Healthcare Resource Use and Costs Associated with Chronic Migraines vs. Non-migraine controls and Episodic Migraines vs. Non-migraine controls

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Abstract

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BACKGROUND: Migraines are a debilitating neurological condition highly prevalent worldwide. Migraines can be characterized as chronic or episodic, depending on frequency and intensity. Chronic migraines are defined by the International Headache Society as ≥15 headache days per month (HDM) for at least 3 months with at least 8 days per month of migraine-specific headaches or treatment with a migraine-specific medication (i.e., triptans). Episodic migraines are defined as <15 headache days per month. Previous studies have examined chronic migraine patients compared to episodic migraine patients, or migraine patients as a whole compared to non-migraine controls. This study serves to compare each subgroup to non-migraine controls within a mixed commercial and Medicare supplemental population for the 2016-2018 study period.

OBJECTIVE: To assess the annual healthcare resource use and costs between chronic migraine patients and non-migraine controls, and episodic migraine patients and non-migraine controls.

METHODS: We conducted a retrospective cohort analysis using health insurance claims data from the IBM Watson Health MarketScan Commercial and Medicare Supplemental database® using data from January 1, 2016 through December 31, 2018. The populations of interest were adults ≥18 years with chronic or episodic migraine defined from migraine-associated claims within the 2017 index year. We then compared chronic and episodic migraine cohorts were to a 36-month continuously enrolled non-migraine cohort. We used multivariable linear regression comparing the incidence of healthcare resource use [inpatient admissions, emergency department (ED) visits, neurologist visits, outpatient services (excluding ED and neurologist visits), and pharmacy services] and costs based on migraine or non-migraine designations were performed and adjusted for covariates and clinical characteristics. Costs were reported in 2018 U.S. dollars.

RESULTS: The analysis compared a chronic migraine cohort (n = 30,004) to a randomly selected 5% non-migraine cohort (n = 343,095), and an episodic migraine cohort (n = 77,835) to the same 5% non-migraine cohort. Cohorts were not matched, but demographic and clinical characteristics were adjusted for in the multivariable regression. Across all outcomes of interest, chronic and episodic migraine patients used more healthcare resources and incurred higher costs when compared to their non-migraine counterparts. Of note, chronic migraine patients used 60 (95% CI: [56, 65]) more all-cause outpatient services and averaged $9,958 (95% CI: [$8,437, $10,893]) higher costs for these outpatient services compared to non-migraine controls. Similarly, but to a lesser degree, episodic migraine patients used 41 (95% CI: [40, 43]) more all-cause outpatient services and $6,132 ([95% CI: $5,413, $6,945]) higher costs compared to non-migraine controls.

CONCLUSION: Our results suggest that chronic and episodic migraine patients have both higher healthcare resource use and higher costs across inpatient admissions, ED visits, neurologist visits, outpatient services, and overall pharmaceutical claims. These results quantify one aspect of the economic burden of migraine compared to a non-migraine, commercially insured population; and to more thoroughly inform direct healthcare resource use and costs that a migraine patient may accrue.

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1. INTRODUCTION

Migraines are a debilitating and often underreported type of headache disorder. The Global Burden of Disease Study of 2010 has ranked migraines as the third most prevalent disorder worldwide, and sixth most debilitating. It is characterized by recurrent, unilateral, pulsating neurological aggravations of a moderate or severe pain intensity that last from 4 to 72 hours when either untreated or treated unsuccessfully.[1] The pathophysiology of migraines, however, is still under debate.[9] The two most popular theories are that it is primarily (1) a vascular disorder, or (2) a neural disorder. With the failure of multiple compounds targeting the vascular pathway and the efficacy of sumatriptan, a drug that had both vascular and neural effects, most theories now consider the neural pathway as the primary pathophysiology of migraines.[9,10]
Migraines tend to be experienced primarily by women, with over 20% of women experiencing them at some point in their lives compared to approximately 10% of men. Of migraine-sufferers at any given time, approximately 85% are women.[11] Fluctuating hormone levels are thought to be the underlying pathophysiology for the higher propensity of migraines in women.[26-28] In accordance with the recent 2018 International Headache Society (IHS) guidance, patients meeting the clinical presentation for migraines and experiencing ≥15 headache days per month (HDM) for at least 3 months with at least 8 days per month of migraine-specific headaches or treatment with a migraine-specific medication (i.e., triptans) are classified as chronic in frequency.[12] Patients experiencing <15 HDM are referred to as episodic.[12]

Previous literature has reported that chronic migraine (CM) patients tend to use more healthcare resources (i.e. emergency department visits, inpatient admissions, outpatient services, and medications) compared to episodic migraine (EM) patients.[1-4, 7,8] Total costs of migraine have been estimated by the GBD to be over $17 billion worldwide, though estimates have ranged from $9 to $28 billion.[4] The extent of healthcare resource utilization (HRU) and associated costs of each are yet to be fully characterized. Prior studies have compared CM to EM[13-17], and migraine to non-migraine.[4,18-19] To our knowledge, a study comparing both (1) CM to non-migraine controls and (2) EM to non-migraine controls within a claims database and with a shared non-migraine cohort comparison group has not been done before.

The primary objective of this study is to quantify the annual incremental all-cause HRUs and costs associated with chronic migraine relative to non-migraine controls, and episodic migraine relative to non-migraine controls.

2. METHODS

2.1 Data Source

We conducted a retrospective observational analysis using administrative claims data collected by Truven Health Analytics, an IBM Watson Health Company. The specific databases used were the IBM Watson Health MarketScan Commercial Claims and Encounters and the Medicare Supplemental and Coordination of Benefits Databases® using data collected between January 1, 2016 and December 31, 2018. All databases contained individual-level, de-identified, HIPAA-compliant insurance claims data for inpatient, outpatient, and pharmacy claims information from over 245 million unique patients since 1995.[5]. This study was reviewed by the University of Washington Human Subjects Division Institutional Review Board (IRB), which determined that it did not meet the definition of human subject research and therefore did not warrant further review.

