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ORIGINAL RESEARCH—BASIC

Productivity Loss and Indirect Burden of Cyclic Vomiting Syndrome in the United States

Xue Song,[1,*] Yaozhu J. Chen,[2] Allison Perry,[1] Jerry Kagan,[1] Sanjay Bhandari,[3] Cristina Almansa,[2] Camilla Richmond,[2] David J. Levinthal,[4] and Thangam Venkatesan[3,‡]

[1]*IBM Watson Health, Cambridge, Massachusetts;* [2]*Takeda Development Center Americas, Inc., Cambridge, Massachusetts;* [3]*Division of Gastroenterology and Hepatology, Medical College of Wisconsin, Milwaukee, Wisconsin; and* [4]*Division of Gastroenterology and Hepatology and Nutrition, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania*

BACKGROUND AND AIMS: To quantify the indirect burden of cyclic vomiting syndrome (CVS), we assessed work-related productivity loss in patients with CVS and caregivers using large-sized databases in the United States. **METHODS:** Patients aged 18–64 years with full-time employment in MarketScan Commercial and Health and Productivity Management Databases were selected if they had ≥1 inpatient or ≥2 outpatient claims for CVS between 2008 and 2018 and continuous enrollment of ≥6 months before and ≥3 months after the initial CVS diagnosis. CVS caregivers were adults with full-time employment and also having dependent(s) with CVS. Propensity scores via multivariable regressions were used to match patients with CVS and their caregivers to non-CVS controls. Productivity loss was assessed by short-term disability (STD) and absenteeism (ABS) days, and the associated costs were also calculated. Differences between the matched cohorts were regarded as the burden attributable to CVS. **RESULTS:** Patients with CVS had longer annualized STD (21.1 vs 7.0, $P < .001$) and ABS days (26.4 vs 22.8, $P < .05$) than their matched controls. CVS caregivers had more annualized STD (3.9 vs 2.6, $P < .001$) and ABS days (20.9 vs 19.5, $P < .05$) than controls. Productivity loss costs for STD or ABS days were greater for patients with CVS and caregivers. Annualized health-care resource utilization (inpatient, emergency room, outpatient) was 5.2–6.0 times higher in patients with CVS ($P < .001$). **CONCLUSION:** CVS is associated with higher productivity loss due to STD/ABS and, therefore, greater indirect costs for patients and caregivers. Further research is needed to assess the full societal burden of CVS. More effective interventions may reduce the disease burden.

Keywords: Cyclic Vomiting Syndrome; Productivity Loss; Indirect Costs; Patient; Caregiver

Introduction

Cyclic vomiting syndrome (CVS) is a chronic disorder of gut-brain interaction, characterized by episodic nausea and repetitive vomiting.[1] It is estimated to affect ~2% of children, with a similar prevalence in adults.[2–4] The pathogenesis of CVS is unknown and appears to be multifactorial, with several potential disease mechanisms.[5,6] This condition is further complicated by comorbid conditions including anxiety, depression, autonomic dysfunction, migraine, and the need for management with lifestyle interventions, supportive care, and abortive and/or prophylactic medications.[7,8]

Several published studies in patients with CVS have noted functional disability, decreased quality of life, and increased health-care costs.[8–15] CVS causes substantial morbidity, with half of the patients requiring emergency room (ER) care and intravenous therapy or inpatient admissions, leading to significant time lost from work or school.[16,17] Such episodic incapacity in adult patients with CVS has led to frequent work absences, delays in education, job loss, and disability.[15,17] Studies on CVS in children estimate an average loss of school days per year between 20 and 24 due to ER visits and scheduling of repetitive testing.[16–18] Because of these repeated school absences, many children have required home tutoring or home schooling, which places additional burdens on their caregivers and is negatively associated with parent emotional functioning.[19] One study found that anxiety and missing school days in children living with CVS strongly predicted lower family health-related quality of life, affecting "family physical functioning, family communication, and family daily activities."[19]

Despite the recognition that patients with CVS and caregivers experience substantial work-related productivity

*Dr Song was employed at IBM Watson Health at the time this study was executed. She is currently employed at Regeneron, Tarrytown, NY, USA.
‡Dr Venkatesan was employed at the Medical College of Wisconsin at the time this study was executed. She is currently employed at the Ohio State Wexner Medical Center, Columbus, OH, USA.

Abbreviations used in this paper: ABS, absenteeism; CVS, cyclic vomiting syndrome; DCI, Deyo-Charlson Comorbidity Index; ER, emergency room; FTE, full-time employee; HRU, health-care resource utilization; HPM, Health Productivity Management; ICD-9, International Classification of Diseases-Ninth Revision; ICD-10, International Classification of Diseases-Tenth Revision; STD, short-term disability.

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loss and associated costs, the extent of this impact has not been well assessed and quantified. To evaluate the magnitude of indirect burden of CVS, this study assessed work-related productivity loss in adults with CVS and their caregivers using large-scaled claims and productivity databases in the United States.

