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ORIGINAL RESEARCH—CLINICAL

Health Care Resource Use and Associated Costs of Cyclic Vomiting Syndrome in the United States

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BACKGROUND AND AIMS: This study aimed to estimate the extent of US health care resource use (HRU) and direct cost burden of cyclic vomiting syndrome (CVS). **METHODS:** We selected patients in the MarketScan Commercial and Medicare Supplemental databases with ≥1 inpatient (IP) or ≥2 outpatient (OP) claims for CVS between October 1, 2015 and June 30, 2019, and continuous insurance enrollment for ≥12 months before (baseline) and ≥3 months after first CVS diagnosis (index). Using propensity scores based on baseline characteristics, each patient with CVS was matched to ∼3 non-CVS controls. We annualized HRU and costs to accommodate varying follow-up periods. Multivariable regressions further balanced CVS and non-CVS groups, and differences in HRU and costs between the matched cohorts were compared to quantify the direct cost burden of CVS. **RESULTS:** Patients with CVS incurred significantly higher average annualized HRU, with the largest differences in emergency room (1.9 vs 0.4) visits and hospital IP (0.9 vs 0.1) stays ($P < .001$). Patients with CVS had significantly higher annual total health care costs ($57,140 vs $14,912), with IP spending as the primary driver ($28,522 vs $3250) of the cost difference (all $P < .001$). After multivariable regression adjustments, total health care costs remained 4.1 times higher for patients with CVS relative to non-CVS controls, with IP costs 12.3 times higher, emergency room costs 5.8 times higher, OP visit costs 2.9 times higher, and OP pharmacy costs 1.5 times higher (all $P < .001$). **CONCLUSION:** Newly diagnosed patients with CVS have greater health care utilization and higher costs than matched non-CVS counterparts, suggesting substantial economic burden of CVS on the US health care system.

Keywords: Cyclic Vomiting Syndrome; Health Care Resource Use; Health Care Costs; Economic Burden

Introduction

Cyclic vomiting syndrome (CVS) is a disorder of gut-brain interaction (DGBI) that is characterized by recurring episodes of severe nausea and repetitive vomiting.[1,2] Although CVS remains poorly understood and generally underdiagnosed, it is far from a rare condition. The prevalence of CVS in the United States is estimated to be approximately 1%–2% among both children and adults, yet it is seldom considered as a potential diagnosis, even among gastroenterologists.[3–5] One recent study of adult patients in an outpatient (OP) gastroenterology clinic found that only a small proportion of the ∼10% of patients who met the diagnostic criteria for CVS were actually diagnosed with the condition.[6] Furthermore, few randomized clinical trials have been conducted among CVS treatments, and treatment recommendations have been based on limited clinical data.[7,8] Clearly, there is a mismatch between the prevalence of CVS with its generally poor clinical recognition.[6]

Diagnosis and treatment of CVS are further complicated by high rates of comorbidities, including other DGBIs, migraine, anxiety, and depression.[1,2,7,9] Previous work has shown a correlation between psychological comorbidities and increased health care utilization in patients with DGBIs, and this association likely is true in patients with CVS.[10–12] The underdiagnosis and delayed diagnosis of CVS, underutilization of existing CVS treatments, and high comorbidity rates, all contribute to excessive, potentially avoidable utilization of health care services by patients with CVS seeking symptom relief during episodes.[1,7] Yet, although CVS clearly imposes a significant burden of health care resource use (HRU) and costs across all health care service settings (ie, inpatient [IP], emergency room [ER], OP, pharmacy), the extent of this impact is not clearly known.

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Abbreviations used in this paper: **CVS, cyclic vomiting syndrome; DGBI, disorder of gut-brain interaction; ER, emergency room; HRU, health care resource utilization; IP, inpatient; OP, outpatient.**

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The objective of this study was to fill this evidence gap and assess the HRU and associated costs attributable to CVS. We hypothesized that patients living with CVS have significantly higher HRU and costs in comparison to their counterparts who do not have CVS. This study also provides a population-level description of demographic and clinical characteristics (eg, comorbidities) of patients with CVS in the United States across all practice or setting types, in contrast to most previous studies that were restricted to tertiary care centers and/or databases linked to specific clinical settings.[1]

Methods

Study Design and Data Source

This observational, retrospective cohort study used deidentified US administrative claims data covering October 1, 2014 to June 30, 2019, housed in the IBM MarketScan Commercial Claims and Encounters (Commercial) Database and the Medicare Supplemental and Coordination of Benefits (Medicare Supplemental) Database. These databases contain all encounters in both IP and OP settings and OP prescription medication use of active and retired employees and their dependents covered under a variety of fee-for-service and managed care health plans. In addition, the analysis was performed for Medicaid patients in the IBM MarketScan Medicaid Multistate Database using claims data covering October 1, 2014 to December 31, 2018. The results from the Medicaid analysis are included as Supplemental Data to provide an additional dimension of CVS burden estimates in the United States. All study data were obtained using International Classification of Diseases, Ninth Revision, Clinical Modification, and International Classification of Diseases, Tenth Revision, Clinical Modification, diagnosis codes, Current Procedural Terminology 4 and Healthcare Common Procedure Coding System procedure codes, and National Drug Codes for prescriptions.

