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A population-based study of patients with Wilson's disease identified in the French national insurance claims database, with a proposal for an exploratory algorithm for improved case identification

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Objective: To investigate the pertinence of different potential markers for case identification of WD patients in the French National Health Data System (SNDS).
Methods: Patients in the SNDS with hospitalization or long-term disease (LTD) status associated with a diagnostic code for WD (E83.0) between 2009 and 2019 were identified and followed from first documentation until 31st December 2019 (or death). Four patient groups were compared. Group A: patients hospitalized for WD, but with neither LTD status nor specific WD treatment. Group B: patients with LTD status, but without treatment. Group C: patients with treatment, but without LTD status. Group D: patients with both LTD status and WD treatment.
Results: 1,520 patients were included (Group A: N = 702; Group B: N = 153; Group C: N = 194; Group D: N = 471). >75% of untreated patients in Groups A and B were never monitored for copper accumulation. The mean number of blood copper tests over the follow-up period was 0.30 ± 2.47 in Group A, 0.76 ± 2.34 in Group B, 3.99 ± 7.66 in Group C and 5.33 ± 7.90 in Group D. Patients in Group A frequently presented LTD status for conditions unrelated to WD, and higher mortality (hazard ratio: 2.87 [95%CI: 1.87–4.41] compared to Group D), frequently dying of causes unrelated to WD.
Conclusions: For many patients identified only by a hospitalization claim, no specific WD treatments or copper monitoring were ever documented. Substantial doubt exists whether these patients actually had WD. Validation studies are needed to find the optimal diagnostic algorithm to identify WD cases unambiguously, which is a prerequisite for collecting reliable information on WD.

KEYWORDS
epidemiology, insurance claims databases, SNDS, survival, treatment, Wilson's disease

1 Introduction

Wilson's disease (WD) is a progressive, potentially fatal degenerative disease principally affecting the liver and the central nervous system (1). It is a hereditary disorder caused by loss-of-function mutations in the gene encoding the Copper Transporting ATPase ATP7B (2, 3), which lead to impaired copper handling and toxic accumulation of copper in the organism. The prevalence of WD in Europe and North America is believed to be in the range of 25–35 cases per million (4).

Given the rarity of the condition, collecting extensive information on patient characteristics, disease management and outcomes in WD is challenging. One approach to collecting data on rare diseases such as WD is to use data from insurance claims databases. In France, all residents are covered by the national health insurance scheme and all reimbursed healthcare resource consumption is documented with reference to a unique patient identifier which remains the same throughout the individual's life. This information is documented in a unique data repository, the *Système national des données de santé* (SNDS). The SNDS is thus a rich source of exhaustive information on healthcare resource utilization in specific diseases (5, 6).

Three studies of WD using data from the SNDS have been published. The first was a cross-sectional study performed in 2013 (7). The other two longitudinal studies covered the periods 2009–2019 inclusive (8) and 2010-2019 (9). All identified WD cases by the presence of an ICD-10 disease code for WD (E83.0) associated with a hospitalization or with long-term disease (LTD) status (entitling the patient to full reimbursement for healthcare) and provided estimates of annual prevalence in the same range (1.5 cases per 100,000 for 2013 in the cross-sectional study, 2.2 cases per 100,000 for 2019 in the first longitudinal study and 3.0 cases per 100,000 for 2019 in the second longitudinal study). In addition, the second longitudinal study reported that prevalence rates had steadily risen between 2010 and 2019.

A surprising feature of these studies was the relatively low proportion of patients who were documented to have received a specific treatment for WD: in the cross-sectional study (7), 37.2% received D-penicillamine at least once and 14.3% received zinc salts; in the longitudinal studies (8, 9), 40.3% and 43.8% received at least one treatment, principally D-penicillamine in both cases. Of interest, similar low treatment rates have been described in insurance claims database studies of patients with WD in the USA (10) and South Korea (11).

Practice guidelines for the management of WD from Europe, North America and Japan recommend lifelong treatment with copper-depleting medication to prevent symptom emergence or progression, unless liver transplantation is undertaken (12–15). If patients are diagnosed and treated early in the disease course, and if patients are adherent and well monitored, then most can be expected to lead a normal life with a normal life expectancy (16–18). In contrast, lack of copper-depleting therapy potentially exposes patients to a high risk of potentially fatal liver injury or severe neurological complications (19). A possible explanation for the lack of documented treatment in these patients may be that they take copper-depleting medication intermittently (20) and indeed several studies have reported that medication adherence is poor (21–24), perhaps due to tolerability issues. However, switching to an alternative treatment remains a possibility (25) and many patients do indeed switch (26). Moreover, intermittent treatment is not a sufficient explanation for the low treatment rates described in the insurance claims database studies, where patients apparently do not receive any treatment for periods of several years. In recent real-world observational studies where data is collected from patient records, the vast majority of patients are prescribed treatment over the long term (26, 27).

The consistently low treatment rates reported in database studies led us, and others (20), to question the accuracy of the case-identification method used, based principally on hospitalization associated with an ICD-10 code for WD. It is possible that this diagnostic algorithm is insufficiently specific and that the study populations evaluated include patients without a fully validated diagnosis of WD.