2.2 Study Cohort Identification / Sample Selection

The migraine cohort was identified using the *International Classification of Diseases, 10th Revision, Clinical Modification* (ICD-10-CM) migraine diagnosis code G43.xxx from at least one inpatient claim, or two outpatient claims from different days [Appendix A]. These diagnosis codes were limited to the primary diagnosis ('PDX', relevant to inpatient claims only), and the first two diagnosis code positions on either an inpatient or outpatient claim ('DX1', "DX2') to more accurately identify a patient's claim as being in relation to migraine.

The study period was from January 1, 2016 through December 31, 2018. Eligible individuals were ≥18 years of age with a diagnosis of migraine recorded between January 1, 2017 and December 31, 2017. The index date was defined as the first qualifying claim within this January 1, 2017 to December 31, 2017 period. Individuals were required to be continuously enrolled for 12 months before and after their index date (for a total enrollment of at least 24 months). The 12-months prior to the index date were considered the pre-index period and were used to identify

demographic and clinical characteristics. The 12-months after the index date were considered the post-index period and used to estimate annual all-cause HRUs and costs (Figure 1). HRUs are characterized as one or more inpatient admissions, outpatient services, emergency department (ED) visits, and/or pharmaceutical claims. Costs were defined as the full associated costs of the healthcare resources without deduction of copays or coinsurance.

Both commercial claim and Medicare supplemental claim cohorts were included. The migraine cohort was divided into a chronic migraine cohort and an episodic migraine cohort. Chronic cohort members were identified based on having ≥1 inpatient or outpatient claim with an ICD-10-CM code G43.7xx, or ≥1 medical claim for BOTOX® with a diagnosis of migraine (ICD-10-CM G43.xxx) in any position between January 1, 2017 to December 31, 2017. Any patients who did not meet the selection criteria for chronic migraine were classified as part of episodic migraine group.

The non-migraine group was identified as a randomly selected 5% cut of individuals who were continuously insured for 36-months (the entire interval between January 1, 2016 to December 31, 2018) with both medical and prescription benefits. Index dates were randomly assigned within the 2017 calendar year (January 1, 2017 to December 31, 2017) with no migraine or headache diagnosis codes for any inpatient or outpatient claims for the entire study period [Appendix A.1 for migraine codes, A.2 for headache]. Patients additionally could not have any claims for BOTOX®. A sensitivity analysis was performed for patients continuously enrolled for only 24-months. The index date was the date in the middle of the 24-month period, with the pre- and post-index periods being the 12-month periods before and after the index date, respectively.

2.3 Patient Characteristics

Baseline demographic and clinical characteristics were identified during each patient's pre-index period and included age, sex, region, and insurance type. The Elixhauser comorbidity index was used to characterize each patient's clinical background.[20]

2.4 Outcomes

The primary study outcomes of interest were average any-cause inpatient admissions, ED visits, neurologist visits, outpatient services (excluding ED and neurologist visits), and pharmaceutical claims in the 12-month period following the patient's index date. The number of patients with at least one visit or claim and average visits among these patients with at least one visit were also calculated.

Negative cost data was excluded for ED visits, neurologist visits, outpatient services, and pharmaceutical claims due the resolved adjustment methods noted by IBM in the Outpatient Services Table and Outpatient Pharmaceutical Claims Tables (from which the aforementioned outcomes were derived).[6] Inpatient services were manually adjusted. All cost data was left in 2018 US dollars($).

Pharmacy claims were reported in both the raw day-supply claims (e.g. 15 days) and associated costs, and additionally in a 30-day supply standardized claims and costs. As an example of the latter, a 15-day supply medication claim would be considered 0.5 of a claim and a 180-day supply would be considered 6 pharmacy claims. 30-day supply standardized costs were derived from the 'PAY' variable divided by the 30-day supply standardized claim variable (i.e. a $10 PAY for a 15-day supply standardized claim, considered 0.5, would be reported as $10/0.5 = $20 within a 30-day supply standardized claim).

2.5 Statistical Analysis

We used means and standard deviations (SDs) and counts and proportions to characterize demographic data. We used regression models to adjust for confounding factors. Specifically, we used generalized linear regression models to adjust for the effects of age, sex, region, insurance plan type (including commercial vs. Medicare Supplemental), and Elixhauser comorbidity scores for both HRUs and associated direct costs. We created separate models for inpatient admissions, ED visits, neurologist visits, outpatient services (excluding ED visits and neurologist visits), and pharmacy claims. To analyze count data (i.e. number of inpatient admissions) in our regression context, we employed quasi-Poisson models to account for the conceptual assumption that an individual's propensity to engage in the associated HRU varied broadly across individuals, thus indicating potential over-dispersion of data.

For the analysis that were limited to those having ≥1 HRU claims, Fisher's exact tests were performed on categorical variables (i.e. proportions of inpatient admission) and analysis of variance (ANOVA) tests were performed for continuous variables (i.e. costs).
All analyses were performed within SAS 9.4 and R.[21, 22S]

3. RESULTS

3.1 Patient Selection

A total of 107,839 individuals met the inclusion criteria for migraine. This cohort was then partitioned into the 30,004 individuals who met the chronic migraine cohort inclusion criteria and the remaining 77,835 individuals who became the episodic migraine cohort. A total of 343,095 individuals were included in the non-migraine cohort. Baseline demographic and clinical characteristics are reported in Table 1.

