Wilson's Disease: An Analysis of Health Care Use and Cost Burden of Commercially Insured Adults in the United States

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The economic and health care use burdens of Wilson's disease (WD) are unknown. In this study, we aimed to quantify this health care resource use and economic burden. We performed a retrospective case-control analysis of individuals in the Truven Health MarketScan Commercial Claims database (2007-2017). Using propensity scores, 424 WD cases were matched 1:1 to chronic liver disease (CLD) controls without WD. Total and service-specific parameters, expressed in monthly averages, were quantified for the 6-month pre-WD diagnosis versus the 12-month period after diagnosis. Wilcoxon signed-rank tests and McNemar tests were used to examine incremental differences in burden between cases and controls. Adjusted multivariable generalized linear regression models were used to compare health care burdens. Relative to the 6-month pre-WD diagnosis, the 12 months after diagnosis had more claims per patient (2.87 vs. 3.35; $P < 0.0001$) and increased per patient health care costs (US $2,089 vs. US $3,887; $P < 0.0001$). WD cases incurred US $1,908 more in total unadjusted costs compared to controls in the 12-month postindex date monthly averages. The increase in claims was primarily due to outpatient visits (1.62 vs. 1.82) and pharmaceutical claims (1.11 vs. 1.37). Cases also had higher health care costs for inpatient admissions (US $559 vs. US $1,264), outpatient visits (US $770 vs. US $1,037), and pharmaceutical claims (US $686 vs. US $1,489). *Conclusion:* WD is associated with significant health care cost and use burdens driven by increased inpatient admissions, outpatient visits, and pharmaceutical claims. (*Hepatology Communications* 2022;6:389-398).

Discovered in 1912 by Samuel Alexander Kinnier Wilson, Wilson's disease (WD), also known as hepatolenticular degeneration, is an autosomal recessive disorder of copper metabolism caused by mutations in the adenosine triphosphate 7B (*ATP7B*) gene.[1,2] More than 600 pathogenic variants in *ATP7B* have been identified, with single nucleotide missense and nonsense mutations being the most common mutations.[3] Although still considered a rare disease, WD has a gene frequency of 1 in 90-150 individuals and an incidence rate as high as 1 in 30,000.[4,5] Recent studies suggest the prevalence to be closer to 1 in 7,000 individuals afflicted and a global genetic prevalence at birth of 13.9 to 15.4 per 100,000.[6,7]

Previous studies have shown a mean delay from symptom onset to diagnosis of WD of 12-36 months,

with a diagnosis being made with less delay in patients with liver dysfunction presenting at a younger age compared to those presenting with neurologic symptoms.[2,8-12] Treatment is based on the removal of copper by chelating agents, such as D-penicillamine, trientine, and tetra-thiomolybdate, or blocking intestinal copper absorption with zinc salts.[1,5] The annual costs for these medications have been extraordinarily high, although generic versions are beginning to mitigate this expense.[13] Liver transplantation corrects the underlying hepatic metabolic defect in WD and is curative.[5,14]

In this case-control study, we used commercial insurance data to quantify the health care resource use and economic burden of WD. Increased costs were ascribed to all the factors of inpatient and outpatient care as well as pharmacy costs. The evaluation of such costs helps to fill the data gap in assessing the cost-effectiveness of intervention strategies.

Materials and Methods

DATA SOURCE

We conducted a case-control study using the Truven Health MarketScan Commercial Claims (MSCC) databases from January 1, 2007, to December 31, 2017. Data included in the MSCC databases represent national health care records from government and public organizations, large employers, and health plans from more than 350 payers annually. The MSCC databases include longitudinal individual-level data for health insurance claims across inpatient, outpatient, and outpatient prescription drug services. Aggregate data on cost of care included in the MSCC represent the amounts eligible for payment before applying coordination of benefits, deductibles, and copayments. All MSCC records are de-identified data that are compliant with all US patient confidentiality requirements. The Internal Review Board of Rutgers Robert Wood Johnson Medical School approved the protocol of this study.

STUDY SAMPLE

Participants with WD were identified as having one primary or secondary record of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code (275.1 or disorders of copper metabolism) along with appropriate medications for WD or the specific ICD-Tenth Revision, CM (ICD-10-CM) code (E83.01) (Supporting Tables S3 and S4). The chronic liver disease (CLD) group included subjects with one primary or secondary ICD-9/ICD-10-CM code for hepatocellular carcinoma, compensated cirrhosis, hepatitis C virus, chronic hepatitis B virus, hepatitis D virus, alcoholic fatty liver, nonalcoholic fatty liver disease, hepatic encephalopathy, autoimmune hepatitis, hepatitis E virus, primary biliary cirrhosis, primary sclerosing cholangitis, or malignant neoplasm of intrahepatic bile ducts.

