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Wilson Disease in the US - Epidemiology and Real-World Patient Characteristics Based on a Claims Database Study

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Abstract

Objectives: To describe the epidemiology, patient characteristics and comorbidities in patients with Wilson disease (WD) in the US.

Design: Retrospective, population-based study

Setting: The study used the US Komodo claims database containing records regarding medical claims for over 120 million individuals.

Participants: Patients with WD were identified via ICD10 code during the study period 2016–2019. A further stratification by disease subtype (hepatic, neurologic and psychiatric) was performed.

Main outcome measures: WD prevalence was reported by age, sex, and US census regions/divisions. Adjusted prevalence was calculated using age-specific prevalence standardized to the US (2010 US census) and to the world (WHO 2000–2025) to enable comparisons across countries, using direct standardization of prevalence estimates by age group.

Results: Overall, 2,115 WD patients were identified during the study period. Among them, 56.8% had hepatic, 57.0% neurologic and 47.4% psychiatric signs and symptoms. The most frequent manifestations in hepatic patients were liver signs and symptoms (90.8%), in neurologic patients cognitive defects (50.7%), and in psychiatric patients mood disorders (86.4%). The mean age in the overall cohort was 39.9 years. Prevalence estimation was based on 1,481 WD patients between 2017 and 2019. The 2017–2019 crude period prevalence was 21.2 patients per million (95% confidence interval: 20.1–22.3), with similar prevalence observed for both sexes.

Conclusions: This study provides important real-world data on the diagnosed prevalence of WD in the US and revealed the comorbidities associated with various disease subtypes, thereby providing a comprehensive basis for guiding physicians and policy makers in the management of this chronic disease.

Strengths and limitations of this study

- This study estimated the diagnosed prevalence of WD for the first time in the US, by using a large, nationally representative claims database. The real-world nature of the data helps estimate the observed frequency of Wilson disease in the US using ICD-10 codes specific to WD.
- The classification of patients into subtypes, and especially the novel approach to differentiate psychiatric symptoms from neurological symptoms, was a further strength of this study.
- Besides general limitations inherent to claims data, the limitations specific to this study included a limited study period after the introduction of a new WD-specific ICD-10 code in 2015.
- The used claims data did not capture information on OTC medications and the treated patients represented the proportion of patients with prescription treatment only.

Introduction

Wilson disease (WD) is an autosomal recessive condition which leads to an excessive copper deposition in body organs, particularly in the liver and the central nervous system.[1] This genetic disorder is caused by mutations of the P-type ATPase copper transporter *ATP7B* gene located in the human chromosome 13.[2] To date, more than 600 variants in the *ATP7B* gene have been described, and most WD patients are compound heterozygous with two different *ATP7B* variants, complicating and prolonging genetic WD diagnosis.[3] WD generally presents in childhood and young adulthood with the most common age of presentation between 10 and 20 years, though patients can occasionally present before the age of 5 years and after the age of 70 years.[4]

Clinical presentation of WD includes a combination of hepatic, neurologic, psychiatric, and ophthalmologic symptoms. Psychiatric symptoms often precede the diagnosis of WD and include personality changes, depression, cognitive changes, and anxiety.[5] The neurologic symptoms of WD mostly refer to dysfunction in the extrapyramidal system including dysarthria, dystonia, gait abnormalities, tremor, parkinsonism, chorea, and seizures.[6] Psychiatric symptoms have been only recently recognized as independent manifestations of WD, as it was previously assumed that they occur together with neurological symptoms, and patients were often referred to as having neuro-psychiatric disorders.[7] The symptoms related to hepatic dysfunction in WD can range from an asymptomatic increase in liver enzyme levels to severe liver failure. Typically, early on in disease progression there is a mild increase in transaminases, which then may progress to chronic active hepatitis, followed by fibrosis and cirrhosis.[8]

WD is a rare disease with recent worldwide clinical prevalence estimates ranging from approximately 16.7 to 25 patients per million,[9] although the prevalence can vary across countries and may be higher in selected regions such as in some Asian communities.[10] Interestingly, there is a discrepancy of WD prevalence estimates originating from epidemiological compared to genetic studies and recent genetic data with a considerably higher prevalence (139 per million) indicate that the prevalence of WD may be underestimated.[11] The possibility of underdiagnosis, misdiagnosis and the lack of accounting for incomplete variant penetrance in the genetic calculations were hypothesized as the main reasons for

the observed inconsistency between genetic vs. clinical data.[11,12] For the US, population-based epidemiological data are still scarce. A previous study reported a genetic birth prevalence of 18.2 per million births,[13] and an abstract on cardiac manifestations in WD reported a prevalence of 26 patients per million, but no details of methodology.[14]

Thus, large population-based studies assessing the epidemiology of WD and its subtypes in the US are needed, allowing for a greater characterization around the spectrum of disease severity and the diagnosed prevalence of WD. Here we present the US-specific data from a recently completed multi-country real-world evidence study that used claims data to investigate various aspects of WD in a real-life setting including epidemiology and patient demographic and clinical characteristics.

Methods

Study design

This retrospective, population-based observational study used health insurance claims data to assess WD epidemiology and patient characteristics using the US Komodo Health claims database available from 2012–2020.[15] Komodo's private payor-complete database contains records regarding prescription and/or medical claims for over 120 million individuals, collected from more than 150 private insurers in the US, including Medicaid managed-care and Medicare Advantage plans. This study used the closed claims available in the database. Closed claims come directly from the payer and provide the complete patient journey, such as full medical and/or prescription benefit information including insurance eligibility.

Population

Patients were selected based on their first reported WD diagnosis (index event) in the claims database between 2016 and 2019 (study period). The diagnosis was based on code (ICD-10 code E83.01 or ICD-9-CM code 275.1 prior to October 1, 2015). The standard ICD-9 diagnostic code for WD could also include another rare condition called Menkes disease. The WD-specific ICD-10 code (E83.01) was introduced in the US on October 1, 2015. A WD diagnosis was defined as at least one inpatient or two outpatient visits with a WD ICD-10 code, separated by at least 30 days during the study period.

No age restriction was imposed. Patients were excluded from the study if they had at least one prescription for a copper replacement drug during the study period. This was applied to rule out patients with Menkes disease which is treated by copper replacement drugs.

Cohorts and subgroups

The cohort presented here includes patients that fulfilled the criteria for at least one WD diagnosis at any time during the study period (2016–2019) and a continuous enrollment for at least one calendar year before the index event. Separately, prevalence was assessed in the period between 2017 and 2019 for patients that had a history of at least one WD diagnosis at any time during that period and a continuous enrollment for at least two calendar years. This separate assessment period for prevalence estimation was based on the WD-specific diagnosis code becoming effective in the US only in 2015. Due to the possibility of miscoding, the most accurate prevalence estimation of WD can be made between 2017 and 2019, as this period includes at least one full calendar year since the introduction of the new code.

A further stratification by WD subtypes was performed. The subtypes “hepatic”, “neurologic” and “psychiatric” were not mutually exclusive or strictly delineated but were based on the presence of signs and symptoms. Patients were assigned to the hepatic subtype if they were diagnosed with liver signs and symptoms, acute hepatitis (not viral), cirrhosis (decompensated or compensated), liver failure, portal hypertension, or hepatocellular carcinoma. Patients assigned to the neurologic subtype had a diagnosis for tremor, parkinsonism or akinetic rigid syndrome, gait abnormalities/ataxia, dysarthria, dystonia, chorea, dysphagia, myopathy, seizures, migraine, somatoform autonomic dysfunction or cognitive disorder. Patients diagnosed with mood disorders, paranoia/schizophrenia, psychosis, or personality disorders were assigned to the psychiatric subtype. WD manifestations were defined as the occurrence of specific signs or symptoms associated with each of the subtypes and were identified using respective ICD-10 codes (see **Supplementary Tables 1–3**).

Variables

Data on patient characteristics (age, sex, region of residence), physician specialty, proportion of patients never treated, distribution of subtypes and manifestations were ascertained at baseline.

Comorbidities were assessed during the study period (2016–2019). Overall, age-, sex-, and region-specific prevalence (crude and age-adjusted period prevalence) were assessed in the period between 2017 and 2019. The rationale for considering a period prevalence rather than an annual prevalence was that the identification of WD patients was based on ICD-10 codes, without considering WD treatment or laboratory records, and the assumption that WD patients who are well managed using over the counter (OTC) or prescription medication may not necessarily visit a health care provider (HCP) each year.

Data analysis

Descriptive statistics were calculated for demographic and baseline characteristics (overall and by subtype). Means and standard deviations (SDs) were provided for continuous or discrete data. Frequencies and percentages were provided for categorical data. For WD manifestations, the frequencies of occurrence of specific ICD-10 codes within subtypes and within the overall patient cohort were calculated and the three most frequent manifestations were listed by subtype. For comorbidities, all recorded diagnoses (ICD-10 codes level-3) at any time during the study period were ranked according to frequency and a list of the 10 most frequent comorbidities in the overall cohort were reported. In addition, the Charlson Comorbidity index (CCI; version of 2011), an assessment tool designed to predict mortality in patients with multiple comorbidities,[16] was assessed for each patient and a mean score including SD (higher scores indicating greater mortality risk and more severe comorbid conditions) was calculated for the overall cohort. Crude period prevalence was calculated from the number of WD cases identified and was expressed as patients per million including 95% confidence intervals (CI). The denominator was the number of patients with continuous enrollment spanning the period of interest (2017–2019) and the numerator was any patient from the denominator with at least one WD diagnosis claim during the period of interest. Prevalence was reported by age, sex, and US census regions/divisions. Adjusted prevalence was calculated using age-specific prevalence standardized to the US (2010 US census) and to the world (WHO 2000–2025) to enable comparisons across countries, using direct standardization of prevalence estimates by age group.

Ethics statement

The final protocol, any amendments, and informed consent documentation of this study were reviewed and approved by an institutional review board (IRB) and/or independent ethics committee (IEC) for each country participating in the study. The IRB for the US was Pearl Pathways. The study was conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor, and followed generally accepted research practices described in Good Pharmacoepidemiology Practices guidelines issued by the International Society for Pharmacoepidemiology.

Data availability statement

The data that support the findings of this study are available from Komodo Health. Restrictions apply to the availability of these data, which were used under license for this study. Access to data must be requested through Cerner Enviza.

Results

WD subtypes and manifestations

The observed cohort included 2,115 WD patients identified between 2016 and 2019. Among these, more than half had hepatic and/or neurologic symptoms (56.8% and 57.0%, respectively) and around half had psychiatric symptoms (47.4%). Most patients had overlapping subtypes, presenting concomitantly with hepatic, neurologic, and/or psychiatric symptoms. **Figure 1** illustrates the distribution of sex (a) and age (b) within subtypes. Slightly more male than female patients had neurologic (54.6%) and psychiatric (55.6%) symptoms, whereas the gender distribution was equal in the hepatic subtype. With regards to age distribution, most patients in all subtypes were in the age groups between 18 to 39 years and 40 to 64 years. The distribution of young (0–17 years) and older (above 65 years) patients was also similar between subtypes, though there were slightly more older patients in the neurologic subtype (21% vs. 16% [hepatic] and 17% [psychiatric]).

The most frequent manifestations associated with the different subtypes and their proportion in the overall cohort are highlighted in **Table 1**. Hepatic patients most frequently experienced liver signs and symptoms (90.8%), cirrhosis (37.9%) and hepatitis (28.9%). Neurologic patients most frequently

experienced cognitive defects (50.7%), ataxia and gait abnormalities (36.2%) and dysphagia (27.2%). Psychiatric patients most frequently experienced mood disorders (86.4%), a mix of symptoms in children (22.3%) and paranoia/schizophrenia (19.8%).

Baseline characteristics

Selected baseline characteristics of the overall cohort and by subtype are displayed in **Table 2**. The mean age in the overall cohort was 39.9 years (SD=20.1 years). The lowest mean age was reported for the psychiatric subtype (39.2 years, SD=20.2 years) and the highest for the neurologic subtype (42.3 years, SD=20.7 years). Overall, 51.8% were male patients. A larger portion of patients came from the South (30.6%) and fewer from the Northeast (21.8%) with little difference between subtypes. While for a majority (54.2%) of overall WD cases no information was available regarding the specialists managing the primary WD diagnosis, the available results showed that patients were mostly in the care of gastroenterologists (13.2%) and general/family practitioners (12.6%). Hepatic patients were more frequently seen by gastroenterologists (16.4%), as compared to the other subtypes (9.7% of neurologic patients and 9.0% of psychiatric patients). On average, patients were followed up for 2.2 years (SD=1.3 years) with little difference between subtypes. Among all patients, the majority (83.0%) were never treated with a reimbursable WD prescription medication during the study period.

Comorbidities

WD patients were diagnosed with a broad spectrum of comorbidities. The most common clinical conditions diagnosed during the study period included other joint disorders (50.9%), unspecified soft tissue disorders (49.3%), dorsalgia (49.1%), disorders of lipoprotein metabolism and other lipidemias (45.9%), essential hypertension (45.2%), anxiety disorders (42.9%), and other diseases of liver (40.0%), **Figure 2**. The extent of comorbidities was also reflected by a mean CCI score of 1.92 (SD=2.68).

Prevalence

Prevalence estimation was based on 1,481 WD patients between 2017 and 2019. The 2017–2019 crude period prevalence was 21.2 patients per million (95% CI: 20.1–22.3), with similar prevalence observed for both sexes (male: 21.2 per million, 95% CI: 19.7–22.8 and female: 21.1 per million, 95%

CI: 19.7–22.6), **Table 3**. The crude period prevalence peaked among young adults in the 18 to 39 years age group (27.1 per million, 95% CI: 24.7–29.5), followed closely by adults 40 to 64 years old (26.1 per million, 95% CI: 24.0–28.2). The highest crude period prevalence was recorded in the Northeast (24.1 per million, 95% CI: 21.6–26.7), followed by the Midwestern (22.2 per million, 95% CI: 19.9–24.5), Western (21.6 per million, 95% CI: 19.2–24.0), and Southern (18.4 per million, 95% CI: 16.7–20.1) regions of the US.

