Received: 7 April 2023 | Accepted: 14 July 2023

DOI: 10.1111/head.14629

RESEARCH SUBMISSIONS

Impact of monthly headache days on migraine-related quality of life: Results from the Chronic Migraine Epidemiology and Outcomes (CaMEO) study

Richard B. Lipton MD[1] | Patricia Pozo-Rosich MD, PhD[2,3] | Serena L. Orr MD, MSc[4,5] | Michael L. Reed PhD[6] | Kristina M. Fanning PhD[7] | Brett Dabruzzo PharmD[8] | Dawn C. Buse PhD[1]

[1]Department of Neurology, Albert Einstein College of Medicine, Bronx, New York, USA

[2]Headache Unit, Neurology Department, Vall d'Hebron University Hospital, Barcelona, Spain

[3]Headache Research Group, VHIR, Universitat Autonoma de Barcelona, Barcelona, Spain

[4]Alberta Children's Hospital, University of Calgary, Calgary, Alberta, Canada

[5]Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada

[6]Vedanta Research, Chapel Hill, North Carolina, USA

[7]MIST Research, Wilmington, North Carolina, USA

[8]Medical Affairs (Neurosciences – Migraine), AbbVie, Illinois, North Chicago, USA

Correspondence
Brett Dabruzzo, PharmD, Director, Medical Affairs (Neurosciences – Migraine) AbbVie, 1 N. Waukegan Road, North Chicago, IL 60064, USA.
Email: brett.dabruzzo@abbvie.com

Funding information
Allergan (prior to its acquisition by AbbVie)

Abstract

Objective: To characterize the direct impact of monthly headache days (MHDs) on health-related quality of life (HRQoL) in people with migraine and the potential mediating effects of anxiety, depression, and allodynia.

Background: Although the general relationship between increased migraine frequency (i.e., MHDs) and reduced HRQoL is well established, the degree to which reduced HRQoL is due to a direct effect of increased MHDs or attributable to mediating factors remains uncertain.

Methods: Cross-sectional baseline data from participants with migraine who completed the Core and Comorbidities/Endophenotypes modules in the 2012–2013 US Chronic Migraine Epidemiology and Outcomes (CaMEO) study, a longitudinal web-based survey study, were analyzed. The potential contribution of depression, anxiety, and/or allodynia to the observed effects of MHDs on HRQoL as measured by the Migraine-Specific Quality-of-Life Questionnaire version 2.1 (MSQ) was evaluated.

Results: A total of 12,715 respondents were included in the analyses. The MSQ domain scores demonstrated progressive declines with increasing MHD categories ($B = -1.23$ to -0.60; $p < 0.001$). The observed HRQoL decrements associated with increasing MHDs were partially mediated by the presence of depression, anxiety, and allodynia. The MHD values predicted 24.0%–32.4% of the observed variation in the MSQ domains. Depression mediated 15.2%–24.3%, allodynia mediated 9.6%–16.1%, and anxiety mediated 2.3%–6.0% of the observed MHD effects on the MSQ.

Conclusions: Increased MHD values were associated with lower MSQ scores; the impact of MHDs on the MSQ domain scores was partially mediated by the presence of depression, anxiety, and allodynia. MHDs remain the predominant driver of the MSQ

Abbreviations: ASC-12, 12-item Allodynia Symptom Checklist; CaMEO, Chronic Migraine Epidemiology and Outcomes; CI, confidence interval; EF, Emotional Function; EM, episodic migraine; GAD-7, seven-item Generalized Anxiety Disorder assessment; HIT-6, Headache Impact Test-6; HRQoL, health-related quality of life; ICHD-3, *International Classification of Headache Disorders*, third edition; MHD, monthly headache day; MSQ, Migraine-Specific Quality-of-Life Questionnaire, version 2.1; PHQ-9, Patient Health Questionnaire-9; RFP, Role Function–Preventive; RFR, Role Function–Restrictive; SF-12, Short Form-12; SF-36, Short Form-36.

variation; moreover, most of the variation in the MSQ remains unexplained by the variables we analyzed. Future longitudinal analyses and studies may help clarify the contribution of MHDs, comorbidities, and other factors to changes in HRQoL.

KEYWORDS
allodynia, anxiety, comorbidity, depression, functional status, health-related quality of life

INTRODUCTION

Migraine is a complex, chronic neurologic disease with recurrent multi-phase attacks characterized by headache as well as neurologic and autonomic symptoms, which may include photophobia, phonophobia, nausea, and/or vomiting as defined by the *International Classification of Headache Disorders*, third edition (ICHD-3) criteria.[1] Migraine is broadly categorized as episodic migraine (EM; < 15 headache days/month) or chronic migraine (≥ 15 headache days/month).[1] Migraine affects an estimated one in seven adults globally. Over 1 billion people experience migraine, and it is the leading cause of years lived with disability in those aged < 50 years.[2,3]

Migraine is associated with substantial decrements in health-related quality of life (HRQoL) across multiple dimensions, confirmed by an abundance of evidence from disease-specific (e.g., Headache Impact Test-6 [HIT-6], Migraine-Specific Quality-of-Life Questionnaire [MSQ]) and generic (e.g., Short Form-12 [SF-12], Short Form-36 [SF-36]) assessments of HRQoL.[4–6]

Moreover, monthly headache day (MHD) frequency has an inverse relationship with HRQoL. HRQoL improves as MHDs are reduced[7–9]; however, the degree to which this improvement is due to a direct effect of reduced MHDs or attributable to mediating factors remains unclear. Because the improvement of HRQoL in persons with migraine is an important patient-centered treatment goal,[10] it is essential to understand the factors that determine HRQoL and how they interact with and respond to treatment.