Patient Selection and Cohort Assignment

Patients with at least 1 IP or 2 OP claims, on different dates, with a diagnosis for CVS (International Classification of Diseases, Ninth Revision, Clinical Modification: G43.A0, G43.A1) between October 1, 2015 and June 30, 2019 (patient selection window) were eligible for study inclusion. The index date was the first claim with a CVS diagnosis during the patient selection window. Patients were required to have continuous enrollment with medical and prescription coverage for at least 12 months before the index date (baseline period) and at least 3 months after index date (follow-up period). Patients were followed from the index date until the database disenrollment or June 30, 2019 (variable-length follow-up period), whichever was earlier. Patients with a CVS diagnosis during the baseline period were excluded to ensure that the study population was comprised of only incident CVS patients.

A non-CVS cohort was selected from a 1% random sample of patients in the Commercial and Medicare Supplemental Databases without evidence of CVS between October 1, 2015 and June 30, 2019. Their index date was randomly assigned to match the distribution of index dates in the CVS cohort. For each patient with CVS, we calculated the number of days between the index date and October 1, 2015 ("interval pool"). For each control, a number was randomly drawn from that interval pool, and their index date was advanced that number of days after October 1, 2015. Controls were required to meet the same inclusion and exclusion criteria of patients with CVS.

Propensity scoring was implemented to match each patient with CVS with up to 3 corresponding non-CVS controls based on baseline demographics, Deyo-Charlson Comorbidity Index, clinical characteristics, and baseline health care costs (Figure 1). The balance between the 2 cohorts postmatching was evaluated using standardized mean differences, with an a priori threshold of $<\pm 10\%$ to indicate balance.

In the Medicaid analysis, CVS patients and non-CVS control patients were selected using the same criteria as used in the primary analysis, except for using data from October 1, 2014 to December 31, 2018. In addition, patients dually enrolled in Medicaid and Medicare were excluded (Supplemental Digital Content 1).

Baseline Characteristics

For CVS patients and non-CVS controls, sociodemographic characteristics, including age, sex, geographic region, population density, and insurance plan type, were assessed on the index date. The duration of follow-up was also captured. We measured and compared baseline clinical characteristics, Deyo-Charlson Comorbidity Index, and the presence of conditions identified in the literature as having a higher burden in CVS patients, including abdominal pain, anxiety (including panic disorder), autonomic dysfunction, cannabis abuse/use, cardiac conditions and risks, depression, fibromyalgia, gastroesophageal reflux disease, gastroparesis, irritable bowel syndrome, migraine, nausea, seizure, and vomiting other than CVS.[7,13,14] We then compared characteristics of matched CVS patients with non-CVS controls on these measures in children to adults within the prematch CVS patient cohort.

HRU and Costs

HRU and costs were measured during the follow-up period to compare all-cause (ie, regardless of reasons) HRU and costs in the CVS patients to their matched non-CVS controls, and the differences between the matched cases and controls were regarded as the burden attributable to CVS. Besides all-cause estimates, CVS-specific HRU and costs, identified by IP claims with a primary diagnosis of CVS and OP claims with CVS in any claim position, were reported among all CVS patients. HRU measures (proportion of patients with an encounter in a care setting, annualized number of HRU) and associated health care costs were reported by service settings (IP, ER, OP office visit, other OP services, and OP pharmacy). Health care costs were inflated to 2019 dollars using the Medical Care Component of the Consumer Price Index and based on paid amounts of adjudicated claims, including insurer payments as well as patient cost sharing (eg, copayment, deductible, and coinsurance).

Statistical Analysis

For all baseline variables and outcome measures, we reported frequencies and percentages for categorical variables and mean and standard deviation for continuous variables. Statistical significance of group differences between CVS patients and non-CVS controls was evaluated using chi-square tests for categorical variables and *t*-tests or analysis of variance for continuous variables. The alpha level for all statistical tests was 0.05.

