Estimating the clinical prevalence of Wilson's disease in the UK

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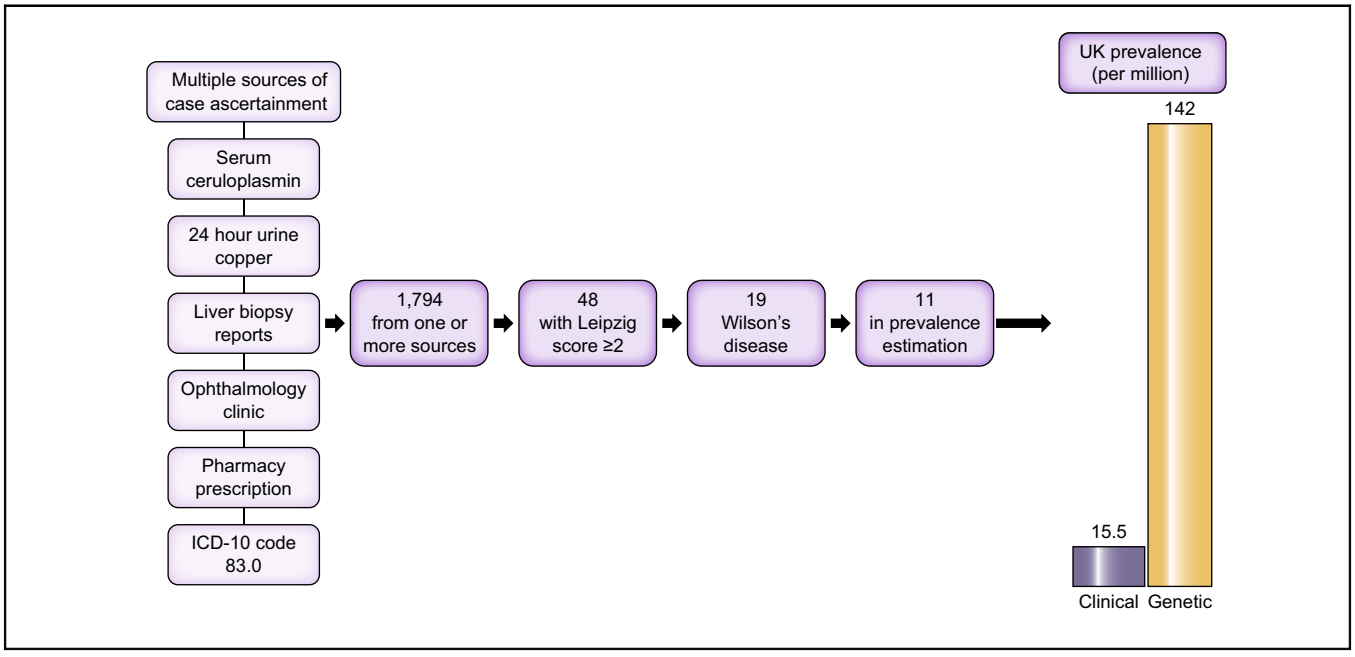
Graphical abstract



Highlights

- The clinical prevalence of Wilson's disease in the UK is estimated to be 15.5/million (1/64,516).
- The clinical prevalence is significantly lower than the previously reported genetic prevalence.
- Routine clinical and laboratory data can be used to not only find existing cases, but also evaluate potential cases.
- Case ascertainment is potentially a cost-effective approach for Wilson's disease and other rare diseases.

Lay summary

Our study estimates the clinical prevalence of Wilson's disease, a rare genetic disorder of copper metabolism, in the UK. The estimated clinical prevalence is this study is markedly lower than the estimated UK genetic prevalence.

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Research article

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Estimating the clinical prevalence of Wilson's disease in the UK

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Background & Aims: The clinical prevalence of Wilson's disease (WD) in the UK remains unknown. The estimated genetic prevalence in the UK, 142/million, is higher than the clinical prevalence (15/million) reported in other European studies. The aim of this study was to estimate the clinical prevalence of WD utilising readily available laboratory and clinical data.
Method: Patients with WD who attended Nottingham University Hospital NHS Trust (NUH) between 2011 and 2018 were identified using multiple sources of case ascertainment: serum ceruloplasmin, 24-hour urinary copper, 'Wilson' in liver biopsy report, hospital prescription for penicillamine/trientine/zinc and admission coded with ICD-10 Code E83.0 (disorder of copper metabolism). Potential cases were identified using the Leipzig score, diagnosis was confirmed in hospital records and the point prevalence was calculated using the Office for National Statistics mid-2017 population estimates.
Results: A total of 1,794 patients were identified from ≥1 source; 19 patients had WD, of whom 11 were from within the study catchment area and alive at the time of point prevalence estimation. Twenty-nine patients had a Leipzig score ≥2 without a diagnosis of WD, but none had WD on screening (n = 16). The overall prevalence of WD was 15.5/million; males 16.9/million and females 14.1/million.
Conclusion: This is the first UK population-based study to assess the clinical prevalence of WD. The reported clinical prevalence is lower than the UK genetic prevalence, but comparable to the clinical prevalence reported in Europe. The case ascertainment approach used in this study may be cost-effective, and similar practises could be adopted nationally.
Lay summary: Our study estimates the clinical prevalence of Wilson's disease, a rare genetic disorder of copper metabolism, in the UK. The estimated clinical prevalence is this study is markedly lower than the estimated UK genetic prevalence.