Adjusted period prevalence was calculated using age-specific prevalence standardized to the US (2010 US census) and to the world (WHO 2000–2025). Between 2017 and 2019, both the US-adjusted and WHO-adjusted period prevalences were similar (22.0 per million, 95% CI: 20.9–23.1 and 21.4 per million, 95% CI: 20.4–22.5, respectively) to the crude period prevalence observed in this study.

Discussion

Principal findings and implications

There is a gap of knowledge regarding the epidemiology and clinical characteristics of WD patients from a national and international perspective. In this large population-based study we assessed WD patient characteristics and epidemiology in the US.

Approximately two-thirds of the cohort showed hepatic and/or neurologic symptoms, which is consistent with the natural disease course, as WD mostly affects the liver and brain.[17] Typically, hepatic symptoms precede the onset of neurologic symptoms and may thus be diagnosed at a younger age[2]. In line with this, though not as evident in the age distribution by subtypes, the mean age at index in the hepatic subtype was slightly lower compared to the neurologic subtype. In agreement with our data on gender distribution in the neurologic and psychiatric subtypes, a registry-based study observed that the neuropsychiatric WD form occurred more frequently in men (67%) vs. women (49%).[18]

Our results also revealed the extent of comorbidities associated with various disease subtypes, as some of the most frequently reported manifestations were quite severe (e.g., around 40% of patients in the hepatic subtype presented with cirrhosis). The frequency of hepatic, neurologic, and psychiatric presentations, as well as the manifestations within these subtypes varies considerably in other

published studies.[4] Considering the great variability in WD symptoms, it is likely that there is referral bias. A review of several independent case series suggested that dysarthria, gait abnormality/ataxia and dystonia are the most frequent manifestations in the neurologic subtype, which partially reflects our findings.[4] The higher rates of dystonia and dysarthria reported in the literature may be explained by the fact that only symptomatic conditions that require treatment get captured in the claims under the ICD-10 diagnosis code. Furthermore, a study from China reported distributions of hepatic manifestations (e.g., 22% cirrhosis and 11% cirrhotic complications) which were similar to our findings.[19]

WD patients in our study were in the typical age range for first symptom onset and disease progression (between the second and sixth decade of life). We found a slightly lower mean age in the psychiatric subtype compared to the other subtypes, which might reflect that psychiatric manifestations are often the first symptoms.[7] The earlier diagnosis of psychiatric WD may highlight a critical gap in care for these patients, as neurologic and psychiatric involvements have been previously assessed in tandem, with neurologic symptoms becoming more apparent later in life. Given the recessive nature of WD, the results confirmed the expectation of a relatively even distribution of cases across genders, which also aligns with previous studies conducted in France,[20] and Hong Kong.[19] The geographical distribution within the US, with a larger portion of patients coming from the South and fewer from the Northeast, might correspond to the distribution of major university centres in the US where WD patients are typically diagnosed. Given the nature of the disease, it is not surprising that patients were primarily in the care of gastroenterologists (most pronounced in hepatic patients), though a considerable fraction of patients was also diagnosed or treated by general or family practitioners who might be the first contact points. The high rate of patients never treated with a reimbursable WD medication during the study period was likely due to the use of OTC zinc preparations which are not covered by insurers in the US, the refusal to take medications and rely solely on a low-copper diet, or the hypothesis that some physicians used the WD diagnosis code to initiate further testing for the patients but did not prescribe a WD medication at that initial stage. Further investigation on this aspect is warranted given the chronic nature of this disease.

Furthermore, our results demonstrated that WD patients were diagnosed with a broad spectrum of comorbidities, most frequently affecting joints, soft tissues, and the cardiovascular system, as well as pain symptoms and metabolic disorders. Comorbidities of WD are rarely described in the literature and vary considerably, however, our findings are at least partially consistent with comorbidities reported in the literature. Kruger et al and Dziezyc et al described that the most common complications in WD patients were pain, renal, neurologic, cardiac, skin, osteoarticular, or endocrinologic complications and included other organ disturbances. [21,22]

Only a few population-based studies assessing WD epidemiology have been performed to date world-wide. It is challenging to compare the results from this study to other reports, because of the heterogeneity of the disease and of the heterogeneity in population, diagnosis, and methodologies employed in other studies assessing WD epidemiology. However, the observed prevalence estimates (US-adjusted prevalence: 22.0 patients per million) align well within the WD prevalence range reported in other claims-based studies in France (15 per million), [23] and China (17.9 per million),[19] while estimates from a claims-based study in South Korea were slightly higher (38.7 per million).[24] Two recent systematic literature reviews assessed WD prevalence data originating from population-based epidemiological as well as genetic studies.[11,25] Sandahl et al. reported a crude population-based prevalence between 25 and 34.5 per million,[25] and underlined that specific populations in Croatia, Sardinia, Israel, Costa Rica, Middle Eastern countries, Pakistan and India had considerably higher prevalence estimates, either related to consanguinity or higher mutation frequencies. Gao et al. performed a meta-analysis resulting in a pooled population-based prevalence of 14 patients per million.[11] Both reviews mentioned that at least in some studies a higher genetic vs. clinically based prevalence could be observed. Gao et al. reported a pooled prevalence at birth of 127 per million.[11] Overall, it seems evident that many factors such as the still uncertain mutational spectrum and penetrance of WD variants, the unclear effect of combined mutations and epigenetic factors, methodological differences in studies, underdiagnosis, changes in diagnostic awareness and treatment options over time, as well as geographic factors may influence WD prevalence estimates. Thus, it is important to assess epidemiological data from large, population-based studies, as the one presented here.

Strengths and limitations

This study benefitted from several strengths. Data elements extracted from claims, some of which are not generally available in literature or patient registries, are collected routinely in clinical practice and represent real-world activities and outcomes. The real-world nature of the data helps estimate the observed frequency of diagnosed diseases using ICD-10 codes. The ICD-10 codes for WD are highly specific, despite any limitations in coding or misdiagnosis which may occur. The Komodo claims data have a large number of patients and are nationally representative based on comparisons made to the US census estimates (by age, sex, and region). The closed claims provide a longitudinal history that facilitates the analysis of the natural history of the disease, healthcare utilization, and treatment dynamics. Of note, the crude prevalence observed in this study between 2017 and 2019 was comparable to the US age-standardized adjusted results, reaffirming the representativeness of the Komodo data for rare disease research in the US. The classification of patients into subtypes, and especially the novel approach to differentiate psychiatric symptoms from neurological symptoms, was a further strength of this study.

There are some general limitations inherent to claims data, such as the potential for errors in diagnosis coding or record keeping at the point of the HCP. Since claims data are used for billing purposes, they only include records for the insured population, therefore projections of the US population assume similarities between the insured and uninsured patients. Leveraging secondary data requires an algorithm for case identification and validated algorithms specific to WD do not currently exist. Claims data contain only reimbursed medical services and thus e.g., results of lab tests or patient-reported outcomes are not captured.

In addition, there were some limitations specific to this study. Epidemiological trends over time were hard to assess given the limited study period and the introduction of the new WD-specific ICD-10 code. Only symptomatic conditions were captured under the ICD-10 code; therefore, no inferences can be made regarding pre-symptomatic patients with WD. The used claims data did not capture information on OTC medications and the treated patients represented the proportion of patients with prescription treatment only.

Conclusions

This claims study provides important real-world data on the prevalence of WD in the US and revealed the extent of comorbidities associated with various disease subtypes. The results of this study extend existing research findings and provide a comprehensive epidemiological basis for guiding physicians and policy makers in the management of this chronic disease.

Declarations

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Authors' Contributions

SF, CS, KHW and PH were responsible for the design, writing and editing of the final version of the manuscript. SF, CS and HC were responsible for the execution of the study and HC was responsible for the analysis of the data. All authors had critically reviewed the manuscript and approved its final version.

Financial Disclosures of all authors (for the preceding 12 months)

PH has no financial relationships to disclose. KHW advises for Alexion, Univar, Orphalan, Desitin, Tilomed, Ultragenyx, Pfizer, Vivet therapeutics, Abbvie. HC is an employee of Cerner Enviza, an Oracle company, which has provided consultancy for Alexion Pharmaceuticals.

Financial Disclosures

PH has no financial relationships to disclose. KHW declares no conflicts of interest that pertains to this work. SF is an employee of Alexion, AstraZeneca Rare Disease and may own stock in AstraZeneca.

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Figure Legends

Figure 1: Distribution of WD subtypes by gender (a) and age (b)

Figure 2: Most frequent (Top-10) comorbidities of WD patients

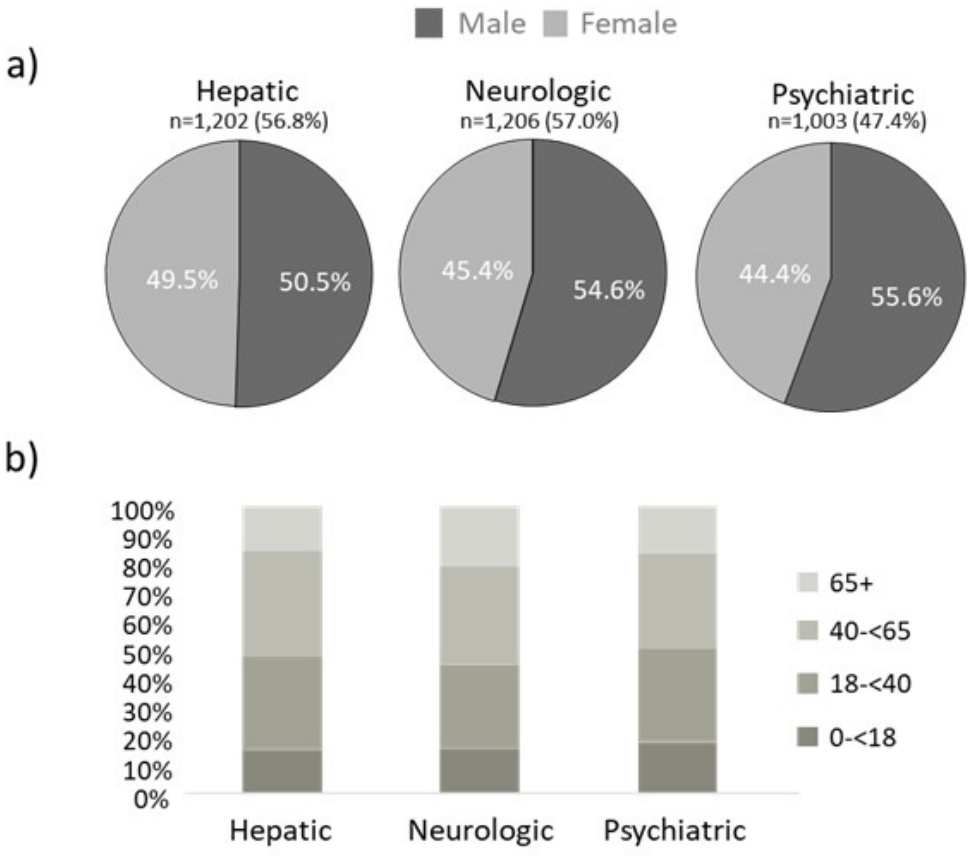

Figure 1: Distribution of WD subtypes by gender (a) and age (b)

98x86mm (150 x 150 DPI)

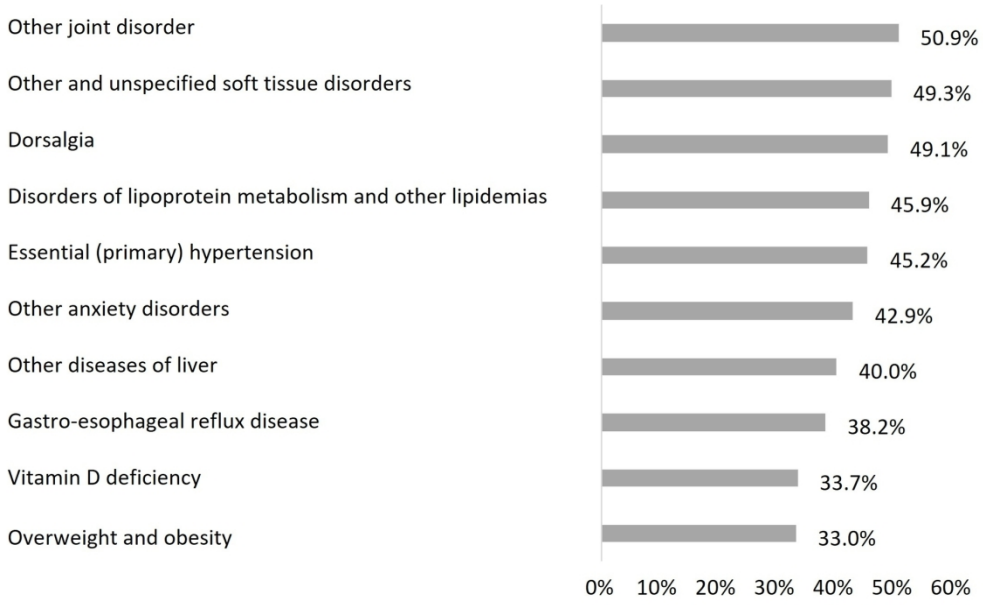

Figure 2: Most frequent (Top-10) comorbidities of WD patients

166x101mm (300 x 300 DPI)

Table 1: *Most frequent (Top-3) WD manifestations by subtype*

Manifestations	***N***	***% subtype***	***% overall cohort (N=2,115)***
Hepatic subtype* (N=1,202)			
Liver signs and symptoms	1,092	90.8%	51.6%
Cirrhosis	456	37.9%	21.6%
Hepatitis	347	28.9%	16.4%
Neurologic subtype* (N=1,206)			
Cognitive defects	611	50.7%	28.9%
Ataxia and gait abnormalities	436	36.2%	20.6%
Dysphagia	328	27.2%	15.5%
Psychiatric subtype* (N=1,003)			
Mood disorders	867	86.4%	41.0%
Mix of symptoms, children	224	22.3%	10.6%
Paranoia and schizophrenia	199	19.8%	9.4%

* These groups are not mutually exclusive.