Methods

Data Sources

This observational retrospective cohort analysis utilized deidentified US administrative claims data covering from July 1, 2007, to December 31, 2018, (study window) in 2 IBM MarketScan Databases: Commercial Claims and Encounters (Commercial) Database and the Health Productivity and Management (HPM) Database. The Commercial Database contains data on the inpatient, outpatient, and outpatient prescription drug use of employees and their dependents, covered under a variety of fee-for-service and managed care health plans. The HPM Database contains lost work days, short-term disability (STD), long-term disability, and workers' compensation data from a subset of MarketScan employer clients. Data elements for a same employee can be fully linked in both databases.

All study data were obtained and classified by International Classification of Diseases, 9th and 10th Revision, Clinical Modification (ICD-9-CM and ICD-10-CM) codes, Current Procedural Terminology 4th edition codes, Healthcare Common Procedure Coding System codes, and National Drug Codes.

Patient Selection: CVS Patients vs non-CVS Controls

Data of patients with ≥1 inpatient or ≥2 outpatient claims, on different dates, with a diagnosis for CVS in any position (ICD-9-CM: 536.2; ICD-10-CM: G43.A0, G43.A1) between January 1, 2008, and December 31, 2018, (patient selection window) were extracted. Index date was the date of first CVS claim in the patient selection window. We included patients who were aged 18–64 years on index date, as active full-time employees (FTEs) (ie, not dependents), and having continuous enrollment with medical and prescription coverages for ≥6 months before the index date (preindex or baseline period) and ≥3 months after the index date (postindex or follow-up period). To ensure that selected patients were newly diagnosed with CVS during the study period, those with any diagnosis claim of CVS or vomiting during the preindex period were excluded. Patients with claims for pregnancy or birth delivery during the study window were also excluded. Two subcohorts of patients with CVS were created: one consisting of patients with work absenteeism (ABS) eligibility, and the other with STD eligibility. We included patients who had ≥6-month preindex and ≥3-month postindex ABS or STD eligibility in each subcohort, respectively (Figure 1). Both subcohorts were followed up for variable lengths of time, until the end of their eligibility with employer-based work absence or STD benefits, disenrollment in the databases, or the end of study window (December 31, 2018), whichever is earlier.

A non-CVS cohort was selected from a 10% random sample of patients without CVS in the linked Commercial and HPM Databases, with ≥1 year of benefit eligibility for absence or STD between January 1, 2008, and December 31, 2018. Index date was randomly assigned to match the distribution of index dates in the CVS cohorts. Controls were required to meet all inclusion and exclusion criteria of patients with CVS.

Propensity score matching was implemented for each CVS patient to up to 3 corresponding non-CVS controls, based on their baseline demographics, Deyo-Charlson Comorbidity Index,[20] clinical characteristics, and baseline work absence or STD days. The balances of postmatching cohorts were evaluated using standardized mean differences, with a threshold of its absolute value <10%, set *a priori*, to indicate balance between cohorts.

Patient Selection: CVS Caregivers vs non-CVS Controls

Caregivers of patients with CVS were also identified: aged 18–64 years, with FTE and benefit eligibility for absence or STD, and having a dependent (ie, child or spouse) who had ≥1 inpatient or ≥2 nondiagnostic outpatient claims for CVS in the selection window but no claim in the preindex period. Index date was the date of first documented CVS diagnosis. We included caregivers who had ≥6 months of preindex and ≥3 months of postindex continuous enrollment of medical and pharmacy benefits. Caregivers were excluded from analysis if they had any claims for CVS, pregnancy, or delivery during the study period. Caregiver controls are those who had no CVS diagnosis, pregnancy or delivery, and no family members with CVS (Figure A1). CVS caregivers and their non-CVS controls were matched by propensity scores from multivariable regressions, which control for baseline characteristics including demographics, number of family members, and baseline lost workdays. Each CVS caregiver was matched with up to 3 controls, with the same standardized mean difference threshold to assess balance level.

Baseline Characteristics

For patients with CVS and controls, we assessed their baseline demographic characteristics, including age, sex, geographic region, population density, and insurance plan type on the index date. Duration of follow-up was also captured. We measured baseline clinical characteristics during the 6-month preindex period and included comorbidities comprising the Deyo-Charlson Comorbidity Index, as well as conditions identified in the literature as having a higher burden in patients with CVS: 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, and seizure. For the CVS caregiver analysis, demographic characteristics, including age, sex, geographic region, population density, and insurance plan type were assessed on the index date. Number of family members was also recorded.

Baseline Productivity Loss

We recorded the number of lost workdays or STD days for patients with CVS, their caregivers, and their corresponding controls during the preindex period.

