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The Healthcare Cost of Migraine: A Retrospective Cohort Study from Alberta, Canada

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ABSTRACT: *Introduction:* The economic burden of migraine is substantial; determining the cost that migraine imposes on the Canadian healthcare system is needed. *Methods:* Administrative data were used to identify adults living with migraine, including chronic migraine (CM) and episodic migraine (EM), and matched controls in Alberta, Canada. One- and two-part generalized linear models with gamma distribution were used to estimate direct healthcare costs (hospitalization, emergency department, ambulatory care, physician visit, prescription medication; reported in 2022 Canadian dollars) of migraine during a 1-year observation period (2017/2018). *Results:* The fully adjusted total mean healthcare cost of migraine ($n = 100{,}502$) was 1.5 times (cost ratio: 1.53 [95% CI: 1.50, 1.55]) higher versus matched controls ($n = 301{,}506$), with a predicted annual incremental cost of $2,806 (95% CI: $2,664, $2,948) per person. The predicted annual incremental cost of CM and EM was $5,059 (95% CI: $4,836, $5,283) and $669 (95% CI: $512, $827) per person, respectively, compared with matched controls. All healthcare cost categories were greater for migraine (overall, CM and EM) compared with matched controls, with prescription medication the primary cost driver (incremental cost – overall: $1,381 [95% CI: $1,234, $1,529]; CM: $2,057 [95% CI: %1,891, $2,223]; EM: $414 [95% CI: $245, $583] per person per year). *Conclusion:* Persons living with migraine had greater direct healthcare costs than those without. With an estimated migraine prevalence of 8.3%–10.2%, this condition may account for an additional $1.05–1.29 billion in healthcare costs per year in Alberta. Strategies to prevent and effectively manage migraine and associated healthcare costs are needed.

RÉSUMÉ : **Le coût des soins de santé relatifs à la migraine : résultats d'une étude de cohorte rétrospective en Alberta (Canada)**
Introduction : Le fardeau économique de la migraine est considérable; il est nécessaire de déterminer le coût que cette affection impose au système de santé au Canada. *Méthode :* L'équipe de recherche a utilisé des données administratives afin de sélectionner des adultes vivant avec la migraine, y compris avec la migraine chronique (MC) ou avec la migraine épisodique (ME), ainsi que des témoins appariés demeurant en Alberta (Canada). Des modèles linéaires généralisés à une et deux parties et avec distribution gamma ont été utilisés aux fins de l'estimation des coûts directs des soins de santé (hospitalisation, service des urgences, soins ambulatoires, consultations médicales, médicaments d'ordonnance; indiqués en dollars canadiens de 2022) relatifs à la migraine au cours d'une période d'observation d'un an (2017-2018). *Résultats :* Le coût moyen total entièrement rajusté des soins de santé relatifs à la migraine (n = 100 502) était 1,5 fois plus élevé (rapport de coûts : 1,53; intervalle de confiance [IC] à 95 % : 1,50 – 1,55) que celui enregistré chez les témoins appariés (n = 301 506), et le coût différentiel annuel prévu était de 2 806 $ (IC à 95 % : 2 664 $ – 2 948 $) par personne. Quant au coût différentiel annuel prévu par personne, il était de 5 059 $ (IC à 95 % : 4 836 $ – 5 283 $) pour la MC et de 669 $ (IC à 95 % : 512 $ – 827 $) pour la ME par rapport à celui établi chez les témoins appariés. Toutes les catégories de coûts de soins de santé indiquaient un coût plus élevé pour les personnes vivant avec la migraine (cohorte générale, MC et ME) que pour les témoins appariés, les médicaments d'ordonnance étant le principal inducteur de coût (coût différentiel : cohorte générale : 1 381 $ [IC à 95 % : 1 234 $ – 1 529 $]; MC : 2 057 $ [IC à 95 % : 1 891 $ – 2 223 $]; ME : 414 $ [IC à 95 % : 245 $ – 583 $] par personne, par année). *Conclusion :* Les coûts directs des soins de santé étaient plus élevés chez les personnes vivant avec la migraine que chez celles qui en étaient exemptes. La prévalence estimée de la migraine variant de 8,3 % à 10,2 %, cette affection pourrait entraîner des coûts additionnels de soins de santé pouvant atteindre de 1,05 à 1,29 milliard de dollars par année, en Alberta. Aussi est-il nécessaire d'élaborer des stratégies visant à prévenir et à prendre en charge efficacement la migraine et les coûts de soins de santé qui y sont associés.

Highlights

- The total mean direct healthcare cost of migraine was 1.5 times higher than matched controls, with a predicted incremental cost of $2,806 per person per year.
- Prescription medication was the primary cost driver.
- Migraine may account for an additional $1.05–1.29 billion in healthcare costs per year in Alberta.

Introduction

Migraine is a common neurological disorder characterized by recurrent headaches that are moderatetosevere in nature and lead to significant symptoms and disability.[1,2] The 2021 Global Burden of Disease study ranked migraine as the second-leading disabling neurological condition in North America.[3] Migraine can be classified as episodic and chronic – episodic migraine (EM) is defined as having <15 headache days per month, and chronic migraine (CM) is defined as headache occurring on ≥15 days per month for >3 months that has the features of migraine headache on ≥8 days per month.[4] Based on data from the Canadian Community Health Survey, between 8.3% and 10.2% of Canadians have reported being diagnosed with migraine by a health professional, of whom females indicated having migraine more than twice as often as males.[5,6] CM is less prevalent than EM, with estimates typically in the range of 1.4%–2.2% of the general population.[7]

Previous studies have shown that persons living with migraine have higher healthcare resource use and costs than those not living with migraine.[8–11] Additionally, those living with CM consistently display higher healthcare resource use and costs compared with those living with EM.[12–15] However, relatively few studies have been conducted on the healthcare cost of persons living with migraine, including CM and EM, in Canada.[13–16] Two recent administrative data claims-based studies described the direct healthcare costs of adults with newly diagnosed/recurrent migraine, including CM and EM, in Alberta.[15,16] The authors found that during a follow-up period, the total mean annual direct healthcare cost of adults living with migraine was $6,403 per person (included costs: all-cause hospitalization, emergency department [ED], non-emergent ambulatory care, physician, diagnostic imaging and migraine-related medication); CM was $12,693, and EM was $4,251 per person (2020 Canadian dollars [$CDN]).[15,16] The additional cost that persons living with migraine may impose on the healthcare system compared with those not living with migraine that accounts for confounders remains to be elucidated within the Canadian healthcare system. The objective of this study was to compare total and incremental direct healthcare costs between adults living with migraine, including CM and EM, and those not living with migraine in Alberta, Canada; costs were also compared between CM and EM.