We therefore decided to return to the SNDS population used for our previous longitudinal study (8) and investigate associations of different potential markers of WD (hospitalization, treatment, monitoring, LTD status, mortality). We aimed to identify a potential case-identification algorithm that could be validated against clinical records in a subsequent study.

2 Methods

This was a retrospective, longitudinal, observational study conducted in the SNDS national database. Data were extracted for an eleven-year period from 1st January 2009 to 31st December 2019 inclusive. For each patient, the index date was defined as the first date at which WD was documented during the selection period. All patients were followed from the index date until 31st December 2019, death or loss from the database, defined as no healthcare consumption documented during 18 consecutive months.

2.1 Data source

The SNDS database contains exhaustive information on reimbursed heath expenditure relating to both hospital and community care and covering the public and private sectors. In France, all residents benefit from healthcare coverage provided by one of a number of profession-based insurance funds, of which the largest is the statutory health insurance scheme (General Fund), which covers 75% – 80% of the French population. Exhaustive data since the SNDS was created are only available for subjects insured through the statutory health insurance scheme, and other insurance funds have been integrated progressively, so that the SNDS now covers >99% of all French residents. Since the present study included patients starting from 2009, recruitment was restricted to individuals insured through the statutory health insurance scheme, to ensure completeness of data retrieval across the study.

In the SNDS, hospitalizations are identified through a disease-related group (DRG) documented on the discharge record. Each DRG is in turn associated with one or more diagnostic codes identified in the International Classification of Diseases 10th

Edition (ICD-10). Diagnoses are labelled as principal diagnoses (PD), which relate to the immediate reason for hospitalization, related diagnoses (RD), which relate to the underlying pathology, and significant associated diagnoses, which relate to any other pathology that may influence the course or cost of the hospitalization. For example, if a patient with WD was hospitalized for an acute episode of jaundice, jaundice would be identified as the PD and WD as the RD; if the patients also had chronic kidney disease, this would be identified as a SAD. The DRG is also associated with a standard unit cost which related to the total cost of hospitalization, including medications, healthcare professional (HCP) time, and any tests or procedures undergone. Medications delivered by community pharmacies are identified by Pack Identifier Codes. From this information, it is possible to identify the medication through the Anatomical, Therapeutic and Chemical (ATC) classification code. In the case of WD, specific copper-depleting medications (D-penicillamine, trientine and zinc salts) are delivered by community pharmacies. Beneficiaries of LTD status are identified through the relevant ICD-10 code.

2.2 Patients

To be eligible, patients were required to have either at least one hospitalization claim associated with the ICD-10 diagnostic code for WD (E83.0*: copper metabolism disorder) as PD, RD or SAD, or to be documented with LTD status associated with this E83.0* diagnostic code for WD.

2.3 Study variables

2.3.1 Demographics

Information was extracted from the database on age at the index date, gender; the presence of LTD status at inclusion for any condition other than WD was also documented. It should be noted that, for patient confidentiality reasons, data cannot be communicated if they concern less than ten patients.

2.3.2 Signs and symptoms

The presence of hepatic, neurological and psychiatric signs and symptoms potentially corresponding to clinical manifestations of WD at the index date was documented from a predefined list using the appropriate ICD-10 codes or ATC codes as previously described (8).

2.3.3 Treatments

All deliveries of specific WD treatments (D-penicillamine, trientine or zinc acetate) during the follow-up period were documented. These treatments were identified through the relevant ATC medication codes (D-penicillamine: M01CC01; trientine: A16AX12; zinc acetate: A16AX05) and corresponding pack identifier codes in the database.

2.3.4 Monitoring

All laboratory tests for determination of copper load performed during the follow-up period were identified from the relevant test codes and documented. These consisted of blood copper (procedure code 0547), urinary copper (code 2008) and blood ceruloplasmin (code 1809).

2.3.5 Liver transplantation

Liver transplantations were identified from the DRG code 27C02.

2.3.6 Mortality

All deaths occurring during follow-up were documented with the year of death. Since the SNDS database is linked to the national mortality registry (Centre d'épidémiologie sur les causes médicales de décès; *CepiDc*), it was possible to collect information on the cause of death, also identified by ICD-10 disease codes. It should be noted that linkage to the CepiDC registry was not available for all the years of study, and, for this reason, information on cause of death is incomplete. In addition, for patient confidentiality reasons, causes of death cannot be communicated if they concern less than ten patients.

2.4 Statistical analysis

Four study groups were identified: Group A consisted of patients with a documented hospitalization for WD, but without LTD status for WD, nor a documented specific WD treatment. Group B consisted of patients with documented LTD status for WD, but without a documented specific WD treatment. Group C consisted of patients with a documented specific WD treatment and a documented hospitalization for WD, but without LTD status for WD. Group D consisted of patients with a documented LTD for WD, as well as a documented specific WD treatment. Group membership was assigned retrospectively, on the basis of hospitalization, LTD status or treatment occurring at any time from the index date up to the end of follow-up inclusive. Patients could not move between groups and each patient is assigned to only one of the four possible groups. There is no missing data in the SNDS.