3.2 Baseline Patient Characteristics

Patients were initially characterized as part of the non-migraine and overall migraine cohorts. The overall migraine cohort was subdivided into chronic and episodic migraine cohorts. Of note, the migraine cohorts were predominantly female compared to the non-migraine cohort [84% overall vs. 49%; Table 1]. The average age of the chronic migraine patients was 44.7 years (SD 12.4), episodic 43.2 years (SD 13.3), and the non-migraine controls was 45.8 years (SD 15.7). The majority of each cohort weas commercially insured (~≥90%), and most had an Exclusive Provider Organization / Preferred Provider Organization (EPO/PPO) plan type (≥50%). The region most frequently represented was the South (≥40%). Of the clinical characteristics, as standardized by the Elixhauser comorbidity score (ECS), the majority of patients had a score of 0 across all cohorts. However, compared to the non-migraine cohort, the migraine cohorts had higher proportions of individuals with an ECS across each level stratification (1, 2, 3, 4+) except for a score of 0. On average, the overall migraine cohort had an Elixhauser comorbidity score of 0.9 (SD 1.1) compared to an average score of 0.5 (SD 0.9) for the non-migraine cohort.

3.3 Chronic Migraine Healthcare Resource Utilization and Costs

In our adjusted analyses versus non-migraine controls, patients in the chronic migraine cohort averaged more inpatient admissions (0.09 [95% Confidence Interval - CI: [0.086, 0.098]]), ED visits (0.93 [0.72, 1.11]), outpatient services (54.7 [49.2, 58.9]), neurologist visits (6.71 [4.22, 9.31]), pharmacy prescriptions (36.84 [30.56, 41.71]), and 30-day supply-standardized prescriptions (39.87 [34.21, 46.13]). This indicates that patients with chronic migraine clearly had a higher average HRU among all subcategories [Table 2a].

Similarly, all-cause direct healthcare associated costs were generally higher for chronic migraine patients compared to their non-migraine counterparts across all outcome measures. Relative to the non-migraine control cohort, patients in the chronic migraine cohort spent on average more on inpatient admissions ($3,271 [$2,985, $3,894]), ED visits ($558 [$508, $611]), outpatient services excluding ED and neurologist visits ($9,958 [$8,437, $10,893]), neurologist visits ($1,844 [$1,113, $2,576]), pharmacy prescriptions ($5,792 [$4,778, $6,830]), and 30-day supply-standardized prescriptions ($1,306 [$1,014, $1,562]). These data cumulatively indicate that chronic migraine patients faced a markedly greater direct healthcare cost burden [Table 2b].

Of the chronic migraine patients and non-migraine that had at least one claim for each HRU, there was a significant difference in total average annual HRUs and costs between the two ($p > 0.001$) [Table 3a, Table 3b].

3.4 Episodic Migraine Healthcare Resource Utilization and Costs

In our adjusted analyses versus non-migraine controls, patients in the episodic migraine cohort averaged more inpatient admissions (0.12 [95% CI: [0.10, 0.13]]), ED visits (0.92 [0.87, 0.99]), outpatient services (41.1 [40.0, 42.9]), neurologist visits (1.87 [1.71, 1.98]), pharmacy prescriptions (20.0 [18.3, 24.9]), and 30-day supply-standardized prescriptions (22.9 [19.2, 26.1]). This indicates that patients with episodic migraine clearly had a higher average HRU among all subcategories [Table 4a].

Similarly, all-cause direct healthcare associated costs were generally higher for episodic migraine patients compared to their non-migraine counterparts across all outcome measures.

Relative to the non-migraine control cohort, patients in the chronic migraine cohort spent on average more on inpatient admissions ($3,126 [$2,578, $3,844]), ED visits ($508 [$410, $593]), outpatient services excluding ED and neurologist visits ($6,132 [$5,413, $6,945]), neurologist visits ($291 [$201, $372]), pharmacy prescriptions ($2,140 [$1,587, $2,711]), and 30-day supply-standardized prescriptions ($2,823 [$2,015, $3,774]). These data cumulatively indicate that chronic migraine patients faced a markedly greater direct healthcare cost burden [Table 4b].

Of the episodic migraine patients and non-migraine that had at least one claim for each HRU, there was a significant difference in total average annual HRUs and costs between the two ($p > 0.001$) [Table 5a, Table 5b].

4. DISCUSSION

4.1 Previous Literature

To our knowledge this is the first study that characterizes the all-cause HRU and direct costs associated with CM patients compared to non-migraine controls, and EM patients compared to non-migraine controls between the 2017-2018 year in an IBM MarketScan database®. While other studies have compared CM to EM[13-17], there has not yet been a study comparing CM to non-migraine controls and EM to non-migraine controls.

From our study, we have found that CM patients had higher average HRUs and costs compared to non-migraine controls [Tables 2a-2b] and EM patients had higher average HRUs and costs compared to non-migraine controls across all subcategories [Tables 4a-4b]. One thing to note is that EM patients had an adjusted 0.12 [95% CI: 0.10, 0.13] average incremental inpatient admissions compared to non-migraine controls, which was higher than the CM adjusted 0.09 [0.086, 0.098] average incremental inpatient admissions compared to non-migraine controls. Since we did not conduct inferential statistics comparing the two, we are unable to interpret these results, but did recognize the discrepancy compared to the other results.

Additionally, compared to their ≥1 HRU non-migraine controls, both ≥1 HRU CM and EM patients had a significant difference in average HRUs and costs across all subcategories [Tables 3a-3b, 5a-5b].