Several factors associated with both MHDs and HRQoL might conceivably influence the observed associations. For example, increased MHD frequency is associated with increased prevalence of depression, anxiety, and cutaneous allodynia during attacks,[11–14] while migraine comorbidity with these disorders and symptoms, in turn, has been associated with HRQoL reductions beyond those from migraine alone.[11,15] As illustrated in Figure 1, we hypothesized that in addition to a direct effect from increased MHD frequency to reduced HRQoL, there are indirect pathways, often referred to as "mediation," leading to reduced HRQoL through depression, anxiety, and/or allodynia.

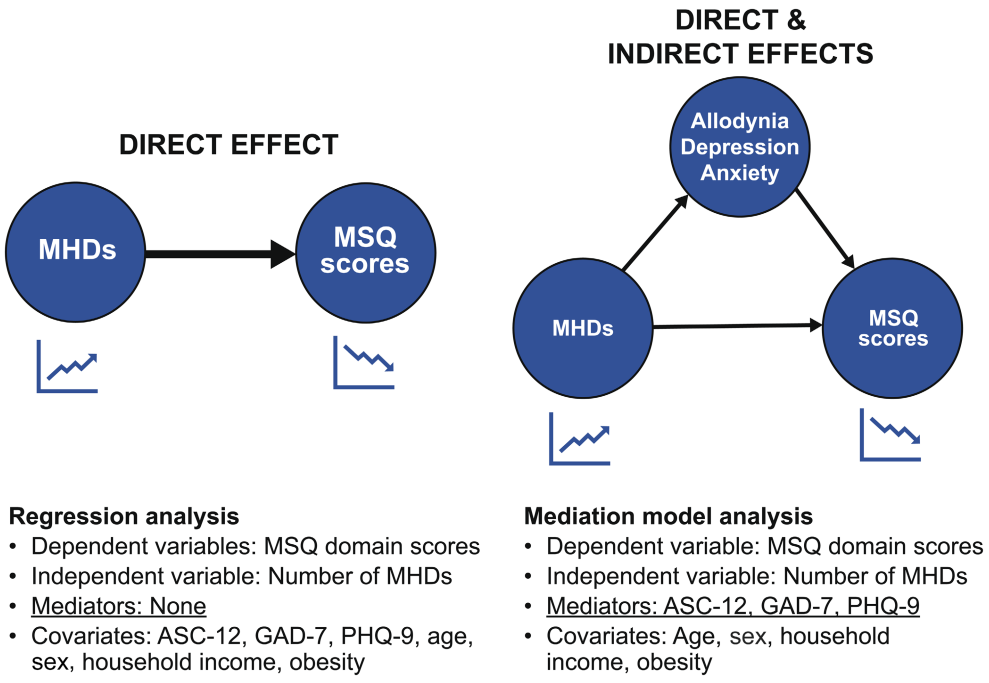

FIGURE 1 Schematic diagram of regression models (left) versus mediation models (right). ASC-12, 12-item Allodynia Symptom Checklist; GAD-7, seven-item Generalized Anxiety Disorder assessment; MHD, monthly headache day; MSQ, Migraine-Specific Quality-of-Life Questionnaire, version 2.1; PHQ-9, Patient Health Questionnaire (nine-item depression module). [Color figure can be viewed at wileyonlinelibrary.com]

The 2012–2013 Chronic Migraine Epidemiology and Outcomes (CaMEO) study is a longitudinal web-based survey study designed to characterize the US population affected by migraine and to explore the natural history of migraine and its correlates and outcomes over the course of 1 year.[16] MHD frequency at baseline was used not only to evaluate the relative proportions of respondents in various MHD frequency ranges, but also to stratify the study population for analytical purposes. The HRQoL measure used was the MSQ. We conducted analyses of cross-sectional baseline data from the CaMEO study, with the objective of characterizing the direct impact of MHDs on HRQoL in persons with migraine and the potential mediating effects of anxiety, depression, and allodynia.

METHODS

Study design and population

This is a post hoc analysis of cross-sectional baseline data from the CaMEO study. The CaMEO study protocol has been described in detail previously[16]; briefly, CaMEO was a prospective, longitudinal, web-based survey with participants drawn from an internet research panel (Research Now, Plano, TX, USA) comprising 2.4 million active US members.[16] Invitations were emailed to nearly half a million panel members selected to be representative of the US population, and respondents completed a validated screening questionnaire. Of 80,783 total returns, 58,418 were usable and 22,365 were removed because they abandoned the survey (< 20% of the survey was complete and headaches status could not be identified), provided unstable data, or were over the predetermined demographics quotas. Of the usable returns, 16,789 respondents met the ICHD-3 beta criteria for migraine and were included in the study. Study data were collected between September 2012 and November 2013.[16] Participants provided electronic consent to participate before initiating the survey, and the Institutional Review Board of the Albert Einstein College of Medicine approved the study.

Assessments

All CaMEO study participants completed a Core Module electronically (at baseline, 6 months, and 12 months) consisting of multiple questions and assessments dealing with information about migraine frequency, symptom severity, treatments, comorbidities, disability, and HRQoL.[16] The Core Module assessments used in the present analyses included baseline headache frequency, the MSQ, Patient Health Questionnaire-9 (PHQ-9), seven-item Generalized Anxiety Disorder Assessment (GAD-7), and 12-item Allodynia Symptom Checklist (ASC-12).