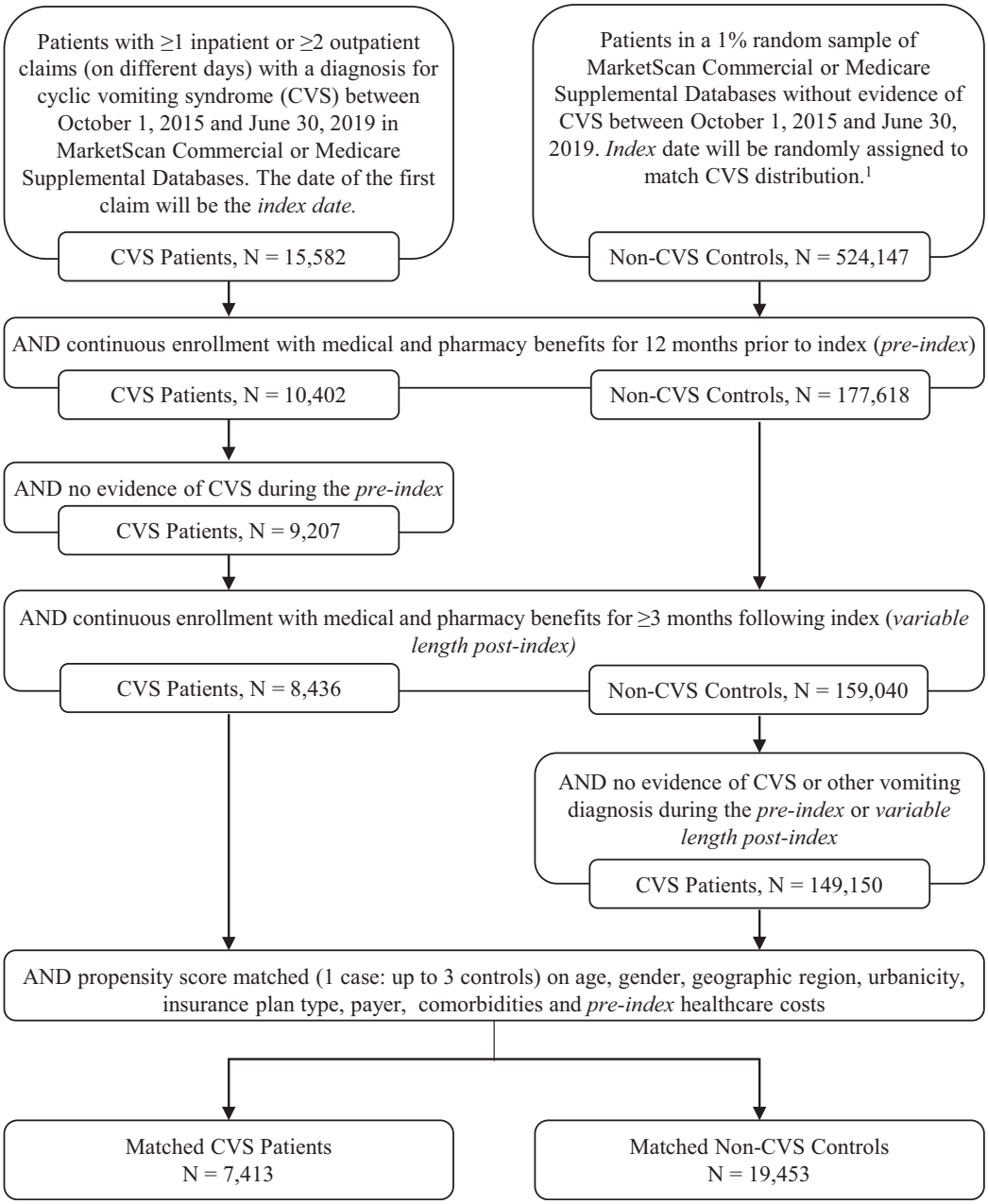

Figure 1. CVS patient attrition. [1]For each patient with CVS, the number of days between *index date* and October 1, 2015, was calculated and referred to as the "interval pool." For each control patient, a number was randomly drawn from that interval pool and the *index date* equals that number of days after October 1, 2015.

Logistic regression models were used to develop propensity scores for matching. Then, generalized linear multivariable regression models were used to further adjust for any remaining imbalances in baseline demographic and clinical characteristics between the matched CVS patients and non-CVS controls. All data analyses were conducted using WPS version 4.1 (World Programming, United Kingdom).

Results

Patient Sample Selection

There were 15,582 patients who had at least 1 IP or 2 distinct OP claims of CVS diagnosis from October 1, 2015 to December 31, 2018 (Figure 1). Among them, a total of 8436 patients with CVS (1878 children and 6558 adults) met the study inclusion and exclusion criteria for analysis. After propensity score matching, 7413 CVS cases and 19,453 controls were included in the final matched comparison (Figure 1).

Patient Demographics and Clinical Characteristics

The prematching data reflect natural patterns in the disease population, where patients with CVS tended to be younger than non-CVS controls (mean age 35.9 vs 38.9 years) and were comprised of more females (63.2% vs

Table 1. Patient Demographics[a] and Baseline Clinical Characteristics[b] Among Children and Adults Prior to Propensity Score Matching

	Children (aged <18 y at index)			Adults (aged ≥18 y at index)		
	CVS patients	Non-CVS controls		CVS patients	Non-CVS controls	
Patient demographics	N = 1878	N = 29,389	*P* value	N = 6558	N = 119,761	*P* value
Age (mean, SD)	10.3 ± 4.5	10.2 ± 4.6	.349	43.2 ± 17.7	46.0 ± 16.1	<.001
Age category (n, %)						
<6	338 (18.0)	5922 (20.2)	.006			<.001
6–11	742 (39.5)	10,610 (36.1)				
12–17	798 (42.5)	12,857 (43.7)				
18–30				2042 (31.1)	24,987 (20.9)	
31–44				1407 (21.5)	28,795 (24.0)	
45–54				1210 (18.5)	26,019 (21.7)	
55–64				1284 (19.6)	28,774 (24.0)	
65–74				288 (4.4)	6470 (5.4)	
75+				327 (5.0)	4716 (3.9)	
Sex (n, %)						
Male	929 (49.5)	14,904 (50.7)	.295	2176 (33.2)	57,844 (48.3)	<.001
Female	949 (50.5)	14,485 (49.3)		4382 (66.8)	61,917 (51.7)	
Geographic region (n, %)						
Northeast	302 (16.1)	5072 (17.3)	<.001	909 (13.9)	22,200 (18.5)	<.001
North Central	392 (20.9)	6631 (22.6)		1695 (25.8)	26,511 (22.1)	
South	912 (48.6)	12,265 (41.7)		3015 (46.0)	51,380 (42.9)	
West	265 (14.1)	5269 (17.9)		920 (14.0)	19,349 (16.2)	
Unknown	7 (0.4)	152 (0.5)		19 (0.3)	321 (0.3)	
Payer (n, %)						
Commercial	1878 (100.0)	29,389 (100.0)		5954 (90.8)	109,364 (91.3)	
Medicare				604 (9.2)	10,397 (8.7)	
Days of follow-up (mean, SD)[c]	617.6 ± 357.0	601.3 ± 352.2	.052	533.8 ± 338.2	578.0 ± 344.5	<.001
DCI (mean, SD)	0.2 ± 0.7	0.1 ± 0.3	<.001	1.5 ± 2.4	0.4 ± 1.0	<.001
Baseline conditions (n, %)[d]						
Abdominal pain	740 (39.4)	1233 (4.2)	<.001	3697 (56.4)	9137 (7.6)	<.001
Anxiety	260 (13.8)	1090 (3.7)	<.001	2044 (31.2)	11,082 (9.3)	<.001
Autonomic dysfunction	21 (1.1)	17 (0.1)	<.001	107 (1.6)	242 (0.2)	<.001
Cannabis abuse/use	19 (1.0)	23 (0.1)	<.001	450 (6.9)	290 (0.2)	<.001
Cardiac conditions and risks[e]	127 (6.8)	356 (1.2)	<.001	3241 (49.4)	33,003 (27.6)	<.001
Depression	147 (7.8)	728 (2.5)	<.001	1770 (27.0)	9480 (7.9)	<.001
Diabetes, type 1	11 (0.6)	73 (0.2)	.006	357 (5.4)	933 (0.8)	<.001
Fibromyalgia	3 (0.2)	41 (0.1)	.747	290 (4.4)	1278 (1.1)	<.001
Gastroesophageal reflux disease (GERD)	318 (16.9)	313 (1.1)	<.001	2047 (31.2)	8591 (7.2)	<.001
Gastroparesis	18 (1.0)	2 (0.0)	<.001	482 (7.3)	78 (0.1)	<.001
Irritable bowel syndrome (IBS)	24 (1.3)	13 (0.0)	<.001	274 (4.2)	618 (0.5)	<.001
Migraine	231 (12.3)	335 (1.1)	<.001	895 (13.6)	4026 (3.4)	<.001
Nausea	213 (11.3)	196 (0.7)	<.001	1587 (24.2)	1758 (1.5)	<.001
Seizure	57 (3.0)	127 (0.4)	<.001	205 (3.1)	651 (0.5)	<.001
Vomiting, other than CVS[f]	1120 (59.6)			3889 (59.3)		
Total health care costs (mean, SD)	$19,935 ± $99,425	$2412 ± $11,086	<.001	$51,301 ± $108,721	$7574 ± $25,451	<.001