Previous literature has reported that chronic migraine patients tend to use more HRUs (i.e., ED visits, inpatient admissions, outpatient services, and medications) compared to episodic migraine

patients. Total costs of migraine have been estimated by the GBD to be over $17 billion worldwide.[23] When migraine patients are matched to non-migraine controls, their direct annual healthcare costs have been significantly higher ($8,033 to $19,663).[4,7,8] Lanteri-Minet conducted a comprehensive review of the American Migraine Prevalence and Prevention and the International Burden of Migraine studies' survey data from 2004 to 2010, two of the largest migraine survey studies conducted worldwide. Our findings are consistent with theirs.[3] One thing to note is that Lanteri-Minet found that HRUs associated with CM were significantly higher than that of EM., though when we performed our regressions, we found that inpatient admissions were higher among EM patients than CM. Issues surrounding HRU and access to care are discussed below in *Section 4.2 Strengths and Limitations*

4.2 Strengths and Limitations

The strengths of this study include examining patients who are part of a mixed commercial and Medicare supplemental population within the 2016-2018 study period, which is a timeline that has not yet been examined. Previous studies using IBM MarketScan data to characterize HRUs and costs examine older study periods and so this study offers an updated report using this data source. An additional strength of this study is the large population size covered by IBM MarketScan (over 245 unique patients).[5] Another strength includes how this study was analyzed. Previous studies analyzed their HRU outcomes using a Poisson or negative binomial distribution, but the use of a quasi-Poisson distribution may be more accurate for migraines for the applicable outcomes examined. Typically, negative binomial and quasi-Poisson distributions are considered interchangeable due to their similar handling of over-dispersed count data. However, the differences between the two distributions are in the effect on the variance. The negative binomial distribution models variance as a quadratic function of the mean while the quasi-Poisson distribution models variance as a linear function of the mean.[31] This affects the weight put on the smaller and larger counts of the data. Due to the downstream significant cost differences between an inpatient admission, ED visit, or neurologist visit, allowing larger healthcare resource users to estimate incremental differences between migraine and non-migraine cohorts is preferrable to account for an upper threshold of possible HRU.

There are several limitations to consider within this study. One to note is that the gradually decreasing numbers of individuals included in the IBM MarketScan database® in the context of a database of employer-based insurance holders may suggest a healthy worker bias. This would diminish the overall applicability of these study outcomes to the general U.S. population. However, studies by Stewart et al. (2010) and Lofland and Frick (2006) conflict in how access to care affects work absenteeism. Stewart et al. (2010) reported that CM patients in their study lost an average of 4.6 hours/week compared to 1.1 hours/week lost by low headache-frequency individuals (1-3 HDM).[29] However, CM patients in this study were additionally 19% less likely to be working for pay compared to 1-3 HDM migraine patients, meaning CM migraine patients may have already exited an employer-based insurance pool by the time any retrospective claims database studies are performed.[29] Alternatively, Lofland and Frick (2006) found that individuals with higher levels of access to care were significantly associated with missing a greater number of workdays.[30] While they had expected higher levels of access to care to be associated with a decrease in number of missed workdays, this may actually indicate that migraine sufferers are less likely to seek care when they have lower levels of access to care. This study did not stratify their migraine cohort by chronic and episodic frequency though, therefore we cannot interpret the effects of access to care between CM and EM patients. Overall, due to these limitations, further studies investigating absenteeism/productivity loss would be beneficial in a migraine population.

The exclusion of Medicaid enrollees may also bias these estimates toward the null. Previous studies have found that Medicaid enrollees tend to not only have significantly higher HRUs and costs compared to non-migraine Medicaid enrollees, but also tend to be younger (at an average age of 31).[24,25] Further studies looking at the Medicaid population compared to their commercial counterparts may be useful.

4.4 Future Directions

Further research into the indirect effects of migraine may be beneficial to adequately assess the overall economic burden of chronic and episodic migraine. Due to potential underreporting and uneven HRUs, especially among episodic migraine patients, additional research into indirect effects of migraine (i.e. productivity loss/absenteeism, caregiver burden) may be warranted. Moreover, since episodic migraines are a definition of exclusion (migraines that do not fit the

chronic migraine definition)[12], they cover a broad range of migraine frequencies (1-14 headache days per month). A future study that stratifies episodic migraine patients into low, middle, and high migraine frequency could better characterize each patient groups HRUs and costs.

5. CONCLUSION

Our results based on IBM MarketScan database records from 2017-2018 quantify the direct economic burden of chronic and episodic migraine, one key aspect of the burden of this neurological condition. We herein demonstrate that chronic and episodic migraine patients have both higher healthcare resource use and incur higher costs across inpatient admissions, ED visits, neurologist visits, outpatient services (excluding ED visits and neurologist visits), and overall pharmaceutical claims when compared to a non-migraine cohort. This study provides a critical snapshot to more comprehensively quantify the economic burden of migraine compared to a broader commercially insured population. Our study adds to and extends upon previous studies designed to better inform the direct healthcare resource use and costs a migraine patient may accrue in the course of disease management.