Methods

Ethics approval was received from the University of Alberta Research Ethics Board (Pro00083495) that granted an exemption from requiring written informed consent (a waiver of consent was applied). Data custodian approvals were received from Alberta Health and Alberta Health Services for the use of administrative health data for this study. This study was reported according to the Reporting of Studies Conducted Using Observational Routinely-Collected Health Data guidelines.[17]

Study design

This retrospective, observational, population-based cohort study was conducted using administrative health data from Alberta between April 1, 2014, and March 31, 2018, with an inclusion period between April 1, 2015, and March 31, 2017; a CM screening period from April 1, 2014, to March 31, 2017; an index date of April 1, 2017; and a 1-year observation period between April 1, 2017, and March 31, 2018.

Data source

Canadian provinces provide publicly funded healthcare for all residents. In Alberta, the fourth most populous province in Canada (4.2–4.3 million people in 2017/2018), healthcare is administered under the Alberta Health Care Insurance Plan (AHCIP), of which over 99% of Albertans participate.[18,19] A person-level data extract from the Discharge Abstract Database (DAD), National Ambulatory Care Reporting System (NACRS), Practitioner Claims, Pharmaceutical Information Network (PIN) and Vital Statistics was linked to the Population Registry using a unique individual identifier (Personal Health Number) and then deidentified and provided to the researchers by the data custodians. DAD and NACRS include demographic, administrative, diagnostic, procedural and resource intensity weight information on people discharged from the hospital (DAD) and ED and facility-based non-emergent ambulatory care clinics (NACRS). Diagnostic fields for each visit include the most responsible diagnosis and room for up to 24 (DAD) and 9 (NACRS) secondary International Classification of Disease Version 10 Canadian Enhancement (ICD-10-CA) codes. Physician visits were obtained from the Practitioner Claims database that include patient, provider and service information such as demographics, physician specialty, date of service, amount paid to the service provider (on fee-for-service, alternative payment plan physician billing and shadow billing) and health service and diagnostic codes; up to ICD – Version 9 – Clinical Modification (ICD-9-CM; Alberta specific) diagnostic codes can be used per visit. The PIN contains information on all dispensed prescription medications from community pharmacies. Vital statistics contains information on all events related to an individual's entrance and departure from life. The Provincial Registry contains demographic information for all Albertans with AHCIP coverage; elements include migration in and out of the province and birth and death indicators. Variables were checked for inconsistencies; inconsistent data were corrected using information majority or most recent data, where applicable.

Cohort selection

The migraine cohort included those who (1) were aged 18–65 years and had ≥1 hospitalization, ED visit, ambulatory care visit (i.e., facility-based non-emergent ambulatory care clinic visit) or physician visit with a recorded diagnostic code for migraine (ICD-10-CA G43 or ICD-9-CM 346 located in any diagnostic field) during the inclusion period;[20] (2) had AHCIP coverage ≥2 years before the index date and ≥1 year after the index or until death, whichever came first; and (3) were matched with three individuals in the control cohort. Among those within the migraine cohort, the CM group was defined as those who had (1) ≥1 botulinum toxin injection for the prophylaxis of CM (available in Alberta for eligible individuals aged 18–65 years; identified by the Health Service Procedure Code 13.59O) during the

inclusion period or (2) had a predicted probability score ≥0.55 from a CM case-finding multivariable logistic regression model during the inclusion period (based on 4 predictors: female vs male sex, ≥24 vs <24 healthcare visits of any type, ≥15 vs <15 acute migraine medication dispensations and 1 or ≥2 vs 0 prophylactic migraine drug class dispensations measured over 1-year increments during the CM screening period).[21] Individuals in the migraine cohort who did not meet the criteria for the CM group were included in the EM group. Age was restricted to allow for the identification of eligible individuals who received a botulinum toxin injection for the prophylaxis of CM during the inclusion period.

The control cohort was initially selected based on adult residents of Alberta who (1) did not have any healthcare encounters with a recorded diagnosis of migraine during the inclusion period and (2) had AHCIP coverage ≥2 years before the index date and ≥1 year after the index or until death, whichever came first. Individuals who met these criteria were then directly matched at a 3:1 ratio with individuals in the migraine cohort where possible. Exact matching factors included age, sex and residence (urban or rural) on the index date, along with the Charlson Comorbidity Index score that was determined during the 2-year pre-index period. Selection criteria for the control cohort and matching were performed by data custodians and provided to the researchers. The researchers conducted balance diagnostics to ensure that the matched groups were comparable on baseline characteristics, and the effectiveness of matching was assessed by examining standardized mean differences between the migraine and control cohorts post-matching.

Study measures

Baseline characteristics
Demographic characteristics included age, sex and residence (based on the second digit of the postal code) on the index date. Clinical characteristics included the Charlson Comorbidity Index and specific migraine-related comorbidities. A Charlson Comorbidity Index score was determined during the 2-year pre-index period that was based on ICD-10-CA and ICD-9-CM codes of 17 different specific medical conditions weighted according to their potential for influencing mortality (Supplementary Table 1).[22,23] Migraine-related comorbidities included anxiety,[24] asthma,[25] cardiovascular disease,[25–29] chronic pain,[25,30] depression,[31,32] epilepsy,[33] hypertension[25] and obstructive sleep apnea;[34] each participant was classified with respect to the presence or absence of a condition determined during the 2-year pre-index period (Supplementary Table 2).