Continuous variables are described by mean values with their standard deviation (SD) or median values with their interquartile range (IQR). Categorical variables are presented as frequency counts and percentage. Continuous variables were compared between the four diagnostic groups using ANOVA and categorical variables compared using the χ^2 test. A four-way comparison across all groups was performed initially; in case of a significant difference being observed, individual comparisons between treated (Groups C and D) and untreated (Groups A and B) individuals and between individuals with (Groups B and D) and without (Groups A and C) LTD status for WD were performed.

All statistical testing between groups was exploratory and no prespecified hypotheses were tested.

Survival was evaluated by Kaplan-Meier analysis. Potential determinants of survival were evaluated between the groups using a Cox proportional hazards model with age (categorized as quartiles), gender and the three classes of clinical manifestations at the index date (present/absent), as independent variables. The proportional hazard assumption was verified. Associations with mortality

were expressed as hazard ratios (HR) with their associated 95% confidence intervals (95% CI).

3 Results

3.1 Study participants

A total of 1,520 patients were available for analysis, of whom 624 (41.1%) had LTD status for WD and 665 (43.8%) had received at least one documented specific WD treatment. The relationship between the four patient subgroups is illustrated in Figure 1. The largest groups were Groups A (702 patients; 46.1%) of patients and Group D (471 patients; 31.0%).

The median follow-up duration in the database following the index date until study end, death or loss to follow-up was 5.1 years (Table 1). Eleven years was the maximum follow-up duration possible. The follow-up duration differed significantly between groups being longer in patients who received a specific WD treatment (Groups C and D) than in those who did not (Groups A and B) (p <0.001) and in patients with LTD status associated with an ICD-10 code for WD (Groups B and D) than in those without (Groups A and C) (p <0.001).

The demographic characteristics of patients in the four groups are presented in Table 1. Significant differences in age were observed between groups, with patients receiving a specific WD treatment (Groups C and D) being younger than those without (Groups A and B). The mean age in Group A, the oldest, was 45.9 years compared to 32.2 years in Group D, the youngest. No differences in gender were observed between groups, with a slight male over-representation in all groups except Group D. Differences in the frequency of symptom occurrence between groups were modest. Psychiatric and neurological symptoms were somewhat more frequent in untreated patients than treated patients and hepatic symptoms were somewhat more frequent in patients with LTD status associated with an ICD-10 code for WD.

Concerning LTD status for conditions other than WD (E83.0), patients who were treated (Groups C and D) were principally registered for ALD status related to other "Disorders of mineral metabolism" (E83 other than E83.0) or "Fibrosis and cirrhosis of liver" (K74) (Table 2). In Group B (untreated with ALD status for WD), patients were also registered related to other "Disorders of mineral metabolism" (E83 other than E83.0) as well as for "Transplanted organ and tissue status" (Z94). In contrast, in Group A, patients were registered for ALD status, in addition to the above three conditions which are potentially relevant to WD, for a variety of common conditions (such as diabetes or heart disease) (Table 2).

3.2 Hospitalizations and monitoring

The mean number of hospitalizations with an ICD-10 code for WD over the course of the follow-up period ranged from 2.56 in Group B to 5.37 in Group C (Table 3). This number was significantly higher in treated patients compared to untreated patients ($p < 0.0001$), but did not differ significantly between patients with and without LTD status for WD ($p = 0.5708$). Median values [IQR] were 2 [1 – 4] in Group A, 1 [0 – 3] in Group B, 3 [1 – 7] in Group C and 2 [1 – 7] in Group D.

Monitoring with blood and urine tests during follow-up was performed more frequently in treated patients than untreated patients ($p < 0.0001$; Table 3), and the majority of untreated patients were never monitored. Median values [IQR] for urine tests were 0 [0 – 0] in Group A, 0 [0 – 0] in Group B, 1 [0 – 4] in Group C and 2 [0 – 7] in Group D. Median values [IQR] for blood tests were 0 [0 – 0] in Group A, 0 [0 – 0] in Group B, 1 [0 – 4] in Group C and 2 [0 – 7] in Group D.

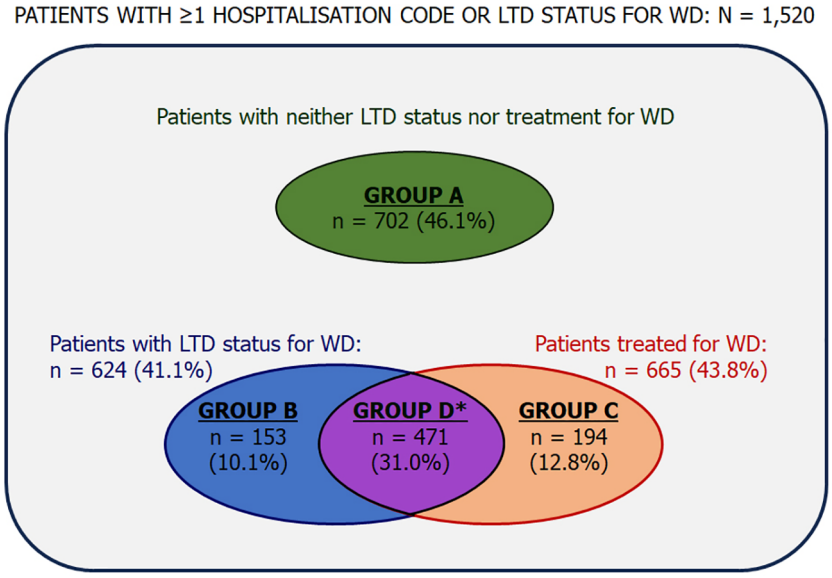


FIGURE 1
Relationship between the four study subgroups. Notes: Group D consisted of patients with both LTD status for WD, and a documented specific treatment for WD.