6. FUNDING

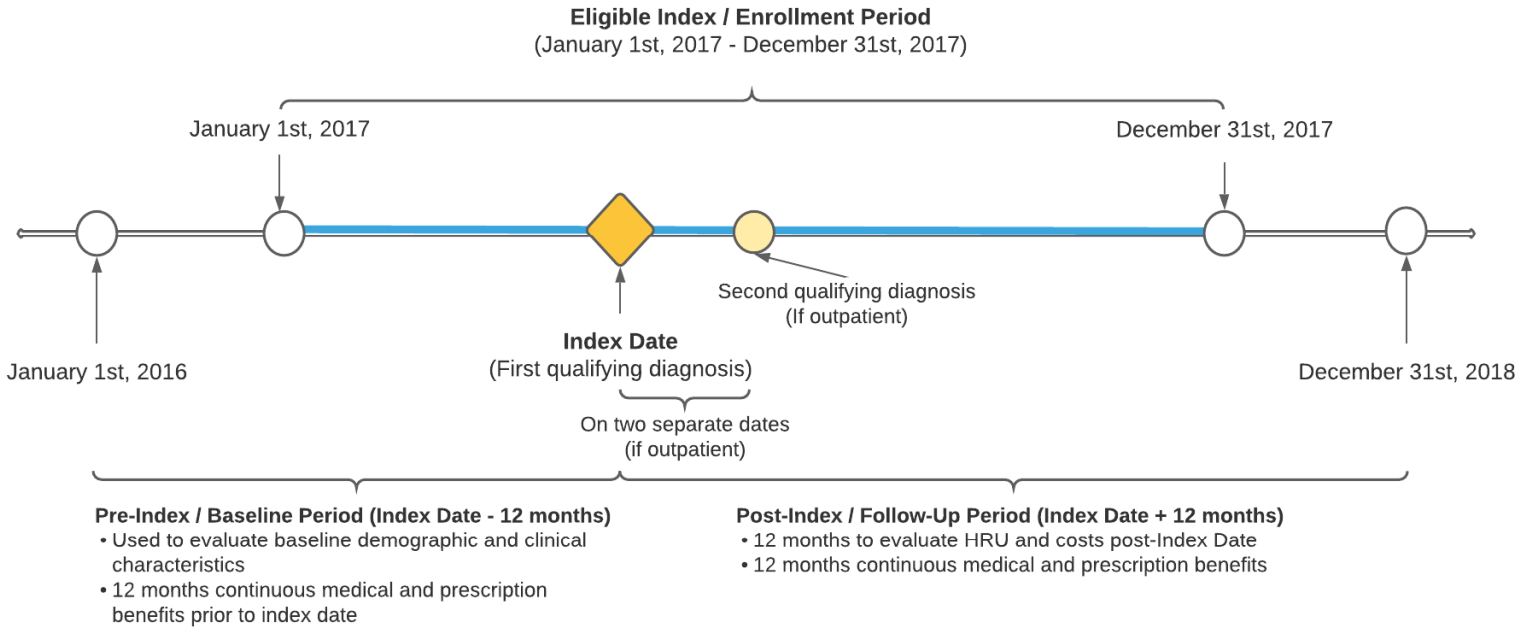
KC was supported by a training grant from AbbVie Pharmaceuticals.

7. DISCLOSURES

MarketScan® is a registered trademark of Truven Health Analytics, an IBM Watson Health Company.

8. FIGURES

Figure 1. Study Timeline



9. TABLES

Table 1. Baseline Demographic and Clinical Characteristics

	Non-migraine control (N = 343,095)		Overall migraine (N = 107,839)		Chronic migraine (N = 30,004)		Episodic migraine (N = 77,835)	
	% / mean	N / SD	% / mean	N / SD	% / mean	N / SD	% / mean	N / SD
Demographics								
Age (years)	45.8	15.7	43.6	13.0	44.7	12.4	43.2	13.3
Female, n, %	49%	168,084	84%	90,150	87%	25,960	82%	64,190
Insurance Type								
Commercial	92%	315,521	96%	103,694	96%	28,885	96%	74,809
Medicare	8%	27,574	4%	4,145	4%	1,119	4%	3,026
Plan type								
EPO/PPO	50%	173,239	54%	57,839	54%	16,155	54%	41,684
HMO	11%	38,010	11%	12,130	11%	3,266	11%	8,864
Non-capitated POS	4%	14,003	5%	5,012	5%	1,543	4%	3,469
CDHP/HDHP	26%	89,606	22%	24,089	22%	6,513	23%	17,576
Comprehensive (COMP)	5%	17,036	4%	4,610	4%	1,171	4%	3,439
Capitated or Part-capitated POS	1%	3,911	1%	1,262	1%	410	1%	852
Missing	2%	7,290	3%	2,897	3%	946	3%	1,951
Geographic Region								
Northeast	20%	69,297	18%	19,725	18%	5,397	18%	14,328
North Central	20%	69,470	20%	21,987	20%	5,936	21%	16,051
South	43%	146,057	45%	48,793	45%	13,456	45%	35,337
West	17%	57,320	16%	17,091	17%	5,142	15%	11,949
Unknown	<1%	951	<1%	243	<1%	73	<1%	170
Clinical								
Elixhauser score								
0	65%	222,886	47%	50,663	43%	12,780	49%	37,883
1	23%	78,517	30.5%	32,931	31%	9,367	30%	23,564
2	8%	27,932	13.5%	14,573	15%	4,521	13%	10,052
3	3%	8,997	6%	6,071	7%	2,035	5%	4,036
4+	1%	4,763	3%	3,601	4%	1,301	3%	2,300
Elixhauser score	0.5	0.9	0.9	1.1	1.0	1.2	0.9	1.1
Comorbidities								
Congestive heart failure	<1%	2,453	<1%	681	<1%	201	<1%	480
Valvular disease	1%	4,423	2%	2,176	2%	641	2%	1,535

Pulmonary circulation disease	<1%	785	<1%	535	<1%	164	<1%	371
Peripheral vascular disease	1%	3,674	1%	1,273	1%	409	1%	864
Hypertension, uncomplicated	14%	49,017	15%	16,608	15%	4,537	16%	12,071
Hypertension, complicated	<1%	2,636	<1%	802	<1%	225	<1%	577
Paralysis	<1%	259	<1%	324	<1%	93	<1%	231
Other neurological diseases	1%	3,128	4%	4,793	5%	1,484	4%	3,309
Chronic pulmonary disease	4%	14,160	9%	9,503	9%	2,776	9%	6,727
Diabetes without chronic complications	6%	19,950	4%	4,630	5%	1,451	4%	3,179
Diabetes with chronic complications	4%	12,440	3%	2,875	3%	892	3%	1,983
Hypothyroidism	4%	14,868	9%	9,383	11%	3,194	8%	6,189
Renal failure	<1%	3,061	<1%	968	1%	362	<1%	606
Liver disease	1%	3,660	2%	2,217	2%	679	2%	1,538
Chronic peptic ulcer disease	<1%	357	<1%	506	<1%	187	<1%	319
HIV and AIDS	<1%	607	<1%	130	<1%	39	<1%	91
Lymphoma	<1%	762	<1%	258	<1%	72	<1%	186
Metastatic cancer	<1%	552	<1%	198	<1%	45	<1%	153
Solid tumor without metastasis	2%	8,221	3%	2,712	3%	796	2%	1,916
Rheumatoid arthritis/collagen vascular diseases	1%	4,652	4%	4,834	6%	1,765	4%	3,069
Coagulation deficiency	<1%	1,254	<1%	896	1%	312	<1%	584
Obesity	2%	5,230	3%	3,672	4%	1,066	3%	2,606
Weight loss	<1%	976	<1%	873	1%	297	<1%	576
Fluid and electrolyte disorders	<1%	2,435	2%	2,553	3%	756	2%	1,797
Blood loss anemia	<1%	742	<1%	598	<1%	189	<1%	409
Deficiency anemia	1%	3,637	3%	3,001	3%	1,037	3%	1,964
Alcohol abuse	<1%	1,270	<1%	456	<1%	104	<1%	352
Drug abuse	<1%	1,210	1%	1,168	1%	396	1%	772
Psychoses	<1%	553	<1%	412	<1%	124	<1%	288
Depression	5%	15,991	14%	15,331	18%	5,370	13%	9,961