An index date was defined for each participant as either the earliest date of WD diagnosis for potential cases or a randomly selected date from all claim records starting with the earliest record with a CLD diagnosis. The random selection of an index date for controls allowed for the comparison between the burden of WD and the average CLD burden across all stages of disease. A baseline period for each participant was defined as the 6 months before the selected index date, while the study follow-up period represented the

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12 months following the defined index date. All participants with at least 6 months of enrollment before and 12 months after the index date were included in the study.

Baseline demographics, including age, sex, the region of residence, and the type of health insurance plan were obtained from the index date records. A comorbidity profile was measured for each participant during the baseline period using ICD-9-CM codes acquired from the inpatient admissions and outpatient services. The profile included participants' status with acute hepatitis, cirrhosis, liver failure, hemolytic anemia, ataxia, dystonia, secondary parkinsonism, tremor, or depression. In addition, a total weighted Charlson Comorbidity Index (CCI) score was calculated for each participant during the baseline period.[15]

MATCHING PROCEDURE

We used propensity score matching to ensure comparability between cases and controls on all observed baseline demographics and comorbidity profiles. A multivariate logistic regression model with WD status as the outcome that included age group, sex, region of residence, type of health insurance, acute hepatitis, cirrhosis, liver failure, hemolytic anemia, ataxia, dystonia, secondary parkinsonism, tremor, and depression was used to estimate the propensity score for each participant (Table 1). In turn, the estimated propensity scores were used to match WD cases 1:1 to WD-free controls, using the nearest neighbor matching without replacement strategy (i.e., GREEDY algorithm) while matching exactly on age group and sex.[16]

HEALTH CARE USE AND COSTS

The health care use parameters included the number of claims per patient for inpatient admissions, Emergency Department (ED) visits, outpatient visits, and pharmaceutical prescriptions. For the additional economic burden, we analyzed monthly averages for service-specific health care charges over claims related to inpatient admissions, ED visits, outpatient visits, and pharmaceutical prescriptions. To assess the burden associated with a new WD diagnosis, we analyzed the health care use and cost parameters over the 6 months before and the 12 months after WD diagnosis by monthly averages.

Measures of health care use included the mean, median, and twenty-fifth/seventy-fifth percentiles of the number of claims per patient for inpatient admissions, ED visits, outpatient visits, and pharmaceutical prescriptions. We also estimated the prevalence of having at least one inpatient admission, ED visit, and outpatient visit. An ED visit denoted emergency services that did not result in a hospital admission.

The mean, median, and twenty-fifth/seventy-fifth percentiles of the health care expenditures were calculated for both the overall and service-specific costs before/after first diagnosis for cases and during the 12 months following the index date for controls. In a subanalysis, we quantified age group-specific health care cost comparisons between the 6 months before vs. 12 months after WD diagnosis for all five expenditure variables. All costs were adjusted to 2020 United States dollar (US $) using the medical care commodities component of the Consumer Price Index.[17]

In addition to the primary analyses, we calculated a comorbidity-specific per patient monthly average health care cost analysis to determine the differences between cases and controls in relation to acute hepatitis, cirrhosis, liver failure, hemolytic anemia, ataxia, dystonia, secondary parkinsonism, tremor, and depression.

STATISTICAL ANALYSIS

We compared baseline characteristics and comorbidity profiles for those with and without WD before and after matching using the standardized differences of means and proportions. We used standardized difference cutoffs of 0.2, 0.5, and 0.8 to indicate small, medium, and large differences, respectively, between means and proportions of the two comparison groups (Table 1).[18,19] Wald chi-square tests were performed to test the associations between WD status, patients' categorical characteristics, and comorbidity profiles in the unmatched sample. Wilcoxon signed-rank tests were used to compare all continuous measures of health care cost and uses. McNemar tests were used to compare dichotomous parameters of health care use in both before and after WD diagnosis and in the case versus control analyses.