The MHD frequency was shown as the number of headache days within the past 30 days only and categorized into four groups (0–3, 4–7, 8–14, and ≥ 15 days) in the sociodemographic table (Table 1); however, MHDs were included as a continuous variable in the linear and mediation models (Figure 1 and described below). The MSQ included 14 items addressing three domains, including Role Function–Restrictive (RFR, seven items covering migraine-related limitations on daily activities); Role Function–Preventive (RFP, four items covering daily activities prevented due to migraine); and Emotional Function (EF, three items covering the emotional impact of migraine); each scored by frequency (1 = none of the time; 6 = all of the time).[17,18] Item scores were summed for each domain and rescaled to a 0–100 scale, with higher scores indicating better HRQoL. The PHQ-9 consisted of the nine-item depression scale from the full PHQ, with symptoms scored on a 4-point frequency scale (0 = not at all; 3 = nearly every day); the total score (range 0–27) was used in the analyses and treated as continuous variables in the mediation models.[19] The GAD-7 is a seven-item scale with symptoms of generalized anxiety disorder rated according to frequency (0 = not at all; 3 = nearly every day); the total score (range 0–21) was used in the analyses.[20] The severities of depression and of anxiety were classified as minimal to mild (total score < 10) or moderate to severe (total score ≥ 10), and scores were treated as continuous variables in the mediation models.

The CaMEO study participants who completed the baseline Comorbidities/Endophenotypes cross-sectional module, a series of patient-reported comorbidity assessments, as well as the baseline Core Module, were included in the current analysis. Allodynia was assessed using the ASC-12, a 12-item list of possible cutaneous allodynia symptoms, rated according to the frequency of occurrence; item scoring is 0 for frequency from "never" to "rarely," 1 for "less than half the time," and 2 for "more than half the time," and responses were summed. The total score cut-off for the presence of allodynia was ≥ 3.[13,16]

Statistical methods

There were no formal sample size calculations conducted for either the full CaMEO study or the present analysis. Baseline responses from participants in the Comorbidities/Endophenotypes module were evaluated using linear regression analysis and an analysis based on mediation models (Figure 1). Multiple linear regression analysis was conducted with MSQ domain scores (RFR, RFP, and EF) as the dependent variables and the independent continuous variable of MHDs. Covariates included ASC-12 score, GAD-7 score, PHQ-9 score, and other covariates with known associations with the MSQ[21] (i.e., age, and binary variables female, household income [≥$50,000], and obesity [body mass index ≥ 30 kg/m^2] as regressors). Unstandardized *B* coefficients, their corresponding 95% confidence intervals (CIs), and *p* values were shown for MHDs, adjusting for covariates. For the mediation models, the number of MHDs was the independent variable and the MSQ domain scores were dependent variables; mediators included ASC-12, GAD-7, and PHQ-9 scores (treated as continuous variables); and covariates included age (continuous) and the binary variables

TABLE 1 Baseline demographics and selected assessments.

	MHD category at baseline ($N = 12,810$)			
Variable	**0–3 ($n = 7416$)**	**4–7 ($n = 2719$)**	**8–14 ($n = 1461$)**	**≥ 15 ($n = 1214$)**
Demographics				
Age, years, mean (SD)	42.2 (14.8)	40.5 (14.0)	40.5 (14.4)	42.1 (13.9)
Female, *n* (%)	5280 (71.2)	2132 (78.4)	1166 (79.8)	1012 (83.4)
Household income, *n* (%) ($N = 12,716$)				
< $30,000	1511 (20.5)	658 (24.4)	401 (27.6)	382 (31.7)
$30,000–$49,999	1348 (18.3)	437 (16.2)	262 (18.0)	240 (19.9)
$50,000–$74,999	1654 (22.5)	622 (23.0)	315 (21.7)	261 (21.7)
≥ $75,000	2844 (38.7)	984 (36.4)	475 (32.7)	322 (26.7)
Race, *n* (%) ($N = 12,771$)				
White	5944 (80.4)	2261 (83.5)	1221 (83.7)	1035 (85.5)
Black	701 (9.5)	221 (8.2)	110 (7.5)	100 (8.3)
American Indian or Native Alaskan	32 (0.4)	10 (0.4)	13 (0.9)	6 (0.5)
Asian	284 (3.8)	77 (2.8)	28 (1.9)	17 (1.4)
Pacific Islander	5 (0.1)	7 (0.3)	0	2 (0.2)
Other race	196 (2.7)	63 (2.3)	31 (2.1)	17 (1.4)
>1 Race	231 (3.1)	70 (2.6)	56 (3.8)	33 (2.7)
Body mass index, *n* (%)				
< 30 kg/m^2 (underweight, normal, or overweight)	4947 (66.7)	1776 (65.3)	889 (60.8)	701 (57.7)
≥ 30 kg/m^2 (obese)	2469 (33.3)	943 (34.7)	572 (39.2)	513 (42.3)
MSQ domain scores, mean (SD)				
Role Function–Restrictive	67.87 (23.0)	56.10 (20.5)	50.86 (20.4)	42.80 (22.3)
Role Function–Preventive	81.03 (21.3)	72.40 (21.8)	68.74 (22.3)	62.29 (26.2)
Emotional Function	79.30 (23.9)	65.93 (26.4)	58.34 (27.4)	47.05 (29.4)
Candidate mediators				
Allodynia (ASC-12 score), mean (SD)	2.59 (3.3)	3.58 (3.7)	4.10 (4.2)	4.95 (4.6)
< 3 (not present), *n* (%)	4579 (61.7)	1326 (48.8)	639 (43.7)	446 (36.7)
≥ 3 (present), *n* (%)	2837 (38.3)	1393 (51.2)	822 (56.3)	768 (63.3)
Depression (PHQ-9 score), mean (SD)	6.40 (5.9)	8.18 (6.1)	9.56 (6.5)	11.55 (7.1)
< 10 (none–mild), *n* (%)	5622 (75.8)	1772 (65.2)	815 (55.8)	537 (44.2)
≥ 10 (moderate–severe), *n* (%)	1794 (24.2)	947 (34.8)	646 (44.2)	677 (55.8)
Anxiety (GAD-7 score), mean (SD)	6.17 (5.3)	7.60 (5.5)	8.70 (5.7)	9.78 (6.0)
< 10 (none–mild), *n* (%)	5715 (77.1)	1829 (67.3)	875 (59.9)	643 (53.0)
≥ 10 (moderate–severe), *n* (%)	1701 (22.9)	890 (32.7)	586 (40.1)	571 (47.0)