Table 1: *Selected baseline characteristics of WD patients, overall and by subtype*

	Hepatic* N=1,202	***Neurologic* N=1,206***	***Psychiatric* N=1,003***	***Overall N=2,115***
Age at index date (years), *mean (SD)*	40.4 (19.08)	42.3 (20.70)	39.2 (20.19)	39.9 (20.06)
Male, *N (%)*	607 (50.5%)	659 (54.6%)	558 (55.6%)	1,096 (51.8%)
US Region of residence at index, *N (%)*				
Northeast	254 (21.1%)	246 (20.4%)	182 (18.2%)	462 (21.8%)
South	376 (31.3%)	398 (33.0%)	332 (33.1%)	647 (30.6%)
Midwest	275 (22.9%)	292 (24.2%)	249 (24.8%)	502 (23.7%)
West	297 (24.7%)	270 (22.4%)	240 (23.9%)	504 (23.8%)
Physician specialty of primary WD diagnosis, *N (%)***				
Gastroenterology	197 (16.4%)	117 (9.7%)	90 (9.0%)	279 (13.2%)
General / Family Practice	136 (11.3%)	133 (11.0%)	124 (12.4%)	266 (12.6%)
Ophthalmology / Optometry	61 (5.1%)	59 (4.9%)	50 (5.0%)	101 (4.8%)
Neurology	41 (3.4%)	75 (6.228%)	48 (4.8%)	88 (4.2%)
Follow-up period (years), *mean (SD)*	2.2 (1.28)	2.1 (1.25)	2.1 (1.26)	2.2 (1.27)
Never treated, *N (%)*	962 (80.0%)	1,044 (86.6%)	881 (87.8%)	1,755 (83.0%)

* These groups are not mutually exclusive.
** This is the primary physician specialty for the first claim with WD as the primary diagnosis. Due to limitations in the analysis of the prevalent WD population, it cannot be inferred with certainty that it represents the first diagnosis.

Table 1: *Crude and age-standardized WD period prevalence 2017–2019*

	N	Prevalence per million (95% CI)
Crude prevalence (overall)	1,481	21.2 (20.1-22.3)
Age		
0- <18	256	12.4 (10.9-14.0)
18-<40	490	27.1 (24.7-29.5)
40-<65	581	26.1 (24.0-28.2)
65+	154	17.1 (14.4-19.8)
Sex		
Male	697	21.2 (19.7-22.8)
Female	784	21.1 (19.7-22.6)
Region		
Northeast	344	24.1 (21.6-26.7)
South	439	18.4 (16.7-20.1)
Midwest	355	22.2 (19.9-24.5)
West	319	21.6 (19.2-24.0)
Missing	24	
US-adjusted prevalence	1,481	22.0 (20.9-23.1)
WHO-adjusted prevalence	1,481	21.4 (20.4-22.5)

**Standardized to the age distribution of the total world population in year 2000-2025, according to WHO
***Standardized to the age distribution of the total US population in year 2010, according to Census Bureau

Fang et al. Supplemental Material

Supplementary Table 1. *ICD-10 Codes for identification of hepatic subtype*

	ICD-10 Code	Description
Elevated serum aminotransferases	R74	Nonspecific elevation of levels of transaminase and lactic acid dehydrogenase [LDH]
Acute hepatitis (not viral)	K72	Acute and subacute hepatic failure
Coagulopathy	D68	Coagulation defect, unspecified
Hepatic encephalopathy	5722	Hepatic encephalopathy
	K727	Hepatic encephalopathy
Cirrhosis (decompensated or compensated)	K717	Toxic liver disease with fibrosis and cirrhosis of liver
	5715	Cirrhosis of liver without mention of alcohol
	K74	Fibrosis and cirrhosis of liver
Liver failure	K704	Alcoholic hepatic failure
	K711	Toxic liver disease with hepatic necrosis
	K720	Acute and subacute hepatic failure
	K721	Chronic hepatic failure
	K729	Hepatic failure, unspecified
Variceal hemorrhage	I8501	Esophageal varices with bleeding
	I8511	Secondary esophageal varices with bleeding
	I983	Esophageal varices with bleeding in diseases classified elsewhere
	4560	Esophageal varices with bleeding
	45620	Esophageal varices in diseases classifies elsewhere, with bleeding
Portal hypertension	K766	Portal hypertension
	5723	Portal hypertension
Hepatocellular carcinoma	C220	Liver cell carcinoma

Supplementary Table 2. *ICD-10 Codes for identification of neurological subtype*

	ICD-10 Code	Description
Tremor	R251	Tremor, unspecified
	G251	Drug-induced tremor
	G252	Other specified forms of tremor
	G250	Essential tremor

	3331	Essential and other specified forms of tremor
Parkinsonism or akinetic rigid syndrome	G20	Parkinson's disease
	G219	Secondary parkinsonism, unspecified
	G218	Other secondary parkinsonism
	G2122	Neuroleptic induced parkinsonism
	G214	Vascular parkinsonism
	G2119	Other drug induced secondary parkinsonism
	3321	Secondary parkinsonism
	G212	Secondary parkinsonism dur to other external agents
	G213	Postencephalitic parkinsonism
	G8903	Parkinson's disease mg
	G211	Other drug induced secondary parkinsonism
	G22	Parkinsonism in diseases classified elsewhere
	G21	Secondary parkinsonism
Gait abnormalities/ataxia	R2689	Other abnormalities of gait and mobility
	R269	Unspecified abnormalities of gait and mobility
	R26	Abnormalities of gait and mobility
	R268	Other abnormalities of gait and mobility
	R270	Ataxia, unspecified
Dysarthria	78451	Dysarthria
	R471	Dysarthria and anarthria
	I69222	Dysarthria following other nontraumatic intracranial hemorrhage
	I69022	Dysarthria following nontraumatic subarachnoid hemorrhage
Dystonia	G249	Dystonia, unspecified
	G248	Other dystonia
	G24	Dystonia
Pseudobulbar palsy	G1220	Motor neuron disease unspecified
	33523	Pseudobulbar palsy
Seizures	G40	Epilepsy and recurrent seizures
	F445	Conversion disorder with seizures or convulsions
	R568	Other and unspecified convulsions
Migraine	G43	Migraine
Somatoform autonomic dysfunction	F45	Somatoform disorders

Cognitive disorder	G3184	Mild cognitive impairment, so stated
	F03	Unspecified dementia
	F05	Delirium due to known physiological condition
	F06	Other mental disorders due to known physiological condition
	331883	Mild cognitive impairment, so stated

Supplementary Table 3. *ICD-10 Codes for identification of psychiatric subtype*

	ICD-10 Code	Description
Depression	F32	Major depressive disorder, single episode
	F33	Major depressive disorder, recurrent
	F34	Persistent mood disorder
Neuroses	F48	Nonpsychotic mental disorder, unspecified
	F40	Phobic anxiety disorder
	F41	Other anxiety disorder
	F42	Obsessive compulsive disorder
	F43	Reaction to severe stress and adjustment disorders
	F44	Dissociative and conversion disorders
	F45	Somatoform disorders
Psychosis	F29	Unspecified psychosis not due to substance or known psychological condition
	F20	Schizophrenia
	F21	Schizotypal disorder
	F22	Delusional disorders
	F23	Brief psychotic disorder
	F24	Shared psychotic disorder
	F25	Schizoaffective disorder
	F28	Other psychotic disorder not due to a substance or known physiological condition
Personality changes	F07	Personality change due to known physiological condition
	F60	Specific personality disorder
	F61	Mixed and other personality disorder
	F62	Enduring personality change
Bipolar disorder	F31	Bipolar affective disorder

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Wilson Disease in the US - Epidemiology and Real-World Patient Characteristics Based on a Retrospective Observational Health Claims Study

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Abstract

Objectives: To describe the epidemiology, patient characteristics and comorbidities in patients with Wilson disease (WD) in the US.

Design: Retrospective, population-based study

Setting: The study used the US Komodo claims database containing records regarding medical claims for over 120 million individuals.

Participants: Patients with WD were identified via ICD10 code during the study period 2016–2019. A further stratification by disease subtype ("hepatic", "neurologic" and "psychiatric") was performed.

Main outcome measures: WD prevalence was reported by age, sex, and US census regions/divisions. Adjusted prevalence was calculated using age-specific prevalence standardized to the US (2010 US census) and to the world (WHO 2000–2025) to enable comparisons across countries, using direct standardization of prevalence estimates by age group.

Results: Overall, 2,115 WD patients were identified during the study period. Among them, 56.8% had hepatic symptoms, 57.0% neurologic symptoms and 47.4% psychiatric symptoms. The most frequent manifestations in hepatic patients were liver signs and symptoms (90.8%), in neurologic patients cognitive defects (50.7%), and in psychiatric patients mood disorders (86.4%). The mean age in the overall cohort was 39.9 years. Prevalence estimation was based on 1,481 WD patients between 2017 and 2019. The 2017–2019 crude period prevalence was 21.2 patients per million (95% confidence interval: 20.1–22.3), with similar prevalence observed for both sexes.

Conclusions: This study provides important real-world data on the diagnosed prevalence of WD in the US and revealed the comorbidities associated with various disease subtypes, thereby providing a comprehensive basis for guiding physicians and policy makers in the management of this chronic disease.

Strengths and limitations of this study

- This study estimated the diagnosed prevalence of WD for the first time in the US, by using a large, nationally representative claims database . The real-world nature of the data helps estimate the observed frequency of Wilson disease in the US using ICD-10 codes specific to WD.
- The classification of patients into subtypes, and especially the novel approach to differentiate psychiatric symptoms from neurological symptoms, was a further strength of this study.
- Besides general limitations inherent to claims data, the limitations specific to this study included a limited study period after the introduction of a new WD-specific ICD-10 code in 2015.
- The used claims data did not capture information on OTC medications and the treated patients represented the proportion of patients with prescription treatment only.

Introduction

Wilson disease (WD) is an autosomal recessive condition which leads to an excessive copper deposition in body organs, particularly in the liver and the central nervous system.[1] This genetic disorder is caused by mutations of the P-type ATPase copper transporter *ATP7B* gene located in the human chromosome 13.[2] To date, more than 600 variants in the *ATP7B* gene have been described, and most WD patients are compound heterozygous with two different *ATP7B* variants, complicating and prolonging genetic WD diagnosis.[3] WD generally presents in childhood and young adulthood with the most common age of presentation between 10 and 20 years, though patients can occasionally present before the age of 5 years and after the age of 70 years.[4]

Clinical presentation of WD includes a combination of hepatic, neurologic, psychiatric, and ophthalmologic symptoms. Psychiatric symptoms often precede the diagnosis of WD and include personality changes, depression, cognitive changes, and anxiety.[5] The neurologic symptoms of WD mostly refer to dysfunction in the extrapyramidal system including dysarthria, dystonia, gait abnormalities, tremor, parkinsonism, chorea, and seizures.[6] Psychiatric symptoms have been only recently recognized as independent manifestations of WD, as it was previously assumed that they occur together with neurological symptoms, and patients were often referred to as having neuro-psychiatric disorders.[7] The symptoms related to hepatic dysfunction in WD can range from an asymptomatic increase in liver enzyme levels to severe liver failure. Typically, early on in disease progression there is a mild increase in transaminases, which then may progress to chronic active hepatitis, followed by fibrosis and cirrhosis.[8]

WD is a rare disease with recent worldwide clinical prevalence estimates ranging from approximately 16.7 to 25 patients per million,[9] although the prevalence can vary across countries and may be higher in selected regions such as in some Asian communities.[10] Interestingly, there is a discrepancy of WD prevalence estimates originating from epidemiological compared to genetic studies and recent genetic data with a considerably higher prevalence (139 per million) indicate that the prevalence of WD may be underestimated.[11] The possibility of underdiagnosis, misdiagnosis and the lack of accounting for incomplete variant penetrance in the genetic calculations were hypothesized as the main reasons for

the observed inconsistency between genetic vs. clinical data.[11,12] For the US, population-based epidemiological data are still scarce. A previous study reported a genetic birth prevalence of 18.2 per million births,[13] and an abstract on cardiac manifestations in WD reported a prevalence of 26 patients per million, but no details of methodology.[14]

Thus, large population-based studies assessing the epidemiology of WD and its subtypes in the US are needed, allowing for a greater characterization around the spectrum of disease severity and the diagnosed prevalence of WD. Here we present the US-specific data from a recently completed multi-country real-world evidence study that used claims data to investigate various aspects of WD in a real-life setting including epidemiology and patient demographic and clinical characteristics.

Methods

Study design

This retrospective, population-based observational study used health insurance claims data to assess WD epidemiology and patient characteristics using the US Komodo Health claims database available from 2012–2020.[15] Komodo's private payor-complete database contains records regarding prescription and/or medical claims for over 120 million individuals, collected from more than 150 private insurers in the US, including Medicaid managed-care and Medicare Advantage plans. This study used the closed claims available in the database. Closed claims come directly from the payer and provide the complete patient journey, such as full medical and/or prescription benefit information including insurance eligibility.

Population

Patients were selected based on their first reported WD diagnosis (index event) in the claims database between 2016 and 2019 (study period). The diagnosis was based on code (ICD-10 code E83.01 or ICD-9-CM code 275.1 prior to October 1, 2015). The standard ICD-9 diagnostic code for WD could also include another rare condition called Menkes disease. The WD-specific ICD-10 code (E83.01) was introduced in the US on October 1, 2015. A WD diagnosis was defined as at least one inpatient or two outpatient visits with a WD ICD-10 code, separated by at least 30 days during the study period.

No age restriction was imposed. Patients were excluded from the study if they had at least one prescription for a copper replacement drug during the study period. This was applied to rule out patients with Menkes disease which is treated by copper replacement drugs.

Cohorts and subgroups

The cohort presented here includes patients that fulfilled the criteria for at least one WD diagnosis at any time during the study period (2016–2019) and a continuous enrollment for at least one calendar year before the index event. Separately, prevalence was assessed in the period between 2017 and 2019 for patients that had a history of at least one WD diagnosis at any time during that period and a continuous enrollment for at least two calendar years. This separate assessment period for prevalence estimation was based on the WD-specific diagnosis code becoming effective in the US only in 2015. Due to the possibility of miscoding, the most accurate prevalence estimation of WD can be made between 2017 and 2019, as this period includes at least one full calendar year since the introduction of the new code.

