and overall work impairment, while all respondents provided data for activity impairment. Respondents with migraine reported statistically significantly higher impairment across all indicators of work productivity compared with individuals without migraine, including absenteeism, presenteeism, and overall work productivity impairment (all $p < 0.001$; Table 3). Additionally, activity impairment among all respondents was significantly higher among patients with migraine than among non-migraine controls ($p < 0.001$; Table 3). Patients with EM and CM reported similar levels of presenteeism, total work productivity impairment, and activity impairment

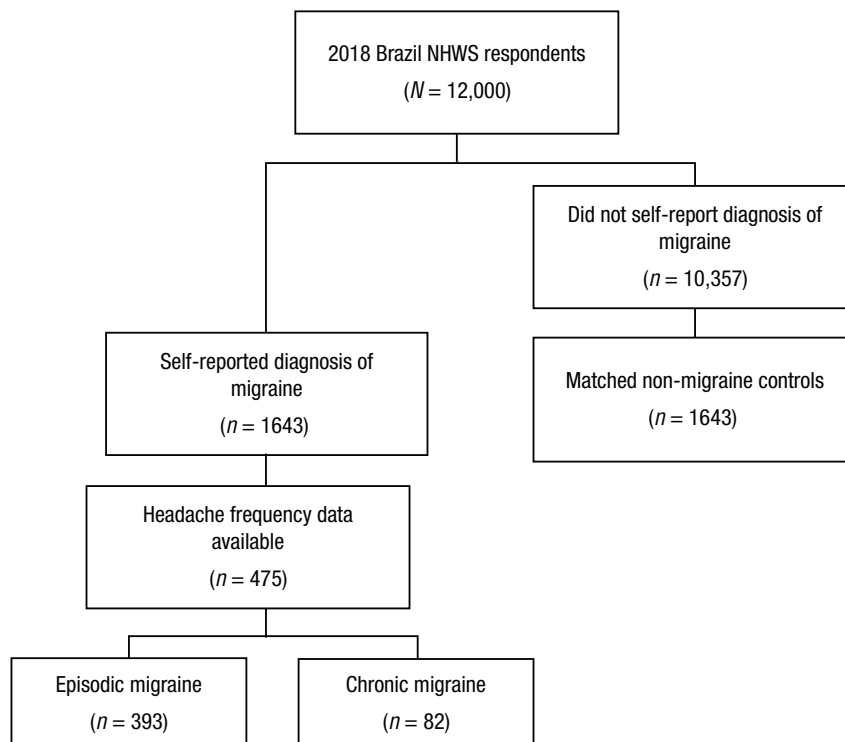


FIGURE 1 Study sample selection flowchart. NHWS, National Health and Wellness Survey.

TABLE 1 Patient demographics and health characteristics for patients with migraine versus matched controls.

	Self-reported diagnosed migraine (n = 1643)	Matched non-migraine control (n = 1643)	Standardized difference
Age, years, mean (\pm SD)	36.3 (11.6)	36.0 (12.4)	0.03
Sex, n (%)			
Male	417 (25.4)	404 (24.5)	0.02
Female	1226 (74.6)	1239 (75.4)	
Ethnicity, n (%)			0.06
White	994 (60.5)	988 (60.1)	
Black	143 (8.7)	145 (8.8)	
Asian	25 (1.5)	37 (2.3)	
Mixed race	454 (27.6)	450 (27.4)	
Indigenous	4 (0.2)	3 (0.2)	
Mixed	19 (1.2)	18 (1.1)	
Declined to answer	4 (0.2)	2 (0.1)	
Married, n (%)			0.03
Married/living with partner	962 (58.6)	939 (57.2)	
Single/divorced/separated/widowed	679 (41.3)	702 (42.7)	
Declined to answer	2 (0.1)	2 (0.1)	
Monthly income, n (%)			0.05
R\$ <250 to R\$ 1000	88 (5.4)	96 (5.8)	
R\$ 1001 to R\$ 5000	940 (57.2)	936 (57.0)	
R\$ 5001 to R\$ 10,000	382 (23.3)	389 (23.7)	
R\$ \geq 10,001	161 (9.8)	143 (8.7)	
Declined to answer	72 (4.4)	79 (4.8)	
Insurance, n (%)			0.04
Private through employer	458 (27.9)	465 (28.3)	
Individual/family plans	414 (25.2)	393 (23.9)	
Public/national/SUS	478 (29.1)	482 (29.3)	
Other	29 (1.8)	36 (2.2)	
None	264 (16.1)	267 (16.3)	
Drinks alcohol, n (%)	1089 (66.3)	1049 (63.8)	0.05
CCI category, n (%)			0.04
0	1410 (85.8)	1420 (86.4)	
1	136 (8.3)	126 (7.7)	
2	60 (3.7)	65 (4.0)	
\geq 3	37 (2.3)	32 (1.9)	