Abbreviations: ASC-12, 12-item Allodynia Symptom Checklist; GAD-7, seven-item Generalized Anxiety Disorder assessment; MHD, monthly headache day; MSQ, Migraine-Specific Quality-of-Life Questionnaire version 2.1; PHQ-9, Patient Health Questionnaire (nine-item depression module); SD, standard deviation.

female, household income (≥ $50,000), and obesity (body mass index ≥ 30 kg/m^2). For each MSQ domain (MSQ-RFR, MSQ-RFP, MSQ-EF), mediators were modeled, along with covariates, one at a time and in pairs (GAD-7 with PHQ-9, ASC-12 with PHQ-9, and ASC-12 with GAD-7) in order to assess the separate and joint contributions of each mediator before the inclusion of the three mediators (ASC-12, GAD-7, PHQ-9) in the final models. Mediation effects and standard errors were reported for the total and direct effects of MHDs on the MSQ, for the indirect effects of mediators on the MSQ, and for the covariates. The *p* values were reported for the total and direct effects of MHDs on the MSQ and for the covariates, and 95% CIs around the indirect effects of mediators on the MSQ were obtained and reported using bootstrapping. In addition, the proportions of all explained variance in the MSQ domain scores attributable to MHDs and the three mediators (ASC-12, GAD-7, PHQ-9) were reported. Inferential tests were two-tailed with significance at $p < 0.05$. The Statistical Package for the Social Sciences (SPSS), version 28.0 (IBM Corp., Armonk, NY,

USA) was used for all statistical analyses; the PROCESS macro was used for mediation models.[22]

RESULTS

Study population

A total of 12,810 respondents completed the baseline Comorbidities/Endophenotypes module. For baseline demographics, income data were missing from 94 respondents and race data were missing from 39 respondents. A total of 12,715 respondents had valid data for all variables of interest and were included in these analyses. Baseline demographic and disease state characteristics are summarized in Table 1. Headache frequency categories of 0–3, 4–7, 8–14, and ≥ 15 MHDs were reported by 7416 (57.9%), 2719 (21.2%), 1461 (11.4%), and 1214 (9.5%) respondents, respectively.

As shown in Table 1, greater baseline MHD frequency was associated with lower mean MSQ-RFR, MSQ-RFP, and MSQ-EM domain scores. In addition, higher mean ASC-12, PHQ-9, and GAD-7 scores were associated with increasing MHD frequency, indicating that greater MHD frequency was associated with increasing levels of allodynia, depression, and anxiety.

Linear regression

In the multiple linear regression analysis models including MHDs, ASC-12, PHQ-9, GAD-7, age, sex, annual household income, and obesity (Table 2), significant negative relationships ($p < 0.001$) were observed between MHDs and MSQ-RFR ($B = -0.92$, 95% CI −0.98 to −0.86), MSQ-RFP ($B = -0.60$, 95% CI −0.66 to −0.54), and MSQ-EF ($B = -1.23$, 95% CI −1.30 to −1.16) domains. These results demonstrate that with each 1-day increase in MHDs there is a 0.92-point decrease (worsening) in MSQ-RFR, a 0.60-point decrease in MSQ-RFP, and a 1.23-point decrease in MSQ-EF. Adjusted R^2 values for MSQ-RFR ($R^2 = 0.305$), MSQ-RFP ($R^2 = 0.240$), and MSQ-EF ($R^2 = 0.324$) indicate that MHD values predicted 30.5%, 24.0%, and 32.4% of the observed variation in the three MSQ domains, respectively.

Mediation models

In the mediation model analysis (Table 3 and Figure 2), the effect of MHDs is shown to be mediated by depression, anxiety, and allodynia. Each mediator (ASC-12, PHQ-9, GAD-7) explained a portion of the observed effect of MHDs on MSQ domain scores, and the size of this portion differed depending on how many mediators were modeled together. For all three MSQ domains (MSQ-RFR, MSQ-RFP, MSQ-EF), when a mediator was modeled one at a time, the indirect effect of that mediator accounted for a greater portion of the effect of MHDs on MSQ compared with when it was modeled along with other mediators.

The MSQ-RFR initial models

Initial models with mediators (ASC-12, PHQ-9, GAD-7) entered one at a time showed that 14.3% of the effect of MHDs on MSQ-RFR is accounted for by allodynia, 25.0% is accounted for by depression, and 18.0% is accounted for by anxiety. When depression and anxiety were entered together, depression accounted for 18.4% of the effect of MHDs on MSQ-RFR and anxiety accounted for 6.7% of the effect. When paired with allodynia, depression accounted for 22.7% of the effect of MHDs on MSQ-RFR and allodynia accounted for 10.8% of the effect. When anxiety was paired with allodynia, anxiety accounted for 16.2% of the effect of MHDs on MSQ-RFR and allodynia accounted for 11.3%.