TABLE 1 Patient characteristics in the four study groups.

	Group				*P* value		
	A N = 702	B N = 153	C N = 194	D N = 471	Overall	A+B vs C+D	A+C vs B+D
Follow-up duration							
Median	5.3	10.6	8.4	11.0	<0.0001	<0.0001	<0.0001
[IQR]	[2.1 – 8.6]	[4.5 – 11.0]	[4.9 – 10.3	[6.8 – 11.0]			
Age							
Mean ± SD	45.9 ± 24.5	39.0 ± 22.3	34.0 ± 19.0	32.2 ± 15.4	<0.0001	<0.0001	0.2156
Median [IQR]	49 [24 – 66]	40 [21 -55]	32 [18 – 46]	33 [20 – 43]			
Gender (male, n, %)	359 (51.1%)	82 (53.6%)	112 (57.7%)	235 (49.9%)	0.2911		
Symptoms at inclusion (n, %)							
Hepatic	332 (47.3%)	79 (51.6%)	109 (56.2%)	222 (47.1%)	0.1172	0.0118	0.4697
Psychiatric	287 (40.9%)	53 (34.6%)	69 (35.6%)	153 (32.5%)	0.0267		
Neurological	230 (32.8%)	48 (31.4%)	54 (27.8%)	121(25.7%)	0.0632		

Group A: patients with neither LTD status for WD nor a specific treatment for WD; Group B: patients with LTD status for WD but without a specific treatment for WD; Group C: patients without LTD status for WD but with a specific treatment for WD; Group D: patients with both LTD status for WD and a specific treatment for WD.
The significance of differences between Groups A+B versus vs Groups C+D and between Groups A+C versus Groups B+D was only tested if the overall difference across all four groups was significant.
IQR: interquartile range; SD: standard deviation.

3.3 Mortality

Over the course of the study, 205 patients (13.5%) died (Table 4). Mortality was highest in Group A (19.7% [95% CI: 16.9 – 22.8]) and lowest in Group D (6.6% [4.7% - 9.2%], being significantly higher ($p < 0.001$; χ^2 test) in untreated patients compared to treated patients (Table 4). Kaplan-Meier survival curves for mortality following the index date are provided in the Supplementary Material. Untreated patients without LTD status (Group A) showed lower survival than did the other three groups. In addition, patients in Group A were older when they died (mean age: 63 years) compared to the other three groups (mean age: ≤51 years; Table 4).

The cause of death was documented in the CepiDC database for 168 of the 205 patients who died (82.0%). The data confidentiality policies of the SNDS preclude providing exact counts for subgroups N <10. For this reason, the cause of death could only be quantified in Group A, which accounted for 67% of deaths. In this group, multiple causes of death were identified, the most frequent of which

TABLE 2 LTD status.

Group			
A N = 702	B N = 153	C N = 194	D N = 471
E11 Type 2 diabetes mellitus: 88 (12.5%) E83 Disorders of mineral metabolism: 43 (6.1%) K74 Fibrosis and cirrhosis of liver: 37 (5.3%) Z94 Transplanted organ and tissue status: 27 (3.8%) I48 Atrial fibrillation and flutter 24 (3.4%) I25 Chronic ischemic heart disease: 23 (3.3%) 10 Essential (primary) hypertension: 22 (3.1%) E10 Type 1 diabetes mellitus: 22 (3.1%) N18 Chronic kidney disease (CKD): 21 (3.0%) F32 Major depressive disorder: 18 (2.6%)	E83 Disorders of mineral metabolism: 21 cases (13.7%) Z94 Transplanted organ and tissue status: 15 cases (9.8%)	K74 Fibrosis and cirrhosis of liver: 27 cases (13.9%) E83* Disorders of mineral metabolism: 16 cases (8.3%)	E83* Disorders of mineral metabolism: 20 cases (4.3%) K74 Fibrosis and cirrhosis of liver: 15 cases (3.2%) Z94 Transplanted organ and tissue status: 10 cases (2.1%)

Group A: patients with neither LTD status for WD nor a specific treatment for WD; Group B: patients with LTD status for WD but without a specific treatment for WD; Group C: patients without LTD status for WD but with a specific treatment for WD; Group D: patients with both LTD status for WD and a specific treatment for WD.
Only LTD status categories documented for more than ten patients are provided.
*Other than E83.0.
IQR, interquartile range; LTD, long-term disease status; SD, standard deviation; WD, Wilson's Disease.

TABLE 3 Hospitalizations and monitoring.