Abbreviations: CCI, Charlson Comorbidity Index; R\$, Brazilian real; SUS, Sistema Único de Saúde (the public health system of Brazil).

(Table S3); however, absenteeism was significantly higher among patients with CM compared with those with EM ($p = 0.029$).

Healthcare resource utilization

HRU was significantly higher among patients with migraine compared with matched controls (Table 4). Overall, 892 (54.3%) patients with self-diagnosed migraine reported a visit to the ED and 291 (17.7%) reported a hospitalization in the prior 6 months compared with 599 (36.5%) and 164 (10.0%) matched controls, respectively. In the 6 months prior to the

questionnaire application, patients with migraine reported significantly more visits to their HCP (mean, 7.2 vs. 4.5; $p < 0.001$), more ED visits (1.7 vs. 0.9; $p < 0.001$), and a higher mean number of hospitalizations compared with individuals without migraine (0.4 vs. 0.2; $p = 0.002$). HRU was comparable among patients with EM and CM (Table S4).

Migraine treatment patterns

Most of the respondents with migraine reported the use of non-specific medications (e.g., non-steroidal anti-inflammatory drugs

TABLE 2 Health-related quality of life for patients with migraine versus matched controls.

Score, mean (\pm SD) [95% CI]	Self-reported diagnosed migraine (n = 1643)	Matched non-migraine control (n = 1643)	p value
SF-36v2 MCS measure	42.9 (10.2) [42.4, 43.4]	46.0 (9.9) [45.5, 46.5]	< 0.001
SF-36v2 PCS measure	50.3 (7.5) [49.9, 50.7]	52.0 (7.6) [51.6, 52.4]	< 0.001
SF-6D health utility index score	0.7 (0.1) [0.7, 0.7]	0.7 (0.1) [0.7, 0.7]	< 0.001
Bodily pain scale	45.4 (9.1) [45.0, 5.8]	49.2 (9.1) [48.8, 49.6]	< 0.001
General health scale	49.8 (9.2) [49.4, 50.2]	52.1 (8.8) [51.7, 52.5]	< 0.001
Mental health scale	44.7 (9.8) [44.2, 45.2]	47.7 (9.7) [47.2, 48.2]	< 0.001
Physical functioning scale	50.2 (8.5) [49.8, 50.6]	51.4 (8.6) [51.0, 51.8]	< 0.001
Role emotional scale	42.4 (11.2) [41.9, 42.9]	45.2 (11.0) [44.7, 45.7]	< 0.001
Role physical scale	47.3 (8.7) [46.9, 47.7]	49.1 (8.9) [48.7, 49.5]	< 0.001
Social functioning scale	43.3 (10.1) [42.8, 43.8]	46.4 (10.1) [45.9, 46.9]	< 0.001
Vitality scale	49.6 (9.4) [49.1, 50.1]	51.5 (9.9) [51.0, 52.0]	< 0.001
EQ-5D-5L utility score	0.7 (0.2) [0.7, 0.7]	0.8 (0.2) [0.8, 0.8]	< 0.001

Abbreviations: CI, confidence interval; EQ-5D-5L, EuroQol 5-dimension 5-level; MCS, mental component summary; PCS, physical component summary; SD, standard deviation; SF-6D, Short Form 6-dimension; SF-36v2, 36-item Short Form Health Survey, version 2.