Healthcare resource utilization and cost
During the 1-year post-index observation period, all-cause and migraine-related (ICD-10-CA G43 located in the most responsible diagnostic field; ICD-9-CM 346 located in any diagnostic field) healthcare resource utilization and costs were determined for acute care (hospitalizations, ED visits), outpatient care (ambulatory care, physician visits) and community pharmacy dispensed prescription medications (all-cause and acute and prophylactic migraine [Supplementary Table 3]). Note that calcitonin gene-related peptide receptor (CGRP) antagonists were not available in Canada during the study period. Acute and ambulatory care costs were derived by multiplying the associated resource intensity weight with the Canadian Institute for Health Information (CIHI) standardized cost for Alberta in 2017/2018.[35,36] Resource intensity

weight is a measure to estimate healthcare resource use and represents the relative value of resources that a given patient, contingent on diagnostic case-mix, would be expected to consume relative to a standard patient; CIHI provides standardized average costs incurred through the direct care of a standardized patient.[35] Physician visit costs were based on the actual amount paid. Drug costs were calculated using the drug product identification number and quantity dispensed, combined with the drug list price (from Alberta Blue Cross); a 3% per unit markup and a $12.15 dispensing fee were included.[37,38] Costs were reported in 2022 $CDN.[39]

Medication use
The proportion of those who received ≥1 dispensation for an all-cause and migraine-related (acute and prophylactic [overall and type]) prescription medication was measured during the 1-year post-index observation period. Among those who received ≥1 dispensation (all-cause, migraine-related [acute and prophylactic]), the total number of dispensations was reported.

Statistical analysis
Descriptive statistics were reported as counts and percentages, means with standard deviations (SD) and/or medians with interquartile ranges (IQR), where appropriate. In accordance with data custodian privacy standards, outcomes with 1–9 individuals were reported as <10. To guide multivariable analyses, a conceptual framework was developed using a structural equation modeling-like directed acyclic graph (DAG) that described the role of covariates in the relationship between migraine and healthcare cost (Supplementary Figure 1).[40] The DAG suggested a minimal sufficient adjustment set for estimating the total effect of migraine on healthcare costs, including demographic characteristics (age, sex and residence), overall health burden (Charlson Comorbidity Index) and the migraine-related comorbidities of anxiety, asthma, cardiovascular disease, depression, epilepsy, hypertension and obstructive sleep apnea; these confounders were matched and/or adjusted for in the multivariable analyses. One- and two-part generalized linear models (GLM) with a gamma distribution and log link function were employed to examine cost differences. When minimal or absent zero cost values were present, a one-part GLM gamma model was used, producing cost ratios. When cost outcomes had prevalent zero values, a two-part GLM approach was adopted.[41] The first part involved using logistic regression to predict the odds of observing a nonzero cost (i.e., having a healthcare encounter), yielding the odds ratios of having a nonzero cost. The second part, conditional on a nonzero cost, involved a GLM gamma model to produce the cost ratios and estimate costs. Incremental cost was presented by cost ratios (accompanied by odds ratios in two-part models) and the difference between predicted costs using an average marginal effect approach.[42] Incremental cost represents the additional healthcare costs incurred by the migraine cohort compared with matched controls (and CM vs EM) during the 1-year observation period. The healthcare cost attributable to persons living with migraine in Alberta was estimated by multiplying the per-person per-year incremental cost of the migraine cohort by the estimated prevalence of migraine (8.3%–10.2%) and the 2022 population of Alberta ($N = 4{,}510{,}891$).[5,18] Analyses were performed using R (v4.2.3; R Core Team 2021) and STATA software (v18; StataCorp LLC, College Station, TX, USA).

Table 1. Baseline characteristics

	Total cohort		Chronic migraine		Episodic migraine	
	Migraine	Control	Migraine	Control	Migraine	Control
	$n = 100,502$	$n = 301,506$	$n = 47,739$	$n = 143,217$	$n = 52,763$	$n = 158,289$
Age, mean (SD)	43[14]	43[14]	44[15]	44[15]	41[14]	41[14]
Sex, *n* (%)						
Female	77,208 (76.8)	23,1624 (76.8)	46,375 (97.1)	139,125 (97.1)	30,833 (58.4)	92,499 (58.4)
Male	23,294 (23.2)	69,882 (23.2)	1,364 (2.9)	4,092 (2.9)	21,930 (41.6)	65,790 (41.6)
Residence, *n* (%)						
Urban	86,692 (86.3)	260,076 (86.3)	40,905 (85.7)	122,715 (85.7)	45,787 (86.8)	137,361 (86.8)
Rural	13,810 (13.7)	41,430 (13.7)	6,834 (14.3)	20,502 (14.3)	6,976 (13.2)	20,928 (13.2)
Charlson Comorbidity Index						
Category, *n* (%)						
0	69,824 (69.5)	200,572 (66.5)	28,634 (60.0)	81,981 (57.2)	41,190 (78.1)	118,517 (74.9)
1–2	25,562 (25.4)	78,928 (26.2)	15,555 (32.6)	46,584 (32.5)	10,007 (19.0)	32,407 (20.5)
3–4	3,512 (3.5)	13,337 (4.4)	2,480 (5.2)	8,992 (6.3)	1,032 (2.0)	4,362 (2.8)
≥5	1,604 (1.6)	8,669 (2.9)	1,070 (2.2)	5,660 (4.0)	534 (1.0)	3,003 (1.9)
Comorbid conditions, *n* (%)						
Chronic pain	19,946 (19.8)	26,799 (8.9)	14,665 (30.7)	15,055 (10.5)	5,281 (10.0)	11,646 (7.4)
Depression	18,259 (18.2)	28,261 (9.4)	12,499 (26.2)	15,862 (11.1)	5,760 (10.9)	12,425 (7.8)
Anxiety	14,149 (14.1)	20,775 (6.9)	9,641 (20.2)	11,578 (8.1)	4,508 (8.5)	9,070 (5.7)
Hypertension	13,969 (13.9)	37,172 (12.3)	8,227 (17.2)	20,367 (14.2)	5,742 (10.9)	16,920 (10.7)
Cardiovascular disease	5,856 (5.8)	12,357 (4.1)	3,549 (7.4)	6,774 (4.7)	2,307 (4.4)	5,641 (3.6)
Asthma	4,244 (4.2)	12,902 (4.3)	3,007 (6.3)	8,017 (5.6)	1,237 (2.3)	4,829 (3.1)
Obstructive sleep apnea	4,203 (4.2)	5,927 (2.0)	2,832 (5.9)	3,283 (2.3)	1,371 (2.6)	2,652 (1.7)
Epilepsy	1,717 (1.7)	1,828 (0.6)	1,038 (2.2)	923 (0.6)	679 (1.3)	855 (0.5)

SD = standard deviation.