DCI, Deyo-Charlson Comorbidity Index.
[a]Demographics were captured on index date.
[b]Baseline clinical characteristics were captured during the 12-mo baseline period.
[c]Length of follow-up comprises time from index until end of follow-up due to end of enrollment or study period (June 30, 2019).
[d]Comorbid conditions identified in the literature as having a high burden in CVS patients.
[e]Defined as acute myocarditis, acute pericarditis, arrhythmias cardiac arrest, cardiomyopathy, cerebrovascular disease, chronic rheumatic heart disease, conduction disorders, diseases of arteries, arterioles and capillaries, diseases of endocardium, diseases of veins, lymphatic vessels and nodes, heart failure, hypertension, hypotension, ischemic heart disease, paroxysmal tachycardia, and pulmonary heart diseases.
[f]Includes diagnosis codes for other types of vomiting, the symptom of vomiting, and nonspecific vomiting.

Table 2. CVS Patient Demographics[a] and Baseline Clinical Characteristics[b] Before and After Propensity Score Matching

	Prematch			Postmatch		
	CVS patients N = 8436	Non-CVS controls N = 149,150	Standardized difference	CVS patients N = 7413	Non-CVS controls N = 19,453	Standardized difference
Age (mean, SD)	35.9 ± 20.9	38.9 ± 20.4	14.84	35.9 ± 21.4	37.1 ± 20.9	5.55
Age category (n, %)						
<6	338 (4.0)	5922 (4.0)	0.18	330 (4.5)	608 (3.1)	6.95
6–11	742 (8.8)	10,610 (7.1)	6.22	702 (9.5)	1716 (8.8)	2.25
12–17	798 (9.5)	12,857 (8.6)	2.93	725 (9.8)	1936 (10.0)	0.58
18–30	2042 (24.2)	24,987 (16.8)	18.55	1670 (22.5)	4310 (22.2)	0.89
31–44	1407 (16.7)	28,795 (19.3)	6.84	1205 (16.3)	3456 (17.8)	4.02
45–54	1210 (14.3)	26,019 (17.4)	8.49	1063 (14.3)	2799 (14.4)	0.14
55–64	1284 (15.2)	28,774 (19.3)	10.79	1142 (15.4)	3048 (15.7)	0.73
65–74	288 (3.4)	6470 (4.3)	4.79	265 (3.6)	716 (3.7)	0.57
75+	327 (3.9)	4716 (3.2)	3.88	311 (4.2)	864 (4.4)	1.21
Sex (n, %)						
Male	3105 (36.8)	72,748 (48.8)	24.37	2820 (38.0)	7587 (39.0)	1.97
Female	5331 (63.2)	76,402 (51.2)	24.37	4593 (62.0)	11,866 (61.0)	1.97
Geographic region (n, %)						
Northeast	1211 (14.4)	27,272 (18.3)	10.65	1083 (14.6)	3589 (18.4)	10.35
North Central	2087 (24.7)	33,142 (22.2)	5.94	1859 (25.1)	4190 (21.5)	8.38
South	3927 (46.6)	63,645 (42.7)	7.81	3413 (46.0)	8818 (45.3)	1.43
West	1185 (14.0)	24,618 (16.5)	6.84	1035 (14.0)	2783 (14.3)	0.99
Unknown	26 (0.3)	473 (0.3)	0.16	23 (0.3)	73 (0.4)	1.11
Payer (n, %)						
Commercial	7832 (92.8)	138,753 (93.0)	0.74	6851 (92.4)	17,926 (92.2)	1.01
Medicare	604 (7.2)	10,397 (7.0)	0.74	562 (7.6)	1527 (7.8)	1.01
Days of follow-up (mean, SD)[c]	552.5 ± 344.2	582.5 ± 346.1	NA	558.5 ± 347.	570.5 ± 342.7	NA
DCI (mean, SD)	1.2 ± 2.2	0.3 ± 0.9	50.96	1.0 ± 2.0	0.8 ± 1.8	9.19
Baseline conditions (n, %)[d]						
Abdominal pain	4437 (52.6)	10,370 (7.0)	115.19	3466 (46.8)	7710 (39.6)	14.41
Anxiety	2304 (27.3)	12,172 (8.2)	51.79	1783 (24.1)	4213 (21.7)	5.71
Autonomic dysfunction	128 (1.5)	259 (0.2)	14.71	71 (1.0)	119 (0.6)	3.92
Cannabis abuse/use	469 (5.6)	313 (0.2)	32.38	227 (3.1)	310 (1.6)	9.75
Cardiac conditions and risks[e]	3368 (39.9)	33,359 (22.4)	38.62	2760 (37.2)	6526 (33.5)	7.71
Depression	1917 (22.7)	10,208 (6.8)	45.90	1469 (19.8)	3425 (17.6)	5.67
Diabetes, type 1	368 (4.4)	1006 (0.7)	NA	250 (3.4)	284 (1.5)	NA
Fibromyalgia	293 (3.5)	1319 (0.9)	17.80	210 (2.8)	473 (2.4)	2.51