To quantify the burden of WD among patients with CLD, we conducted secondary multivariate regression analyses using generalized linear models (GLMs), models with negative binomial distributions

TABLE 1. BASELINE CHARACTERISTICS OF THE STUDY SAMPLE BY WD STATUS BEFORE AND AFTER MATCHING

Patient Characteristics*	Unmatched				Matched[†]		
	WD (n = 425)	No WD (n = 1,250,532)	Standardized Difference[§]	P Value	WD (n = 424)	No WD (n = 424)	Standardized Difference[§]
Age (years), mean (SD)	35.12 (15.98)	47.60 (12.44)	0.8720	<0.0001	35.19 (15.93)	35.84 (16.14)	0.0406
Age group, n (%)			0.8409	<0.0001			0.0000
<18	82 (19.29)	33,612 (2.69)			81 (19.10)	81 (19.10)	
18-34	120 (28.24)	154,763 (12.38)			120 (28.30)	120 (28.30)	
35-44	74 (17.41)	228,076 (18.24)			74 (17.45)	74 (17.45)	
45-54	96 (22.59)	387,162 (30.96)			96 (22.64)	96 (22.64)	
55+	53 (12.47)	446,919 (35.74)			53 (12.50)	53 (12.50)	
Sex, n (%)			0.1225	0.0117			0.0000
Male	230 (54.12)	600,338 (48.01)			229 (54.01)	229 (54.01)	
Female	195 (45.88)	650,194 (51.99)			195 (45.99)	195 (45.99)	
Region of residence, n (%)			0.1645	0.0020			0.1428
Northeast	95 (22.35)	257,442 (20.59)			95 (22.41)	94 (22.17)	
North Central	107 (25.18)	237,269 (18.97)			107 (25.24)	106 (25.00)	
South	149 (35.06)	507,826 (40.61)			148 (34.91)	152 (35.85)	
West	72 (16.94)	225,320 (18.02)			72 (16.98)	70 (16.51)	
Unknown	2 (0.47)	22,675 (1.81)			2 (0.47)	2 (0.47)	
Type of health insurance, n (%)			0.1112	0.4035			0.0335
Preferred provider organization	250 (58.82)	768,325 (61.44)			249 (58.73)	255 (60.14)	
Health maintenance organization	47 (11.06)	149,405 (11.95)			47 (11.08)	44 (10.38)	
Comprehensive	9 (2.12)	31,721 (2.54)			9 (2.12)	10 (2.36)	
Point-of-service with capitation	42 (9.88)	100,187 (8.01)			42 (9.91)	42 (9.91)	
Other	77 (18.12)	200,894 (16.06)			77 (18.16)	73 (17.22)	
Comorbidity profile[‡]							
CCI, mean (SD)	0.37 (0.77)	0.75 (1.06)	0.4117	<0.0001	0.37 (0.77)	0.38 (0.78)	0.0091
CCI, n (%)			0.4714	<0.0001			0.0825
0	317 (74.59)	678,524 (54.26)			316 (74.53)	315 (74.29)	
1	78 (18.35)	347,362 (27.78)			78 (18.40)	78 (18.40)	
2	19 (4.47)	137,508 (11.00)			19 (4.48)	19 (4.48)	
3	7 (1.65)	53,852 (4.31)			7 (1.65)	8 (1.89)	
4+	4 (0.94)	33,286 (2.66)			4 (0.94)	4 (0.94)	
Acute hepatitis, n (%)	25 (5.88)	78,737 (6.30)	0.0173	0.7254	25 (5.90)	26 (6.13)	0.0099
Cirrhosis, n (%)	69 (16.24)	97,365 (7.79)	0.2621	<0.0001	69 (16.27)	64 (15.09)	0.0324
Liver failure, n (%)	27 (6.35)	16,951 (1.36)	0.2618	<0.0001	27 (6.37)	24 (5.66)	0.0298
Hemolytic anemia, n (%)	10 (2.35)	3,169 (0.25)	0.1859	<0.0001	10 (2.36)	11 (2.59)	0.0152
Ataxia, n (%)	5 (1.18)	2,511 (0.20)	0.1182	<0.0001	4 (0.94)	6 (1.42)	0.0437
Dystonia, n (%)	4 (0.94)	1,125 (0.09)	0.1191	<0.0001	3 (0.71)	5 (1.18)	0.0488
Secondary parkinsonism, n (%)	0 (0)	538 (0.04)	0.0293	0.6689	0 (0)	0 (0)	0.0000
Tremor, n (%)	27 (6.35)	13,637 (1.09)	0.2807	<0.0001	26 (6.13)	28 (6.60)	0.0193
Depression, n (%)	45 (10.59)	66,886 (5.35)	0.1944	<0.0001	45 (10.61)	44 (10.38)	0.0077