Results

Cohort selection

After applying selection criteria and conducting matching, a total of 100,502 were included in the migraine cohort (CM group: $n = 47,739$; EM group: $n = 52,763$); 301,506 were in the control cohort (Figure 1; Supplementary Figure 2). The matching rate was high – only 1.6% ($n = 1,594$) of those that met the criteria for the migraine cohort had <3 matched controls (Figure 1).

Baseline characteristics

Individuals within the control cohort were exactly matched on age, sex and residence to those in the migraine cohort (Table 1). The Charlson Comorbidity Index scores of the control cohort were not exactly matched to the migraine cohort (standardized mean difference = 0.10); to remove this potential residual confounding bias, the Charlson Comorbidity Index score was used as a covariate in the adjusted cost analysis models.[43]

The average age of the migraine and control cohorts was 43 (SD 14) years, comprised predominantly of females (76.8%) and mostly lived in urban areas (86.3%) (Table 1). The CM group (and their matched controls) was more likely to be older (45 [SD 15] vs 41 [SD 14] years of age) and had a higher proportion of females (97.1% vs 58.4%) compared with the EM group (and their matched controls) (Table 1). Persons living with migraine (migraine cohort, CM and

EM) were more likely to have a higher proportion of migraine-related comorbidities (anxiety, depression, epilepsy, hypertension, obstructive sleep apnea, chronic pain and cardiovascular disease) compared with matched controls (Table 1). The CM group was more likely to have a larger proportion of migraine-related comorbidities compared with the EM group (Table 1).

Healthcare resource utilization and medication use

The migraine cohort was more likely to have had a higher proportion with ≥1 all-cause hospitalization (9.2% vs 7.4%), ED visit (37.9% vs 24.5%), ambulatory care visit (47.8% vs 33.6%) and physician visit (95.7% vs 84.1%) compared with the matched control cohort during the 1-year post-index observation period; the CM and EM groups were also more likely to have a larger proportion with ≥1 all-cause visit for all healthcare resources compared with matched controls (Table 2). Compared with EM, the CM group was more likely to have a larger proportion with ≥1 all-cause hospitalization (CM vs EM: 13.1% vs 5.7%), ED visit (45.9% vs 30.6%), ambulatory care visit (61.1% vs 35.7%) and physician visit (98.5% vs 93.1%) (Table 2). See Supplementary Table 4 for migraine-related healthcare resource utilization.

A higher proportion of persons living with migraine were more likely to have had ≥1 dispensation for any medication compared with matched controls (migraine cohort: 91.0% vs 75.5%; CM: 96.2% vs 80.2%; EM: 86.2% vs 71.2%) during the 1-year post-index
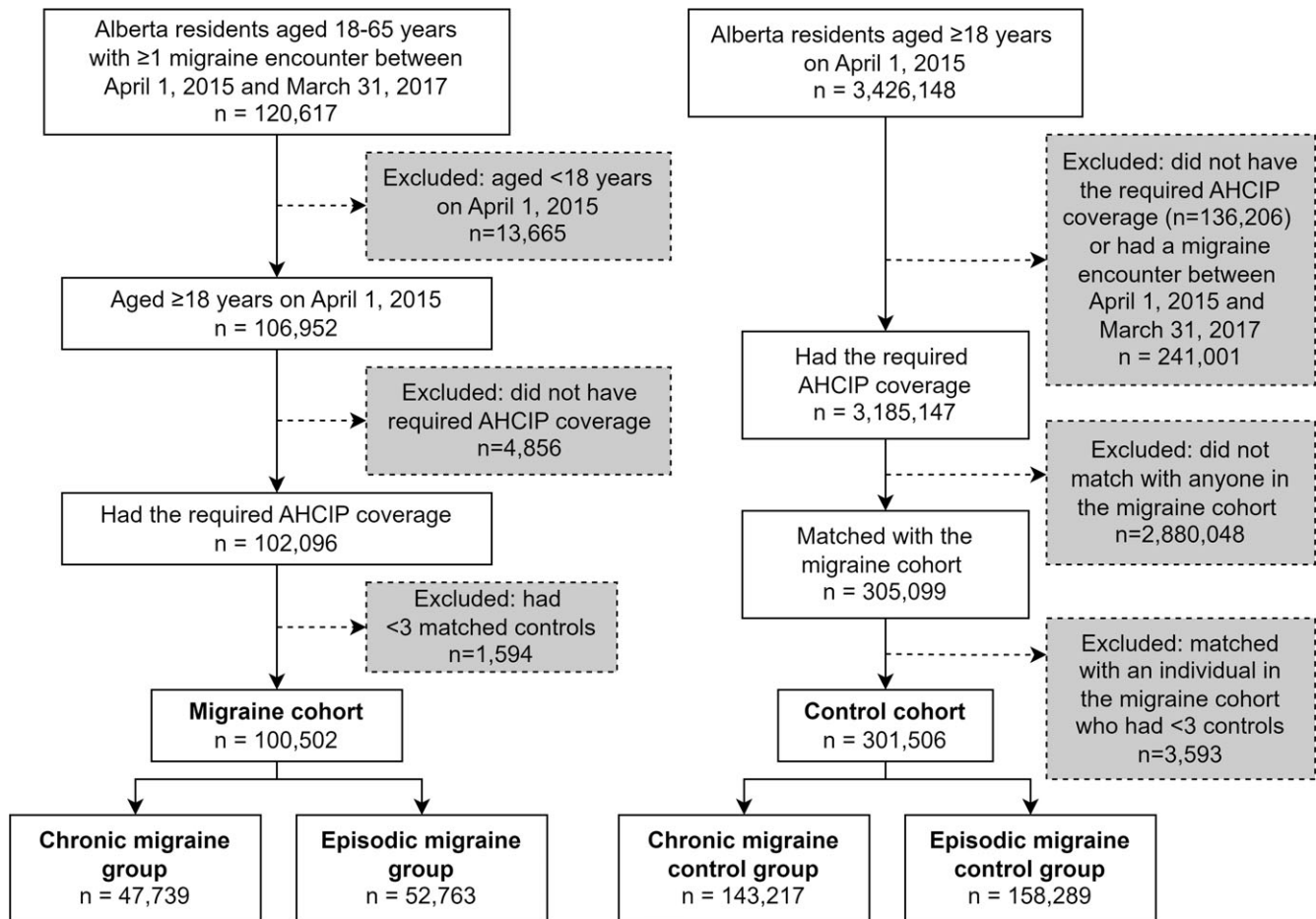
Figure 1. Migraine and control cohort selection flow diagram. AHCIP = Alberta Health Care Insurance Plan.