The MSQ-RFP initial models

Modeling MSQ-RFP initially with single mediators showed that 20.4% of the effect of MHDs on MSQ-RFP is accounted for by allodynia, 30.4% was accounted for by depression, and 20.1% was accounted for by anxiety. When paired with anxiety, depression accounted for 26.8% of the effect and anxiety accounted for 3.7%. When depression and allodynia were entered together, depression accounted for 26.5% of the effect of MHDs on MSQ-RFP and allodynia accounted for 16.2% of the effect. When anxiety was paired with allodynia, anxiety accounted for 17.0% of the effect of MHDs on MSQ-RFP and allodynia accounted for 17.2%.

The MSQ-EF initial models

Mediation models in which mediators were entered one at a time showed that 13.1% of the effect of MHDs on MSQ-EF was accounted for by allodynia, 23.5% was accounted for by depression, and 16.8% was accounted for by anxiety. When paired with anxiety, depression accounted for 17.4% of the effect of MHDs on MSQ-EF and anxiety accounted for 6.2% of the effect. Allodynia accounted for 9.9% of the effect when entered with depression in the model, while depression accounted for 20.6% of the effect of MHDs on MSQ-EF. When anxiety was paired with allodynia, anxiety accounted for 14.8% of the effect of MHDs on MSQ-EF and allodynia accounted for 10.4%.

Final mediation model

In the final models, all mediators were added simultaneously (Table 3 and Figure 2). For the MSQ-RFR domain, allodynia accounted for 10.5%, depression accounted for 16.9%, and anxiety accounted for 6.0% of the association with MHDs. For the MSQ-RFP domain, allodynia accounted for 16.1%, depression accounted for 24.3%, and anxiety accounted for 2.3% of the association with MHDs. For the MSQ-EF domain, allodynia accounted for 9.6%,

TABLE 2 Linear regression models.

Dependent variable: MSQ score at baseline	Role Function–Restrictive				Role Function–Preventive				Emotional Function			
			95% CI				95% CI				95% CI	
	B	*p*	Low	High	*B*	*p*	Low	High	*B*	*p*	Low	High
MHDs[a]	−0.92	<0.001	−0.98	−0.86	−0.60	<0.001	−0.66	−0.54	−1.23	<0.001	−1.30	−1.16
Demographic covariates												
Female	−4.40	<0.001	−5.20	−3.59	−1.74	<0.001	−2.55	−0.92	−0.98	0.039	−1.90	−0.05
Age	0.07	<0.001	0.04	0.09	0.06	<0.001	0.03	0.08	0.12	<0.001	0.09	0.15
Household annual income, ≥ $50,000	−0.44	0.237	−1.17	0.29	−0.10	0.788	−0.84	0.64	−0.62	0.147	−1.45	0.22
Obesity (BMI ≥ 30 kg/m^2)	−0.19	0.623	−0.93	0.55	−0.48	0.204	−1.23	0.26	0.06	0.896	−0.79	0.90
Candidate mediators												
ASC-12 score, baseline	−1.16	<0.001	−1.26	−1.06	−1.34	<0.001	−1.44	−1.24	−1.37	<0.001	−1.48	−1.26
PHQ-9 score, baseline	−0.88	<0.001	−0.97	−0.79	−0.96	<0.001	−1.05	−0.87	−1.02	<0.001	−1.13	−0.92
GAD-7 score, baseline	−0.44	<0.001	−0.54	−0.34	−0.13	0.015	−0.23	−0.03	−0.53	<0.001	−0.64	−0.41
Adjusted R^2	0.305				0.240				0.324			

Note: Female sex, annual household income ≥ $50,000, and obesity were entered into the model as dichotomous variables, while MHDs, age, ASC-12, PHQ-9, and GAD-7 were entered as continuous variables.

Abbreviations: ASC-12, 12-item Allodynia Symptom Checklist; BMI, body mass index; CI, confidence interval; GAD-7, seven-item Generalized Anxiety Disorder assessment; MHD, monthly headache day; MSQ, Migraine-Specific Quality-of-Life Questionnaire version 2.1; PHQ-9, Patient Health Questionnaire (nine-item depression module); R^2, coefficient of determination; SD, standard deviation.

[a]Over previous 30 days.

TABLE 3 Mediation model analysis.

	Role Function–Restrictive				Role Function–Preventive				Emotional Function			
	Effect	SE	p		Effect	SE	p		Effect	SE	p	
Total effect	−1.38	0.03	<0.001		−1.05	0.03	<0.001		−1.77	0.04	<0.001	
Direct effect of MHDs	−0.92	0.03	<0.001		−0.60	0.03	<0.001		−1.23	0.04	<0.001	
			95% CI				95% CI				95% CI	
Indirect effects	Effect	SE	Low	High	Effect	SE	Low	High	Effect	SE	Low	High
ASC-12 (allodynia)	−0.15	0.01	−0.17	−0.13	−0.17	0.01	−0.19	−0.15	−0.17	0.01	−0.20	−0.15
PHQ-9 (depression)	−0.23	0.02	−0.27	−0.20	−0.25	0.02	−0.29	−0.22	−0.27	0.02	−0.31	−0.23
GAD-7 (anxiety)	−0.08	0.01	−0.11	−0.06	−0.02	0.01	−0.05	−0.00	−0.10	0.01	−0.13	−0.07
Covariates	Effect	SE	p		Effect	SE	p		Effect	SE	p	
Female	−5.89	0.45	<0.001		−3.22	0.45	<0.001		−2.74	0.52	<0.001	
Age	0.14	0.01	<0.001		0.12	0.01	<0.001		0.21	0.02	<0.001	
Household income, annual, ≥$50,000	1.80	0.05	<0.001		1.95	0.41	<0.001		2.01	0.47	<0.001	
Obesity	−2.14	0.41	<0.001		−2.40	0.41	<0.001		−2.23	0.47	<0.001	

Note: Female sex, annual household income ≥$50,000, and obesity were entered into the model as dichotomous variables, while MHDs, age, ASC-12, PHQ-9, and GAD-7 were entered as continuous variables.