*All demographics data were obtained on the first date of WD diagnosis for cases and random record after first CLD for controls.
[†]WD cases and WD-free controls were matched 1:1 using propensity scoring. The logistic regression model used to estimate propensity scores included age group, region of residence, sex, type of health insurance, CCI, acute hepatitis, cirrhosis, liver failure, hemolytic anemia, ataxia, dystonia, secondary parkinsonism, tremor, and depression.
[‡]Estimated from records before the first date of WD diagnosis for cases and records before the random date for controls.
[§]Difference in means or proportions divided by standard error. Imbalance between the two groups is defined as absolute value greater than 0.10; smaller values indicate better balance.

for health care use rates, and gamma distributions for cost estimates. We used a generalized estimation equation with an exchangeable structure to account for the correlation between cases and controls. All GLMs were adjusted for age group, sex, region of residence, type of health insurance, acute hepatitis, cirrhosis, liver failure, hemolytic anemia, ataxia, dystonia, secondary parkinsonism, tremor, and depression. $P < 0.05$ was considered statistically significant. All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

Results

SAMPLE CHARACTERISTICS

The study sample included 3,125,201 participants in MSCC databases with CLD or WD in either inpatient admission or outpatient services (Fig. 1). Of all patients with CLD or WD, 1,255,572 met the inclusion criteria of continuous enrollment for 6 months before and 12 months after the index date. A further 5,040 potential patients with WD were identified; however, of this group, 425 patients with WD met all inclusion criteria, including use of WD medications. Of the 425 patients, 331 were identified using ICD-10-CM codes; 424 of the 425 were then matched 1:1 using propensity scores to CLD controls. The incidence of WD in the unmatched sample was 0.03%.

Between-group differences in the unmatched and matched samples are summarized in (Table 1). Compared to those without WD, patients with WD were slightly younger (35.12 vs. 47.60 years; $P < 0.0001$) with a lower proportion of women (45.88% vs. 51.99%; $P < 0.05$) and a lower CCI (0.37 vs. 0.75; $P < 0.0001$). Patients with WD had a numerically lower prevalence of acute hepatitis (5.88% vs. 6.30%; $P > 0.05$) and secondary parkinsonism (0% vs. 0.04%; $P > 0.05$) that did not reach statistical significance compared to the WD-free CLD cohort. On the other hand, patients with WD had a higher prevalence of cirrhosis (16.24% vs. 7.79%; $P < 0.0001$), liver failure (6.35% vs. 1.36%; $P < 0.0001$), hemolytic anemia (2.35% vs. 0.25; $P < 0.0001$), ataxia (1.18% vs. 0.20%; $P < 0.0001$), dystonia (0.94% vs. 0.09%; $P < 0.0001$), tremor (6.35% vs. 1.09%; $P < 0.0001$), and depression (10.59% vs. 5.35%; $P < 0.0001$) compared to the WD-free CLD cohort. The distribution of all baseline characteristics was balanced between the matched WD cases and controls (standardized difference <0.2) (Table 1).

HEALTH CARE USE

Monthly health care use was compared between the 6-month baseline period (before WD) and 12 months following the index date (after WD) in the 424 patients with a record of WD (Table 2). The total number of claims per patient was significantly higher in the period after WD than before the WD baseline period (3.35 vs. 2.87; $P < 0.0001$), representing an increase of 0.47 (95% confidence interval [CI], 0.24, 0.71) claims per patient after diagnosis. The period after WD was characterized by a significantly higher number of outpatient visits (1.82 vs. 1.62; $P < 0.0001$) and pharmaceutical claims (1.34 vs. 1.11; $P < 0.0001$) compared to before WD but not inpatient admissions (0.14 vs. 0.10; $P = 0.1324$). The average length of inpatient stays for patients with WD was numerically slightly higher after versus before the first diagnosis period (0.13 days vs. 0.10 days; $P = 0.2597$).

The monthly average health care use was next compared between matched WD cases and CLD controls (Supporting Table S1). The total number of claims per patient over the 12 months following the index date was significantly higher in the case group than in the control group (case vs. control, 3.35 vs. 2.65; $P < 0.0001$). This increase was related to outpatient visits (case vs. control, 1.82 vs. 1.41; $P < 0.0001$). The prevalence of at least one inpatient admission was not statistically signficantly different for WD cases compared to controls (15.33% vs. 16.51%; $P = 0.6311$). We also observed a minimally higher average length of inpatient stays between cases and controls (0.13 days vs. 0.11 days; $P = 0.5876$).