	Group				*P* value[a]		
	A N = 702	B N = 153	C N = 194	D N = 471	Overall	A+B vs C+D	A+C vs B+D
Number of hospital stays with Wilson's disease during follow-up[b]							
Mean ± SD	3.78 ± 6.86	2.56 ± 2.56	5.37 ± 6.35	5.01 ± 7.77	<0.0001	<0.0001	0.5708
Median [IQR]	2 [1 – 4]	1 [0 – 3]	3 [1 – 7]	2 [1 – 7]			
Blood tests for copper or ceruloplasmin							
Mean ± SD	0.30 ± 2.47	0.76 ± 2.34	3.99 ± 7.66	5.33 ± 7.90	<0.0001	<0.0001	0.0457
Median [IQR]	0 [0 – 0]	0 [0 – 0]	1 [0 – 5]	2 [0 – 8]			
Urinary tests for copper							
Mean ± SD	0.05 ± 0.28	0.30 ± 1.16	2.98 ± 5.19	4.55 ± 5.93	<0.0001	<0.0001	0.0014
Median [IQR]	0 [0 – 0]	0 [0 – 0]	1 [0 – 4]	2 [0 – 7]			

Group A: patients with neither LTD status for WD nor a specific treatment for WD; Group B: patients with LTD status for WD but without a specific treatment for WD; Group C: patients without LTD status for WD but with a specific treatment for WD; Group D: patients with both LTD status for WD and a specific treatment for WD.
[a]ANOVA.
[b]Hospitalizations with a diagnosis code for Wilson's disease as principal, related or significant associated diagnosis.
IQR, interquartile range; LTD, long-term disease status; SD, standard deviation; WD, Wilson's Disease.

was respiratory arrest, whereas WD accounted for <18% of deaths in Group A. Combining Groups C and D (treated patients), WD was the only cause of death documented in ≥10 patients, accounting for 17/37 of deaths (45.9%).

Given the important differences in characteristics observed between the four groups, a Cox proportional hazards model was performed to investigate whether group attribution was independently associated with mortality risk (Figure 2). The hazard ratio for death increased with age, and was higher in men than in women. Compared to Group D as the reference group, patients in Group A presented a higher mortality risk with a hazard ratio of 2.87 [95% CI: 1.87 – 4.41] ($p < 0.0001$). A trend towards higher mortality was also observed in Group C, but did not reach statistical significance (HR: 1.65 [95% CI: 0.94 – 2.87]; $p = 0.079$).

3.4 Liver transplantation

A total of 153 patients (10.1%) underwent liver transplantation over the course of follow-up (Table 4). This was most frequent in Group B (44 patients; 28.8%) and least frequent in Group D (11 patients; 2.3%). The proportion of patients undergoing liver transplantation was significantly higher in untreated patients than in treated patients ($p < 0.0001$) whereas no difference was observed between patients with and without LTD status ($p = 0.97$).

4 Discussion

The objective of this analysis was to evaluate the reliability of association of different coding definitions for identification of cases of WD. We observed important differences in healthcare resource utilization according to the definition used, implying that the most accurate way to identify patients with WD remains to be determined.

A number of limitations of the present analysis should be emphasized. Firstly, the analysis was performed on a prevalent population of all patients with an ICD-10 code for WD associated with hospitalization or LTD status at any time during follow-up. No information was available on where individual patients were on their disease trajectories. Ideally, it would have been more informative to perform the present analysis on patients followed from

TABLE 4 Mortality and liver transplantation. .

	Group				*P* value		
	A N = 702	B N = 153	C N = 194	D N = 471	Overall	A+B vs C+D	A+C vs B+D
Mortality	138						
Number of patients (%) [95% CI]	(19.7%) [16.9 – 22.8]	14 (9.2%) [5.5 – 14.8]	22 (11.3%) [7.6 6 16.6]	31 (6.6%) [4.7 – 9.2]	<0.0001	<0.0001	0.1761
Age at death (years) Mean ± SD	63.1 ± 22.1	41.7 ± 33.5	45.9 ± 20.1	50.7 ± 14.8	<0.0001	0.0007	0.3247
Liver transplantation Number of patients (%[95% CI])	71 (10.1%) [8.1 – 12.6]	44 (28.8%) [22.2 – 36.4]	27 (13.9%) [9.8 – 19.5]	11 (2.3%) [1.3 – 4.1]	<0.0001	<0.0001	<0.0001

CI, confidence interval; SD, standard deviation.

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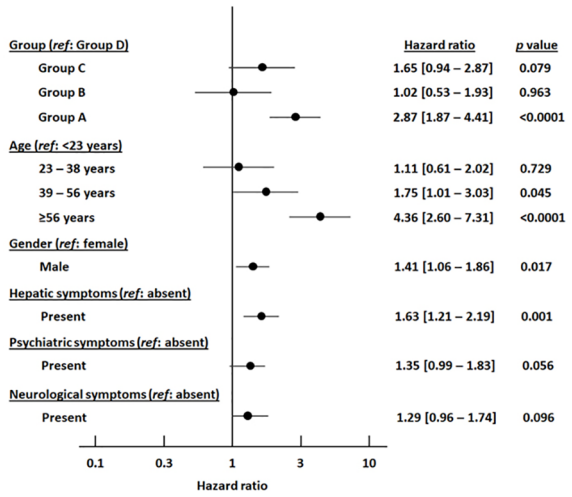