Table 2. Continued

	Prematch			Postmatch		
	CVS patients N = 8436	Non-CVS controls N = 149,150	Standardized difference	CVS patients N = 7413	Non-CVS controls N = 19,453	Standardized difference
Gastroesophageal reflux disease	2365 (28.0)	8904 (6.0)	61.45	1785 (24.1)	3934 (20.2)	9.30
Gastroparesis	500 (5.9)	80 (0.1)	35.01	123 (1.7)	80 (0.4)	12.35
Irritable bowel syndrome	298 (3.5)	631 (0.4)	22.47	182 (2.5)	380 (2.0)	3.42
Migraine	1126 (13.3)	4361 (2.9)	38.84	870 (11.7)	2008 (10.3)	4.51
Nausea	1800 (21.3)	1954 (1.3)	66.61	1124 (15.2)	1692 (8.7)	20.04
Seizure	262 (3.1)	778 (0.5)	19.46	195 (2.6)	429 (2.2)	2.77
Vomiting, other than CVS[f]	5009 (59.4)			4097 (55.3)		
Total health care costs (mean, SD)[g]	$44,319 ± $107,511	$6557 ± $23,421	NA	$34,565 ± $89,103	$18,050 ± $47,900	NA
Median	$11,698	$1333		$9133	$4928	

CVS, cyclic vomiting syndrome; DCI, Deyo-Charlson Comorbidity Index.
[a]Demographics were captured on index date.
[b]Baseline clinical characteristics were captured during the 12-mo baseline period.
[c]Length of follow-up comprises time from index until end of follow-up due to end of enrollment or study period (June 30, 2019).
[d]Comorbid conditions identified in the literature as having a high burden in CVS patients.
[e]Defined as acute myocarditis, acute pericarditis, arrhythmias cardiac arrest, cardiomyopathy, cerebrovascular disease, chronic rheumatic heart disease, conduction disorders, diseases of arteries, arterioles and capillaries, diseases of endocardium, diseases of veins, lymphatic vessels and nodes, heart failure, hypertension, hypotension, ischemic heart disease, paroxysmal tachycardia, and pulmonary heart diseases.
[f]Includes diagnosis codes for other types of vomiting, the symptom of vomiting, and nonspecific vomiting.
[g]Log (total health care costs) was used as a matching factor. Standardized difference was NA, when the covariate was not used in the matching.

Table 3. Annualized All-Cause Health Care Utilization in Variable-Length Follow-Up Period for Matched CVS and Non-CVS Patients

	Matched CVS patients	Matched non-CVS controls	*P* value
Inpatient admissions			
Patients with an admission (n, %)	3348 (45.2)	1942 (10.0)	<.001
Average length of stay in days per admission (mean, SD)	11.69 ± 23.55	7.13 ± 12.14	<.001
Number of admissions, annualized (mean, SD)	0.90 ± 1.81	0.11 ± 0.49	<.001
Emergency room (ER) visits			
Patients with an ER visit (n, %)	4548 (61.4)	5670 (29.1)	<.001
Number of ER visits, annualized (mean, SD)	1.91 ± 3.48	0.39 ± 0.99	<.001
Outpatient services			
Outpatient office visits			
Patients with an office visit (n, %)	7226 (97.5)	17,742 (91.2)	<.001
Number of office visits, annualized (mean, SD)	11.16 ± 10.03	6.74 ± 7.09	<.001
Other outpatient services			
Patients with other outpatient services (n, %)	7333 (98.9)	17,740 (91.2)	<.001
Number of other outpatient services, annualized (mean, SD)	79.91 ± 114.33	33.43 ± 52.52	<.001
Outpatient pharmacy			
Patients with an outpatient prescription (n, %)	7171 (96.7)	17,029 (87.5)	<.001
Number of outpatient prescriptions, annualized (mean, SD)	31.58 ± 32.59	18.89 ± 24.31	<.001