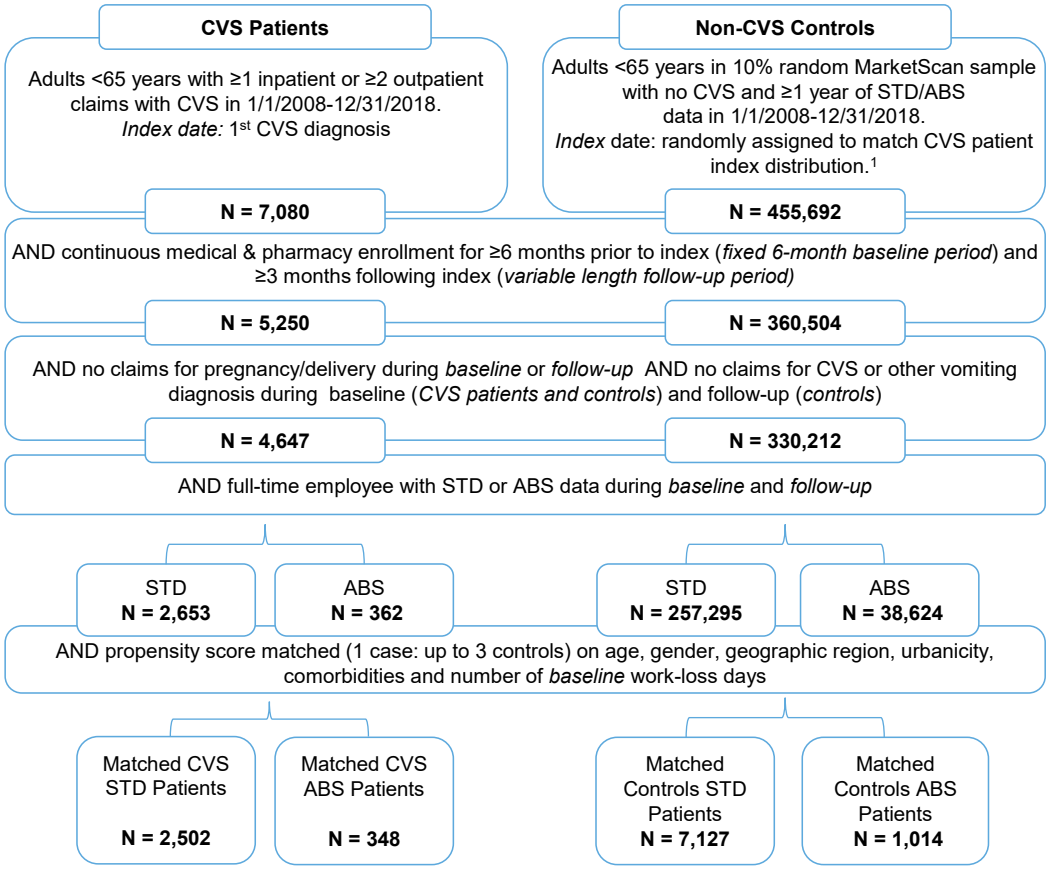

Figure 1. Cyclic vomiting syndrome (CVS) patient attrition. [1]For each patient with CVS, the number of days between the *index date* and January 1, 2008, was calculated and referred to as the "interval pool." For each control patient, a number was randomly drawn from that interval pool, and the *index date* equals that number plus January 1, 2008.

Productivity Loss and Indirect Costs in the Follow-up Period

Number and proportion of patients with an absence or STD claim were reported during the follow-up period. We annualized number of lost workdays and associated costs (per-patient per-year) to account for variable length of follow-up period. Indirect costs associated with ABS were calculated as number of absent days multiplied by a wage constant of $177.2 per day (ie, $22.15 per hour), which is an equivalent to the median hourly rate for the employed full-time US workers in 2018.[21] Indirect costs associated with STD were calculated using the same wage constant but multiplied by a discounting factor of 60%, which is the typical percentage of an employee's income that STD policies compensate for.

All-Cause Health-Care Resource Utilization in the Follow-up Period for Patients With CVS and Controls

Among the patients with CVS and their matched controls included in this study, we also compared their all-cause health-care resource utilization (HRU), including ER visits, inpatient admissions, outpatient services (such as physician office visits and other outpatient visits), and outpatient pharmacy claims. The proportion of patients with any claim as well as the number of annualized visits or services in each care setting were captured; in addition, length of stay in days per admission was also reported for the inpatient setting. These assessments on HRU provide additional data to inform to what extent the impact of CVS on ABS/STD may relate to the elevated use of medical services.

Statistical Analysis

For all baseline characteristics, frequencies and percentages were reported for categorical variables, and mean and standard deviation were reported for continuous variables. The alpha level for all statistical tests was 0.05. All analyses were conducted using WPS version 4.1 (World Programming, United Kingdom). Data are owned by IBM Watson Health and can be accessed through a licensing agreement https://www.ibm.com/products/marketscan-research-databases.