TABLE 3 Work productivity and activity impairment for patients with migraine versus matched controls.

	Self-reported diagnosed migraine (n = 1643)		Matched non-migraine control (n = 1643)		p value
	Valid no.	Mean (\pm SD) [95% CI]	Valid no.	Mean (\pm SD) [95% CI]	
Absenteeism (work time missed), % ^a	1196	12.8 (19.1) [11.9, 13.7]	1119	8.4 (17.1) [7.6, 9.2]	< 0.001
Presenteeism (impairment while working), % ^a	1223	35.0 (28.7) [33.6, 36.4]	1143	24.8 (28.0) [23.4, 26.2]	< 0.001
Total work productivity impairment (overall productivity loss), % ^a	1196	40.6 (31.4) [39.1, 42.1]	1119	28.6 (30.9) [27.1, 30.1]	< 0.001
Activity impairment (impairment), %	1643	36.0 (28.8) [34.6, 37.4]	1643	25.5 (28.1) [24.1, 26.9]	< 0.001

Abbreviations: CI, confidence interval; SD, standard deviation.

^aOnly employed patients responded to work impairment items; all patients responded to activity impairment items.

TABLE 4 Healthcare resource utilization in the past 6 months for patients with migraine versus matched controls.

	Self-reported diagnosed migraine (n = 1643)	Matched non-migraine control (n = 1643)
Patients with ED visits or hospitalizations, n (%) [95% CI]		
ED visit	892 (54.3) [51.9, 56.7]	599 (36.5) [34.1, 38.8]
Hospitalization	291 (17.7) [15.9, 20.0]	164 (10.0) [8.5, 11.4]
No. of visits or hospitalizations, mean (\pm SD) [95% CI]		
No. of visits to HCP	7.2 (9.5) ^a [6.7, 7.7]	4.5 (6.3) [4.2, 4.8]
No. of ED visits	1.7 (3.8) ^a [1.5, 1.9]	0.9 (2.2) [0.8, 1.0]
No. of times hospitalized	0.4 (2.7) ^b [0.3, 0.5]	0.2 (1.1) [0.1, 0.3]

Abbreviations: CI, confidence interval; ED, emergency department; HCP, healthcare provider; SD, standard deviation.

^ap < 0.001 versus matched non-migraine control.

^bp = 0.002 versus matched non-migraine control.

(NSAIDs) and analgesics) for acute migraine treatment by the time of questionnaire completion, most commonly ibuprofen (79.4%), followed by acetaminophen (30.7%; Table 5). Approximately 48% of respondents with migraine reported the use of drug combinations

of acetaminophen or metamizole with dihydroergotamine and other compounds. Only 24.9% of patients with migraine reported the use of any kind of triptan. Of patients taking acute treatments (n = 631), 3.6% reported taking an opioid analgesic. A total of 225 (13.7%)

TABLE 5 Current prescribed migraine treatments for the self-reported diagnosed migraine group.