A further stratification by WD subtypes was performed. The subtypes “hepatic”, “neurologic” and “psychiatric” were not mutually exclusive or strictly delineated but were based on the presence of signs and symptoms. Patients were assigned to the hepatic subtype if they were diagnosed with liver signs and symptoms, acute hepatitis (not viral), cirrhosis (decompensated or compensated), liver failure, portal hypertension, or hepatocellular carcinoma. Patients assigned to the neurologic subtype had a diagnosis for tremor, parkinsonism or akinetic rigid syndrome, gait abnormalities/ataxia, dysarthria, dystonia, chorea, dysphagia, myopathy, seizures, migraine, somatoform autonomic dysfunction or cognitive disorder. Patients diagnosed with mood disorders, paranoia/schizophrenia, psychosis, or personality disorders were assigned to the psychiatric subtype. WD manifestations were defined as the occurrence of specific signs or symptoms associated with each of the subtypes and were identified using respective ICD-10 codes (see **Supplementary Tables 1–3**).

Variables

Data on patient characteristics (age, sex, region of residence), physician specialty, proportion of patients never treated, distribution of subtypes and manifestations were ascertained at baseline.

Comorbidities were assessed during the study period (2016–2019). Overall, age-, sex-, and region-specific prevalence (crude and age-adjusted period prevalence) were assessed in the period between 2017 and 2019. A rationale for considering a period prevalence rather than an annual prevalence was that the identification of WD patients was based on ICD-10 codes, without considering WD treatment or laboratory records, and the assumption that WD patients who are well managed using over the counter (OTC) or prescription medication may not necessarily visit a health care provider (HCP) each year. A further reason for using a period prevalence was to account for possible misdiagnosis in the first year after the introduction of the ICD-10 code for WD.

Data analysis

Descriptive statistics were calculated for demographic and baseline characteristics (overall and by subtype). Means and standard deviations (SDs) were provided for continuous or discrete data. Frequencies and percentages were provided for categorical data. For WD manifestations, the frequencies of occurrence of specific ICD-10 codes within subtypes and within the overall patient cohort were calculated and the three most frequent manifestations were listed by subtype. For comorbidities, all recorded diagnoses (ICD-10 codes level-3) at any time during the study period were ranked according to frequency and a list of the 10 most frequent comorbidities in the overall cohort were reported. In addition, the Charlson Comorbidity index (CCI; version of 2011), an assessment tool designed to predict mortality in patients with multiple comorbidities,[16] was assessed for each patient and a mean score including SD (higher scores indicating greater mortality risk and more severe comorbid conditions) was calculated for the overall cohort. Crude period prevalence was calculated from the number of WD cases identified and was expressed as patients per million including 95% confidence intervals (CI). The denominator was the number of patients with continuous enrollment spanning the period of interest (2017–2019) and the numerator was any patient from the denominator with at least one WD diagnosis claim during the period of interest. Prevalence was reported by age, sex, and US census regions/divisions. Adjusted prevalence was calculated using age-specific prevalence standardized to the US (2010 US census) and to the world (WHO 2000–2025) to enable comparisons across countries, using direct standardization of prevalence estimates by age group.

Ethics statement

This was a multinational study which was approved by an institutional review board (IRB) and/or independent ethics committee (IEC) in each participating country. The IRB for the US was Pearl Pathways. The study was conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor, and followed generally accepted research practices described in Good Pharmacoepidemiology Practices guidelines issued by the International Society for Pharmacoepidemiology. The Institutional board and approval were: Pearl Pathways IRB and Approval number is #20-KANT-224

Patient and public involvement

Patients or the public were not actively involved in this observational study.

Data availability statement

The data that support the findings of this study are available from Komodo Health. Restrictions apply to the availability of these data, which were used under license for this study. Access to data must be requested through Oracle.

Results

WD subtypes and manifestations

The observed cohort included 2,115 WD patients identified between 2016 and 2019. Among these, more than half had hepatic and/or neurologic symptoms (56.8% and 57.0%, respectively) and around half had psychiatric symptoms (47.4%). Most patients had overlapping subtypes, presenting concomitantly with hepatic, neurologic, and/or psychiatric symptoms, presenting concomitantly with hepatic, neurologic, and/or psychiatric signs and symptoms (see **Supplementary Figure 1**). For instance, 734 (34.7%) had 2 overlapping conditions of hepatic, neurologic, and/or psychiatric and 422 (20.0%) WD patients presented with concomitant hepatic, neurological, and psychiatric conditions. **Figure 1** illustrates the distribution of sex (a) and age (b) within subtypes. Slightly more male than female patients had neurologic (54.6%) and psychiatric (55.6%) symptoms, whereas the sex distribution was equal in the hepatic subtype. With regards to age distribution, most patients in all subtypes were in the age groups between 18 to 39 years and 40 to 64 years. The distribution of young

(0–17 years) and older (above 65 years) patients was also similar between subtypes, though there were slightly more older patients in the neurologic subtype (21% vs. 16% [hepatic] and 17% [psychiatric]).

The most frequent manifestations associated with the different subtypes and their proportion in the overall cohort are highlighted in **Table 1**. Hepatic patients most frequently experienced liver signs and symptoms (90.8%), cirrhosis (37.9%) and hepatitis (28.9%). Neurologic patients most frequently experienced cognitive defects (50.7%), ataxia and gait abnormalities (36.2%) and dysphagia (27.2%). Psychiatric patients most frequently experienced mood disorders (86.4%), a mix of symptoms in children (22.3%) and paranoia/schizophrenia (19.8%).

Baseline characteristics

Selected baseline characteristics of the overall cohort and by subtype are displayed in **Table 2**. The mean age in the overall cohort was 39.9 years (SD=20.1 years). The lowest mean age was reported for the psychiatric subtype (39.2 years, SD=20.2 years) and the highest for the neurologic subtype (42.3 years, SD=20.7 years). Overall, 51.8% were male patients. A larger portion of patients came from the South (30.6%) and fewer from the Northeast (21.8%) with little difference between subtypes. While for a majority (54.2%) of overall WD cases no information was available regarding the specialists managing the primary WD diagnosis, the available results showed that patients were mostly in the care of gastroenterologists (13.2%) and general/family practitioners (12.6%). Hepatic patients were more frequently seen by gastroenterologists (16.4%), as compared to the other subtypes (9.7% of neurologic patients and 9.0% of psychiatric patients). On average, patients were followed up for 2.2 years (SD=1.3 years) with little difference between subtypes. Among all patients, the majority (83.0%) were never treated with a reimbursable WD prescription medication during the study period.

Comorbidities

WD patients were diagnosed with a broad spectrum of comorbidities. The most common clinical conditions diagnosed during the study period included other joint disorders (50.9%), unspecified soft tissue disorders (49.3%), dorsalgia (49.1%), disorders of lipoprotein metabolism and other lipidemias (45.9%), essential hypertension (45.2%), anxiety disorders (42.9%), and other diseases of liver

(40.0%), **Figure 2**. The extent of comorbidities was also reflected by a mean CCI score of 1.92 (SD=2.68).

Prevalence

Prevalence estimation was based on 1,481 WD patients between 2017 and 2019. The 2017–2019 crude period prevalence was 21.2 patients per million (95% CI: 20.1–22.3), with similar prevalence observed for both sexes (male: 21.2 per million, 95% CI: 19.7–22.8 and female: 21.1 per million, 95% CI: 19.7–22.6), **Table 3**. The crude period prevalence peaked among young adults in the 18 to 39 years age group (27.1 per million, 95% CI: 24.7–29.5), followed closely by adults 40 to 64 years old (26.1 per million, 95% CI: 24.0–28.2). The highest crude period prevalence was recorded in the Northeast (24.1 per million, 95% CI: 21.6–26.7), followed by the Midwestern (22.2 per million, 95% CI: 19.9–24.5), Western (21.6 per million, 95% CI: 19.2–24.0), and Southern (18.4 per million, 95% CI: 16.7–20.1) regions of the US.

Adjusted period prevalence was calculated using age-specific prevalence standardized to the US (2010 US census) and to the world (WHO 2000–2025). Between 2017 and 2019, both the US-adjusted and WHO-adjusted period prevalences were similar (22.0 per million, 95% CI: 20.9–23.1 and 21.4 per million, 95% CI: 20.4–22.5, respectively) to the crude period prevalence observed in this study.

Discussion

Principal findings and implications

There is a gap of knowledge regarding the epidemiology and clinical characteristics of WD patients from a national and international perspective. In this large population-based study we assessed WD patient characteristics and epidemiology in the US.

Approximately two-thirds of the cohort showed hepatic and/or neurologic symptoms, which is consistent with the natural disease course, as WD mostly affects the liver and brain.[17] Typically, hepatic symptoms precede the onset of neurologic symptoms and may thus be diagnosed at a younger age[2]. In line with this, though not as evident in the age distribution by subtypes, the mean age at index in the hepatic subtype was slightly lower compared to the neurologic subtype. In agreement with our

data on sex distribution in the neurologic and psychiatric subtypes, a registry-based study observed that the neuropsychiatric WD form occurred more frequently in men (67%) vs. women (49%).[18]

Our results also revealed the extent of comorbidities associated with various disease subtypes, as some of the most frequently reported manifestations were quite severe (e.g., around 40% of patients in the hepatic subtype presented with cirrhosis). The frequency of hepatic, neurologic, and psychiatric presentations, as well as the manifestations within these subtypes varies considerably in other published studies.[4] Considering the great variability in WD symptoms, it is likely that there is referral bias. A review of several independent case series suggested that dysarthria, gait abnormality/ataxia and dystonia are the most frequent manifestations in the neurologic subtype, which partially reflects our findings.[4] The higher rates of dystonia and dysarthria reported in the literature may be explained by the fact that only symptomatic conditions that require treatment get captured in the claims under the ICD-10 diagnosis code. Furthermore, a study from China reported distributions of hepatic manifestations (e.g., 22% cirrhosis and 11% cirrhotic complications) which were similar to our findings.[19]

WD patients in our study were in the typical age range for first symptom onset and disease progression (between the second and sixth decade of life). We found a slightly lower mean age in the psychiatric subtype compared to the other subtypes, which might reflect that psychiatric manifestations are often the first symptoms.[7] The earlier diagnosis of psychiatric WD may highlight a critical gap in care for these patients, as neurologic and psychiatric involvements have been previously assessed in tandem, with neurologic symptoms becoming more apparent later in life. Given the recessive nature of WD, the results confirmed the expectation of a relatively even distribution of cases across sexes, which also aligns with previous studies conducted in France,[20] and Hong Kong.[19] The geographical distribution within the US, with a larger portion of patients coming from the South and fewer from the Northeast, might correspond to the distribution of major university centres in the US where WD patients are typically diagnosed. Given the nature of the disease, it is not surprising that patients were primarily in the care of gastroenterologists (most pronounced in hepatic patients), though a considerable fraction of patients was also diagnosed or treated by general or family practitioners who might be the first contact points. The high rate of patients never treated with a reimbursable WD medication during the study

period was likely due to the use of OTC zinc preparations which are not covered by insurers in the US, the refusal to take medications and rely solely on a low-copper diet, or the hypothesis that some physicians used the WD diagnosis code to initiate further testing for the patients but did not prescribe a WD medication at that initial stage. Further investigation on this aspect is warranted given the chronic nature of this disease.

Furthermore, our results demonstrated that WD patients were diagnosed with a broad spectrum of comorbidities, most frequently affecting joints, soft tissues, and the cardiovascular system, as well as pain symptoms and metabolic disorders. Comorbidities of WD are rarely described in the literature and vary considerably, however, our findings are at least partially consistent with comorbidities reported in the literature. Kruger et al and Dziezyc et al described that the most common complications in WD patients were pain, renal, neurologic, cardiac, skin, osteoarticular, or endocrinologic complications and included other organ disturbances. [21,22]

Only a few population-based studies assessing WD epidemiology have been performed to date world-wide. It is challenging to compare the results from this study to other reports, because of the heterogeneity of the disease and of the heterogeneity in population, diagnosis, and methodologies employed in other studies assessing WD epidemiology. However, the observed prevalence estimates (US-adjusted prevalence: 22.0 patients per million) align well within the WD prevalence range reported in other claims-based studies in France (15 per million), [23] and China (17.9 per million),[19] while estimates from a claims-based study in South Korea were slightly higher (38.7 per million).[24] Two recent systematic literature reviews assessed WD prevalence data originating from population-based epidemiological as well as genetic studies.[11,25] Sandahl et al. reported a crude population-based prevalence between 25 and 34.5 per million,[25] and underlined that specific populations in Croatia, Sardinia, Israel, Costa Rica, Middle Eastern countries, Pakistan and India had considerably higher prevalence estimates, either related to consanguinity or higher mutation frequencies. Gao et al. performed a meta-analysis resulting in a pooled population-based prevalence of 14 patients per million.[11] Both reviews mentioned that at least in some studies a higher genetic vs. clinically based prevalence could be observed. Gao et al. reported a pooled prevalence at birth of 127 per million.[11]

Overall, it seems evident that many factors such as the still uncertain mutational spectrum and penetrance of WD variants, the unclear effect of combined mutations and epigenetic factors, methodological differences in studies, underdiagnosis, changes in diagnostic awareness and treatment options over time, as well as geographic factors may influence WD prevalence estimates. Thus, it is important to assess epidemiological data from large, population-based studies, as the one presented here.

Strengths and limitations

This study benefitted from several strengths. Data elements extracted from claims, some of which are not generally available in literature or patient registries, are collected routinely in clinical practice and represent real-world activities and outcomes. The real-world nature of the data helps estimate the observed frequency of diagnosed diseases using ICD-10 codes. The ICD-10 codes for WD are highly specific, despite any limitations in coding or misdiagnosis which may occur. The Komodo claims data are large and nationally representative based on comparisons made to the US census estimates (by age, sex, and region). The closed claims provide a longitudinal history that facilitates the analysis of the natural history of the disease, healthcare utilization, and treatment dynamics. Of note, the crude prevalence observed in this study between 2017 and 2019 was comparable to the US age-standardized adjusted results, reaffirming the representativeness of the Komodo data for rare disease research in the US. The classification of patients into subtypes, and especially the novel approach to differentiate psychiatric symptoms from neurological symptoms, was a further strength of this study.