Results

Patients With CVS vs non-CVS: Demographics and Clinical Characteristics

A total of 7080 patients with CVS were identified (Figure 1). After applying study selection criteria and

Table 1. Matched CVS Patient Demographics,[a] Baseline Clinical Characteristics, and Productivity Loss[b]

	Short-term disability (STD)			Absenteeism (ABS)		
Characteristics	CVS patients N = 2502	Non-CVS controls N = 7127	% Standardized difference	CVS patients N = 348	Non-CVS controls N = 1014	% Standardized difference
Age (mean, SD)	43.7 ± 10.9	44.9 ± 10.9	10.69	46.0 ± 11.2	45.7 ± 11.1	2.23
Age group (N, %)						
18–30	370 (14.8)	941 (13.2)	4.57	43 (12.4)	123 (12.1)	0.69
31–44	905 (36.2)	2415 (33.9)	4.79	104 (29.9)	309 (30.5)	1.28
45–54	729 (29.1)	2151 (30.2)	2.29	106 (30.5)	322 (31.8)	2.80
55–64	498 (19.9)	1620 (22.7)	6.91	95 (27.3)	260 (25.6)	3.76
Sex (N, %)						
Male	1086 (43.4)	3069 (43.1)	0.7	199 (57.2)	555 (54.7)	4.9
Female	1416 (56.6)	4058 (56.9)	0.7	149 (42.8)	459 (45.3)	4.9
Days of follow-up (mean, SD)[c]	874.9 (729.5)	876.3 (669.0)	0.20	1093.3 (886.9)	1179.8 (837.1)	10.03
Median	663.5 (0.0)	687.0 (0.0)		846.5 (0.0)	1058.5 (0.0)	
DCI (mean, SD)	1.0 (2.0)	0.9 (1.8)	5.46	1.1 (2.1)	0.9 (1.9)	8.70
Baseline conditions (N, %)[d,e]						
Abdominal pain	954 (38.1)	2570 (36.1)	4.29	109 (31.3)	299 (29.5)	3.99
Anxiety	314 (12.6)	926 (13.0)	1.33	39 (11.2)	115 (11.3)	0.42
Panic disorder	37 (1.5)	97 (1.4)	1.00	5 (1.4)	7 (0.7)	7.28
Cardiac conditions and risks[f]	902 (36.1)	2585 (36.3)	0.46	128 (36.8)	366 (36.1)	1.43
Depression	289 (11.6)	862 (12.1)	1.69	37 (10.6)	117 (11.5)	2.89
Fibromyalgia	78 (3.1)	217 (3.0)	0.42	9 (2.6)	25 (2.5)	0.77
GERD	441 (17.6)	1248 (17.5)	0.30	45 (12.9)	136 (13.4)	1.42
Gastroparesis	44 (1.8)	40 (0.6)	11.20	3 (0.9)	4 (0.4)	5.92
Irritable bowel syndrome (IBS)	49 (2.0)	128 (1.8)	1.20	4 (1.1)	15 (1.5)	2.90
Migraine	174 (7.0)	476 (6.7)	1.09	24 (6.9)	76 (7.5)	2.32
Nausea	220 (8.8)	476 (6.7)	7.92	22 (6.3)	49 (4.8)	6.49
Geographic region (N, %)						
Northeast	286 (11.4)	895 (12.6)	3.5	39 (11.2)	123 (12.1)	2.9
North Central	605 (24.2)	1669 (23.4)	1.8	70 (20.1)	190 (18.7)	3.5
South	1137 (45.4)	3167 (44.4)	2.0	121 (34.8)	343 (33.8)	2.0
West	473 (18.9)	1383 (19.4)	1.3	117 (33.6)	355 (35.0)	2.9
Unknown	1 (0.0)	13 (0.2)	4.3	1 (0.3)	3 (0.3)	0.2
Baseline productivity loss[b]						
Days with STD/ABS (mean, SD)	7.3 (21.0)	6.0 (20.3)	6.6	15.2 (14.5)	15.0 (14.2)	1.6

DCI, Deyo-Charlson Comorbidity Index; GERD, gastroesophageal reflux disease.
[a]Demographics were captured on *index*.
[b]Baseline clinical characteristics and productivity loss were captured during the 6-month preindex period.
[c]Length of follow-up comprises the time from *index* until the end of follow-up due to end of eligibility, enrollment, or study period (December 31, 2018).
[d]Comorbid conditions identified in the literature as having a high burden in CVS patients.[6,10,11]
[e]Additional baseline comorbidities captured include autonomic dysfunction, cannabis abuse/use, and seizure, which occurred at a rate of less than 2.0%.
[f]Defined as acute myocarditis, acute pericarditis, arrhythmias (including atrial fibrillation and flutter), 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 lymph nodes, heart failure, hypertension, hypotension, ischemic heart disease, paroxysmal tachycardia, and pulmonary heart diseases.

propensity score matching process, 2502 CVS cases and 7127 controls were included in the STD analysis, and 348 CVS cases and 1014 controls were included in the ABS analysis (Figure 1).