HEALTH CARE COSTS

In the analysis, the per patient monthly average cost of health care services was US $2,089 and $3,887 before and after WD diagnosis, respectively (Table 3). The difference in the total unadjusted cost was significant with postdiagnosis cases costing US $1,798 (95% CI, $772, $2,825) more than prediagnosis cases on a monthly basis. The incremental difference in monthly average health care costs after versus before WD diagnosis was related to US $706 (126%) in inpatient costs, $22 (30%) from ED costs, $268 (35%)
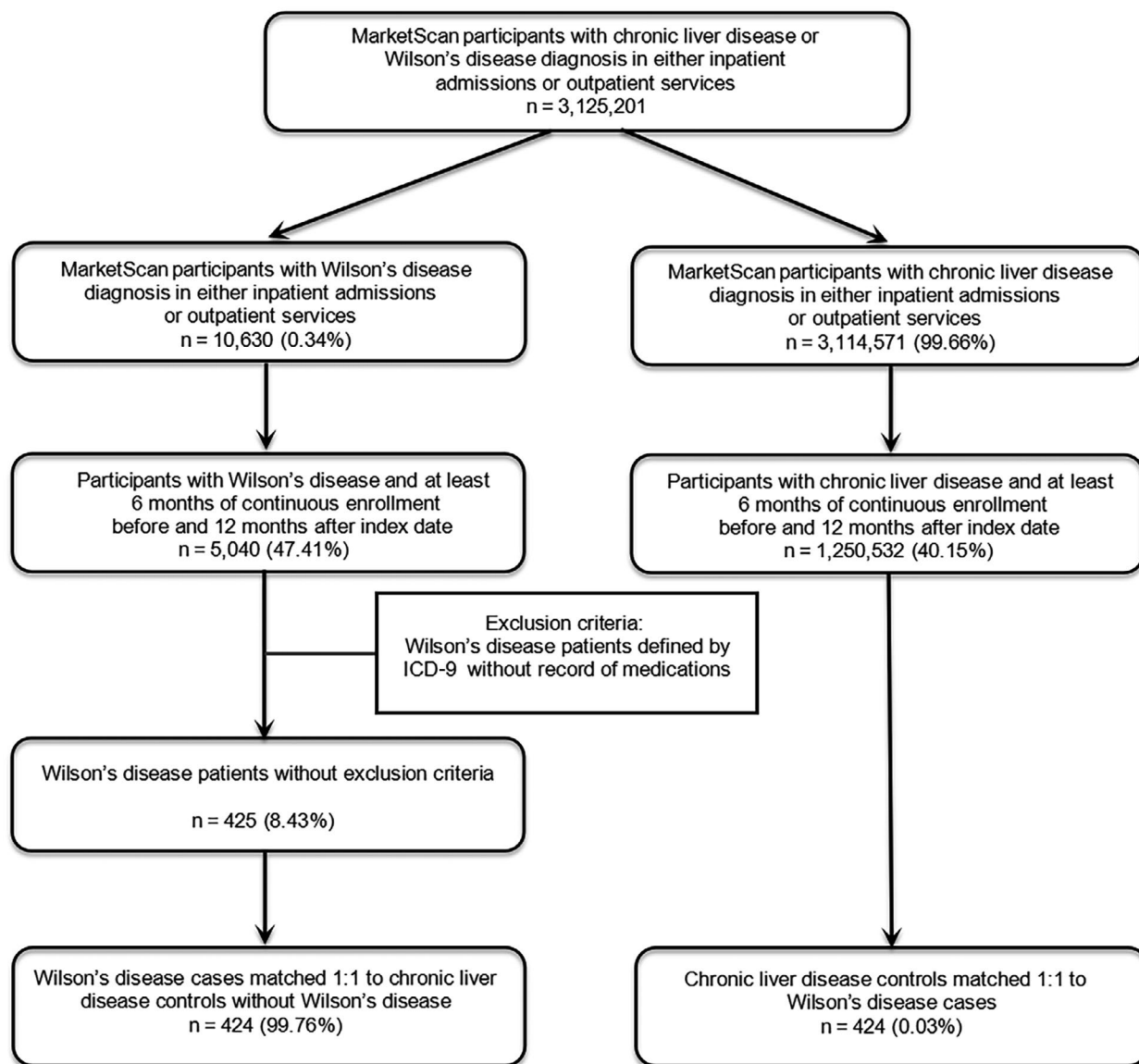
FIG. 1. Diagram for study selection.

from cost of outpatient visits, and $803 (117%) from outpatient prescription costs.

Health care costs were then compared between matched WD cases and CLD controls without WD (Table 4). The monthly average costs of health care services over the 12 months following the index dates were significantly higher in WD cases than in controls (case vs. control, US $3,887 vs. $1,979; $P < 0.0001$), with an excess per patient cost of $1,908 (95% CI, $657, $3,159). Incremental monthly average cost in WD compared to controls was related to higher expenditures for inpatient admissions (US $1,264 vs.