51.2%). Among the baseline conditions measured, patients with CVS exhibited higher rates of all conditions when compared with non-CVS controls before matching but had particularly high proportions of patients with abdominal pain (52.6% vs 7.0%), anxiety (27.3% vs 8.2%), depression (22.7% vs 6.9%), migraine (13.3% vs 2.9%), and nausea (21.3% vs 1.3%). This pattern of comorbidities held in the pediatric CVS cohort as well (Table 1). We note that the female predominance of our cohort of adult CVS patients is similar to prior reports.[4] However, we did not observe a female predominance in our cohort of pediatric CVS patients.[15–21]

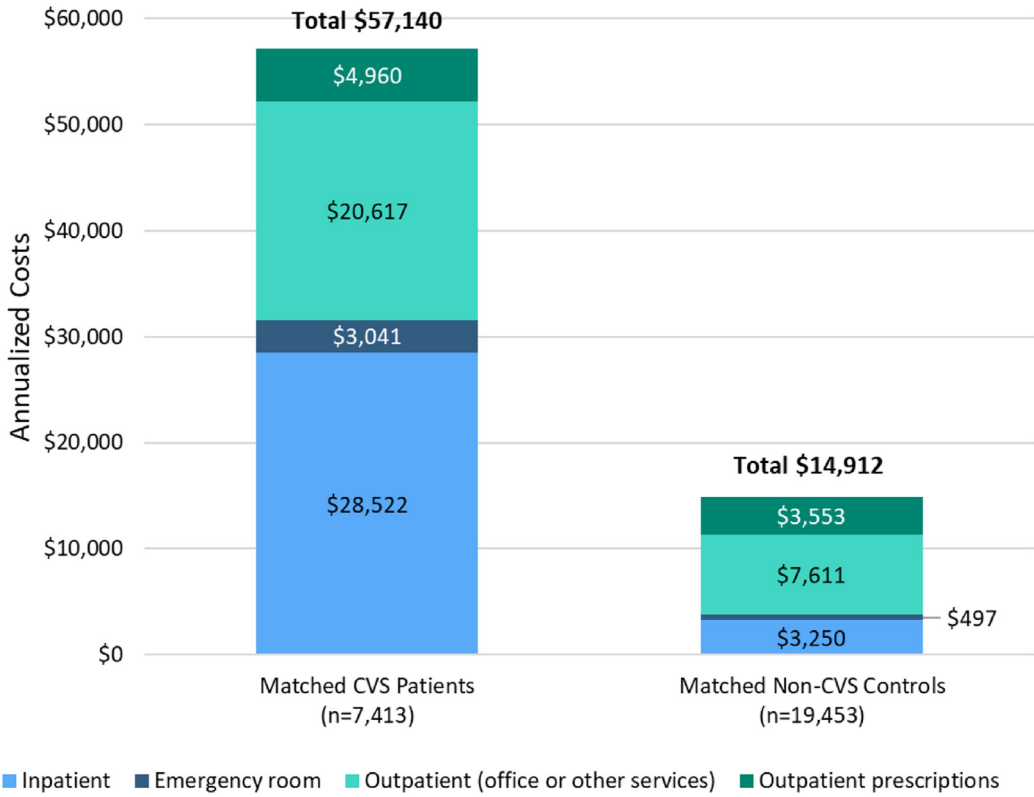

Figure 2. Annualized all-cause health care costs during follow-up for matched CVS and non-CVS patients. All comparisons between matched CVS patients and non-CVS controls were $P < .001$.

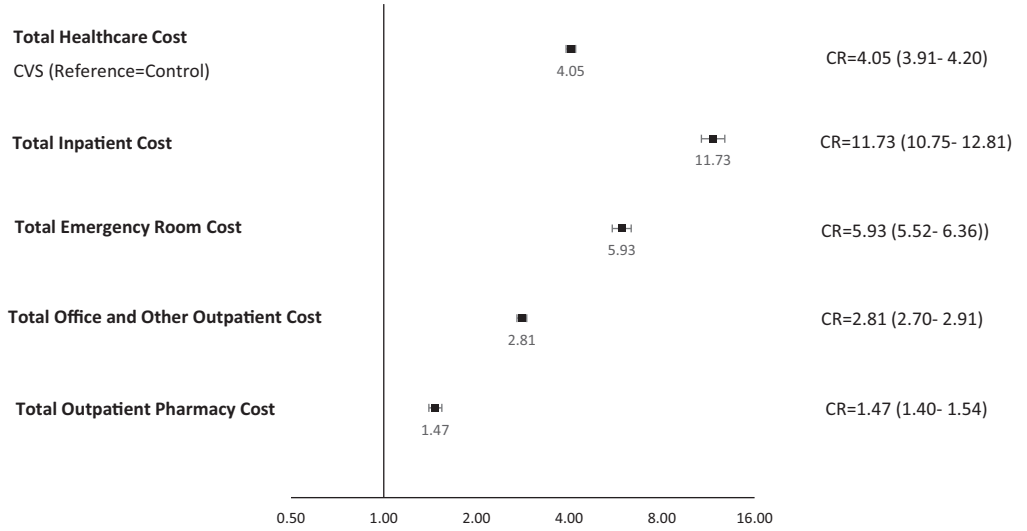

Figure 3. General linear model estimating cost ratio adjusting for differences in demographic and clinical characteristics and baseline costs for matched CVS and non-CVS patients.