Currently taking prescription medication, n (%)	Acute (n = 631)	Analgesics ^a	Acetaminophen	194 (30.7)	
			Metamizole + caffeine	75 (11.9)	
		NSAIDs ^a	Ibuprofen	501 (79.4)	
			Acetylsalicylic acid	131 (20.8)	
			Diclofenac sodium	47 (7.4)	
			Ketorolac tromethamine	40 (6.3)	
			Naproxen	33 (5.2)	
			Loxoprofen sodium hydrate	3 (0.5)	
			Acetylsalicylic acid + caffeine	37 (5.9)	
			Triptans ^a	Naratriptan	90 (14.3)
				Sumatriptan	48 (7.6)
		Rizatriptan		11 (1.7)	
		Zolmitriptan		8 (1.3)	
		Sumatriptan + naproxen		14 (2.2)	
		Ergotamines ^a	Dihydroergotamine + acetaminophen + caffeine + metoclopramide	155 (24.6)	
			Dihydroergotamine + metamizole + caffeine	148 (23.5)	
		Opioids	Tramadol hydrochloride	23 (3.6)	
		Muscle relaxants	Cyclobenzaprine	22 (3.5)	
		Preventive (n = 225)	Antiseizure medications	Topiramate	103 (45.8)
	Sodium valproate			22 (9.8)	
	Gabapentin			13 (5.8)	
	Beta blockers			Propranolol	40 (17.8)
			Metoprolol	11 (4.9)	
			Nadolol	7 (3.1)	
	Tricyclic antidepressants		Amitriptyline	40 (17.8)	
	Calcium channel blockers		Flunarizine	36 (16.0)	
	Neuromuscular blockers		OnabotulinumtoxinA	11 (4.9)	
Central alpha agonists	Clonidine		9 (4.0)		
Serotonin antagonist	Pizotifen	4 (1.8)			

Abbreviation: NSAID, non-steroidal anti-inflammatory drug.

^aIncluding combinations.

patients with migraine were taking preventive medications, most commonly topiramate (45.8%), followed by amitriptyline and propranolol (17.8% each). A higher proportion of patients with CM reported the use of acute medication compared with patients with EM (83.3% vs. 65.0%, respectively), primarily driven by NSAID utilization. By contrast, a higher proportion of patients with EM reported the use of preventive medication (35.0%) compared with those with CM (16.7%), with higher proportions of patients with EM utilizing nearly all categories of preventive medication (Table S5).

DISCUSSION

The results of this cross-sectional, nationally representative survey showed that Brazilian individuals with migraine had significantly poorer HRQoL indicators than their non-migraine matched controls

and higher HRU, which may result in greater costs to the health-care system. Additionally, respondents with migraine also reported greater loss of work productivity and activity impairment than their matched controls, indicating that migraine negatively impacts the well-being, productivity, and HRQoL of affected individuals.

In this study, individuals with migraine, when compared with those without it, showed significantly lower SF-36v2 PCS and MCS scores and utility scores (derived from both the SF-6D and EQ-5D-5L), indicating worse physical, mental, and overall health status. These results are consistent with those of previously published studies, which also demonstrated lower HRQoL scores among patients with migraine in the United States and Europe.^{6,23,24} In the present study, the differences between patients with migraine and non-migraine controls in these health status scores met the established MIDs and were thus considered clinically meaningful, reinforcing the burden of the disease.

The impacts on the personal, familial, social, and professional lives of individuals affected by migraine have been investigated in studies across multiple countries, like the Eurolight project, a survey conducted in 10 European countries in which individuals with migraine reported losing workdays, housework days, and social activities due to migraine attacks.²⁵ In My Migraine Voice, a global transversal study conducted in 2018 in several countries, including Brazil, among patients with migraine with >4 headache attacks per month, 87% of patients reported impacts on their personal, social, and professional lives.⁵ Particularly in Brazil, the majority of patients reported impacts on social and daily activities.²⁶ The present study also showed statistically significantly higher levels of absenteeism, presenteeism and total work productivity impairment among respondents living with migraine in Brazil, consistent with previously published studies in other countries.^{6,25} This emphasizes the indirect economic burden of migraine related to decreased work productivity, mainly when considering that the pre-retired population groups (aged 15–49 years) are the ones most affected by migraine disability.¹

Although migraine has a major burden on private, professional, and social domains of an individual's life,⁵ data regarding the economic and social burden of migraine in the Brazilian population are still scarce. A previous Brazilian study showed that patients with primary headache disorders (largely migraine) missed an average of 4.2 days of work over 3 months and reported presenteeism ($\geq 50\%$ reduced productivity) on an average of 5.7 days over 3 months.²⁷ A study among beneficiaries from a Brazilian health plan showed a higher use of outpatient services by patients with migraine compared with individuals without migraine.²⁸ In a retrospective review of records from 66,808 patients admitted to an ED in Brazil, inpatient treatment was more common among patients with multiple headache-related ED visits.²⁹ The present study also indicated higher HRU among Brazilian patients with migraine compared with their matched controls, including significantly more HCP and ED visits, as well as a higher mean number of hospitalizations in 6 months. Although this study improves the understanding of the substantial societal and healthcare system burden of migraine in Brazil, additional research is needed to better understand the direct and indirect cost implications.