observation period (Table 3). Overall, 52.3% of the migraine cohort (CM: 62.8%; EM: 42.8%) was dispensed an acute migraine medication (Table 3); the most common (>10%) types were opioids (migraine cohort: 28.4%; CM: 38.5%; EM: 19.3%), nonsteroidal anti-inflammatory drugs (migraine cohort: 22.7%; CM: 28.2%; EM: 17.7%) and triptans (migraine cohort: 22.0%; CM: 25.6%; EM: 18.8%) (Figure 2). During the 1-year post-index observation period, 31.3% of the migraine cohort (CM: 44.7%; EM: 19.2%) received ≥1 dispensation for a prophylactic migraine medication (Table 3). The most common types were antidepressants (migraine cohort: 15.1%; CM: 21.1%; EM: 9.6%) and antiseizure medications (migraine cohort: 12.2%; CM: 19.2%; EM: 5.9%); botulinum toxin (12.1%) and antihypertensives (11.0%) were also common among the CM group (Figure 2).

Healthcare cost of migraine

After matching and adjusting for confounding factors, the fully adjusted total healthcare cost was 1.5 times higher (cost ratio: 1.53 [95% confidence interval [CI]: 1.50, 1.55) in the migraine cohort ($8,126 [95% CI: $7,914, $8,339] per person per year) compared with the matched control cohort ($5,320 [95% CI: $5,197, $5,443] per person per year), with persons living with migraine having a predicted incremental cost of $2,806 (95% CI: $2,664, $2,948) per person per year (Table 4). The total healthcare cost of the CM group was 1.9 times higher (cost ratio: 1.88 [95% CI: 1.84, 1.92]) than matched controls ($10,796 [95% CI: $10,513, $11,078] vs

$5,736 [95% CI: $5,602, $5,870] per person per year), with persons living with CM having a predicted incremental cost of $5,059 (95% CI: $4,836, $5,283) per person per year (Table 4). The total healthcare cost of the EM group was 1.1 times higher (cost ratio: 1.14 [95% CI: 1.11, 1.18]) than matched controls ($5,394 [95% CI: $5,112, $5,676] vs $4,725 [95% CI: $4,507, $4,943] per person per year), with persons living with EM having a predicted incremental cost of $669 (95% CI: $512, $827) per person per year (Table 4). The full multivariable regression model is shown in Supplementary Table 5. Similar patterns were observed in sensitivity analysis that did not adjust for migraine-related comorbidities, with an increased effect size; for example, the incremental cost of persons living with CM was $6,644 (95% CI: $6,358, $6,930) compared with $5,059 (Supplementary Table 6). Hospitalization, ED, ambulatory care, physician and prescription drug costs all significantly contributed to the higher cost of persons living with migraine (migraine cohort, CM and EM [with the exception of hospitalization for EM]); prescription drugs were the primary cost driver, especially for the CM group (Table 5).

After adjusting for confounding factors (age, sex, residence, overall health burden [Charlson Comorbidity Index] and migraine-related comorbidities), the total healthcare cost was higher (all-cause cost ratio: 2.25 [95% CI: 2.19, 2.31]; migraine-related cost ratio: 4.10 [95% CI: 3.97, 4.24]) in the CM group (all-cause: $8,367 [95% CI: $8,207, $8,526]; migraine-related: $870 [95% CI: $852, $888]) compared with the EM group (all-cause: $3,721 [95% CI: $3,638, $3,804]; migraine-related: $212 [95% CI:

Table 2. All-cause healthcare resource utilization during the 1-year post-index observation period

	Total cohort		Chronic migraine		Episodic migraine	
	Migraine	Control	Migraine	Control	Migraine	Control
	$n = 100{,}502$	$n = 301{,}506$	$n = 47{,}739$	$n = 143{,}217$	$n = 52{,}763$	$n = 158{,}289$
Hospitalization						
Had ≥1 visit, n (%)	9,248 (9.2)	22,397 (7.4)	6,266 (13.1)	12,449 (8.7)	2,982 (5.7)	10,010 (6.3)
Number of visits, mean (SD)	1.4 (0.8)	1.4 (0.9)	1.4 (0.9)	1.4 (1.0)	1.3 (0.8)	1.3 (0.9)
Number of visits, median [IQR]	1 [1, 1]	1 [1, 1]	1 [1, 1]	1 [1, 1]	1 [1, 1]	1 [1, 1]
Length of stay, mean (SD)	9.4 (18.5)	10.3 (21.6)	9.7 (18.3)	11.0 (22.9)	8.8 (19.1)	9.9 (21.4)
Length of stay, median [IQR]	4 [2, 7]	3 [2, 8]	4 [2, 8]	4 [2, 8]	4 [2, 7]	3 [2, 7]
Emergency department						
Had ≥1 visit, n (%)	38,061 (37.9)	73,946 (24.5)	21,915 (45.9)	37,581 (26.2)	16,146 (30.6)	36,466 (23.0)
Number of visits, mean (SD)	2.7 (4.1)	2.2 (3.0)	3.1 (4.7)	2.2 (3.1)	2.2 (2.9)	2.1 (3.0)
Number of visits, median [IQR]	2 [1, 3]	1 [1, 2]	2 [1, 3]	1 [1, 2]	1 [1, 2]	1 [1, 2]
Ambulatory care						
Had ≥1 visit, n (%)	48,011 (47.8)	101,272 (33.6)	29,152 (61.1)	54,560 (38.1)	18,859 (35.7)	46,863 (29.6)
Number of visits, mean (SD)	5.4 (12.9)	5.5 (14.9)	6.3 (14.9)	5.7 (14.5)	4.1 (8.9)	5.2 (14.3)
Number of visits, median [IQR]	2 [1, 5]	2 [1, 5]	3 [1, 6]	2 [1, 5]	2 [1, 4]	2 [1, 5]
Physician visits						
Had ≥1 visit, n (%)	96,156 (95.7)	253,649 (84.1)	47,032 (98.5)	125,505 (87.6)	49,124 (93.1)	128,025 (80.9)
Number of visits, mean (SD)	14.3 (15.8)	11.0 (14.8)	19.0 (17.6)	12.2 (15.8)	9.9 (12.4)	9.8 (13.7)
Number of visits, median [IQR]	10 [5, 18]	7 [3, 13]	15 [9, 24]	8 [4, 15]	7 [4, 12]	6 [3, 12]
Total healthcare use						
Had ≥1 visit, n (%)	96,328 (95.8)	254,408 (84.4)	47,062 (98.6)	125,737 (87.8)	49,266 (93.4)	128,549 (81.2)
Number of visits, mean (SD)	18.2 (22.7)	13.9 (21.7)	24.5 (26.3)	15.5 (23.0)	12.2 (16.5)	12.3 (20.0)
Number of visits, median [IQR]	12 [6, 23]	8 [4, 16]	18 [10, 30]	9 [5, 18]	8 [4, 15]	7 [3, 14]

IQR = interquartile range; SD = standard deviation.