There are some general limitations inherent to claims data, such as the potential for errors in diagnosis coding or record keeping at the point of the HCP. Since claims data are used for billing purposes, they only include records for the insured population, therefore projections of the US population assume similarities between the insured and uninsured patients. Leveraging secondary data requires an algorithm for case identification and validated algorithms specific to WD do not currently exist. Claims data contain only reimbursed medical services and thus e.g., results of lab tests or patient-reported outcomes are not captured.

In addition, there were some limitations specific to this study. Epidemiological trends over time were hard to assess given the limited study period and the introduction of the new WD-specific ICD-10 code. Only symptomatic conditions were captured under the ICD-10 code; therefore, no inferences can be made regarding pre-symptomatic patients with WD. The claims data did not capture information on laboratory testing well, and results are not available in claims data. Further the claims data did not capture OTC medications and thus the treated patients represented the proportion of patients with prescription treatment only. The proportion of patients without a claim for a WD-specific treatment was quite high and unexpected however and whether this truly reflects a large proportion of patients on OTC zinc is unclear. Further investigation is needed as to the proportion of WD patients receiving treatment in the US.

Conclusions

This claims study provides important real-world data on the prevalence of WD in the US and revealed the extent of comorbidities associated with various disease subtypes. The results of this study extend existing research findings and provide a comprehensive epidemiological basis for guiding physicians and policy makers in the management of this chronic disease.

Declarations

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Authors' Contributions

SF, CS, KHW and PH were responsible for the design, writing and editing of the final version of the manuscript. SF, CS and HC were responsible for the execution of the study and HC was responsible for the analysis of the data. SF is the guarantor. All authors had critically reviewed the manuscript and approved its final version.

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PH has no financial relationships to disclose. KHW advises for Alexion, Univar, Orphalan, Desitin, Tilomed, Ultragenyx, Pfizer, Vivet therapeutics, Abbvie. HC is an employee of Oracle America, which has provided consultancy for Alexion Pharmaceuticals.

Financial Disclosures

PH has no financial relationships to disclose. KHW declares no conflicts of interest that pertains to this work. SF is an employee of Alexion, AstraZeneca Rare Disease and may own stock in AstraZeneca.

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Tables

Table 1: *Most frequent (Top-3) WD manifestations by subtype*

Manifestations	*N*	*% subtype*	*% overall cohort (N=2,115)*
Hepatic subtype* (N=1,202)			
Liver signs and symptoms	1,092	90.8%	51.6%
Cirrhosis	456	37.9%	21.6%
Hepatitis	347	28.9%	16.4%
Neurologic subtype* (N=1,206)			
Cognitive defects	611	50.7%	28.9%
Ataxia and gait abnormalities	436	36.2%	20.6%
Dysphagia	328	27.2%	15.5%
Psychiatric subtype* (N=1,003)			
Mood disorders	867	86.4%	41.0%
Mix of symptoms, children	224	22.3%	10.6%
Paranoia and schizophrenia	199	19.8%	9.4%

* These groups are not mutually exclusive.

448

449 ***Table 2:*** *Selected baseline characteristics of WD patients, overall and by subtype*

	Hepatic* N=1,202	***Neurologic* N=1,206***	***Psychiatric* N=1,003***	***Overall N=2,115***
Age at index date (years), *mean (SD)*	40.4 (19.08)	42.3 (20.70)	39.2 (20.19)	39.9 (20.06)
Male, *N (%)*	607 (50.5%)	659 (54.6%)	558 (55.6%)	1,096 (51.8%)
US Region of residence at index, *N (%)*				
Northeast	254 (21.1%)	246 (20.4%)	182 (18.2%)	462 (21.8%)
South	376 (31.3%)	398 (33.0%)	332 (33.1%)	647 (30.6%)
Midwest	275 (22.9%)	292 (24.2%)	249 (24.8%)	502 (23.7%)
West	297 (24.7%)	270 (22.4%)	240 (23.9%)	504 (23.8%)
Physician specialty of primary WD diagnosis, *N (%)***				
Gastroenterology	197 (16.4%)	117 (9.7%)	90 (9.0%)	279 (13.2%)
General / Family Practice	136 (11.3%)	133 (11.0%)	124 (12.4%)	266 (12.6%)
Ophthalmology / Optometry	61 (5.1%)	59 (4.9%)	50 (5.0%)	101 (4.8%)
Neurology	41 (3.4%)	75 (6.228%)	48 (4.8%)	88 (4.2%)
Follow-up period (years), *mean (SD)*	2.2 (1.28)	2.1 (1.25)	2.1 (1.26)	2.2 (1.27)
Never treated, *N (%)*	962 (80.0%)	1,044 (86.6%)	881 (87.8%)	1,755 (83.0%)

450 * These groups are not mutually exclusive.
451 ** This is the primary physician specialty for the first claim with WD as the primary diagnosis. Due to limitations in the analysis of the
452 prevalent WD population, it cannot be inferred with certainty that it represents the first diagnosis.
453
454

Table 3: *Crude and age-standardized WD period prevalence 2017–2019*

	N	Prevalence per million (95% CI)
Crude prevalence (overall)	1,481	21.2 (20.1-22.3)
Age		
0- <18	256	12.4 (10.9-14.0)
18-<40	490	27.1 (24.7-29.5)
40-<65	581	26.1 (24.0-28.2)
65+	154	17.1 (14.4-19.8)
Sex		
Male	697	21.2 (19.7-22.8)
Female	784	21.1 (19.7-22.6)
Region		
Northeast	344	24.1 (21.6-26.7)
South	439	18.4 (16.7-20.1)
Midwest	355	22.2 (19.9-24.5)
West	319	21.6 (19.2-24.0)
Missing	24	
US-adjusted prevalence	1,481	22.0 (20.9-23.1)
WHO-adjusted prevalence	1,481	21.4 (20.4-22.5)

**Standardized to the age distribution of the total world population in year 2000-2025, according to WHO
***Standardized to the age distribution of the total US population in year 2010, according to Census Bureau

Figure Legends

Figure 1: Distribution of WD subtypes by sex (a) and age (b)

Figure 2: Most frequent (Top-10) comorbidities of WD patients

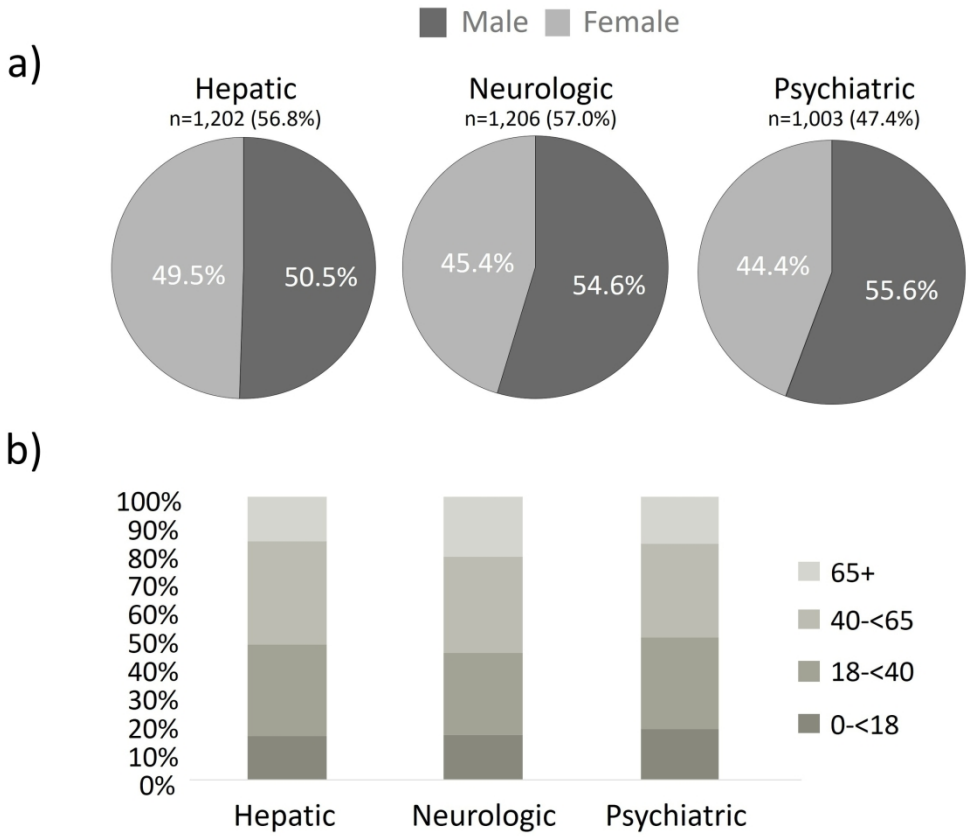


Figure 1: Distribution of WD subtypes by sex (a) and age (b)

214x184mm (300 x 300 DPI)

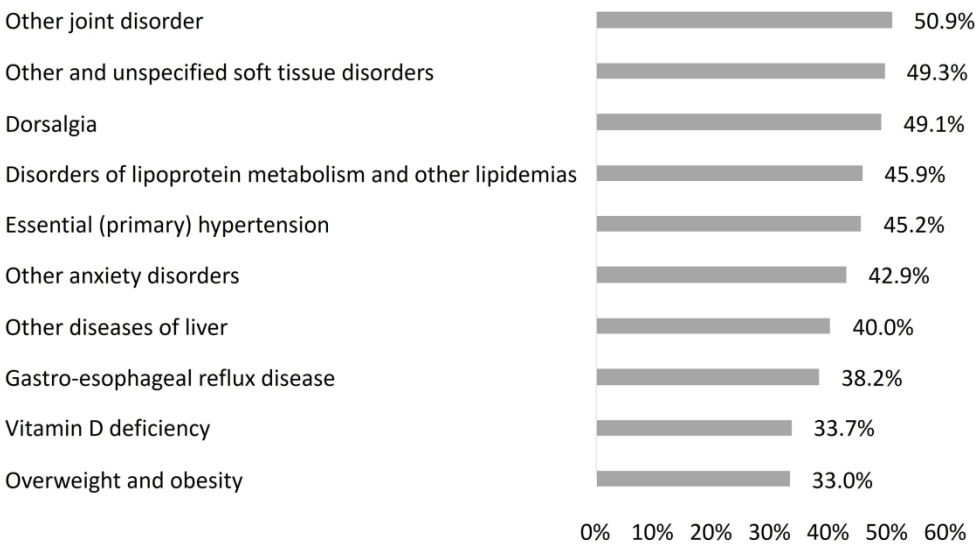


Figure 2: Most frequent (Top-10) comorbidities of WD patients

286x160mm (300 x 300 DPI)

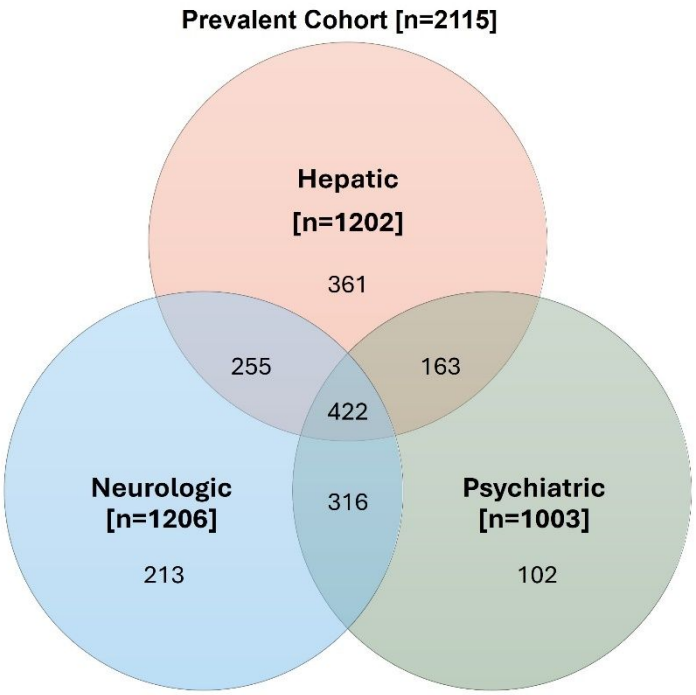
Wilson Disease in the US - Epidemiology and Real-World Patient Characteristics Based on a Retrospective Observational Health Claims Database Study - Supplementary Materials

Supplementary Methods

Data source

Komodo Health is a healthcare technology company that has built an expansive Healthcare Map including de-identified claims (>65 billion clinical, pharmacy and lab encounters) for more than 320 million U.S. patients. These encounters represent census level representation across populations (e.g., age, geography, risk pools) in the United States (US), including hospital networks, physician networks, healthcare claim processing companies (i.e. claims clearinghouses), pharmacies, and health insurers. Nearly half of the data in Komodo's Healthcare Map is comprised of "closed" datasets, which come directly from the payer and provide insight regarding the complete patient journey, such as full medical and/or prescription benefit information, including insurance eligibility. Komodo's private payer-complete population contains prescription and/or medical claims of over 120 million individuals collected from 150+ private insurers in the US. Data that is rooted in a complete patient journey provides an optimal basis for a variety of research focuses, including adherence studies, treatment pattern studies and comparative effectiveness studies within an insured population.