A majority of the patients in CVS case and matched non-CVS control cohorts were female (56.6%–56.9% female), while more men were seen in the final ABS cohorts (42.8%–45.3% female) (Table 1). The STD and ABS cohorts were fairly similar in age (mean 43.7–46.0 years) and prevalence of other digestive problems, such as abdominal pain (29.5%–38.1%) and gastroesophageal reflux disease (12.9%–17.6%). Also, prevalent comorbidities among the patients in CVS cohorts and their matched non-CVS controls include cardiac conditions/risks (36.1%–36.8%), anxiety (11.2%–13.0%), and depression (10.6%–12.1%). In the STD analysis, close to half of the cases and controls were from

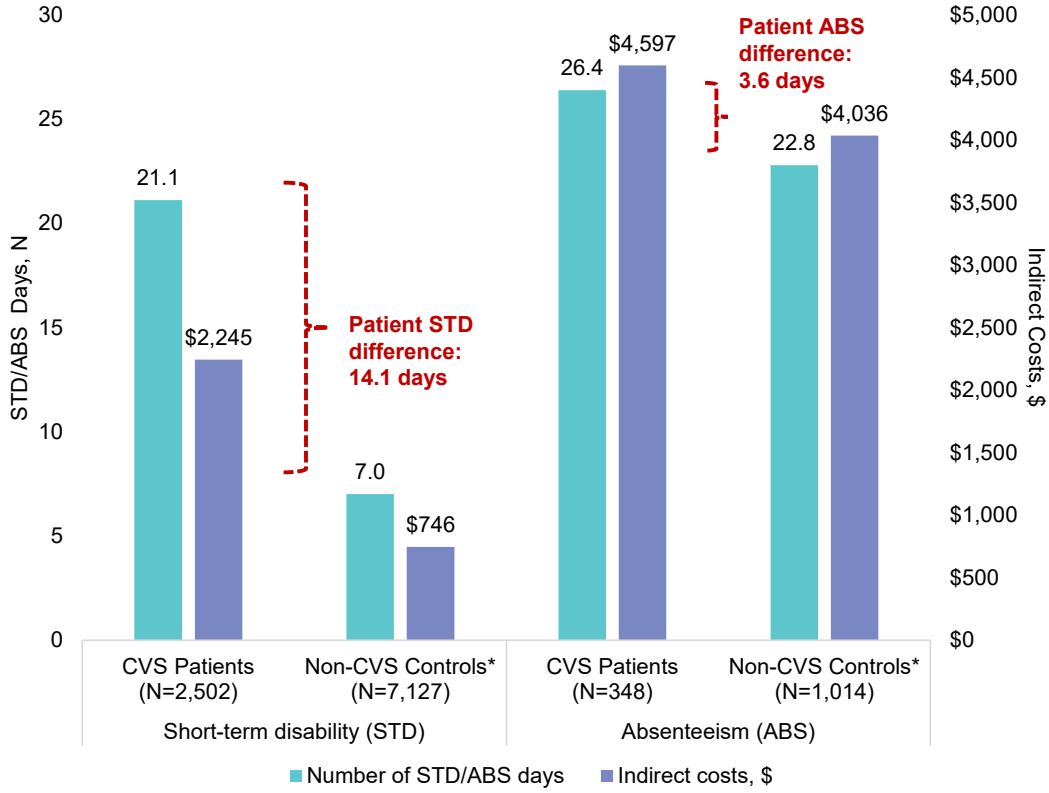

Figure 2. Patient annualized number of short-term disability (STD) and absenteeism (ABS) days and related costs during follow-up. Costs for STD = (number of days lost) × (2018 daily wage of $106.3 [which is 60% of the 2018 US national median daily wage $177.2] for STD). Costs for ABS = (number of days lost) × (2018 US national median daily wage of $177.2 for ABS); *$P < .001$.

the South region (44.4%–45.4%); while in the ABS analysis, more patients were from South or West regions (33.8%–34.8% South, 33.6%–35.0% West). In addition, the lengths of follow-up in databases were on average 2.4 years for STD and 3.1 years for ABS.

Patients With CVS and non-CVS: Annualized Productivity Loss and Related Costs

During variable-length follow-up period, a significantly greater proportion of patients with CVS used STD time during follow-up than controls (41.5% vs 18.2%, $P < .001$), whereas a comparable proportion of cases and controls used ABS time (73.0% vs 76.6%, $P = .172$). Patients with CVS used 3 times greater average number of annualized STD days (21.1 vs 7.0) and incurred significantly greater corresponding indirect costs ($2245.06 vs $745.60) than controls ($P < .001$) (Figure 2). Patients with CVS also had a significantly greater number of annualized ABS days (25.9 vs 22.8) and associated costs ($4597.49 vs $4036.43) than controls ($P < .05$).

Patients With CVS vs non-CVS: Annualized All-Cause HRU

Table 2 presents annualized all-cause HRU during the follow-up period for matched patients with CVS and non-CVS controls in the STD and ABS subcohorts. Across all service categories, HRU was higher for patients with CVS than for non-CVS controls (Table 2). Specifically, the proportion of patients with CVS with an inpatient admission was between 5.2 and 6.0 times higher than controls, with a prevalence of 70.5% in cases and 11.7% in controls in the STD subcohort and 68.4% vs 13.0% in the ABS subcohort ($P < .001$). The average number of postindex inpatient admissions among patients with CVS was 12 times higher than that in controls although mean lengths of stay per admission were comparable. This trend held when comparing mean annual ER visits, outpatient services, and prescription fills (all $P < .001$).

Caregiver CVS vs non-CVS: Demographics and Clinical Characteristics

A total of 92,509 adult family members of patients with CVS were identified (Figure A1). After the employment of selection criteria and propensity score matching, 7342 CVS caregivers and 22,013 non-CVS caregiver controls were included for the STD analysis, and 1318 CVS caregivers and 3942 non-CVS caregiver controls were captured for the ABS analysis.