Table 3. Medication use during the 1-year post-index observation period

	Total cohort		Chronic migraine		Episodic migraine	
	Migraine	Control	Migraine	Control	Migraine	Control
	$n = 100{,}502$	$n = 301{,}506$	$n = 47{,}739$	$n = 143{,}217$	$n = 52{,}763$	$n = 158{,}289$
All-cause medication						
Had ≥1 dispensation, n (%)	91,423 (91.0)	227,674 (75.5)	45,936 (96.2)	11,4918 (80.2)	45,487 (86.2)	112,775 (71.2)
Total number of dispensations						
Mean (SD)	29.9 (112.1)	21.9 (89.2)	42.5 (142.0)	25.1 (97.1)	17.1 (67.6)	18.7 (81.1)
Median [IQR]	13 [5, 27]	8 [3, 18]	20 [9, 39]	9 [4, 21]	8 [4, 16]	7 [3, 15]
Migraine-related acute medication						
Had ≥1 dispensation, n (%)	52,585 (52.3)	70,274 (23.3)	30,000 (62.8)	36,870 (25.7)	22,585 (42.8)	33,276 (21.0)
Total number of dispensations						
Mean (SD)	7.4 (20.2)	5.0 (21.4)	9.5 (22.6)	5.4 (21.6)	4.7 (16.2)	4.6 (19.5)
Median [IQR]	3 [1, 8]	2 [1, 4]	4 [2, 11]	2 [1, 4]	2 [1, 5]	2 [1, 3]
Migraine-related prophylactic medication						
Had ≥1 dispensation, n (%)	31,491 (31.3)	32,973 (10.9)	21,342 (44.7)	18,755 (13.1)	10,149 (19.2)	14,319 (9.0)
Total number of dispensations						
Mean (SD)	8.8 (28.9)	9.8 (30.1)	10.3 (33.2)	10.1 (30.0)	5.8 (16.1)	9.2 (30.5)
Median [IQR]	4 [2, 9]	4 [2, 9]	5 [3, 10]	4 [2, 9]	4 [2, 6]	4 [2, 8]

Note that calcitonin gene-related peptide (CGRP) inhibitors were not available in Canada during the observation period. IQR = interquartile range; SD = standard deviation.
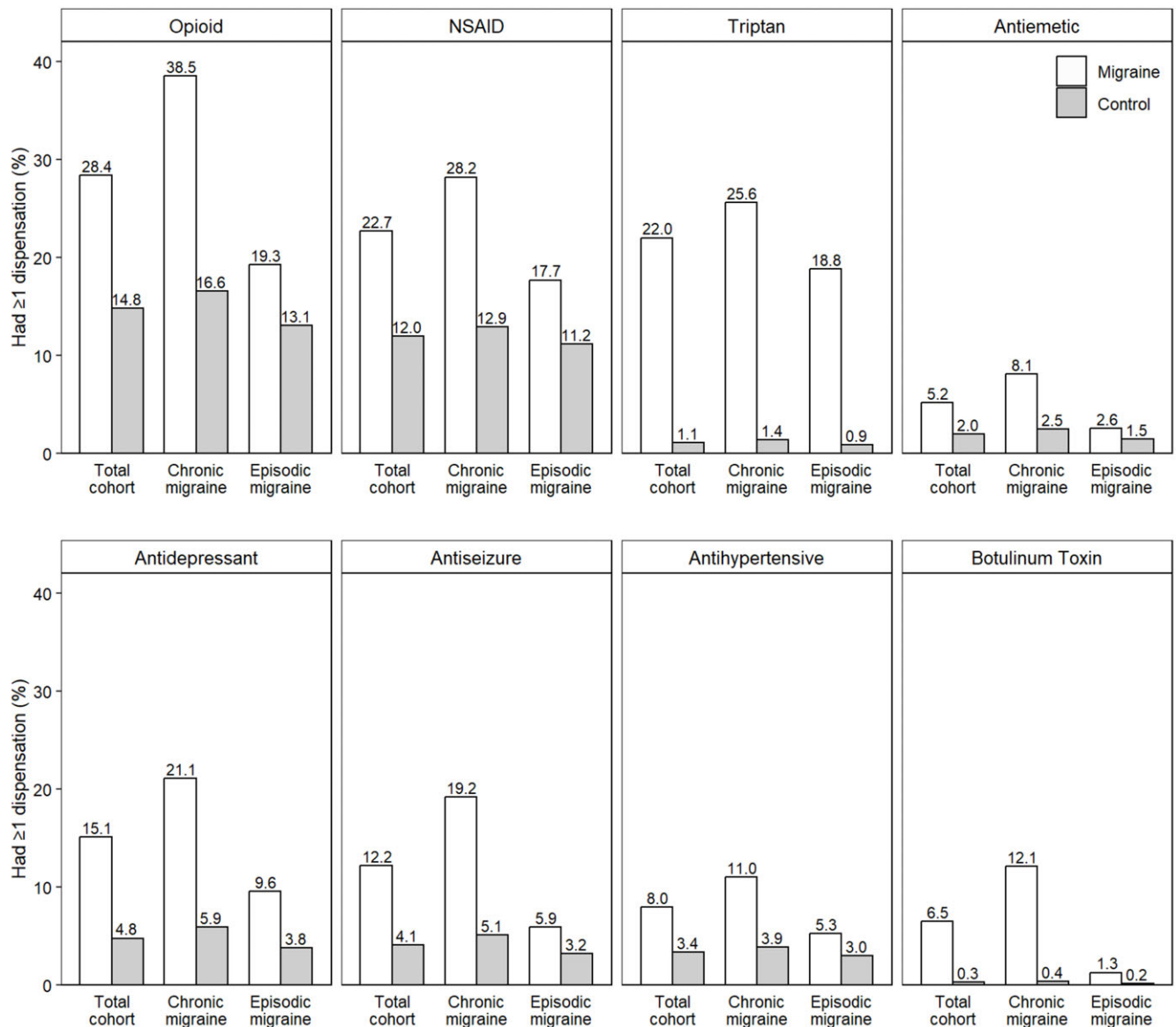
Figure 2. Types of acute and prophylactic migraine medication used during the 1-year post-index observation period. Less than 0.5% received an ergot (migraine cohort: 0.2%; CM group: 0.3%; EM group: 0.1%; matched control groups: 0.0% each), calcium antagonist (migraine cohort: 0.3%; CM group: 0.4%; EM group: 0.1%; matched control groups: 0.0% each) or antihistamine (migraine cohort: 0.0%; CM group: 0.1%; EM group: 0.0%; matched control groups: 0.0% each). NSAID = nonsteroidal anti-inflammatory drug.