Supplementary Figures



Supplementary Figure 1. *Distribution of hepatic, neurologic and psychiatric Wilson disease subtypes*

Supplementary Tables

Supplementary Table 1. *ICD-10 Codes for identification of hepatic Wilson disease subtype*

	ICD-10 Code	Description
Elevated serum aminotransferases	R74	Nonspecific elevation of levels of transaminase and lactic acid dehydrogenase [LDH]
Acute hepatitis (not viral)	K72	Acute and subacute hepatic failure
Coagulopathy	D68	Coagulation defect, unspecified
Hepatic encephalopathy	5722	Hepatic encephalopathy
	K727	Hepatic encephalopathy
Cirrhosis (decompensated or compensated)	K717	Toxic liver disease with fibrosis and cirrhosis of liver
	5715	Cirrhosis of liver without mention of alcohol
	K74	Fibrosi and cirrhosis of liver
Liver failure	K704	Alcoholic hepatic failure
	K711	Toxic liver disease with hepatic necrosis
	K720	Acute and subacute hepatic failure
	K721	Chronic hepatic failure
	K729	Hepatic failure, unspecified
Variceal hemorrhage	I8501	Esophageal varices with bleeding
	I8511	Secondary esophageal varices with bleeding
	I983	Oesophageal varices with bleeding in diseases classified elsewhere
	4560	esophageal varices with bleeding
	45620	esophageal varices in diseases classifies elsewhere, with bleeding
Portal hypertension	K766	portal hypertension
	5723	portal hypertension
Hepatocellular carcinoma	C220	liver cell carcinoma

Supplementary Table 2. *ICD-10 Codes for identification of neurological Wilson disease subtype*

	ICD-10 Code	Description
Tremor	R251	tremor, unspecified
	G251	Drug-induced tremor
	G252	other specified forms of tremor
	G250	essential tremor

	3331	essential and other specified forms of tremor
Parkinsonism or akinetic rigid syndrome	G20	parkinson's disease
	G219	secondary parkinsomism, unspecified
	G218	other secondary parkinsonism
	G2122	neuroleptic induced parkinsonism
	G214	vascular parkinsomism
	G2119	other drug induced secondary parkinsonism
	3321	secondary parkinsonism
	G212	secondary parkinsonism dur to other external agents
	G213	postencephalitic parkinsonism
	G8903	Parkinson's disease mg
	G211	other drug induced secondary parkinsonism
	G22	Parkinsonism in diseases classified elsewhere
	G21	secondary parkinsonism
Gait abnormalities/ataxia	R2689	other abnormalities of gait and mobility
	R269	unspecified abnormalities of gait and mobility
	R26	abnormalities of gait and mobility
	R268	other abnormalities of gait and mobility
	R270	ataxia, unspecified
Dysarthria	78451	Dysarthria
	R471	Dysarthria and anarthria
	I69222	Dysarthria following oth nontraumatic intrcrn hemorrhage
	I69022	Dysarthria followin nontraumatic subarachnoid hemorrhage
Dystonia	G249	Dystonia, unspecified
	G248	Other dystonia
	G24	Dystonia
Pseudobulbar palsy	G1220	Motor neuron disease unspecified
	33523	Pseudobulbar palsy
Seizures	G40	Epilepsy and recurrent seizures
	F445	Conversion disorder with seizures or convulsions
	R568	Other and unspecified convulsions
Migraine	G43	Migraine
Somatoform autonomic dysfunction	F45	Somatoform disorders

Cognitive disorder	G3184	Mild cognitive imparment, so stated
	F03	Unspecified dementia
	F05	Delirium due to known physiological condition
	F06	Other mental disorders due to known physiological condition
	331883	Mild cognitive imparment, so stated

Supplementary Table 3. *ICD-10 Codes for identification of psychiatric Wilson disease subtype*

	ICD-10 Code	Description
Depression	F32	Major depressive disorder, single episode
	F33	Major depressive disorder, recurrent
	F34	Persistent mood disorder
Neuroses	F48	Nonpsychotic mental disorder, unspecified
	F40	Phobic anxiety disorder
	F41	Other anxiety disorder
	F42	Obsessive compulsive disorder
	F43	Reaction to severe stress and adjustment disorders
	F44	Dissociative and conversion disorders
	F45	Somatoform disorders
Psychosis	F29	Unspecified physchosis not due to substance or known psychological condition
	F20	Schizophrenia
	F21	schizotypal disorder
	F22	delusional disorders
	F23	brief psychotic disorder
	F24	shared psychotic disorder
	F25	schizoaffective disorder
	F28	other psychotic disorder not due to a substance or known physioogical condition
Personality changes	F07	Personality change due to known physiological condition
	F60	Specific personality disorder
	F61	Mixed and other personality disorder
	F62	Enduring personality change
Bipolar disorder	F31	Bipolar affective disorder

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Wilson Disease in the US - Epidemiology and Real-World Patient Characteristics Based on a Retrospective Observational Health Claims Study

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Abstract

Objectives: To describe the epidemiology, patient characteristics and comorbidities in patients with Wilson disease (WD) in the US.

Design: Retrospective, population-based study

Setting: The study used the US Komodo claims database containing records regarding medical claims for over 120 million individuals.

Participants: Patients with WD were identified via ICD-10 code during the study period 2016–2019 and no age restriction was applied. A further stratification by disease subtype ("hepatic", "neurologic" and "psychiatric") was performed.

Main outcome measures: WD prevalence was reported by age, sex, and US census regions/divisions. Adjusted prevalence was calculated using age-specific prevalence standardized to the US (2010 US census) and to the world (WHO 2000–2025) to enable comparisons across countries, using direct standardization of prevalence estimates by age group.

Results: Overall, 2,115 WD patients were identified during the study period. Among them, 56.8% had hepatic symptoms, 57.0% neurologic symptoms and 47.4% psychiatric symptoms. The most frequent manifestations in hepatic patients were liver signs and symptoms (90.8%), in neurologic patients cognitive defects (50.7%), and in psychiatric patients mood disorders (86.4%). The mean age in the overall cohort was 39.9 years. Prevalence estimation was based on 1,481 WD patients between 2017 and 2019. The 2017–2019 crude period prevalence was 21.2 patients per million (95% confidence interval: 20.1–22.3), with similar prevalence observed for both sexes.

Conclusions: This study provides important real-world data on the diagnosed prevalence of WD in the US and revealed the comorbidities associated with various disease subtypes, thereby providing a comprehensive basis for guiding physicians and policy makers in the management of this chronic disease.

Strengths and limitations of this study

- This study estimated the diagnosed prevalence of WD for the first time in the US, by using a large, nationally representative claims database. The real-world nature of the data helps estimate the observed frequency of Wilson disease in the US using ICD-10 codes specific to WD.
- The classification of patients into subtypes, and especially the novel approach to differentiate psychiatric symptoms from neurological symptoms, was a further strength of this study.
- Besides general limitations inherent to claims data, the limitations specific to this study included a limited study period after the introduction of a new WD-specific ICD-10 code in 2015.
- The used claims data did not capture information on OTC medications and the treated patients represented the proportion of patients with prescription treatment only.

Introduction

Wilson disease (WD) is an autosomal recessive condition which leads to an excessive copper deposition in body organs, particularly in the liver and the central nervous system.[1] This genetic disorder is caused by mutations of the P-type ATPase copper transporter *ATP7B* gene located in the human chromosome 13.[2] To date, more than 600 variants in the *ATP7B* gene have been described, and most WD patients are compound heterozygous with two different *ATP7B* variants, complicating and prolonging genetic WD diagnosis.[3] WD generally presents in childhood and young adulthood with the most common age of presentation between 10 and 20 years, though patients can occasionally present before the age of 5 years and after the age of 70 years.[4]

Clinical presentation of WD includes a combination of hepatic, neurologic, psychiatric, and ophthalmologic symptoms. Psychiatric symptoms often precede the diagnosis of WD and include personality changes, depression, cognitive changes, and anxiety.[5] The neurologic symptoms of WD mostly refer to dysfunction in the extrapyramidal system including dysarthria, dystonia, gait abnormalities, tremor, parkinsonism, chorea, and seizures.[6] Psychiatric symptoms have been only recently recognized as independent manifestations of WD, as it was previously assumed that they occur together with neurological symptoms, and patients were often referred to as having neuro-psychiatric disorders.[7] The symptoms related to hepatic dysfunction in WD can range from an asymptomatic increase in liver enzyme levels to severe liver failure. Typically, early on in disease progression there is a mild increase in transaminases, which then may progress to chronic active hepatitis, followed by fibrosis and cirrhosis.[8]

WD is a rare disease with recent worldwide clinical prevalence estimates ranging from approximately 16.7 to 25 patients per million,[9] although the prevalence can vary across countries and may be higher in selected regions such as in some Asian communities.[10] Interestingly, there is a discrepancy of WD prevalence estimates originating from epidemiological compared to genetic studies and recent genetic data with a considerably higher prevalence (139 per million) indicate that the prevalence of WD may be underestimated.[11] The possibility of underdiagnosis, misdiagnosis and the lack of accounting for incomplete variant penetrance in the genetic calculations were hypothesized as the main reasons for

the observed inconsistency between genetic vs. clinical data.[11,12] For the US, population-based epidemiological data are still scarce. A previous study reported a genetic birth prevalence of 18.2 per million births,[13] and an abstract on cardiac manifestations in WD reported a prevalence of 26 patients per million, but no details of methodology.[14]

Thus, large population-based studies assessing the epidemiology of WD and its subtypes in the US are needed, allowing for a greater characterization around the spectrum of disease severity and the diagnosed prevalence of WD. Here we present data from a recently completed real-world evidence study that used US claims data to investigate various aspects of WD in a real-life setting including epidemiology and patient demographic and clinical characteristics.

Methods

Study design

This retrospective, population-based observational study used health insurance claims data to assess WD epidemiology and patient characteristics using the US Komodo Health claims database available from 2012–2020.[15] Komodo's private payor-complete database contains records regarding prescription and/or medical claims for over 120 million individuals, collected from more than 150 private insurers in the US, including Medicaid managed-care and Medicare Advantage plans. This study used the closed claims available in the database. Closed claims come directly from the payer and provide the complete patient journey, such as full medical and/or prescription benefit information including insurance eligibility. For more details on the data source, see **Supplementary Methods**.

Population

Patients were selected based on their first observed WD diagnosis (index event) in the claims database between 2016 and 2019 (study period). The diagnosis was based on code (ICD-10 code E83.01 or ICD-9-CM code 275.1 prior to October 1, 2015). The standard ICD-9 diagnostic code for WD was not specific to WD and could also include another rare condition called Menkes disease. The WD-specific ICD-10 code (E83.01) was introduced in the US on October 1, 2015. A WD diagnosis was defined as at least one inpatient or two outpatient visits with a WD ICD-10 code, separated by at least 30 days

during the study period. For the selected WD patients a follow-up period of at least one calendar year (defined as post-index period) was examined, to observe their treatment journey. The follow-up period was defined from index until the last available claim. No age restriction was imposed. Patients were excluded from the study if they had at least one prescription for a copper replacement drug, a drug used to treat Menkes disease, during the study period.

Cohorts and subgroups

The cohort presented here includes patients that fulfilled the criteria for at least one WD diagnosis at any time during the study period (2016–2019) and a continuous enrollment for at least one calendar year before the index event. Separately, prevalence was assessed in the period between 2017 and 2019 for patients that had a history of at least one WD diagnosis at any time during that period and a continuous enrollment for at least two calendar years. This separate assessment period for prevalence estimation was based on the WD-specific diagnosis code becoming effective in the US only in 2015. Due to the possibility of miscoding, the most accurate prevalence estimation of WD can be made between 2017 and 2019, as this period includes at least one full calendar year since the introduction of the new code.

A further stratification by WD subtypes was performed, according to ICD-10 codes (see **Supplementary Tables 1–3**) based on the presence of signs and symptoms for each category. The subtypes “hepatic”, “neurologic” and “psychiatric” were not mutually exclusive or strictly delineated but were based on the presence of signs and symptoms. Patients were assigned to the hepatic subtype if they were diagnosed with liver signs and symptoms, acute hepatitis (not viral), cirrhosis (decompensated or compensated), liver failure, portal hypertension, or hepatocellular carcinoma. Patients assigned to the neurologic subtype had a diagnosis for tremor, parkinsonism or akinetic rigid syndrome, gait abnormalities/ataxia, dysarthria, dystonia, chorea, dysphagia, myopathy, seizures, migraine, somatoform autonomic dysfunction or cognitive disorder. Patients diagnosed with mood disorders, paranoia/schizophrenia, psychosis, or personality disorders were assigned to the psychiatric subtype.

Variables

Data on patient characteristics (age, sex, region of residence) and physician specialty at baseline (i.e., at first observed WD diagnosis during the study period) were ascertained. In addition, the proportion of patients never treated and distribution of subtypes and manifestations were ascertained during the study period. Comorbidities /concurrent diagnoses were assessed during the study period (2016–2019). Overall, age-, sex-, and region-specific prevalence (crude and age-adjusted period prevalence) were assessed in the period between 2017 and 2019. A rationale for considering a period prevalence rather than an annual prevalence was that the identification of WD patients was based on ICD-10 codes, without considering WD treatment or laboratory records, and the assumption that WD patients who are well managed using over the counter (OTC) or prescription medication may not necessarily visit a health care provider (HCP) each year. A further reason for using a period prevalence was to account for possible misdiagnosis in the first year after the introduction of the ICD-10 code for WD.

Data analysis

Descriptive statistics were calculated for demographic and baseline characteristics (overall and by subtype). Means and standard deviations (SDs) were provided for continuous or discrete data. Frequencies and percentages were provided for categorical data. For WD manifestations, the frequencies of occurrence of specific ICD-10 codes within subtypes and within the overall patient cohort were calculated and the three most frequent manifestations were listed by subtype. For comorbidities, all recorded diagnoses (ICD-10 codes level-3) at any time during the study period were ranked according to frequency and a list of the 10 most frequent comorbidities in the overall cohort were reported. In addition, the Charlson Comorbidity index (CCI; version of 2011), an assessment tool designed to predict mortality in patients with multiple comorbidities,[16] was assessed for each patient and a mean score including SD (higher scores indicating greater mortality risk and more severe comorbid conditions) was calculated for the overall cohort. Crude period prevalence was calculated from the number of WD cases identified and was expressed as patients per million including 95% confidence intervals (CI). The denominator was the number of patients with continuous enrollment spanning the period of interest (2017–2019) and the numerator was any patient from the denominator with at least one WD diagnosis claim during the period of interest. Prevalence was reported by age,

sex, and US census regions/divisions. Adjusted prevalence was calculated using age-specific prevalence standardized to the US (2010 US census) and to the world (WHO 2000–2025) to enable comparisons across countries, using direct standardization of prevalence estimates by age group.

Ethics statement

This was study was approved by the IRB Pearl Pathways. The study was conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor, and followed generally accepted research practices described in Good Pharmacoepidemiology Practices guidelines issued by the International Society for Pharmacoepidemiology.

Patient and public involvement

Patients or the public were not actively involved in this observational study.

Data availability statement

The data that support the findings of this study are available from Komodo Health. Restrictions apply to the availability of these data, which were used under license for this study. Access to data must be requested through Oracle.