The mean ages of CVS caregivers and their matched non-CVS controls were between 43.9 and 46.1 years, and those

Table 2. Annualized All-Cause Health-care Utilization in Follow-Up for Matched CVS and Non-CVS Patients

	Short-term disability (STD)			Absenteeism (ABS)		
	CVS patients	Non-CVS controls		CVS patients	Non-CVS controls	
Characteristics	N = 2502	N = 7127	*P* value	N = 348	N = 1014	*P* value
Inpatient admissions						
Patients with an admission (N, %)	1764 (70.5)	836 (11.7)	<.001	238 (68.4)	132 (13.0)	<.001
Avg. length of stay per admission, d (mean ± SD)	3.93 ± 3.93	3.86 ± 4.45	.48	4.08 ± 3.58	3.75 ± 3.64	.14
Number of admissions, annualized (mean ± SD)	1.20 ± 1.98	0.10 ± 0.54	<.001	1.17 ± 2.17	0.09 ± 0.44	<.001
Emergency room (ER) visits						
Patients with an ER visit (N, %)	1762 (70.4)	2503 (35.1)	<.001	243 (69.8)	392 (38.7)	<.001
Number of ER visits, annualized (mean ± SD)	1.92 ± 3.48	0.40 ± 1.17	<.001	1.34 ± 2.16	0.40 ± 1.30	<.001
Outpatient services						
Outpatient office visits						
Patients with an office visit (N, %)	2443 (97.6)	6658 (93.4)	<.001	345 (99.1)	957 (94.4)	<.001
Number of office visits, annualized (mean ± SD)	287.13 ± 347.35	187.41 ± 244.11	<.001	341.10 ± 407.45	224.32 ± 243.43	<.001
Other outpatient services						
Patients with other outpatient services (N, %)	2476 (99.0)	6636 (93.1)	<.001	346 (99.4)	950 (93.7)	<.001
Number of other outpatient services, annualized (mean ± SD)	84.82 ± 115.74	37.11 ± 55.80	<.001	84.52 ± 128.53	37.31 ± 57.53	<.001
Outpatient pharmacy						
Patients with an outpatient prescription (N, %)	2455 (98.1)	6602 (92.6)	<.001	338 (97.1)	949 (93.6)	.01
Number of outpatient prescriptions, annualized (mean ± SD)	33.81 ± 30.17	20.66 ± 21.80	<.001	33.73 ± 28.96	22.25 ± 24.88	<.001

of their dependents with CVS were between 23.5 and 25.8 years on average (Table 3). Most of the CVS caregivers and non-CVS controls included in this study were male (72.2%–82.9%), with a mean of 2.6–2.7 family members per caregiver. Caregivers and controls were followed up for an average of 2.8–4.0 years.

Caregiver CVS vs non-CVS: Annualized Productivity Loss and Related Costs

During the follow-up, more CVS caregivers used STD time than their controls (16.1% vs 10.3%, $P < .001$), whereas the proportions with ABS time use were more comparable between CVS caregivers and non-CVS controls (75.2% vs 74.7%, $P = .741$). In comparison to the matched non-CVS controls, CVS caregivers had a higher number of STD and ABS days (Figure 3), and consequently, their annualized productivity loss in workdays and associated indirect costs were 1.5 times higher for STD (3.9 vs 2.6 days, $410.04 vs $273.60; $P < .001$) and 1.1 times higher for ABS (20.9 vs 19.5, $3700.20 vs $3460.92; $P < .05$).

Conclusions

While the previous literature established that CVS imposes significant burden due to health-care use and costs, increased work and school ABS, as well as reduced quality of life, these prior studies also had limitations, such as a small sample size, reliance on survey data, or restriction to specific settings of care.[9,10,12,13,19,22–25] Our study methods leveraged population-level administrative databases to quantify the indirect burden of work productivity loss and associated costs which are attributable to CVS. The results of the current study clearly demonstrate that CVS is associated with significant productivity loss and a substantial indirect burden in the United States.

We found that indirect costs are an important component of the economic burden of CVS. In our study, newly diagnosed patients had an annualized average of 14.1 more days than non-CVS controls for STD (resulting in 3 times higher costs, $P < .001$) and 3.6 days more for ABS (leading to 1.1 times higher costs, $P < .05$). Increased workday loss in patients with CVS may relate to their higher use of health-care resource, primarily due to ER and inpatient care. We found that patients with CVS were 5.2–6.0 times more likely to have an inpatient admission (70.5% vs 11.7% in STD and 68.4% vs 13.0% in ABS, $P < .001$), and their average number of annualized inpatient admissions were 12 times higher than those of controls (1.20 vs 0.10 for STD and 1.17 vs 0.09 for ABS, $P < .001$).