$655; $P = 0.3426$) but reached statistical significance for outpatient visits ($1,037 vs. $869; $P = 0.0035$) and pharmaceutical claims ($1,489 vs. $344; $P < 0.0001$)

The differences in monthly average health care cost between patients before and after WD diagnosis were significant among all age groups. The highest difference of US $3,916 (95% CI, –$532, $8,363) in monthly average cost between before and after diagnosis was observed in patients aged <18 years. Relative to prediagnosis, the cost of inpatient services after diagnosis was higher in ages <18 years (US $3,129 vs. $1,156; $P = 0.3572$) and 35-44 years ($415 vs. $1,155;

TABLE 2. MONTHLY AVERAGE HEALTH CARE RESOURCE USE FOR PATIENTS WITH WD DURING THE 6 MONTHS BEFORE VERSUS 12 MONTHS AFTER FIRST DIAGNOSIS DATE, 2007 TO 2017

Health Care Use	Prediagnosis (n = 424)	Postdiagnosis (n = 424)	P Value*
Total Number of claims			
Mean (SD)	2.87 (3.49)	3.35 (3.54)	<0.0001
Median (25th, 75th percentile)	1.83 (0.83, 3.67)	2.33 (1.17, 4.25)	
Inpatient admissions			
Prevelance of at least one visit, n (%)	44 (10.38)	65 (15.33)	0.0127
Number of admissions			
Mean (SD)	0.10 (0.52)	0.14 (0.57)	0.1324
Median (25th, 75th percentile)	0 (0, 0)	0 (0, 0)	
Total length of stay, days			
Mean (SD)	0.10 (0.63)	0.13 (0.58)	0.2597
Median (25th, 75th percentile)	0 (0, 0)	0 (0, 0)	
ED visits			
Prevelance of at least one visit, n (%)	73 (17.22)	120 (28.30)	<0.0001
Number of visits			
Mean (SD)	0.05 (0.13)	0.05 (0.14)	0.6201
Median (25th, 75th percentile)	0 (0, 0)	0 (0, 0.08)	
Outpatient visits			
Prevelance of at least one visit, n (%)	367 (86.56)	424 (100.00)	<0.0001
Number of visits			
Mean (SD)	1.62 (2.61)	1.82 (2.39)	0.0001
Median (25th, 75th percentile)	1 (0.33, 2.00)	1.17 (0.50, 2.25)	
Pharmaceutical claims			
Number of claims			
Mean (SD)	1.11 (1.29)	1.34 (1.37)	<0.0001
Median (25th, 75th percentile)	0.67 (0.17, 1.50)	1 (0.33, 1.92)	

*For comparisons between before versus after first WD diagnosis; all P values were obtained from Wilcoxon signed-rank tests for continuous variables and McNemar tests for binary variables.

P = 0.0833). The monthly average costs related to outpatient care had a higher difference in patients' postdiagnosis in ages 45-54 years (US $459 vs. $1,058; P = 0.0021) and 55+ ($661 vs. $829; P = 0.0350). Postdiagnosis cases aged <18, 18-34, 35-44, 45-54 and 55+ years incurred higher pharmaceutical costs compared to prediagnosis (Supporting Table S2).

The adjusted per person monthly average health care cost by comorbidity was higher for WD cases compared to controls (Table 5). Similar to the results from the main analysis, WD was associated with increases in per person annual cost among all comorbidities except for hemolytic anemia. With acute hepatitis, cirrhosis, liver failure, ataxia, dystonia, tremor, and depression, WD resulted in US $3,121, $6,630, $16,590, $2,377, $2,674, $467, and $885 higher adjusted per person monthly average health care cost, respectively, compared to CLD controls.

Discussion

In this retrospective case-control study that identified 3,125,201 individuals with CLD and/or WD, 1,250,532 met the inclusion criteria for our study. Of that sample population, 5,040 had a diagnosis of WD, mainly from ICD-9-CM coding. By restricting confirmation of the diagnosis with patients who had claims data identifying medications used to treat WD (Supporting Table 4) and by propensity matching, we were able to match 424 cases from this group 1:1 to patients with CLD who did not have WD.