SD = standard deviation

EPO = Exclusive Provider Organization; PPO = Preferred Provider Organization; HMO = Health Maintenance Service; POS = Point-of-Service

HIV = Human Immunodeficiency Virus; AIDS = Acquired Immunodeficiency Syndrome

Table 2a. Chronic vs. Non-migraine controls: All-cause Healthcare Resource Utilization

	Chronic migraine (N = 30,004)		Non-migraine controls (N = 343,095)		Incremental		95% CI
	Mean	SD	Mean	SD	Unadjusted	Adjusted	Adjusted
Inpatient admissions§							
# admission	0.13	0.52	0.05	0.27	0.08*	0.09***	(0.086, 0.098)
ED visits§							
# visits	1.03	3.45	0.18	0.72	0.85*	0.93***	(0.72, 1.11)
Outpatient services±							
# service claims (excl. ED)	80.96	77.52	25.3	38.8	55.66**	60.02***	(56.24, 65.19)
# service claims (excl. ED, neurologist visits)	74.3	75.26	22.4	34.3	51.9***	54.7***	(49.2, 58.9)
Neurologist visits§							
# visits	5.63	10.29	0.08	1.03	5.55**	6.71***	(4.22, 9.31)
Pharmacy claims±							
# 30-day supply standardized prescriptions	51.31	41.76	14.11	20.32	37.2**	39.87***	(34.21, 46.13)
# prescriptions	45.17	35.91	12.44	17.57	32.73**	36.84**	(30.56, 41.71)

§ = GLM, quasi-Poisson distribution, log-link; ± GLM, Gaussian distribution, log-link

*p<0.05, **p<0.01, ***p<0.001

Adjusted models controlled for age, sex, geographic region, insurance type, commercial or Medicare supplemental insurance, and Elixhauser Comorbidity Score

Table 2b. Chronic vs. Non-migraine controls: All-cause Direct Healthcare Costs (US$)

	Chronic migraine (N = 30,004)		Non-migraine controls (N = 343,095)		Incremental		95% CI
	Mean	SD	Mean	SD	Unadjusted	Adjusted	Adjusted
Inpatient admissions							
Costs of admissions	$3,411	$18,980	$1,517	$13,833	$3,260	$3,271***	($2,985, $3,894)
ED visits							
Costs of visits	$604	$2,318	$102	$510	$502	$558**	($508, $611)
Outpatient services							
Costs of service claims (excl. ED)	$12,326	$22,597	$3,365	$15,300	$8,981	$10,165***	($9,114, $12,004)
Costs of service claims (excl. ED, neurologist visits)	$10,713	$21,217	$2,123	$14,593	$8,590	$9,958***	($8,437, $10,893)
Neurologist visits							
Costs of visits	$1,391	$4,308	$19	$822	$1,672	$1,844***	($1,113, $2,576)
Pharmacy claims							
Costs of 30-day supply standardized prescriptions	$7,429	$29,916	$6,380	$14,909	$1,049	$1,306**	($1,014, $1,562)
Costs of prescriptions	$6,380	$14,909	$1,759	$8,829	$4,621	$5,792***	($4,778, $6,830)

*p<0.05, **p<0.01, ***p<0.001
All adjustments made using GLM, Gamma distribution, identity link
Adjusted models controlled for age, sex, geographic region, insurance type, commercial or Medicare supplemental insurance, and Elixhauser Comorbidity Score

Table 3a. Chronic vs. Non-migraine controls: All-cause Healthcare Resource Utilization (≥1 use)

	Chronic Migraine (N = 30,004)		Non-migraine controls (N = 343,095)		P-value
Inpatient admissions	% / mean	N / SD	% / mean	N / SD	
# patients with ≥1 admission	9%	2,816	4%	14,488	<.001
# visits amongst patients with ≥1 visit	1.41	1.03	1.2	0.61	
ED visits					
# patients with ≥1 visit	30%	8,920	9%	31,371	<.001
# visits amongst patients with ≥1 visit	3.46	5.63	2	1.43	
Outpatient services (excl. ER visits)					
# patients with ≥1 service claim	99%	30,002	85%	293,094	<.001
# service claims among patients with ≥1 visit	80.96	77.52	29.66	40.44	
Neurologist visits					
# patients with ≥1 visit	72%	21,504	2%	8,019	<.001
# visits amongst patients with ≥1 visit	7.86	11.42	3.35	5.84	
Pharmacy claims					
# patients with ≥1 prescription	99%	29,595	78%	266,468	<.001
# prescriptions amongst patients with ≥1 prescription	45.79	35.76	16.04	18.47	
# prescriptions amongst patients with ≥1 30-day standardized prescription	52.02	41.61	18.44	19.91	

Table 3b. Chronic vs. Non-migraine controls: All-cause Direct Healthcare Costs (≥1 use) (US$)