Results

Baseline characteristics

The observed cohort included 2,115 WD patients identified between 2016 and 2019. Selected baseline characteristics of the overall cohort and by subtype are displayed in **Table 1** The mean age in the overall cohort was 39.9 years (SD=20.1 years). The lowest mean age was reported for the psychiatric subtype (39.2 years, SD=20.2 years) and the highest for the neurologic subtype (42.3 years, SD=20.7 years). Overall, 51.8% were male patients. A larger portion of patients came from the South (30.6%) and fewer from the Northeast (21.8%) with little difference between subtypes. While for a majority (54.2%) of overall WD cases no information was available regarding the specialists managing the primary WD diagnosis, the available results showed that patients were mostly in the care of gastroenterologists (13.2%) and general/family practitioners (12.6%). Hepatic patients were more frequently seen by gastroenterologists (16.4%), as compared to the other subtypes (9.7% of neurologic

patients and 9.0% of psychiatric patients). On average, the follow-up time in the study was 2.2 years (SD=1.3 years) with little difference between subtypes. Among all patients, the majority (83.0%) were never treated with a reimbursable WD prescription medication during the study period.

WD subtypes and manifestations

Among the cohort, more than half had hepatic and/or neurologic symptoms (56.8% and 57.0%, respectively) and around half had psychiatric symptoms (47.4%). Most patients had overlapping subtypes, presenting concomitantly with hepatic, neurologic, and/or psychiatric signs and symptoms (see **Supplementary Figure 1**). For instance, 734 (34.7%) presented with at least two concomitant conditions, whereas 422 (20.0%) WD patients presented with the three of them together. **Figure 1** illustrates the distribution of sex (a) and age (b) within subtypes. Slightly more male than female patients had neurologic (54.6%) and psychiatric (55.6%) symptoms, whereas the sex distribution was equal in the hepatic subtype. With regards to age distribution, most patients in all subtypes were in the age groups between 18 to 39 years and 40 to 64 years. The distribution of young (0–17 years) and older (above 65 years) patients was also similar between subtypes, though there were slightly more older patients in the neurologic subtype (21% vs. 16% [hepatic] and 17% [psychiatric]).

The most frequent manifestations associated with the different subtypes and their proportion in the overall cohort are highlighted in **Table 2**. Hepatic patients most frequently experienced liver signs and symptoms (90.8%), cirrhosis (37.9%) and hepatitis (28.9%). Neurologic patients most frequently experienced cognitive defects (50.7%), ataxia and gait abnormalities (36.2%) and dysphagia (27.2%). Psychiatric patients most frequently experienced mood disorders (86.4%), a mix of symptoms in children (22.3%) and paranoia/schizophrenia (19.8%).

Comorbidities/Concurrent diagnoses

WD patients were diagnosed with a broad spectrum of comorbidities. The most common clinical conditions diagnosed during the study period included other joint disorders (50.9%), unspecified soft tissue disorders (49.3%), dorsalgia (49.1%), disorders of lipoprotein metabolism and other lipidemias (45.9%), essential hypertension (45.2%), anxiety disorders (42.9%), and other diseases of liver

(40.0%), **Figure 2**. The extent of concurrent diagnoses and comorbidities was also reflected by a mean CCI score of 1.92 (SD=2.68).

Prevalence

Prevalence estimation was based on 1,481 WD patients between 2017 and 2019. The 2017–2019 crude period prevalence was 21.2 patients per million (95% CI: 20.1–22.3), with similar prevalence observed for both sexes (male: 21.2 per million, 95% CI: 19.7–22.8 and female: 21.1 per million, 95% CI: 19.7–22.6), **Table 3**. The crude period prevalence peaked among young adults in the 18 to 39 years age group (27.1 per million, 95% CI: 24.7–29.5), followed closely by adults 40 to 64 years old (26.1 per million, 95% CI: 24.0–28.2). The highest crude period prevalence was recorded in the Northeast (24.1 per million, 95% CI: 21.6–26.7), followed by the Midwestern (22.2 per million, 95% CI: 19.9–24.5), Western (21.6 per million, 95% CI: 19.2–24.0), and Southern (18.4 per million, 95% CI: 16.7–20.1) regions of the US.

Adjusted period prevalence was calculated using age-specific prevalence standardized to the US (2010 US census) and to the world (WHO 2000–2025). Between 2017 and 2019, both the US-adjusted and WHO-adjusted period prevalences were similar (22.0 per million, 95% CI: 20.9–23.1 and 21.4 per million, 95% CI: 20.4–22.5, respectively) to the crude period prevalence observed in this study.

Discussion

Principal findings and implications

There is a gap of knowledge regarding the epidemiology and clinical characteristics of WD patients from a national and international perspective. In this large population-based study we assessed WD patient characteristics and epidemiology in the US.

Approximately two-thirds of the cohort showed hepatic and/or neurologic symptoms, which is consistent with the natural disease course, as WD mostly affects the liver and brain.[17] Typically, hepatic symptoms precede the onset of neurologic symptoms and may thus be diagnosed at a younger age[2]. In line with this, though not as evident in the age distribution by subtypes, the mean age at index in the hepatic subtype was slightly lower compared to the neurologic subtype. In agreement with our

data on sex distribution in the neurologic and psychiatric subtypes, a registry-based study observed that the neuropsychiatric WD form occurred more frequently in men (67%) vs. women (49%).[18]

Our results also revealed the extent of comorbidities associated with various disease subtypes, as some of the most frequently reported manifestations were quite severe (e.g., around 40% of patients in the hepatic subtype presented with cirrhosis). The frequency of hepatic, neurologic, and psychiatric presentations, as well as the manifestations within these subtypes varies considerably in other published studies.[4] Considering the great variability in WD symptoms, it is likely that there is referral bias. A review of several independent case series suggested that dysarthria, gait abnormality/ataxia and dystonia are the most frequent manifestations in the neurologic subtype, which partially reflects our findings.[4] The higher rates of dystonia and dysarthria reported in the literature may be explained by the fact that only symptomatic conditions that require treatment get captured in the claims under the ICD-10 diagnosis code. Furthermore, a study from China reported distributions of hepatic manifestations (e.g., 22% cirrhosis and 11% cirrhotic complications) which were similar to our findings.[19]

WD patients in our study were in the typical age range for first symptom onset and disease progression (between the second and sixth decade of life). We found a slightly lower mean age in the psychiatric subtype compared to the other subtypes, which might reflect that psychiatric manifestations are often the first symptoms.[7] The earlier diagnosis of psychiatric WD may highlight a critical gap in care for these patients, as neurologic and psychiatric involvements have been previously assessed in tandem, with neurologic symptoms becoming more apparent later in life. Given the recessive nature of WD, the results confirmed the expectation of a relatively even distribution of cases across sexes, which also aligns with previous studies conducted in France,[20] and Hong Kong.[19] The geographical distribution within the US, with a larger portion of patients coming from the South and fewer from the Northeast, might correspond to the distribution of major university centres in the US where WD patients are typically diagnosed. Given the nature of the disease, it is not surprising that patients were primarily in the care of gastroenterologists (most pronounced in hepatic patients), though a considerable fraction of patients was also diagnosed or treated by general or family practitioners who might be the first contact points. The high rate of patients never treated with a reimbursable WD medication during the study

period was likely due to the use of OTC zinc preparations which are not covered by insurers in the US, the refusal to take medications and rely solely on a low-copper diet, or the hypothesis that some physicians used the WD diagnosis code to initiate further testing for the patients but did not prescribe a WD medication at that initial stage. Further investigation on this aspect is warranted given the chronic nature of this disease.

Furthermore, our results demonstrated that WD patients were diagnosed with a broad spectrum of comorbidities, most frequently affecting joints, soft tissues, and the cardiovascular system, as well as pain symptoms and metabolic disorders. Comorbidities of WD are rarely described in the literature and vary considerably, however, our findings are at least partially consistent with comorbidities reported in the literature. Kruger et al and Dziezyc et al described that the most common complications in WD patients were pain, renal, neurologic, cardiac, skin, osteoarticular, or endocrinologic complications and included other organ disturbances. [21,22]

Only a few population-based studies assessing WD epidemiology have been performed to date world-wide. It is challenging to compare the results from this study to other reports, because of the heterogeneity of the disease and of the heterogeneity in population, diagnosis, and methodologies employed in other studies assessing WD epidemiology. However, the observed prevalence estimates (US-adjusted prevalence: 22.0 patients per million) align well within the WD prevalence range reported in other claims-based studies in France (15 per million), [23] and China (17.9 per million),[19] while estimates from a claims-based study in South Korea were slightly higher (38.7 per million).[24] Two recent systematic literature reviews assessed WD prevalence data originating from population-based epidemiological as well as genetic studies.[11,25] Sandahl et al. reported a crude population-based prevalence between 25 and 34.5 per million,[25] and underlined that specific populations in Croatia, Sardinia, Israel, Costa Rica, Middle Eastern countries, Pakistan and India had considerably higher prevalence estimates, either related to consanguinity or higher mutation frequencies. Gao et al. performed a meta-analysis resulting in a pooled population-based prevalence of 14 patients per million.[11] Both reviews mentioned that at least in some studies a higher genetic vs. clinically based prevalence could be observed. Gao et al. reported a pooled prevalence at birth of 127 per million.[11]

Overall, it seems evident that many factors such as the still uncertain mutational spectrum and penetrance of WD variants, the unclear effect of combined mutations and epigenetic factors, methodological differences in studies, underdiagnosis, changes in diagnostic awareness and treatment options over time, as well as geographic factors may influence WD prevalence estimates. Thus, it is important to assess epidemiological data from large, population-based studies, as the one presented here.

Strengths and limitations

This study benefitted from several strengths. Data elements extracted from claims, some of which are not generally available in literature or patient registries, are collected routinely in clinical practice and represent real-world activities and outcomes. The real-world nature of the data helps estimate the observed frequency of diagnosed diseases using ICD-10 codes. The ICD-10 codes for WD are highly specific, despite any limitations in coding or misdiagnosis which may occur. The Komodo claims data are large and nationally representative based on comparisons made to the US census estimates (by age, sex, and region). The closed claims provide a longitudinal history that facilitates the analysis of the natural history of the disease, healthcare utilization, and treatment dynamics. Of note, the crude prevalence observed in this study between 2017 and 2019 was comparable to the US age-standardized adjusted results, reaffirming the representativeness of the Komodo data for rare disease research in the US. The classification of patients into subtypes, and especially the novel approach to differentiate psychiatric symptoms from neurological symptoms, was a further strength of this study.

There are some general limitations inherent to claims data, such as the potential for errors in diagnosis coding or record keeping at the point of the HCP. Since claims data are used for billing purposes, they only include records for the insured population, therefore projections of the US population assume similarities between the insured and uninsured patients. Leveraging secondary data requires an algorithm for case identification and validated algorithms specific to WD do not currently exist. Claims data contain only reimbursed medical services and thus e.g., results of lab tests or patient-reported outcomes are not captured. In addition, these claims data in general have limited follow-up,

e.g., due to patients switching insurance plan or losing coverage or privacy restrictions limiting data linkage.

In addition, there were some limitations specific to this study. Epidemiological trends over time were hard to assess given the limited study period and the introduction of the new WD-specific ICD-10 code. Only symptomatic conditions were captured under the ICD-10 code; therefore, no inferences can be made regarding pre-symptomatic patients with WD. The claims data did not capture information on laboratory testing well, and results are not available in claims data. Further the claims data did not capture OTC medications and thus the treated patients represented the proportion of patients with prescription treatment only. The proportion of patients without a claim for a WD-specific treatment was quite high and unexpected however and whether this truly reflects a large proportion of patients on OTC zinc is unclear. Further investigation is needed as to the proportion of WD patients receiving treatment in the US.

Conclusions

This claims study provides important real-world data on the prevalence of WD in the US and revealed the extent of comorbidities associated with various disease subtypes. The results of this study extend existing research findings and provide a comprehensive epidemiological basis for guiding physicians and policy makers in the management of this chronic disease.

Declarations

Acknowledgments

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Authors' Contributions

SF, CS, KHW and PH were responsible for the design, writing and editing of the final version of the manuscript. SF, CS and HC were responsible for the execution of the study and HC was responsible for the analysis of the data. SF is the guarantor. All authors had critically reviewed the manuscript and approved its final version.

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PH has no financial relationships to disclose. KHW advises for Alexion, Univar, Orphalan, Desitin, Tilomed, Ultragenyx, Pfizer, Vivet therapeutics, Abbvie. HC is an employee of Oracle America, which has provided consultancy for Alexion Pharmaceuticals.

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PH has no financial relationships to disclose. KHW declares no conflicts of interest that pertains to this work. SF is an employee of Alexion, AstraZeneca Rare Disease and may own stock in AstraZeneca.

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Tables

Table 1: *Selected baseline characteristics of WD patients, overall and by subtype*

	Hepatic* N=1,202	***Neurologic* N=1,206***	***Psychiatric* N=1,003***	***Overall N=2,115***
Age at index date (years), *mean (SD)*	40.4 (19.08)	42.3 (20.70)	39.2 (20.19)	39.9 (20.06)
Male, *N (%)*	607 (50.5%)	659 (54.6%)	558 (55.6%)	1,096 (51.8%)
US Region of residence at index, *N (%)*				
Northeast	254 (21.1%)	246 (20.4%)	182 (18.2%)	462 (21.8%)
South	376 (31.3%)	398 (33.0%)	332 (33.1%)	647 (30.6%)
Midwest	275 (22.9%)	292 (24.2%)	249 (24.8%)	502 (23.7%)
West	297 (24.7%)	270 (22.4%)	240 (23.9%)	504 (23.8%)
Physician specialty of primary WD diagnosis, *N (%)***				
Gastroenterology	197 (16.4%)	117 (9.7%)	90 (9.0%)	279 (13.2%)
General / Family Practice	136 (11.3%)	133 (11.0%)	124 (12.4%)	266 (12.6%)
Ophthalmology / Optometry	61 (5.1%)	59 (4.9%)	50 (5.0%)	101 (4.8%)
Neurology	41 (3.4%)	75 (6.228%)	48 (4.8%)	88 (4.2%)
Follow-up period (years), *mean (SD)*	2.2 (1.28)	2.1 (1.25)	2.1 (1.26)	2.2 (1.27)
Never treated, *N (%)*	962 (80.0%)	1,044 (86.6%)	881 (87.8%)	1,755 (83.0%)

* These groups are not mutually exclusive.
** This is the primary physician specialty for the first claim with WD as the primary diagnosis. Due to limitations in the analysis of the prevalent WD population, it cannot be inferred with certainty that it represents the first diagnosis.