TABLE 3. MONTHLY AVERAGE HEALTH CARE COSTS FOR PATIENTS WITH WD DURING THE 6 MONTHS BEFORE VERSUS 12 MONTHS AFTER THE INDEX DATE, 2007 TO 2017

Health Care Cost (US $)	Prediagnosis (n = 424)	Postdiagnosis (n = 424)	P Value
Total Cost			
Mean (SD)	2,089 (4,882)	3,887 (11,501)	<0.0001
Median (25th, 75th percentile)	549 (173, 1,473)	919 (327, 2,348)	
Inpatient admissions			
Mean (SD)	559 (2,728)	1,264 (9,114)	0.1369
Median (25th, 75th percentile)	0 (0, 0)	0 (0, 0)	
ED visits			
Mean (SD)	74 (256)	97 (276)	0.0037
Median (25th, 75th percentile)	0 (0, 0)	0 (0, 42)	
Outpatient visits			
Mean (SD)	770 (2,283)	1,037 (3,369)	<0.0001
Median (25th, 75th percentile)	221 (45, 688)	369 (125, 839)	
Pharmaceutical claims			
Mean (SD)	686 (3,099)	1,489 (4,833)	<0.0001
Median (25th, 75th percentile)	70 (5, 327)	159 (17, 616)	

TABLE 4. MONTHLY AVERAGE HEALTH CARE COSTS FOR WD CASES AND WD-FREE CONTROLS DURING THE 12 MONTHS POST-INDEX DATE, 2007 TO 2017

Case Versus Control

Health care Cost (US $)	WD (n = 424)	No WD (n = 424)	P Value
Total number of claims			
Mean (SD)	3,887 (11,501)	1,979 (7,170)	<0.0001
Median (25th, 75th percentile)	919 (327, 2,348)	479 (147, 1,367)	
Inpatient admissions			
Mean (SD)	1,264 (9,114)	655 (3,823)	0.3426
Median (25th, 75th percentile)	0 (0, 0)	0 (0, 0)	
ED visits			
Mean (SD)	97 (276)	111 (345)	0.3065
Median (25th, 75th percentile)	0 (0, 42)	0 (0, 93)	
Outpatient visits			
Mean (SD)	1,037 (3,369)	869 (3,429)	0.0035
Median (25th, 75th percentile)	369 (125, 839)	222 (73, 644)	
Pharmaceutical claims			
Mean (SD)	1,489 (4,833)	344 (1,366)	<0.0001
Median (25th, 75th percentile)	159 (17, 616)	26 (0, 171)	

When comparing baseline characteristics to the group of patients with CLD but without WD, those with WD were slightly younger (35.19 vs. 35.84 years; $P = 0.0406$) with a slightly lower weighted CCI score (0.37 vs. 0.38; $P = 0.0091$) and a higher proportion of men to women (54.01% vs. 45.99%). Patients with WD had a statistically significant increase in cirrhosis (16.24% vs. 7.79%; $P < 0.0001$), liver failure (6.35% vs. 1.36%; $P < 0.0001$), hemolytic anemia (2.35% vs. 0.25%; $P < 0.0001$), ataxia (1.18% vs. 0.20%; $P < 0.0001$), dystonia (0.94% vs. 0.09%; $P < 0.0001$), tremor (6.35% vs. 1.09%; $P < 0.0001$), and depression

TABLE 5. PER PATIENT MONTHLY AVERAGE HEALTH CARE COSTS BY COMORBIDITY STATUS FOR MATCHED PATIENTS WITH AND WITHOUT WD (12 MONTHS AFTER INDEX FOR BOTH)

Health Care Cost*	Number of Pairs	WD n = 424 (US $) (95% CI)	No WD n = 424 (US $) (95% CI)	P Value[†]
CCI group				
0	313	3,374 (2,063, 4,685)	1,635 (856, 2,413)	<0.0001
1	75	4,847 (2,498, 7,195)	1,598 (1,048, 2,147)	0.0053
2	18	3,319 (312, 6,326)	1,586 (693, 2,478)	0.2121
3	6	12,081 (−9,532, 33,693)	3,291 (−422, 7,005)	0.6875
4+	4	7,598 (−7,203, 22,398)	2,278 (−3,229, 7,784)	0.6250
Acute hepatitis	23	4,981 (1,815, 8,146)	1,860 (855, 2,864)	0.0770
Cirrhosis	64	10,649 (4,368, 16,931)	4,019 (1,808, 6,230)	0.0509
Liver failure	21	21,578 (3,246, 39,911)	4,989 (2,348, 7,629)	0.0995
Hemolytic anemia	7	10,772 (−6,679, 28,224)	15,843 (−6,862, 38,548)	0.9375
Ataxia	4	2,927 (−1,645, 7,498)	550 (63, 1,037)	0.2500
Dystonia	2	4,518 (−42,961, 51,997)	1,844 (−6,759, 10,447)	1.0000
Secondary parkinsonism	0	N/A	N/A	N/A
Tremor	24	4,264 (468, 8,059)	3,797 (434, 7,159)	0.6373
Depression	40	5,662 (2,389, 8,935)	4,777 (−916, 10,470)	0.0756

*All costs were adjusted to 2020 US $ using the medical care component of the Consumer Price Index.
[†]Obtained from Wilcoxon signed-rank tests for cost comparisons between cases versus controls in the 12 months following the index date.
Abbreviation: N/A, not available.