	Chronic Migraine (N = 30,004)		Non-migraine controls (N = 343,095)		P-value
Inpatient admissions	% / mean	N / SD	% / mean	N / SD	
# patients with ≥1 admission	9%	2,816	4%	14,488	<.001
Costs amongst patients with ≥1 visit	$36,345	$51,401	$35,928	$57,413	
ED visits					
# patients with ≥1 visit	30%	8,920	9%	31,371	<.001
Costs amongst patients with ≥1 visit	$2,032	$3,895	$1,118	$1,309	
Outpatient services (excl. ER visits)					
# patients with ≥1 service claim	99%	30,002	85%	293,094	<.001
Costs of service claims among patients with ≥1 visit	$12,327	$22,597	$3,943	$16,487	
Neurologist visits					
# patients with ≥1 visit	72%	21,504	2%	8,019	<.001
Costs of visits amongst patients with ≥1 visit	$1,941	$4,983	$826	$5,312	
Pharmacy claims					
# patients with ≥1 prescription	99%	29,595	78%	266,468	<.001
Costs of prescriptions amongst patients with ≥1 prescription	$6,476	$15,022	$2,268	$9,966	
Costs of prescriptions amongst patients with ≥1 30-day standardized prescription	$7,532	$30,109	$2,977	$10,421	

Table 4a. Episodic vs. Non-migraine controls: All-cause Healthcare Resource Utilization

	Episodic migraine (N = 77,835)		Non-migraine controls (N = 343,095)		Incremental		95% CI
	Mean	SD	Mean	SD	Unadjusted	Adjusted	Adjusted
Inpatient admissions§							
# admission	0.16	0.58	0.05	0.27	0.11***	0.12***	(0.10, 0.13)
ED visits§							
# visits	0.92	2.87	0.18	0.72	0.74***	0.92***	(0.87, 0.99)
Outpatient services±							
# service claims (excl. ED)	63.9	68.24	25.3	38.8	38.6***	40.4**	(38.2, 43.1)
# service claims (excl. ED, neurologist visits)	62.1	66.3	22.4	34.3	39.7***	41.1***	(40.0, 42.9)
Neurologist visits§							
# visits	1.60	4.33	0.08	1.03	1.52***	1.87***	(1.71, 1.98)
Pharmacy claims±							
# 30-day supply standardized prescriptions	34.91	30.44	14.11	20.32	20.8***	22.9***	(19.2, 26.1)
# prescriptions	30.78	28.62	12.44	17.57	18.34***	20.0***	(18.3, 24.9)

§ = GLM, quasi-Poisson distribution, log-link; ± GLM, Gaussian distribution, log-link

*p<0.05, **p<0.01, ***p<0.001

Adjusted models controlled for age, sex, geographic region, insurance type, commercial or Medicare supplemental insurance, and Elixhauser Comorbidity Score

Table 4b. Episodic vs. Non-migraine controls: All-cause Direct Healthcare Costs (US$)

	Episodic Migraine (N = 77,835)		Non-migraine controls (N = 343,095)		Incremental		95% CI
	Mean	SD	Mean	SD	Unadjusted	Adjusted	Adjusted
Inpatient admissions							
Costs of admissions	$4,045	$23,763	$1,517	$13,833	$2,528**	$3,126***	($2,578, $3,844)
ED visits							
Costs of visits	$538	$1,888	$102	$510	$436***	$508***	($410, $593)
Outpatient services							
Costs of service claims (excl. ED)	$8,361	$18,950	$3,365	$15,300	$4,996***	$5,254	($4,395, $6,116)
Costs of service claims (excl. ED, neurologist visits)	$7,993	$17,901	$2,123	$14,593	$5,870**	$6,132	($5,413, $6,945)
Neurologist visits							
Costs of visits	$269	$1,924	$19	$822	$250***	$291***	($201, $372)
Pharmacy claims							
Costs of 30-day supply standardized prescriptions	$8,877	$16,921	$6,380	$14,909	$2,497**	$2,823**	($2,015, $3,774)
Costs of prescriptions	$3,576	$15,290	$1,759	$8,829	$1,817**	$2,140**	($1,587, $2,711)

*p<0.05, **p<0.01, ***p<0.001
All adjustments made using GLM, Gamma distribution, identity link
Adjusted models controlled for age, sex, geographic region, insurance type, commercial or Medicare supplemental insurance, and Elixhauser Comorbidity Score

Table 5a. Episodic vs. Non-migraine controls: All-cause Direct Healthcare Costs (≥1 use)

	Episodic Migraine (N = 77,835)		Non-migraine controls (N = 343,095)		P-value
Inpatient admissions	% / mean	N / SD	% / mean	N / SD	
# patients with ≥1 admission	11%	8,634	4%	14,488	<.001
# visits amongst patients with ≥1 visit	1.42	1.13	1.2	0.61	
ED visits					
# patients with ≥1 visit	29%	22,285	9%	31,371	<.001
# visits amongst patients with ≥1 visit	3.21	4.62	2	1.43	
Outpatient services (excl. ER visits)					
# patients with ≥1 service claim	99%	77,800	85%	293,094	<.001
# service claims among patients with ≥1 visit	64.03	68.25	29.66	40.44	
Neurologist visits					
# patients with ≥1 visit	40%	30,900	2%	8,019	<.001
# visits amongst patients with ≥1 visit	4.03	6.13	3.35	5.84	
Pharmacy claims					
# patients with ≥1 prescription	97%	75,835	78%	266,468	<.001
# prescriptions amongst patients with ≥1 prescription	31.6	28.54	16.04	18.47	
# prescriptions amongst patients with ≥1 30-day standardized prescription	35.7	30.22	18.44	19.91	

Table 5b. Episodic vs. Non-migraine controls: All-cause Direct Healthcare Costs (≥1 use) (US$)