453 ***Table 2:*** *Most frequent (Top-3) WD manifestations by subtype*

Manifestations	*N*	*% subtype*	*% overall cohort (N=2,115)*
Hepatic subtype* (N=1,202)			
Liver signs and symptoms	1,092	90.8%	51.6%
Cirrhosis	456	37.9%	21.6%
Hepatitis	347	28.9%	16.4%
Neurologic subtype* (N=1,206)			
Cognitive defects	611	50.7%	28.9%
Ataxia and gait abnormalities	436	36.2%	20.6%
Dysphagia	328	27.2%	15.5%
Psychiatric subtype* (N=1,003)			
Mood disorders	867	86.4%	41.0%
Mix of symptoms, children	224	22.3%	10.6%
Paranoia and schizophrenia	199	19.8%	9.4%

454 * These groups are not mutually exclusive.

455

Table 1: *Crude and age-standardized WD period prevalence 2017–2019*

	N	Prevalence per million (95% CI)
Crude prevalence (overall)	1,481	21.2 (20.1-22.3)
Age		
0- <18	256	12.4 (10.9-14.0)
18-<40	490	27.1 (24.7-29.5)
40-<65	581	26.1 (24.0-28.2)
65+	154	17.1 (14.4-19.8)
Sex		
Male	697	21.2 (19.7-22.8)
Female	784	21.1 (19.7-22.6)
Region		
Northeast	344	24.1 (21.6-26.7)
South	439	18.4 (16.7-20.1)
Midwest	355	22.2 (19.9-24.5)
West	319	21.6 (19.2-24.0)
Missing	24	
US-adjusted prevalence	1,481	22.0 (20.9-23.1)
WHO-adjusted prevalence	1,481	21.4 (20.4-22.5)

**Standardized to the age distribution of the total world population in year 2000-2025, according to WHO
***Standardized to the age distribution of the total US population in year 2010, according to Census Bureau

Figure Legends

Figure 1: Distribution of WD subtypes by sex (a) and age (b)

Figure 2: Most frequent (Top-10) comorbidities/concurrent diagnoses of WD patients

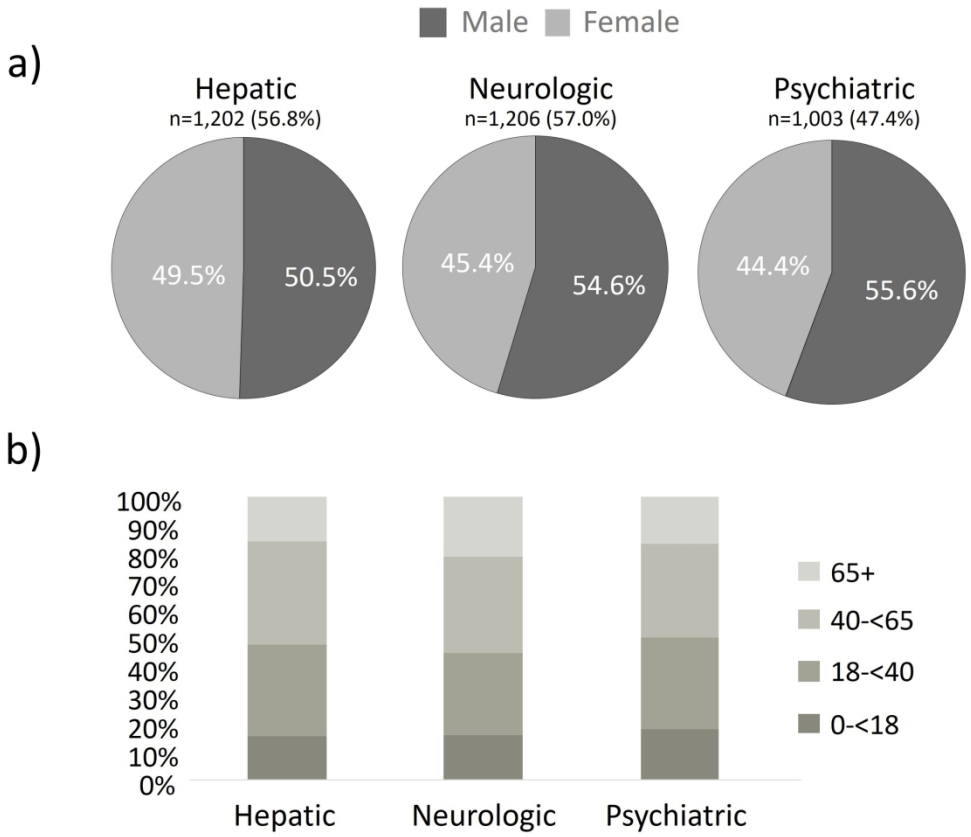


Figure 1: Distribution of WD subtypes by sex (a) and age (b)

214x184mm (300 x 300 DPI)

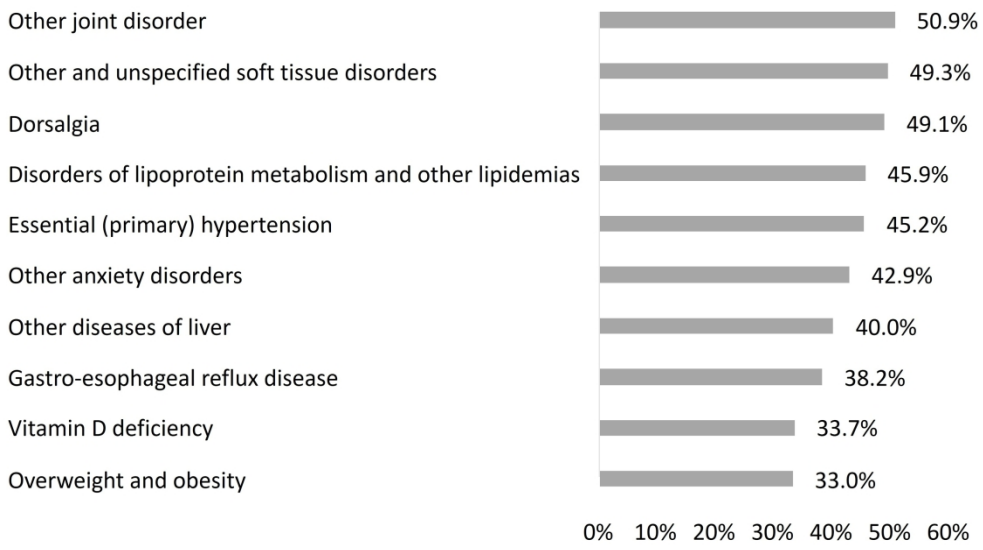


Figure 2: Most frequent (Top-10) comorbidities/concurrent diagnoses of WD patients

286x160mm (300 x 300 DPI)

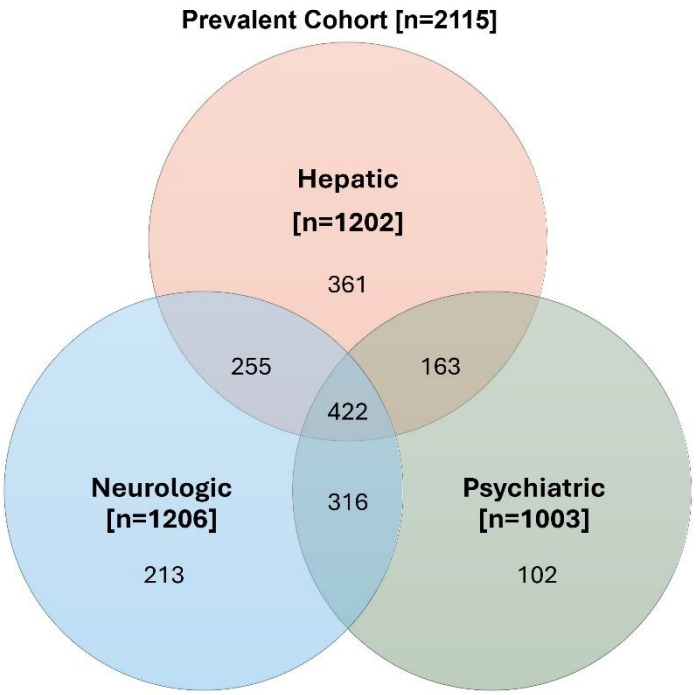
Wilson Disease in the US - Epidemiology and Real-World Patient Characteristics Based on a Retrospective Observational Health Claims Database Study - Supplementary Materials

Supplementary Methods

Data source

Komodo Health is a healthcare technology company that has built an expansive Healthcare Map including de-identified claims (>65 billion clinical, pharmacy and lab encounters) for more than 320 million U.S. patients. These encounters represent census level representation across populations (e.g., age, geography, risk pools) in the United States (US), including hospital networks, physician networks, healthcare claim processing companies (i.e. claims clearinghouses), pharmacies, and health insurers. Nearly half of the data in Komodo's Healthcare Map is comprised of "closed" datasets, which come directly from the payer and provide insight regarding the complete patient journey, such as full medical and/or prescription benefit information, including insurance eligibility. Komodo's private payer-complete population contains prescription and/or medical claims of over 120 million individuals collected from 150+ private insurers in the US. Data that is rooted in a complete patient journey provides an optimal basis for a variety of research focuses, including adherence studies, treatment pattern studies and comparative effectiveness studies within an insured population.

Supplementary Figures



Supplementary Figure 1. *Distribution of hepatic, neurologic and psychiatric Wilson disease subtypes*

Supplementary Tables

Supplementary Table 1. *ICD-10 Codes for identification of hepatic Wilson disease subtype*

	ICD-10 Code	Description
Elevated serum aminotransferases	R74	Nonspecific elevation of levels of transaminase and lactic acid dehydrogenase [LDH]
Acute hepatitis (not viral)	K72	Acute and subacute hepatic failure
Coagulopathy	D68	Coagulation defect, unspecified
Hepatic encephalopathy	5722	Hepatic encephalopathy
	K727	Hepatic encephalopathy
Cirrhosis (decompensated or compensated)	K717	Toxic liver disease with fibrosis and cirrhosis of liver
	5715	Cirrhosis of liver without mention of alcohol
	K74	Fibrosi and cirrhosis of liver
Liver failure	K704	Alcoholic hepatic failure
	K711	Toxic liver disease with hepatic necrosis
	K720	Acute and subacute hepatic failure
	K721	Chronic hepatic failure
	K729	Hepatic failure, unspecified
Variceal hemorrhage	I8501	Esophageal varices with bleeding
	I8511	Secondary esophageal varices with bleeding
	I983	Oesophageal varices with bleeding in diseases classified elsewhere
	4560	esophageal varices with bleeding
	45620	esophageal varices in diseases classifies elsewhere, with bleeding
Portal hypertension	K766	portal hypertension
	5723	portal hypertension
Hepatocellular carcinoma	C220	liver cell carcinoma

Supplementary Table 2. *ICD-10 Codes for identification of neurological Wilson disease subtype*

	ICD-10 Code	Description
Tremor	R251	tremor, unspecified
	G251	Drug-induced tremor
	G252	other specified forms of tremor
	G250	essential tremor

	3331	essential and other specified forms of tremor
Parkinsonism or akinetic rigid syndrome	G20	parkinson's disease
	G219	secondary parkinsomism, unspecified
	G218	other secondary parkinsonism
	G2122	neuroleptic induced parkinsonism
	G214	vascular parkinsomism
	G2119	other drug induced secondary parkinsonism
	3321	secondary parkinsonism
	G212	secondary parkinsonism dur to other external agents
	G213	postencephalitic parkinsonism
	G8903	Parkinson's disease mg
	G211	other drug induced secondary parkinsonism
	G22	Parkinsonism in diseases classified elsewhere
	G21	secondary parkinsonism
Gait abnormalities/ataxia	R2689	other abnormalities of gait and mobility
	R269	unspecified abnormalities of gait and mobility
	R26	abnormalities of gait and mobility
	R268	other abnormalities of gait and mobility
	R270	ataxia, unspecified
Dysarthria	78451	Dysarthria
	R471	Dysarthria and anarthria
	I69222	Dysarthria following oth nontraumatic intrcrn hemorrhage
	I69022	Dysarthria followin nontraumatic subarachnoid hemorrhage
Dystonia	G249	Dystonia, unspecified
	G248	Other dystonia
	G24	Dystonia
Pseudobulbar palsy	G1220	Motor neuron disease unspecified
	33523	Pseudobulbar palsy
Seizures	G40	Epilepsy and recurrent seizures
	F445	Conversion disorder with seizures or convulsions
	R568	Other and unspecified convulsions
Migraine	G43	Migraine
Somatoform autonomic dysfunction	F45	Somatoform disorders

Cognitive disorder	G3184	Mild cognitive imparment, so stated
	F03	Unspecified dementia
	F05	Delirium due to known physiological condition
	F06	Other mental disorders due to known physiological condition
	331883	Mild cognitive imparment, so stated

Supplementary Table 3. *ICD-10 Codes for identification of psychiatric Wilson disease subtype*

	ICD-10 Code	Description
Depression	F32	Major depressive disorder, single episode
	F33	Major depressive disorder, recurrent
	F34	Persistent mood disorder
Neuroses	F48	Nonpsychotic mental disorder, unspecified
	F40	Phobic anxiety disorder
	F41	Other anxiety disorder
	F42	Obsessive compulsive disorder
	F43	Reaction to severe stress and adjustment disorders
	F44	Dissociative and conversion disorders
	F45	Somatoform disorders
Psychosis	F29	Unspecified physchosis not due to substance or known psychological condition
	F20	Schizophrenia
	F21	schizotypal disorder
	F22	delusional disorders
	F23	brief psychotic disorder
	F24	shared psychotic disorder
	F25	schizoaffective disorder
	F28	other psychotic disorder not due to a substance or known physioogical condition
Personality changes	F07	Personality change due to known physiological condition
	F60	Specific personality disorder
	F61	Mixed and other personality disorder
	F62	Enduring personality change
Bipolar disorder	F31	Bipolar affective disorder