FIGURE 2
Cox relative hazard model. Notes: the number of events (deaths) was 138/702 in Group A; 14/153 in Group 8; 22/194 in Group C and 31/194 IN Group D.

their first documented claim. This is challenging due to the absence of any data on WD claims prior to 2009. However, restricting the analysis to patients with no claim during the first year of database availability (2009) would have reduced the number of patients available. Moreover, for patients identified in the SNDS at a later date, it cannot be guaranteed that they are really 'incident' patients: since patients have on average less than one WD claim a year, leading to a lag-time of an unknown duration when 'heritage' patients with WD diagnosed before 2009 are recruited. It should also be noted that the ICD-10 code used to identify patients with WD (E83.0) also covers Menkes disease, an extremely rare disease of copper metabolism, which is usually fatal in infancy with life expectancy generally not exceeding three years (28). Although we did not use a formal age filter, less than ten patients in our sample were aged ≤3 years (due to the data confidentiality policies of the SNDS precluding providing exact counts for numbers less than ten, there could have been between one and nine patients aged ≤3 years). Another limitation relates to the high-level diagnostic classification used for the ALD. For example, the Z94 code refers to all transplanted patients, and includes, for example, liver transplants, which may be part of WD care as well as kidney transplants which would be unrelated to WD. Patients in the different subgroups were also followed for different lengths of time, which introduces some confounding when comparing monitoring rates between groups. Nonetheless, differences in monitoring rates were much larger than differences in follow-up durations, suggesting that the former differences are real. The findings concerning cause of death should be interpreted cautiously, since this information was missing for one-quarter of the patients and confidentiality restrictions from the database provider prevented providing information on causes of death concerning <10 patients. Assessment of cause of death is thus incomplete and only the most frequent causes of death can be identified. The hazard ratios estimated in the Cox analysis should also be interpreted with caution: the four groups A-D were defined on a categorical basis through the presence of a treatment claim or LTD status at any time between the index event (generally a hospitalization with an E.83.0* diagnostic code) and the end of follow-up. Since the Cox analysis is a time-to-event analysis of mortality, the fact that group allocation is also time-dependent (receipt of treatment of LTD status could occur anytime over the lifetime of the model) adds a potential confounding factor to estimates of the hazard ratio. Finally, this cohort is now rather old, the last patients having been recruited in 2019. We fixed the end of the enrolment period at the end of 2019, after ten years of inclusion, due to the emergence of the COVID-19 pandemic in France at the beginning of 2020 which disrupted medical care provision for most of 2020 and 2021. However, the basic structure of the SNDS has not changed over the last twenty years and guidelines for the management of WD remain the same. The quality of data coding has nevertheless improved over time, and it is possible that if we repeated the study today, we might have found less potential misclassification. We chose to perform the analysis on the earlier ten-year cohort rather than on a post-2021 five-year cohort which would necessarily have comprised much fewer patients. However, this trade-off between cohort date and cohort size may mean that our findings do not exactly reflect current practice, and it will be important to reiterate the findings at a future date, including at least 10 years follow-up too, perhaps using a more accurate diagnostic approach, and linking to a patient registry for case ascertainment, as discussed below.

Patients in Group D were registered for LTD status with a WD diagnostic code and with at least one delivery of a copper-chelating treatment specific for WD. These patients also underwent regular monitoring for blood or urinary copper, as recommended in practice guidelines for WD (12, 15). The profile of these patients is consistent with them being true patients with WD. Although mortality was lowest in this group, patients in Group D who died did so at a relatively young age (mean age at death: 51 years). Such a reduction in life expectancy for patients with WD has been observed in several other studies, for example in Poland (27), UK (29), South Korea (11), and the USA (10, 30).

On the other hand, the patients in Group A, who constituted 46% of the original study population, were identified solely on the basis of at least one hospitalization associated with an ICD-10 diagnostic code for WD. These patients were not treated for WD, rarely underwent blood or urine monitoring and were not registered for LTD status for WD. Patients in this group were older than those in the other groups, and had higher mortality, independently of their age-associated mortality risk. This high mortality may possibly be explained by the presence of other pathologies, since they frequently had LTD status for diseases other than WD. In particular, we observed a high proportion of patients in this group with LTD status for liver fibrosis or cirrhosis (5.3% of patients in Group A) and transplanted organ or tissue status (3.8%). In addition, liver cirrhosis was one of the more frequent causes of death. However, the cause of death for 21 untreated patients was declared as WD (although these patients may be in Group B, since we were obliged to pool groups A and B in order to have sufficient numbers to identify causes of death in >10 patients).

It seems very improbable that so many patients with WD should be receiving non-optimal care and we would infer that

most of them did not have WD. The question thus arises as to why they had a WD diagnostic code in their hospitalization discharge summary. One hypothesis would be that they presented symptoms consistent with WD and were hospitalized for exploratory tests to confirm or refute a suspected diagnosis of WD. For example, patients in Group A had a higher incidence of psychiatric and neurological symptoms than the other patients. These symptoms are not specific for WD and some are very common in the general population. For example, depressive disorders, anxiety disorders and sleep disorders occur in at least 20% of the French adult population (31, 32). It is possible that the presence of these symptoms in patients who also have hepatic symptoms, may have been a 'flag' for physicians to consider a diagnosis of WD, which resulted in a diagnostic code in the database that was never rectified.