$207, $217]); the CM group had a predicted all-cause incremental cost of $4,646 (95% CI: $4,478, $4,813) and migraine-related incremental cost of $658 (95% CI: $639, $677) per person per year versus the EM group (Table 4).

Discussion

In this retrospective, observational, population-based cohort study of adults living with and without migraine in Alberta, the incremental direct healthcare cost of persons living with migraine (overall, CM and EM) and cost by migraine classification between CM and EM was determined between April 1, 2017, and March 31, 2018, using administrative health data (reported in 2022 $CDN). After adjusting for confounders, the annual total mean healthcare cost of persons living with migraine was 1.5 times higher than matched controls, with a predicted incremental cost of $2,806 per person per year; the CM group was 1.9 times higher, and the EM group was 1.1 times higher than respective matched controls. While all healthcare cost categories contributed to the higher cost of persons living with migraine (overall, CM and EM), prescription medication was the primary cost driver. The cost of the CM group was 2.3 times higher than the EM group, with a predicted incremental cost of $4,646 per person per year. Findings show that persons living with migraine had greater direct healthcare costs than those without, particularly for those living with CM, which persisted after matching and adjustment for confounders, including comorbid conditions commonly observed in persons living with migraine.

Previous studies indicate that persons living with migraine have higher healthcare costs compared with those not living with migraine.[8–11] Findings from a large commercial administrative claims database in the USA (Truven Health MarketScan; covers approximately 38 million employees and their dependents) showed that adults living with migraine had a higher total all-

Table 4. Total healthcare cost comparisons between those living with migraine and matched controls, and between chronic and episodic migraine, measured during the 1-year post-index observation period

	Total cost ($CDN)	95% CI		Cost ratio	95% CI		Incremental cost ($CDN)	95% CI	
Migraine versus control									
All-cause									
Migraine	8,126	7,914	8,339	1.53	1.50	1.55	2,806	2,664	2,948
Control (reference)	5,320	5,197	5,443	—	—	—	—	—	—
Chronic migraine	10,796	10,513	11,078	1.88	1.84	1.92	5,059	4,836	5,283
Control (reference)	5,736	5,602	5,870	—	—	—	—	—	—
Episodic migraine	5,394	5,112	5,676	1.14	1.11	1.18	669	512	827
Control (reference)	4,725	4,507	4,943	—	—	—	—	—	—
Chronic migraine versus episodic migraine									
All-cause									
Chronic migraine	8,367	8,207	8,526	2.25	2.19	2.31	4,646	4,478	4,813
Episodic migraine (reference)	3,721	3,638	3,804	—	—	—	—	—	—
Migraine-related									
Chronic migraine	870	852	888	4.10	3.97	4.24	658	639	677
Episodic migraine (reference)	212	207	217	—	—	—	—	—	—

Estimated by one-part generalized linear model with log link and gamma distribution. Individuals in the control cohort were exactly matched with individuals in the migraine cohort on age, sex and urban/rural residence; the Charlson Comorbidity Index was not exactly matched and therefore further adjusted in the cost analysis model. Adjustments for the migraine-related comorbidities of anxiety, asthma, depression, epilepsy, cardiovascular disease, hypertension and obstructive sleep apnea were included. CDN = Canadian; CI = confidence interval.

cause mean annual direct healthcare cost compared with propensity score matched individuals who were not living with migraine ($13,032 [95% CI: $12,919, $13,144] vs $3,234 [95% CI: $3,202, $3,266] per person; 2016 $USD).[11] Relatively few studies have been conducted on the healthcare cost of persons living with migraine in Canada.[13–16] McMullen et al. (2023) and Graves et al. (2023) described the total direct healthcare cost of a retrospective population-based cohort living with incident (newly diagnosed/recurrent) migraine among adults between 2012 and 2018 using administrative data from Alberta.[15,16] During a follow-up period after the incident date, the total all-cause mean annual direct healthcare cost was $6,403 (SD $39,880) for persons living with migraine, $12,693 (SD $40,644) for CM and $4,251 (SD $40,637) for EM per person (2020 $CDN).[15,16] Results of the current study extend findings by reporting the annual incremental all-cause direct healthcare cost of adults living with migraine ($2,806), including CM ($5,059) and EM ($669) per person, compared with matched controls. With an estimated migraine prevalence of 8.3%–10.2%, this condition may account for an additional $1.05–1.29 billion in healthcare costs per year in Alberta.

Among the different types of migraine, individuals living with CM consistently display higher healthcare resource use and costs compared with those living with EM.[12–15] Based on survey responses from Canadian participants of the International Burden of Migraine Study (*n* = 679), those living with CM reported higher healthcare resource use and had a total direct healthcare cost that was 2.7 times higher than EM as determined during a 3-month period.[13] McMullen et al. (2023) described higher rates of healthcare use and an average annual total direct healthcare cost that was 3.0 times higher for those living with CM compared with EM in Alberta.[15] Collectively, findings from previous reports and the current study help elucidate the economic burden associated with CM and EM; this has implications for guiding treatment

decisions and the management of persons living with migraine. To this end, opioids were the most common migraine-related drug used by persons living with migraine in this study, particularly CM; higher use of opioids has been shown to be associated with higher healthcare use and costs among persons living with migraine.[44] While opioids may be helpful in some persons living with migraine, routine use is not recommended as it increases the propensity of developing medication-overuse headache, the risk of developing new-onset CM and the likelihood of becoming more refractory to other acute migraine medications and may lead to misuse or abuse resulting in dependence.[45–49] Providing care management and effective treatments for migraine that result in reduced opioid use may represent a potentially modifiable factor that could facilitate a reduction in healthcare costs and an improvement in quality of life for those living with migraine.