	Episodic Migraine (N = 77,835)		Non-migraine controls (N = 343,095)		P-value
Inpatient admissions	% / mean	N / SD	% / mean	N / SD	
# patients with ≥1 admission	11%	8,634	4%	14,488	<.001
Costs amongst patients with ≥1 visit	$36,465	$62,520	$35,928	$57,413	
ED visits					
# patients with ≥1 visit	29%	22,285	9%	31,371	<.001
Costs amongst patients with ≥1 visit	$1,882	$3,151	$1,118	$1,309	
Outpatient services (excl. ER visits)					
# patients with ≥1 service claim	99%	77,800	85%	293,094	<.001
Costs of service claims among patients with ≥1 visit	$8,379	$18,982	$3,943	$16,487	
Neurologist visits					
# patients with ≥1 visit	40%	30,900	2%	8,019	<.001
Costs of visits amongst patients with ≥1 visit	$679	$3,008	$826	$5,312	
Pharmacy claims					
# patients with ≥1 prescription	97%	75,835	78%	266,468	<.001
Costs of prescriptions amongst patients with ≥1 prescription	$3,670	$15,480	$2,268	$9,966	
Costs of prescriptions amongst patients with ≥1 30-day standardized prescription	$5,136	$17,162	$2,977	$10,421	

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10. APPENDIX

Table A.1 International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) Diagnosis Codes

ICD-10-CM Code	ICD-10-CM Diagnosis Description
G43.109	Migraine with aura, not intractable without status migrainosus
G43.119	Migraine with aura, intractable without status migrainosus
G43.101	Migraine with aura, not intractable with status migrainosus
G43.111	Migraine with aura, intractable with status migrainosus
G43.009	Migraine without aura, not intractable without status migrainosus
G43.019	Migraine without aura, intractable without status migrainosus
G43.001	Migraine without aura, not intractable with status migrainosus
G43.011	Migraine without aura, intractable, with status migrainosus
G43.809	Other migraine, not intractable, without status migrainosus
G43.A0	Cyclical vomiting, not intractable
G43.B0	Ophthalmoplegic migraine, not intractable
G43.C0	Periodic headache syndromes in child or adult, not intractable
G43.D0	Abdominal migraine, not intractable
G43.819	Other migraine, not intractable, without status migrainosus
G43.A1	Cyclical vomiting, intractable
G43.B1	Ophthalmoplegic migraine, intractable
G43.C1	Periodic headache syndromes in child or adult, intractable
G43.D1	Abdominal migraine, intractable
G43.801	Other migraine, not intractable, with status migrainosus
G43.811	Other migraine, intractable, with status migrainosus
G43.409	Hemiplegic migraine, not intractable without status migrainosus
G43.419	Hemiplegic migraine, intractable without status migrainosus
G43.401	Hemiplegic migraine, not intractable with status migrainosus
G43.411	Hemiplegic migraine, intractable with status migrainosus
G43.829	Menstrual migraine, not intractable, without status migrainosus
G43.839	Menstrual migraine, intractable, without status migrainosus
G43.821	Menstrual migraine, not intractable, with status migrainosus
G43.831	Menstrual migraine, intractable, with status migrainosus
G43.509	Persistent migraine aura without cerebral infarction, not intractable, without status migrainosus
G43.501	Persistent migraine aura without cerebral infarction, without mention of intractable migraine with status migrainosus
G43.511	Persistent migraine aura without cerebral infarction, with intractable migraine, so stated, with status migrainosus
G46.609	Persistent migraine aura with cerebral infarction, without mention of intractable migraine, without mention of status migrainosus
G43.619	Persistent migraine aura with cerebral infarction, with intractable migraine, so stated, without mention of status migrainosus
G43.601	Persistent migraine aura with cerebral infarction, without mention of intractable migraine with status migrainosus
G43.611	Persistent migraine aura with cerebral infarction, with intractable migraine, so stated, with status migrainosus

ICD-10-CM Code	ICD-10-CM Diagnosis Description
G43.709	Chronic migraine without aura, without mention of intractable migraine without mention of status migrainosus
G43.719	Chronic migraine without aura, with intractable migraine, so stated, without mention of status migrainosus
G43.701	Chronic migraine without aura, without mention of intractable migraine, with status migrainosus
G43.711	Chronic migraine without aura, with intractable migraine, so stated, with status migrainosus
G43.809	Other forms of migraine, without mention of intractable migraine without mention of status migrainosus
G43.819	Other forms of migraine, with intractable migraine, so stated, without mention of status migrainosus
G43.801	Other forms of migraine, without mention of intractable migraine, with status migrainosus
G43.811	Other forms of migraine, with intractable migraine, so stated, with status migrainosus
G43.909	Migraine, unspecified, not intractable, without status migrainosus
G43.919	Migraine, unspecified, intractable, without status migrainosus
G43.901	Migraine, unspecified, not intractable, with status migrainosus
G43.911	Migraine, unspecified, intractable, with status migrainosus

Table A.2 ICD codes for Headaches (non-inclusive of Migraine)

ICD-10-CM Code	ICD-10-CM Diagnosis Description
G44.209	Tension-type headache, unspecified, not intractable
G44.219	Episodic tension-type headache, not intractable
G44.221	Chronic tension-type headache, intractable
G44.229	Chronic tension-type headache, not intractable
N94.3	Premenstrual tension syndrome
G97.1	Other reaction to spinal and lumbar puncture (applicable to Headache due to lumbar puncture)
G44.1	Vascular headache, not elsewhere classified
R51	Headache

Table B. Abbreviations and Definitions

Abbreviation	Definition
AIDS	Acquired immunodeficiency syndrome
CI	Confidence interval
CM	Chronic Migraine
ECI	Elixhauser Comorbidity Index
ED	Emergency department
EM	Episodic Migraine
EPO	Exclusive provider organization
GLM	Generalized linear regression
HDM	Headache days per month
HIV	Human immunodeficiency virus
HMO	Health maintenance organization
HRU	Healthcare resource use
1CD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
IHS	International Headache Society
POS	Point-of-service
PPO	Preferred provider organization
SD	Standard deviation