The hospital stay may then have been labelled for reimbursement purposes with an ICD-10 code at the time of the test for WD, even though the diagnosis was not subsequently confirmed. In addition, individuals who are screened following diagnosis of WD in a relative, as part of genetic counselling, may also acquire a diagnostic code for WD in the SNDS. However, since ICD-10 coding may never be subsequently corrected in the SNDS, this may lead to incorrect case identification when this is the only criterion used in insurance claims database studies. In this respect, it is of interest that, in a study using a German insurance claims database, the use of an ICD-10 code alone identified twice as many cases than when requiring, in addition to the ICD-10 code, documentation of a WD medication or a laboratory test for both copper and ceruloplasmin (33).

The treated patients who did not have LTD status for WD (Group C) were generally similar to the treated patients with LTD status, and we would hypothesize that most of these were true patients with WD. In France, registration for LTD status is the shared responsibility of the primary care physician and the specialist. However, irrespective of disease, a significant proportion of patients who are eligible for LTD status do not get registered (34). In addition, for patients who are eligible for LTD status for more than one disease may only be declared by their general practitioner to social security for the disease that was identified first. Alone, LTD status is thus not sufficiently sensitive for case identification.

Patients with LTD status for WD who were not treated (Group B) represent ten percent of the population identified in the SNDS. In principle, LTD status should only be assigned once the diagnosis has been confirmed, and status is then reviewed every five years, and revoked if no longer relevant. Exceptionally, this may not happen, and it is possible that some patients initially received LTD status before a definitive diagnosis had been assigned, and that this was never subsequently revoked. However, if this does occasionally happen, it is likely to be a rare event and unlikely to account for more than a handful of patients in Group B. A more likely explanation is incomplete capture of patients with liver transplants. Some untreated patients with LTD status in Group B had received a liver transplant and therefore no longer required copper-chelating treatment and copper monitoring. Indeed, liver transplantation during the follow-up period was most frequent in this group, accounting for 28.8% of the group. Liver transplantations are identified from procedure codes at the time of the event, and thus patients who had undergone liver transplantation prior to the start of the study period in 2009 cannot be identified. There is thus left-censoring of the data and we may be failing to identify a significant number of patients who received a liver transplant prior to 2009. Given that our population was a mature one (mean age at the index date: 40 years), it cannot be excluded that we are missing patients who received a liver transplant when young. Several retrospective cohort studies from other countries have indeed indicated that liver transplantation in WD is typically performed before the age of twenty (35–38). It is also possible that patients with WD who were not treated with medication for whatever reason more frequently undergo liver transplantation, since this is the only other treatment available. Finally, it cannot be excluded that certain patients refuse pharmacotherapy in favor of alternative medicine approaches. However, this would not be expected to concern many patients, since interruption or refusal of copper-depleting medications leads to rapid progression of hepatic disease and early death (19, 21). Indeed, the mean age of death was ten years lower in Group B than in Group D, which would be consistent with this explanation.

Correctly identifying patients with WD in insurance claims databases may require combining ICD-10 diagnostic codes, treatment and monitoring of relevant biological markers. The most specific combination may be for an ICD-10 code for WD and a specific treatment and blood or urine tests for copper or caeruloplasmin before and after initiation of treatment. We would suggest requiring at least two hospitalizations since, if the patient was initially hospitalized for a diagnostic work-up following suspicion of WD, a hospitalization claim may persist in the database even though a diagnosis of WD was finally excluded. Many database claims studies performed in the United States in a range of diseases, including the study of WD (10), require two hospitalizations for this very reason. Similarly, requiring a single copper test may not be informative since the claim will be documented in the SNDS regardless of whether the results (which are not available in the database) were positive or negative; requiring the test to be performed more than once provides some reassurance that the initial test was positive and follow-up monitoring has been initiated. However, this may be insufficiently sensitive for exhaustive case detection if copper monitoring is not performed in accordance with practice guidelines. For example, in a retrospective medical chart review reported from the United States copper monitoring was not performed systematically and one quarter of patients did not undergo a laboratory test for copper at the time of diagnosis (39). A possible case identification algorithm for use in insurance claims databases is proposed in Table 5; currently, this is just a proposition and the algorithm would need to be validated against clinical records to determine its performance and reliability, notably in determining its sensitivity, specificity, and positive and negative predictive value.

To take this approach a step further, such a case-identification algorithm should be validated with respect to the clinical diagnosis made by the treating physician. The French national health insurance fund has developed a mapping system (Healthcare Expenditures and Conditions Mapping) for identifying common pathologies in the SNDS database, which is updated annually (40). This was done in order to monitor the cost to the health service of

TABLE 5 Proposed diagnostic algorithm to identify patients with Wilson's disease in insurance claims databases.