Lastly, this study examined treatment patterns for Brazilian patients with migraine. Most of the reported drugs were indicated for acute therapy, which aims to treat migraine attacks once they have begun, limiting disability, and reducing pain and associated symptoms (e.g., nausea or vomiting).³⁰ Among these acute treatments, NSAIDs and analgesics, such as ibuprofen and acetaminophen, were the most used. Only 24.9% of respondents used migraine-specific therapies like triptans. These findings are in line with previous Brazilian observational studies, which reported a greater use of non-specific drugs for the acute treatment of migraine attacks over specific drugs, like triptans.^{8,31}

Drugs indicated for migraine preventive treatment were less frequently reported. In this study, treatment with topiramate was the most frequently reported (45.8%), followed by amitriptyline (17.8%) and propranolol (17.8%). Preventive treatment of migraine aims to reduce the severity, frequency, and duration of expected attacks

in those with a significant headache burden to improve HRQoL.³² However, only ~14% of Brazilian patients in the present study were receiving a preventive treatment. Interestingly, rates of preventive treatment use were lower in patients with CM than in those with EM despite preventive treatment being indicated for all patients with CM. A study by Peres et al.³³ showed that the five most common preventive classes in Brazil were antidepressants (44%), beta blockers (41%), antiseizure medications (39%), non-medicinal therapy (32%), and vitamins/herbal therapies (24%). In a separate study by Carod-Artal et al.,³¹ only approximately one-fifth of patients in Brazil were using preventive treatments; however, those study results are >12 years old and may not represent current rates of preventive treatment use.

Our study has several limitations. As the NHWS is a cross-sectional study, no causal conclusions may be drawn. It allows for insights into different interpretations, but a longitudinal study is needed to tease out bidirectional effects. Considering that the NHWS study consists of a standardized questionnaire to assess general health status across several therapeutic areas, there was no specific questionnaire to assess whether HRU was for migraine (e.g., migraine-related hospitalizations) or for other disease states. Furthermore, ~80% of diagnosed migraine respondents were classified as having EM, potentially weighing the results in favor of that population. However, the classification of migraine as EM or CM in the present study should be interpreted with caution. The available data for headache days (i.e., 30 days) were shorter than the required time frame of ≥ 3 months for appropriate classification as CM per *International Classification for Headache Disorders, Third Edition* criteria.³⁴ This potential bias in classification may have contributed to the unexpected finding of higher preventive treatment use among patients with EM as compared with those with CM. While NHWS is broadly representative of the corresponding national adult population, as with other patient-reported surveys, it likely underrepresents several populations, such as people with limited access to online administration, less healthy elderly people, patients who are institutionalized, and those with severe comorbidities and disabilities. Additionally, 60.3% of individuals in this study population were White compared with 44.2% of the general Brazilian population, resulting in an overrepresentation of this demographic, as the NHWS was representative of the general population but not necessarily representative for specific conditions.³⁵ The self-reported nature of the NHWS also is associated with potential corresponding biases, such as inaccurate recall due to a lengthy recall period for some questions and false reporting (whether intentional or unintentional). For example, diagnoses and medications are self-reported as being provided by a physician and were not confirmed by a physician. Although self-reported diagnosis has been previously used in studies, an additional limitation was the exclusion of patients with migraine who did not receive a medical consultation, which may result in underdiagnosed migraine. Very low rates of migraine diagnosis have been reported in epidemiologic studies, including those in Brazil; in a population-based study in Brazil, the 1-year sex- and age-adjusted prevalence of migraine was reported at 15.2%,³⁶ indicating that the burden of

migraine identified in this study was likely underestimated and the total burden could be greater than reported.