Abbreviations: ASC-12, 12-item Allodynia Symptom Checklist; CI, confidence interval; GAD-7, seven-item Generalized Anxiety Disorder assessment; MHD, monthly headache day; MSQ, Migraine-Specific Quality-of-Life Questionnaire, version 2.1; PHQ-9, Patient Health Questionnaire (nine-item depression module); SE, standard error.

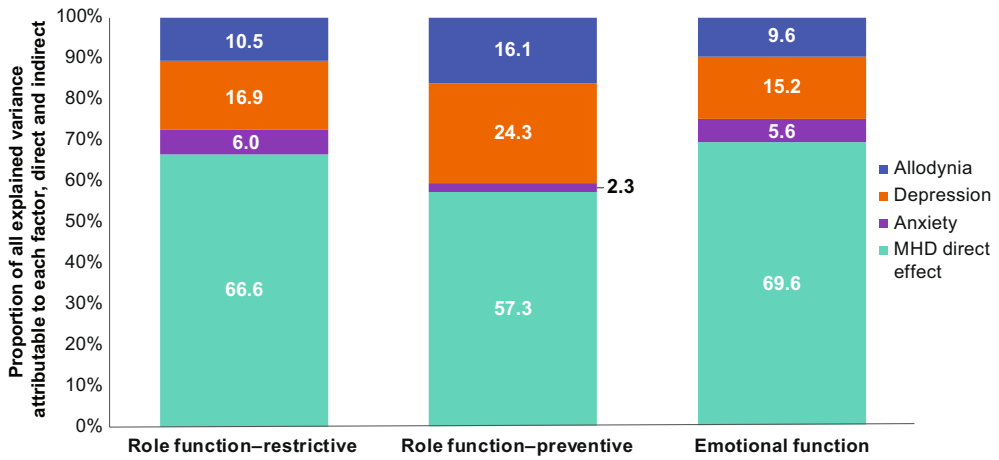

FIGURE 2 The proportional contribution of direct effect (from MHDs) and mediated effects (from allodynia, depression, and anxiety) to the total observed effect of MHDs on MSQ scores, based on mediation modeling. MHDs, ASC-12, PHQ-9, and GAD-7 were entered into the mediation models as continuous variables; all mediators were added to the models simultaneously. ASC-12, 12-item Allodynia Symptom Checklist; GAD-7, seven-item Generalized Anxiety Disorder assessment; MHD, monthly headache day; MSQ, Migraine-Specific Quality-of-Life Questionnaire, version 2.1; PHQ-9, Patient Health Questionnaire (nine-item depression module). [Color figure can be viewed at wileyonlinelibrary.com]

depression accounted for 15.2%, and anxiety accounted for 5.6% of the association with MHDs.

DISCUSSION

In this analysis of baseline data from people with migraine from the CaMEO study, MHD frequency was inversely associated with MSQ scores across all three domains (RFR, RFP, and EF). Linear regression models demonstrated a negative effect of MHDs on MSQ subscales such that, as MHDs increase HRQoL decreases. The mediation models demonstrated that a portion of the total effect of MHDs on the MSQ subscales could be explained by an indirect effect of depression, allodynia, and anxiety for all domains. To better understand the unique and joint effects of the mediators, additional models were conducted that added the three mediators alone and in pairs. Here, we saw that the portion of the total effect of MHDs accounted for by these mediators was larger when

each mediator was entered alone compared with when entered together, suggesting that the variables are associated. When including the three mediators together, some portion of the variance explained by one mediator could also be explained by the others. For example, some proportion of the mediating effect of depression on the relationship between MHDs and the MSQ can also be explained by anxiety and allodynia. Overall, the indirect effects of MHDs on MSQ domain scores were greatest for depression, followed by allodynia, and then anxiety for all domains. In the final models with all mediators entered together, depression explained approximately 15.2%–24.3%, allodynia explained 9.6%–16.1%, and anxiety explained 2.3%–6.0% of the total observed effect of MHDs across the MSQ subscales.

An overarching goal of migraine treatment is to improve HRQoL in people with migraine.[10] Migraine treatments targeting attack frequency, headache pain intensity, and migraine-associated symptoms can be viewed according to their ultimate effects on HRQoL. Findings from the present analysis showing that MHDs have a substantial direct negative effect on HRQoL suggest that HRQoL can be improved by reducing MHD frequency. Consistent with these results, clinical trials of anti-calcitonin gene-related peptide monoclonal antibodies and calcitonin gene-related peptide receptor inhibitors, such as erenumab, galcanezumab, and atogepant, have demonstrated that these preventive treatments are effective in reducing the number of migraine days and in improving HRQoL, as measured by the MSQ.[23–25] The results of the regression and mediation models in the present analysis also suggest that the benefits of MHD reduction on HRQoL could be augmented by targeting comorbidities such as depression and anxiety as well as migraine features of the attack itself, such as allodynia. People with migraine might benefit from preventive medications for migraine that do not have the potential to exacerbate depression and anxiety, and behavioral treatment and lifestyle modifications that specifically target improving depression and/or anxiety. Allodynia is generally treated by reducing attack frequency and reducing trigeminovascular sensitization with effective preventive therapy.[26]

Allodynia, depression, and anxiety were included in this analysis due to their high prevalence in people with migraine and their recognized impact on HRQoL. Given that only a portion of the total effect of MHDs on HRQoL could be explained by an indirect effect of allodynia, depression, and anxiety in this analysis, additional studies are needed to identify other indirect mediators. Potential contributors to MSQ variation not included in these analyses include additional features of the migraine attack that could modify the influence of migraine on HRQoL (e.g., presence and severity of aura, nausea and/or vomiting, premonitory and postdromal features, headache pain intensity, and associated symptom burden [e.g., interictal burden], other comorbid conditions, including other pain disorders, respiratory disorders, cardiovascular conditions, as well as interpersonal, family, and social factors, such as internalized stigma).