Productivity loss patterns in caregivers were similar. CVS caregivers used, on average, 1.3 more STD days and

Table 3. Matched Caregiver Demographics[a] and Productivity Loss

	Short-term disability (STD)			Absenteeism (ABS)		
Characteristics	Caregivers N = 7342	Caregiver controls N = 22,013	% Standardized difference	Caregivers N = 1318	Caregiver controls N = 3942	% Standardized difference
Age (mean, SD)	43.9 (9.1)	44.1 (9.0)	2.54	45.5 (8.9)	46.1 (9.0)	5.84
Age group (N, %)						
18–30	566 (7.7)	1643 (7.5)	0.93	80 (6.1)	203 (5.1)	4.00
31–44	3289 (44.8)	9856 (44.8)	0.05	493 (37.4)	1416 (35.9)	3.08
45–54	2458 (33.5)	7365 (33.5)	0.04	520 (39.5)	1578 (40.0)	1.18
55–64	1029 (14.0)	3149 (14.3)	0.83	225 (17.1)	745 (18.9)	4.76
Sex (N, %)						
Male	5300 (72.2)	16,026 (72.8)	1.4	1092 (82.9)	3268 (82.9)	0.1
Days of follow-up (mean, SD)[c]	1158.7 (851.3)	1037.2 (737.5)	NA	1462.4 (973.5)	1272.1 (848.0)	NA
Median	975.0	884.0		1326.0	1205.5	
No. of family members (mean, SD)	2.7 (1.3)	2.7 (1.3)	0.23	2.6 (1.3)	2.6 (1.3)	0.84
Median	3.0	3.0		3.0	3.0	
CVS patient characteristics[d]						
Age (mean, SD)	23.5 (18.1)	—	—	25.8 (18.1)	—	—
Sex (N, %)						
Male	2706 (36.9)	—	—	411 (31.2)	—	—
Relationship to caregiver (N, %)						
Spouse	2615 (35.6)	—	—	514 (39.0)	—	—
Child/Other	4727 (64.4)	—	—	804 (61.0)	—	—
Baseline productivity loss[b]						
Days with STD/ABS (mean, SD)	1.9 (10.7)	1.6 (10.5)	2.6	12.2 (10.5)	11.9 (10.7)	2.9

[a]Demographics were captured on *index*.
[b]Baseline clinical characteristics and productivity loss were captured during the 6-mo preindex period.
[c]Length of follow-up comprises the time from *index* until the end of follow-up due to end of eligibility, enrollment, or study period (December 31, 2018).
[d]Relationship to caregiver also evaluated employee and dependent relation unknown, which had an N (%) of 0 for both STD and ABS CVS caregiver cohorts.

were absent for 1.4 more days from work, which translated into an annual average of 1.5 times higher indirect costs in STD ($410 vs $274, $P < .001$) and 1.1 times higher costs in ABS ($3700 vs $3,461, $P < .05$). These results in combination suggest a substantial productivity loss due to CVS, which imposes an economic burden not only for patients and their caregivers but to society at large.

This study has several notable strengths. The data source was based on national databases from many large employers and represents a broad range of insurance plans, which result in large sample sizes that are much larger than those used in the previous CVS literature. As the data are suitable to support the estimations at population level, this study is among the first population-level analyses to quantify the indirect burden of CVS on patients and caregivers. Also, this study has the strength in design to quantify the indirect burden of CVS based on the differences of all-cause ABS and STD between CVS cases and non-CVS controls who were matched via propensity scores based on patients' baseline characteristics.

However, several limitations need to be considered when interpreting the results. First, like in any claims-based study, the databases were developed for administrative purposes rather than for research and, thus, are subject to coding misclassifications and data entry errors. Additionally, prior to 2016, there was no ICD diagnosis code specific to CVS. To address this issue, our analysis focused entirely on incident cases of CVS, as the additional restrictions allowed us to more specifically identify CVS patients. As additional time elapses, future analysis should be performed using only post-2016 data in which longstanding CVS patients may be identified. Furthermore, future work should be performed to validate via chart review the ICD coding for CVS in a linked EMR-claims database. The reliance of claims databases on ICD coding makes the data readily accessible as compared to Electronic Medical Records (EMR) data. Therefore, despite its limitations, claims databases provide a strong framework for these future analyses.

Second, the study focused on full-time employment and did not include other employment status (eg, part time, transition from full time to part time, or in early retirement) or no employment (eg, homemaker) due to data availability. Therefore, this study tends to undercapture employment types associated with productivity loss. Additionally, CVS is known to be more common in female patients, yet in this study, we see a higher proportion of male patients in the