(10.59% vs. 5.35%; P < 0.0001). These findings in our study mirror previous studies in terms of age and clinical symptom distribution.[15,12,20]

Our findings demonstrate that a new WD diagnosis results in excess monthly average health care use of 0.47 (95% CI, 0.24, 0.71) claims per patient and an additional US $1,799 (95% CI, $772 to $2,825) in per patient monthly average health care costs. The increased burden was primarily attributed to pharmaceutical claims (0.23; 95% CI, 0.16, 0.30) and costs (US $803; 95% CI, $372, $1,234).

Our case-control analysis also demonstrated a significant increase in health care use (0.70 claims; 95% CI, 0.29, 1.11) and cost (US $1,908; 95% CI, $657, $3,159) in patients with WD when compared to CLD controls with similar demographics and comorbidity profiles. The difference could primarily be attributed to an increase in inpatient admissions (US $609; 95% CI, −$340 to $1,558; P = 0.3426), outpatient visits ($168; 95% CI, −$268, $604; P = 0.0035), and pharmaceutical claims ($1,145; 95% CI, $666, $1,625; P < 0.0001).

The difference in monthly average health care cost between patients with WD patient's before and after

diagnosis was statistically significant among all age groups, with a difference of US $1,799 (95% CI, $772, $2,825; P < 0.0001). The highest per month average patient cost was observed in patients younger than 18 years of age, with a difference of US $3,916 (95% CI, −$532, $8,363; P = 0.3832) and was driven primarily by the cost of inpatient admissions (US $1,973; 95% CI, −$1,884, $5,830; P = 0.3572) and pharmaceutical claims (US $2,043; 95% CI, $588, $3,497; P < 0.0001). These results follow findings in previous reports that patients diagnosed at a younger age have more liver involvement and require more aggressive treatment to stabilize the disease.[5,12,21-23]

Comorbidity-specific analysis showed that patients with WD presenting with a CCI of 0 had a statistically significant increase in monthly health care costs when compared to patients with CLD without WD (US $3,211 to $1,740; 95% CI, $269; P < 0.0001). This difference could be mainly attributed to an increase in monthly expenditures on pharmaceutical therapy to treat WD. When further analyzing the comorbidity costs of patients with WD, patients having WD with liver failure or cirrhosis had higher per patient monthly average costs by US $16,590 and US

$6,630, respectively, compared to patients with CLD with liver failure or cirrhosis but without WD.

The MSCC database is based on ICD-9-CM and ICD-10-CM codes; this creates limitations that are present in our study and analysis. Demographic data, such as ethnicity and race, are not present. Laboratory data are not available for the years analyzed, precluding calculations of Leipzig scores. While National Drug Code package codes for D-penicillamine, trientine, and zinc salts were searched in the database, retail pharmacy costs presented may vary widely. The retrospective nature of the study is also problematic given that details of treatment failures and nonadherence are not available.

Our study has several strengths, including a large matched-control group. This allowed for the estimation of incremental differences in health care use and cost parameters. Use of a nested case-control study design within a cohort of insured patients with continuous 6-month enrollment during the baseline period and for 12-months following the index date eliminates any bias in selecting appropriate cases and controls. The use of a score-matching system ensured high comparability between cases and controls in relation to risk factors associated with WD.

The present findings indicate that the diagnosis of WD imposes higher health care cost and use burdens compared to CLD controls without WD who have the same demographics and comorbidity profiles. This has been mainly due to higher pharmaceutical costs, although generic versions of trientine have now decreased prices drastically. A higher cost differential in patients with WD under 18 years of age compared to controls indicates the need and disproportionately greater benefit of earlier diagnosis. The statistically significant increased prevalence of depression in addition to acute hepatitis, cirrhosis, liver failure, hemolytic anemia, disease, ataxia, dystonia, and tremor in patients with WD points out the importance of considering the diagnosis of Wilson's disease, especially in our younger patients.

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