The period over which this study was conducted occurred before CGRP antagonists were available in Canada. This new class of drug for the prophylactic treatment of CM and EM has a favorable safety and tolerability profile and displays promising efficacy in a significant number of persons living with migraine.[50–53] However, these drugs are costly. Considering that prescription medication was the primary direct healthcare cost driver of persons living with migraine in this study, the use of CGRP antagonists may additionally increase this cost category if widely used. Therefore, the rationale use of this new drug class will need to consider possible reductions in other healthcare cost categories and the benefits in quality of life that may be realized, as well as the societal cost of migraine. To this end, CGRP antagonists have shown improved quality of life and productivity and reduced the number of monthly migraine days and the use of acute migraine medication in persons living with migraine.[50–53] Health economic and cost-effectiveness models have shown that treatment with CGRP antagonists has the potential to reduce both

Table 5. Comparison of healthcare cost components between those living with migraine and matched controls and between chronic and episodic migraine, measured during the 1-year post-index observation period

	Odds ratio of encounter (nonzeros)			Cost ratio			Incremental cost ($CDN)		
	Point estimate	95% CI		Point estimate	95% CI		Point estimate	95% CI	
Migraine versus control									
Hospitalization	1.22	1.19	1.25	0.94	0.91	0.98	122	64	180
Emergency department	1.78	1.75	1.81	1.19	1.17	1.21	166	160	173
Ambulatory care	1.80	1.77	1.83	1.05	1.03	1.08	269	249	290
Physician visit	NA	NA	NA	1.49	1.47	1.51	618	600	636
Medication	NA	NA	NA	1.82	1.76	1.89	1,381	1,234	1,529
Chronic migraine versus control									
Hospitalization	1.51	1.46	1.56	0.91	0.87	0.96	377	279	475
Emergency department	2.18	2.13	2.23	1.30	1.27	1.33	282	271	294
Ambulatory care	2.51	2.46	2.57	1.17	1.13	1.20	575	537	613
Physician visit	NA	NA	NA	1.78	1.75	1.80	1,125	1,095	1,156
Medication	NA	NA	NA	2.36	2.26	2.46	2,057	1,891	2,223
Episodic migraine versus control									
Hospitalization	0.90	0.86	0.94	0.93	0.86	1.01	−142	−214	−70
Emergency department	1.47	1.44	1.51	1.03	1.01	1.06	69	61	76
Ambulatory care	1.35	1.32	1.38	0.90	0.87	0.93	29	10	49
Physician visit	NA	NA	NA	1.19	1.17	1.21	201	181	221
Medication	NA	NA	NA	1.24	1.16	1.32	414	245	583
Chronic migraine versus episodic migraine									
Hospitalization	2.15	2.04	2.28	1.20	1.12	1.28	954	851	1,056
Emergency department	1.82	1.76	1.88	1.45	1.42	1.50	292	277	306
Ambulatory care	2.42	2.35	2.50	1.43	1.38	1.49	690	649	731
Physician visit	NA	NA	NA	1.91	1.87	1.95	1,107	1,074	1,139
Medication	NA	NA	NA	2.78	2.66	2.91	1,573	1,486	1,660

Estimated by two-part gamma hurdle models (hospitalizations, emergency department visits and ambulatory care visits) or a one-part generalized linear model with log link and gamma distribution (physician visits and outpatient medication) and matched on or adjusted for age, sex, residence, Charlson Comorbidity Index score and the migraine-related comorbidities of anxiety, asthma, depression, epilepsy, cardiovascular disease, hypertension and obstructive sleep apnea. CI = confidence interval, NA = not applicable (for the one-part model).

direct healthcare costs and the societal burden of migraine.[54–56] This is important as direct non-healthcare costs (e.g., transportation for medical appointments, childcare costs) and indirect costs (e.g., productivity loss) may account for the majority (52%–64%) of the overall economic burden of migraine in Canada;[14] indirect costs have been reported to account for 87% of the annual cost of migraine in Canada among those living with moderate-to-severe migraine.[57]

Important strengths of this study are the large population-based design, high-quality source of administrative health data that contains information on comprehensive healthcare resources in Alberta and analytical approach (multivariable analyses guided by a pre-defined conceptual framework). However, this study is also subject to several limitations that should be taken into consideration when interpreting results. Retrospective administrative claims-based studies use administrative data as opposed to medical records, and therefore, there is a potential for misclassification of the study groups or measures. Previously detailed, although migraine diagnostic codes from administrative claims data have been shown to reliably detect migraine status, this strategy may have missed a large number of persons living with migraine in the population, as many persons living with migraine either do not seek medical care for their condition or are not properly diagnosed.[21] As a validated case-finding algorithm was not available at the time of this study for the identification of individuals living with CM using Canadian administrative data, adaptation of a case definition from the USA was used.[58] This case definition does preferentially include females. While receipt of ≥1 botulinum toxin injection for the prophylaxis of CM was an inclusion criterion for the CM group, some individuals living with CM who respond to botulinum toxin treatment will convert to EM.[59,60] Therefore, the misclassification of some individuals within the CM and EM groups may have occurred. The PIN database only provides information on prescription medication dispensations (over-the-counter medications excluded) from community pharmacies and may not represent actual medication uptake by individuals. This study was conducted from the perspective of the Canadian healthcare system and did not include costs borne by individuals or indirect costs. Previous studies have shown that when a societal perspective is considered, costs outside the healthcare system account for the majority of the economic burden of migraine in Canada.[14,57]

Conclusions

This study provides insights into the direct healthcare costs associated with persons living with migraine, including CM and EM in Alberta. Adults living with migraine, particularly those living with CM, used greater healthcare resources and incurred higher incremental costs compared with those not living with migraine that was primarily driven by prescription medication cost. Findings from this study support the rationale for strategies to prevent and effectively manage migraine that reduce associated healthcare and societal costs, along with improving the quality of life for persons living with migraine.

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