EITHER
At least two hospitalizations associated with a documented ICD-10 code for WD (E83.0*: copper metabolism disorder) (PD, RD or SAD).
OR
LTD status for WD (ICD-10 code: E83.0*).
AND
No subsequent loss of LTD status for WD.
AND
Age ≥4 years[1]
AND
At least two documented claims for a blood or urine test for copper or caeruloplasmin (procedure codes 0547, 2008 or 1809).
AND
At least two deliveries of a WD-specific medication (D-penicillamine: M01CC01; trientine: A16AX12; zinc acetate: A16AX05), one of which should be subsequent to a blood or urine test for copper or caeruloplasmin.

[1]To exclude patients with Menkes disease.
ICD-10: International Classification of Diseases – 10th Edition; LTD, long-term disease; PD, primary diagnosis; RD, related diagnosis; SAD, significant associated diagnosis; WD, Wilson's disease.

different pathologies over time and to serve as a benchmark for evaluating the effectiveness of health interventions and for prioritizing healthcare policy. It should be noted that, for most pathologies, this mapping system has not been validated against data from patient records, although a network (REDSIAM) has been established to develop and validate algorithms to identify common pathologies from hospital claims in the SNDS (41). Given the number of possible pathologies, mapping operates at a relatively high level of disease classification, and individual case identification algorithms are not available for WD or other rare diseases.

The creation of a national rare disease registry represents a promising approach to validating algorithms for identifying patients in the SNDS reliably. In 2014, the management of WD (and other rare diseases) in France was centralized in a small number of reference centers, with the goal of improving the quality of care. In parallel, a French national registry for rare diseases (Banque Nationale de Données Maladies Rares; BNDMR) was set up with the objective of collecting data on all patients with rare diseases cared for by reference centers across the country in a standardized electronic database (42, 43). Since the database was opened, the number of rare diseases represented and patient recruitment have progressively accrued (44, 45). To our knowledge, there have been no studies of WD performed in the BNDMR published to date. However, as of 1st May 2024, this database had enrolled 1,238 patients with WD, of whom >90% were still alive (46). It should thus be possible to link patients with a validated diagnosis of WD in the BNDMR to the same individual in the SNDS and thus assess the quality of case identification in the SNDS, identify any miscoding issues and thereby establish the most accurate diagnostic algorithm to retrieve patients with WD from the SNDS. Such a linkage approach between the SNDS and local patient registries has been previously used successfully to validate diagnostic algorithms and to evaluate the quality of coding in the SNDS in common diseases such as heart failure (47–49), diabetes (50) and cancer (51, 52).

An alternative approach used to validate diagnostic algorithms in the SNDS, applied to multiple sclerosis and prostate cancer, has been to reconstitute patient care pathways from claims history in the SNDS and then subject these to review by an expert panel who adjudicated on whether they were true cases or not (47). The latter approach may be well-suited to a rare disease such as WD, since it would not require the active involvement of multiple reference centers across the country.

5 Conclusion

This study of 1,520 patients with a documented insurance claim for WD in the SNDS and followed for up to eleven years suggests that there is substantial doubt about the optimal way to identify unambiguously cases of WD in the SNDS. For this reason, it is important to perform validation studies with the goal of identifying a diagnostic algorithm with optimal accuracy. This could be done by linking data from the SNDS to medical records of the same patients in a dedicated patient registry for WD containing high-quality medical data. The ability to identify these patients correctly in the national insurance database is a prerequisite for collecting exhaustive and accurate information on epidemiology, healthcare utilization and outcomes in the real-world treatment setting, which is needed for planning of resource allocation and evaluating the cost-effectiveness of innovative treatments.

Data availability statement

Access to data in the SNDS is available exclusively to institutions who meet the criteria for access to confidential data, following procurement of consent from the National Health Data Hub (HDH) and the French data protection authority (CNIL), and following signature of a contractual agreement with the data provider (the CNAM). Requests to access the datasets should be directed to Health Data Hub https://www.health-data-hub.fr.

Ethics statement

The studies involving humans were approved by the Comité éthique et scientifique pour les recherches, les études et les évaluations dans le domaine de la santé (CESRESS). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin because the data retrieved from the SNDS was anonymized before extraction. Patients cannot be identified and obtaining written informed consent is neither possible nor relevant.

Author contributions

CL: Conceptualization, Writing – original draft, Project administration, Investigation, Formal analysis, Supervision, Methodology, Writing – review & editing, Data curation, Validation. TD: Writing – review & editing, Validation, Conceptualization, Methodology. BB: Validation, Conceptualization, Writing – review & editing, Methodology. SB: Conceptualization, Writing – review & editing, Validation, Methodology. J-PC: Project administration, Supervision, Validation, Funding acquisition, Conceptualization, Writing – review & editing, Writing – original draft.

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Conflict of interest

J-PC is an employee and shareholder of Vivet Therapeutics, a biotechnology company involved in the development of gene therapies for rare diseases, including Wilson's disease. BB and TD were also employees and shareholders of Vivet Therapeutics at the time of the study. CL and SB are employees of Putnam, a company with expertise in database studies, who performed the analysis on behalf of Vivet Therapeutics.

Generative AI statement

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Supplementary material

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