Matching resolved most imbalances between patients with CVS and their controls, although some minor differences remained in the prevalence of abdominal pain (46.8% vs 39.6%), gastroparesis (1.7% vs 0.4%), and nausea (15.2% vs 8.7%; Table 2). To adjust for these remaining imbalances, generalized linear multivariable regression models were estimated as part of the health care cost analysis.

Patient Annualized HRU

During the variable-length follow-up, matched CVS patients had higher all-cause annualized HRU than matched non-CVS controls across all service types, but with particularly striking differences in ER and IP utilization (Table 3). Matched CVS patients were significantly more likely than matched non-CVS controls to have an all-cause IP admission (45.2% vs 10.0%; $P < .001$), and the duration of these IP stays was longer (mean 11.69 vs 7.13 days; $P < .001$; Table 3). Also, matched CVS patients were more than twice as likely to have an ER visit (61.4% vs 29.1%; $P < .001$) and had almost 5 times as many annualized ER visits (1.91 vs 0.39 visits; $P < .001$; Table 3) compared with non-CVS controls.

In addition to estimating burden via the delta of all-cause HRUs between matched cases and controls, we also assessed the HRUs with CVS claims among all CVS patients ($N = 8436$). Only 5.0% of CVS patients had hospitalizations with a CVS claim as the primary discharge diagnosis, and 22.3% had ER visits with a CVS claim. This "narrow view" approach indicates that the sole use of claims with CVS diagnosis will undercapture the impact on CVS patients (Supplemental Digital Content 2).

Patient Annualized Health Care Costs

Figure 2 presents unadjusted annualized all-cause health care costs during follow-up for matched CVS patients and non-CVS controls in total and by setting. Across all service categories, total health care costs were higher among patients with CVS compared with those without CVS (all $P < .001$). IP costs accounted for nearly half of the total health care costs of CVS patients and were almost 9 times higher in CVS patients than their matched controls ($28,522 vs $3250), whereas ER costs were 6 times higher ($3041 vs $497; all $P < .001$). Although OP services accounted for a smaller proportion of total costs, they still contributed to significantly higher costs among CVS cases compared with matched non-CVS controls ($20,617 vs $7611; $P < .001$; Figure 2).

We also examined CVS-specific costs for all CVS patients. On average, the annual IP costs were $836, ER costs were $782, physician office visit costs were $216, and other OP costs were $1294, with 5.0%, 22.3%, 58.4%, and 61.7% of patients using each type of CVS-specific services, respectively (Supplemental Digital Content 2).

After multivariable adjustments were performed to further balance the matched CVS cases and non-CVS controls, the difference in costs between the 2 cohorts remained (Figure 3, Supplemental Digital Content 3). Total health care costs were 4.05 times higher for CVS patients compared with their matched non-CVS controls, with IP costs 11.73 times higher, ER costs 5.93 times higher, OP costs 2.81 times higher, and OP pharmacy costs 1.47 times higher (all $P < .001$; Figure 3). In addition, adult CVS patients incurred significantly higher total costs in all individual cost components than did pediatric CVS patients (Supplemental Digital Content 3).

Medicaid Analysis

Replication of the analyses in Medicaid data revealed that the demographic and clinical characteristics among the matched Medicaid cohorts are similar to those in the Commercial and Medicare analyses, with the exception that

Medicaid patients were 7–8 years younger and had baseline health care costs only half of those in the Commercial and Medicare cohorts (Supplemental Digital Content 4). Similarly, consistent with the prior findings, Medicaid CVS patients had significantly higher HRU, annualized total costs ($25,745 vs $8.075; $P < .001$), and adjusted total cost ratios (3.09; $P < .001$) than their matched non-CVS controls. IP costs were the largest driver of overall CVS costs ($16,277 vs $2431; $P < .001$), accounting for 77% of the total cost difference between CVS patients and matched non-CVS controls (Supplemental Digital Contents 5 and 6).

Conclusions

Our results highlight a significant, under-recognized economic burden of CVS. CVS patients with poorly controlled illness often seek treatment in ER and IP settings during acute episodes, with providers who are unfamiliar with CVS, who may administer unproductive diagnostic tests, and ultimately neither properly diagnose the condition nor refer the patient to a specialist.[22,23] Not only does this result in repetitive avoidable costs but imposes stress on the patient and a longer, frustrating patient journey that likely worsens CVS symptoms and negatively impacts the quality of life.[22,24]

This study quantified the direct burden of HRU and costs attributable to CVS across all health care service settings. In the year before initial diagnosis, patients with CVS incurred more than $10,000 in excess median health care costs compared with non-CVS controls, representing a substantial cost burden associated with the CVS diagnostic journey. After the first confirmed CVS diagnosis, adjusted annualized costs were 4 times higher in CVS patients than their matched non-CVS controls, driven primarily by ER costs (6 times higher) and IP costs (12 times higher). These findings are consistent with prior literature documenting patterns of health care utilization in CVS patients.[1,23] Indeed, we found that CVS patients were twice as likely to visit the ER and 4.5 times more likely to have an IP admission compared with matched controls. Close to half (45%) of matched CVS patients had all-cause hospitalizations compared with only 10% of matched non-CVS controls, suggesting that CVS patients have a much poorer overall health with elevated risks for hospitalization. Thus, if CVS attacks can be potentially prevented or aborted via more effective OP care and therapies, the majority of CVS total care costs could be substantially decreased.