The strengths of the CaMEO study include the large sample size (nearly 17,000 respondents) and representative recruitment strategy, both of which led to the inclusion of a typical sample of the US population with migraine in the study. Another strength of the study is the modular structure, including modules that assessed previously unexplored aspects of barriers to care and family burden of migraine, as well as comorbidities. The present analysis is cross-sectional, providing a static snapshot of the study population, and limiting conclusions regarding causality between the variables, given that temporality is not present in these data. Additionally, these analyses did not evaluate whether patients were currently on preventive treatment for migraine. While these results allow for a clear characterization of the direct and indirect impact of MHDs on HRQoL, additional analyses are warranted to explore how changes in MHDs over time are associated with a corresponding change in the MSQ score and how mediators play into this relationship in a longitudinal data set. Additionally, the MSQ may be a lagging indicator of treatment benefit. Additional studies could help to elucidate whether improvements in HRQoL are reported concurrent with reductions in MHDs (within the same 30-day window) or are more prominent in the weeks or months following a reduction in MHDs.

CONCLUSIONS

These analyses of data from the CaMEO study demonstrated that although increased MHDs among people with migraine have a substantial direct negative effect on the MSQ domain scores, the observed HRQoL decrements associated with increasing MHDs are at least partially mediated by the presence of depression, allodynia, and anxiety. Across all domains, the indirect effects of MHDs on the MSQ domain scores were most substantial for depression, followed by allodynia and anxiety. To optimize improvements in HRQoL in people living with migraine, treatment should be focused on both reducing the frequency of attacks and addressing other indirect mediators, such as depression and anxiety.

AUTHOR CONTRIBUTIONS

Study concept and design: Richard B. Lipton, Michael L. Reed, Dawn C. Buse. *Acquisition of data*: Michael L. Reed. *Analysis and interpretation of data*: All authors. *Drafting of the manuscript*: Richard B. Lipton, Kristina M. Fanning. *Revising it for intellectual content*: All authors. *Final approval of the completed manuscript*: All authors.

ACKNOWLEDGMENTS

AbbVie and the authors thank the CaMEO survey respondents and investigators who participated in this clinical trial. Medical writing and editorial assistance were provided to the authors by Peloton Advantage, LLC, an OPEN Health company, Parsippany, NJ, USA, and were funded by AbbVie.

FUNDING INFORMATION

Allergan (prior to its acquisition by AbbVie) funded this trial and contributed to the study design, the collection, analysis, and interpretation of data, and the review and approval of the final version for

publication. All authors had access to relevant data and participated in the drafting, review, and approval of this publication. No honoraria or payments were made for authorship.

CONFLICT OF INTEREST STATEMENT

Richard B. Lipton, MD, has received research support from the National Headache Foundation, the National Institutes of Health, and the US Food and Drug Administration. He serves as a consultant or advisory board member or has received honoraria or research support from AbbVie/Allergan, Amgen, Biohaven, Dr. Reddy's Laboratories (Promius), electroCore, Eli Lilly, GlaxoSmithKline, Lundbeck, Merck, Novartis, Teva, Vector, and Vedanta Research. He receives royalties from *Wolff's Headache*, 8th edition (Oxford University Press, 2009), and Informa. He holds stock/options in Biohaven and Manistee. **Patricia Pozo-Rosich, MD, PhD**, has received personal compensation for serving as a consultant for AbbVie, Biohaven, Eli Lilly, Lundbeck, Medscape, Novartis, Pfizer, and Teva Pharmaceuticals, and for serving on a scientific advisory board for Lilly Foundation Spain. **Serena L. Orr, MD, MSc**, has received publishing royalties from Cambridge University Press for a publication related to health care. She is an associate editor for *Headache* and is on the editorial boards of *Neurology* and the American Migraine Foundation. She also has received funding from Alberta Children's Hospital Research Institute and the Canadian Institutes of Health Research. **Michael L. Reed, PhD**, is Managing Director of Vedanta Research, which has received research funding from AbbVie, Allay Lamp, Dr. Reddy's Laboratories, Eli Lilly, and GlaxoSmithKline via grants to the National Headache Foundation. Vedanta Research has received funding directly from AbbVie for work on the CaMEO and CaMEO-I studies. **Kristina M. Fanning, PhD**, is Managing Director of MIST Research, which has received research funding from AbbVie, Allay Lamp, GlaxoSmithKline, Juva Health, and NYU Langone Health via grants to the National Headache Foundation. **Brett Dabruzzo, PharmD**, is an employee of AbbVie and may own AbbVie stock. **Dawn C. Buse, PhD**, has received grant support and honoraria from AbbVie/Allergan, Amgen, Biohaven, Eli Lilly and Company, Lundbeck, and Teva, and for work on the editorial board of *Current Pain and Headache Reports*.

DATA AVAILABILITY STATEMENT

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual, and trial-level data (analysis data sets), as well as other information (e.g., protocols, clinical study reports, or analysis plans), if the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent, scientific research, and will be provided following review and approval of a research proposal, Statistical Analysis Plan (SAP), and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time after approval in the United States and Europe and after acceptance of this manuscript for publication. The data will be accessible for 12 months, with possible extensions considered. For more information on the process or to submit a request, visit the following link: https://www.abbvieclinicaltrials.com/hcp/data-sharing/.