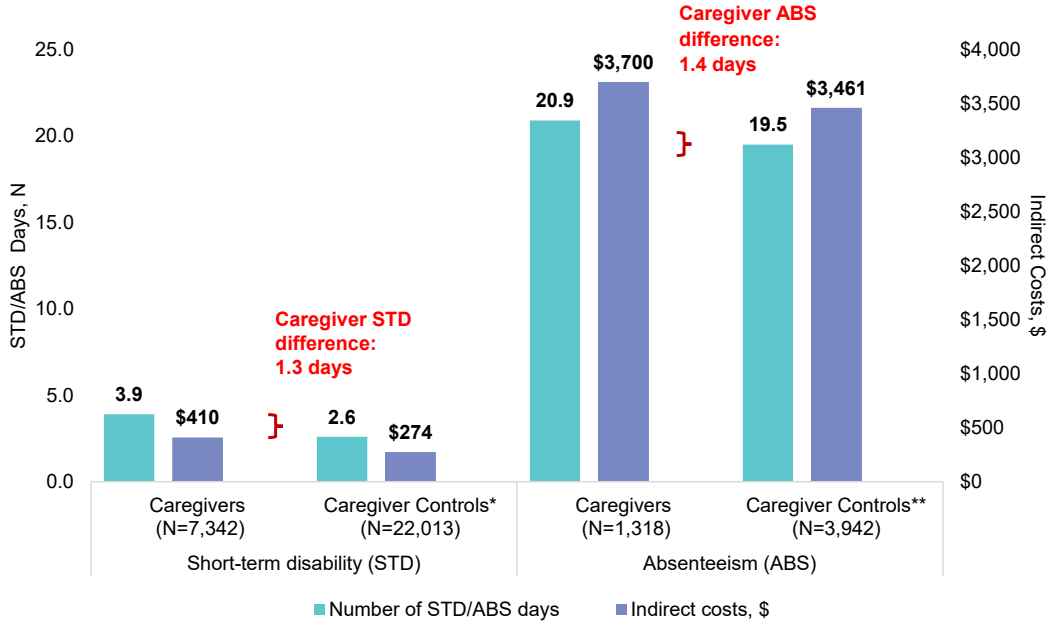

Figure 3. Caregiver annualized number of short-term disability (STD) and absenteeism (ABS) days and related costs during follow-up. Costs for STD = (number of days lost) × (2018 daily wage of $106.3 [which is 60% of the 2018 US national median daily wage $177.2] for STD). Costs for ABS = (number of days lost) × (2018 US national median daily wage of $177.2 for ABS); *$P < .01$; **$P < .05$.

ABS analysis. This may be associated with a higher proportion of men in the underlying HPM Database, reflecting the sex distribution of FTEs in the United States.[5,26] With regard to the sex distribution in the caregiver burden analysis, women are more likely than men to drop out of the work force to take care of a sick family member,[27] which was not captured by the HPM Database, leading to an underestimation of the indirect burden of CVS if family member caregivers were not FTEs at the same time. Furthermore, the approach of propensity score matching may underestimate the attributable productivity loss, as the cohort-matching process excluded the most severe patients with CVS who may not find a well-matched non-CVS control. On the other hand, the matched non-CVS controls tend to be sicker than the general population, which may further narrow the difference between CVS and controls and indicate that the burden estimates from this study are conservative. In addition, it often takes months or even years for a CVS patient to be diagnosed, so this study focusing on the newly diagnosed patients does not reflect the productivity loss prior to the first diagnosis of CVS. Another type of productivity loss, also underestimated in this study due to lack of data, is presenteeism (ie, being at work while ill and performing at a lower level than usual). However, since STD benefits are typically used for one's own medical condition, rather than caring for a sick family member, the STD days of caregivers may overestimate the impact of CVS on indirect costs of caregivers. Finally, our estimates on CVS indirect burden reflect those in a commercially insured population with full-time employment, which may not be generalizable to those with other or no insurance, whose employers do not provide STD or ABS benefits, part-time employees, or homemakers.

Patients with CVS and their caregivers experience substantial productivity loss with economic implications that extend well beyond the direct costs for medical services and treatment. This study adds quantifiable evidence on the impact of CVS and highlights the critical need for new and more-effective treatment options and management strategies. These may reduce the burden due to CVS on patients, their caregivers, employers, and society at large.

Supplementary Materials

Material associated with this article can be found in the online version at https://doi.org/10.1016/j.gastha.2022.06.017.

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Correspondence:
Address correspondence to: Thangam Venkatesan, MD, The Ohio State University College of Medicine, 395 W 12th Avenue, Columbus, Ohio 43210. e-mail: Thangam.Venkatesan@osumc.edu.

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Xue Song, Yaozhu J. Chen, and Allison Perry contributed to conception, design, and planning of the study, analysis of the data, interpretation of the results, and drafting of the manuscript. Jerry Kagan led acquisition and analysis of the data. Sanjay Bhandari, Cristina Almansa, Camilla Richmond, David J. Levinthal, and Thangam Venkatesan contributed to conception of the study and interpretation of the results, as well as critically reviewing the manuscript for important intellectual content. Propensity score matching was provided by David Smith of IBM Watson Health.

Conflicts of Interest:
These authors disclose the following: Yaozhu J. Chen, Camilla Richmond, and Cristina Almansa are current or former employees of Takeda Development Center Americas, Inc and may own stock and/or options. Cristina Almansa is a current employee of and owns stocks in Ironwood Pharmaceuticals. Xue Song, Allison Perry, and Jerry Kagan are employed by IBM Watson Health, which received funding from Takeda to conduct this study. David J. Levinthal and Thangam Venkatesan are consultants for Takeda and Alexza Pharmaceuticals. The remaining author has no disclosures.

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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 https://www.ibm.com/products/marketscan-research-databases.