This study also revealed the first assessment of the impact of CVS on the number of OP visits and services and their associated costs. CVS patients were significantly more likely to use OP care. Particularly striking was the number of visits—67% more OP office visits and 139% more other OP services—when compared with matched controls. Nonetheless, the total proportion of excess costs incurred by OP care was smaller than ER and IP care, and OP prescription costs were the smallest component of total costs. Clearly, CVS imposes substantial excess HRU and costs on the US health care system. Our data also imply that improved CVS management, even if requiring increases in spending on prophylactic and abortive medications, could substantially reduce the cost burden by shifting more expensive emergent and IP care to OP visits. Furthermore, improvements in the clinical recognition of CVS should reduce the costs of unnecessary diagnostic testing in the OP settings.

Further bolstering these findings, the Medicaid analysis confirmed many similar trends found among the Commercial and Medicare patients. One notable difference in our findings was that Medicaid-insured CVS patients tended to receive more ER- and IP-based care than the CVS patients with Commercial or Medicare coverage. As has been demonstrated in other chronic conditions, this study may reflect the fact that Medicaid insurance status serves as a proxy for factors that drive more severe forms of CVS.[25] Alternatively, there could be disparities in CVS treatment that Medicaid patients receive. Regardless of mechanism, the results from the Medicaid analysis reinforce the notion that more robust management of CVS in the OP settings that prevents CVS attacks could save overall costs by preempting the need for ER and IP care.

Finally, our analysis revealed that several comorbid conditions are quite prevalent in CVS patients. First, mood disorders are common in both pediatric and adult patients. We found that diagnoses of anxiety and/or depression were comorbid in ~22% of pediatric patients and ~58% of adult patients. This finding reinforces the importance of psychosocial context in CVS and the concept that optimal CVS management should incorporate mental health interventions.[12] Second, we found that the prevalence of comorbid episodic disorders (eg, migraine or seizure) was much higher in CVS patients in comparison to their controls, no matter in pediatric or adult patients. Specifically, there was a ~6-fold higher rate of seizures in CVS patients than non-CVS patients. These findings lend support to the concept that CVS may share neurobiological mechanisms, such as increased neural excitability, with migraine and seizure disorders.[7,26] Lastly, our analysis found a notably high prevalence of cardiac conditions and risks (nearly 50%) in adult CVS patients. This latter issue has not been explored in the existing CVS literature and warrants further attention, given the implications for screening and prevention of heart diseases in this population. In addition, future research is warranted to describe what happened between CVS initial symptom onset and a confirmed diagnosis and to elaborate the burden of CVS diagnostic journey.

There are several limitations to this study, and the majority likely result in an underreporting of CVS-related HRU. First, as the primary purpose of administrative claims has been for reimbursement and not for research, symptoms experienced by CVS patients (eg, nausea, vomiting, or pain) tend to be underreported and not captured in billing codes. In addition, test procedure results are not recorded in claims data, and therefore, this information was unavailable for analysis. Underreporting could be further reflected in under or delayed diagnosis of CVS, as it takes time for providers to recognize a pattern of discrete vomiting

episodes in the prior year to inform the diagnosis of CVS based on the Rome IV criteria.[13] Similar to all other studies based on administrative claims data, misclassification of the study variables may occur, particularly among providers other than the primary treating physician, because of miscoding, undercoding, and data entry error. Although the awareness of CVS is increasing among providers, previous work has shown CVS to be underdiagnosed in both specialist and emergency settings.[6,23] Second, the study results were based on individuals with Commercial, Medicare supplemental, or Medicaid health insurance coverage and may not be generalizable to patients with other insurance types or no insurance. Third, the goal of propensity score matching CVS patients with non-CVS controls (ie, to achieve balanced comparisons) resulted in disproportionate removal of more severe CVS patients in cases as well as the disproportionate removal of non-CVS patients with fewer comorbidities in controls to achieve the balance in matching. Therefore, the direct burden of CVS estimated by cost difference between the 2 matched cohorts in this study is likely an underestimate of the true direct burden of CVS.

In summary, our study shows that patients with CVS have significantly higher health care resource utilization, particularly in ER and IP settings, compared with patients without this disorder, leading to much higher total annualized costs. CVS imposes an excessive burden on patients and the health care delivery system, but greater awareness of CVS among both health care providers and the broader population holds promise in reducing these burdens. Earlier diagnosis and more effective management and therapies could substantially improve not only CVS patient outcomes but also reduce health care costs.

Supplementary Materials

Material associated with this article can be found in the online version at https://doi.org/10.1016/j.gastha.2022.06.013.

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Authors' Contributions:
Y.J.Chen, X.Song, and I.Winer contributed to conception, design, and planning of the study, analysis of the data, interpretation of the results, and drafting of the article. P. Smith led acquisition, propensity score matching, and analysis of the data. S.Bhandari, C.Almansa, C.Richmond, T.Venkatesan, and D.J.Levinthal contributed to conception of the study and interpretation of the results, as well as critically reviewing the manuscript for important intellectual content.

Conflicts of Interest:
These authors disclose the following: Y.J.C., C.R., and C.A. are current or former employees of Takeda Development Center Americas, Inc, and may own stock and/or options. X.S., I.W., and P.S. are used by IBM Watson Health, which received funding from Takeda to conduct this study. D.J.L. and T.V. are consultants for Takeda and Alexza Pharmaceuticals. The remaining authors disclose no conflicts.

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Ethical Statement:
The corresponding author, on behalf of all authors, jointly and severally, certifies that their institution has approved the protocol for any investigation involving humans or animals and that all experimentation was conducted in conformity with ethical and humane principles of research.

Data Transparency Statement:
Data are owned by IBM Watson Health and can be accessed through a licensing agreement via https://www.ibm.com/products/marketscan-research-databases.