ORCID

Serena L. Orr https://orcid.org/0000-0002-2879-811X

REFERENCES

1. Headache Classification Committee of the International Headache Society. The international classification of headache disorders, 3rd edition. *Cephalalgia*. 2018;38:1-211.
2. 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*. 2017;390:1211-1259.
3. Steiner TJ, Stovner LJ, Vos T, Jensen R, Katsarava Z. Migraine is first cause of disability in under 50s: will health politicians now take notice? *J Headache Pain*. 2018;19:17.
4. Lipton RB, Liberman JN, Kolodner KB, Bigal ME, Dowson A, Stewart WF. Migraine headache disability and health-related quality-of-life: a population-based case-control study from England. *Cephalalgia*. 2003;23:441-450.
5. Doane MJ, Gupta S, Vo P, Laflamme AK, Fang J. Associations between headache-free days and patient-reported outcomes among migraine patients: a cross-sectional analysis of survey data in Europe. *Pain Ther*. 2019;8:203-216.
6. Lipton RB, Lee L, Saikali NP, Bell J, Cohen JM. Effect of headache-free days on disability, productivity, quality of life, and costs among individuals with migraine. *J Manag Care Spec Pharm*. 2020;26:1344-1352.
7. Lipton RB, Varon SF, Grosberg B, et al. OnabotulinumtoxinA improves quality of life and reduces impact of chronic migraine. *Neurology*. 2011;77:1465-1472.
8. Alpuente A, Gallardo VJ, Caronna E, Torres-Ferrus M, Pozo-Rosich P. In search of a gold standard patient-reported outcome measure to use in the evaluation and treatment-decision making in migraine prevention. A real-world evidence study. *J Headache Pain*. 2021;22:151.
9. Johnston K, Harris L, Powell L, et al. Monthly migraine days, tablet utilization, and quality of life associated with rimegepant – post hoc results from an open label safety study (BHV3000-201). *J Headache Pain*. 2022;23:10.
10. Ailani J, Burch RC, Robbins MS. The American Headache Society consensus statement: update on integrating new migraine treatments into clinical practice. *Headache*. 2021;61:1021-1039.
11. Lipton RB, Hamelsky SW, Kolodner KB, Steiner TJ, Stewart WF. Migraine, quality of life, and depression: a population-based case-control study. *Neurology*. 2000;55:629-635.
12. Irimia P, Garrido-Cumbrera M, Santos-Lasaosa S, et al. Impact of monthly headache days on anxiety, depression and disability in migraine patients: results from the Spanish Atlas. *Sci Rep*. 2021;11:8286.
13. Lipton RB, Bigal ME, Ashina S, et al. Cutaneous allodynia in the migraine population. *Ann Neurol*. 2008;63:148-158.
14. Torres-Ferrús M, Quintana M, Fernandez-Morales J, Alvarez-Sabin J, Pozo-Rosich P. When does chronic migraine strike? A clinical comparison of migraine according to the headache days suffered per month. *Cephalalgia*. 2017;37:104-113.
15. Lanteri-Minet M, Radat F, Chautard MH, Lucas C. Anxiety and depression associated with migraine: influence on migraine subjects'

disability and quality of life, and acute migraine management. *Pain*. 2005;118:319-326.
16. Manack Adams A, Serrano D, Buse DC, et al. The impact of chronic migraine: the Chronic Migraine Epidemiology and Outcomes (CaMEO) Study methods and baseline results. *Cephalalgia*. 2015;35:563-578.
17. Martin BC, Pathak DS, Sharfman MI, et al. Validity and reliability of the migraine-specific quality of life questionnaire (MSQ version 2.1). *Headache*. 2000;40:204-215.
18. Rendas-Baum R, Bloudek LM, Maglinte GA, Varon SF. The psychometric properties of the Migraine-Specific Quality of Life Questionnaire version 2.1 (MSQ) in chronic migraine patients. *Qual Life Res*. 2013;22:1123-1133.
19. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*. 2001;16:606-613.
20. Spitzer RL, Kroenke K, Williams JB, Lowe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med*. 2006;166:1092-1097.
21. Gillard PJ, Devine B, Varon SF, Liu L, Sullivan SD. Mapping from disease-specific measures to health-state utility values in individuals with migraine. *Value Health*. 2012;15:485-494.
22. Hayes AF. *Introduction to Mediation, Moderation, and Conditional Process Analysis Third Edition: A Regression-Based Approach*. Guilford Press; 2022.
23. Ailani J, Lipton RB, Goadsby PJ, et al. Atogepant for the preventive treatment of migraine. *N Engl J Med*. 2021;385:695-706.
24. Dodick DW, Ashina M, Brandes JL, et al. ARISE: a phase 3 randomized trial of erenumab for episodic migraine. *Cephalalgia*. 2018;38:1026-1037.
25. Skljarevski V, Matharu M, Millen BA, Ossipov MH, Kim BK, Yang JY. Efficacy and safety of galcanezumab for the prevention of episodic migraine: results of the EVOLVE-2 phase 3 randomized controlled clinical trial. *Cephalalgia*. 2018;38:1442-1454.
26. Landy S, Rice K, Lobo B. Central sensitisation and cutaneous allodynia in migraine: implications for treatment. *CNS Drugs*. 2004;18:337-342.

How to cite this article: Lipton RB, Pozo-Rosich P, Orr SL, et al. Impact of monthly headache days on migraine-related quality of life: Results from the Chronic Migraine Epidemiology and Outcomes (CaMEO) study. *Headache*. 2023;63:1448-1457. doi:10.1111/head.14629