Despite the noted limitations, this study also has several strengths. It used self-reported data from the 2018 Brazil NHWS, which is a validated survey with standardized questionnaires that have been used to study the burden of illness across several therapeutic areas in Brazil and in multiple countries,^{11,37–40} with a methodology that ensures representativeness of the general population. The NHWS, hence, provides an opportunity to analyze real-world data outside the highly controlled setting of clinical trials for representative information on clinical characteristics, treatment patterns, and patient-reported outcomes that might not otherwise be available in administrative data, such as insurance claims.

The present study is the first to present comprehensive data on the burden of migraine in Latin America. It originated from a nationally representative survey conducted in Brazil, and its findings indicate an increased burden of migraine by demonstrating that Brazilian individuals with migraine have poorer HRQoL (i.e., mental, physical, and overall health status), greater loss of work productivity (both presenteeism and absenteeism), more activity impairment, and higher HRU compared with those without migraine. Due to the higher HRU and work productivity loss among patients with migraine, results might suggest important direct and indirect costs associated with migraine. However, further research is needed to better understand these economic implications. We speculate that allocating resources toward the treatment of migraine may reduce absenteeism and presenteeism, thereby improving productivity and providing an economic return in the investment in public health.

CONCLUSIONS

Cumulatively, these study findings reveal substantial unmet needs among individuals with migraine. Although more research is needed into the economic implications and the differences between EM and CM burden in Brazil, results from this study indicate that those with migraine have poorer HRQoL and higher work productivity loss and HRU compared with those without migraine. These study results suggest that treatments that reduce symptom burden and the number of headache days may have a positive impact on patients' HRQoL and, therefore, on the costs to the healthcare system and to society. Thus, these findings are relevant for HCPs treating patients with migraine, as well as for employers, payers, and health authorities.

AUTHOR CONTRIBUTIONS

Study concept and design: Joshua M. Cohen, Tony Piha, Rinat Ribalov, Tamar Lengil, Andressa van der Laan. **Acquisition of data:** Lulu K. Lee. **Analysis and interpretation of data:** Marcio Nattan Portes Souza, Joshua M. Cohen, Tony Piha, Rinat Ribalov, Tamar Lengil, Andressa van der Laan, Marcelo Calderaro, Lulu K. Lee. **Drafting of the manuscript:** Marcio Nattan Portes Souza, Joshua M. Cohen, Tony Piha, Rinat

Ribalov, Tamar Lengil, Andressa van der Laan, Marcelo Calderaro, Lulu K. Lee. *Revising it for intellectual content:* Marcio Nattan Portes Souza, Joshua M. Cohen, Tony Piha, Rinat Ribalov, Tamar Lengil, Andressa van der Laan, Marcelo Calderaro, Lulu K. Lee. *Final approval of the completed manuscript:* Marcio Nattan Portes Souza, Joshua M. Cohen, Tony Piha, Rinat Ribalov, Tamar Lengil, Andressa van der Laan, Marcelo Calderaro, Lulu K. Lee.

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CONFLICT OF INTEREST

Marcio Nattan Portes Souza has received honoraria for oral presentations from Teva, Lilly, Novartis, Allergan/AbbVie, Sanofi, Lundbeck and Libbs. **Tony Piha, Rinat Ribalov, Tamar Lengil, and Andressa van der Laan** are employees of Teva Pharmaceuticals. **Joshua M. Cohen** is a former employee of Teva Pharmaceuticals. **Marcelo Calderaro** has received grants for lectures for Allergan/AbbVie, Boehringer Ingelheim, Novartis, and Teva Pharmaceuticals. **Lulu K. Lee** is an employee of Kantar Health who received funding to conduct this study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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