Introduction

Wilson's disease (WD), first reported in 1912,[1] is a rare, autosomal recessive disease of copper metabolism that leads to multi-organ damage through excess intracellular copper accumulation.[2] Early diagnosis and life-long copper chelation is lifesaving, without which WD is usually fatal.[3,4] Although the ability to diagnose and manage WD have improved globally, estimation of its true prevalence remains a challenge, at least in part due to the lack of a single diagnostic test and the wide range of phenotypes presenting to various medical specialities.

Since the first identification of variants in the *ATP7B* gene being responsible for WD nearly 30 years ago,[5-7] more than 500 variants have been linked to development of the disease.[8,9] A more recent study reviewed a total of 1,458 unique variants in the *ATP7B* gene identified from previous literature and data resources.[10] They were annotated using American College of Medical Genetics and Genomics and the Association for Molecular Pathology criteria and a total of 656 pathogenic or likely pathogenic variants were curated into their database.[10] Variable penetrance of disease-causing mutations is being considered a contributor to the poor correlation between the genetic and clinical prevalence.[11] Further, the identification of pathogenic mutations based on algorithmic predictions[10] may also contribute the discrepancy through mislabelling of benign mutations as pathogenic.

In the UK, the only prevalence study to date estimates the genetic prevalence to be as high as 142/million, by sequencing the entire *ATP7B* gene of 1,000 new-borns for variants that had *in silico* evidence of causing WD.[12] The clinical prevalence of WD in the UK has not been established, which was the aim of this study.

Keywords: Wilson's disease; Copper metabolism disorder; Clinical prevalence; Multiple sources of case ascertainment.
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Materials and methods

Patient selection

A retrospective analysis was undertaken to identify patients with confirmed or probable WD in Nottingham University Hospital NHS Trust (NUH) catchment area using multiple sources of case

ascertainment. All patients who, between 01 January 2011 and 31 December 2018, had i) a 24-hour urinary copper measurement, ii) a serum ceruloplasmin level <0.2 g/L iii) the term 'Wilson' in their liver biopsy report, iv) received a hospital prescription for penicillamine, trientine, or zinc, v) an admission to NUH with a recorded primary or comorbid diagnosis of disorder of copper metabolism (ICD-10-CM Diagnosis Code E83.0) and vi) identification of Kayser-Fleischer ring or sunflower cataracts in ophthalmology clinics, were included in this study (study cohort).

Data collection

To ensure completeness, data collection of the patients included in the study cohort was not limited to the study period that was used for patient selection. Regardless of which source(s) a case originated from, every patient case record was searched manually for a serum caeruloplasmin level (lowest value if more than 1 entry), a 24-hour urinary copper level (highest value if more than 1 entry), any liver histology, any ophthalmology encounter and *ATP7B* gene analysis, if available. All clinic letters/clinical correspondence, hospital discharge summaries and hospital prescriptions were also reviewed. Demographic details included Clinical Commissioning Group (CCG) determined by the General Practice at which the patient is registered. CCGs are geographically grouped, clinically led statutory bodies that are responsible for commissioning most health and care services for patients in their area.

Case definition

Leipzig score[13-15] was calculated for all patients included in the study cohort using the above collected data. To increase the sensitivity, a Leipzig score of 2 or more was used for the identification of potential patients with WD; those with Leipzig score of 0 or 1 were deemed unlikely to have WD. Based on the 8th International Meeting on Wilson's disease recommendation[15] and our laboratory reference range, a serum ceruloplasmin level of <0.2 g/L and a 24-hour urinary copper excretion of >0.95 μmol/day (>0.64 μmol/day for children) were considered abnormal.

Patients were deemed to have confirmed WD if the calculated Leipzig score was 4 or more and they were on treatment for WD, and/or the diagnosis of WD had been mentioned on at least 2 written communications, be it clinic letter, clinical correspondence or hospital discharge summary. Patients with Leipzig score of 2 or more and without a confirmed diagnosis of WD were considered as 'possible' WD and were invited to a WD screening clinic.

Screening clinic

Patients who were categorised as 'WD diagnosis possible' and resident within the NUH catchment area at the time of this study were invited to a screening clinic. A thorough clinical assessment, laboratory investigations including 24-hour urinary copper estimation, *ATP7B* gene analysis and slit lamp examination were undertaken as part of the screening. Liver biopsy and magnetic resonance imaging of the brain were reserved only for those who were suspected to have WD based on above clinical assessment and investigations.

Gene analysis was undertaken by sequencing the entire coding region of the *ATP7B* gene, including all intron/exon boundaries, which has a sensitivity of >99% for identifying all reported pathogenic variants.

Ethical approval

This study was approved by the Nottingham University Hospitals Trust Clinical Effectiveness Board (19- 061C) and did not require informed patient consent from individual patients to access their medical records held within NUH.

General Practitioners of patients who were deemed 'WD diagnosis possible' were contacted in writing to seek confirmation of appropriateness before inviting the patients to the screening clinic. Those who were deemed not appropriate (*e.g.*, terminal illness) were not approached.

Study area and denominator population

NUH is a tertiary centre covering a wide population base across the East Midlands. However, for the purposes of this study only patients identified from within Greater Nottingham, which represents NHS Nottingham City CCG, NHS Nottingham North and East CCG, NHS Nottingham West CCG and NHS Rushcliffe CCG, were included in the analysis. The population of all 4 CCGs was derived from the Office for National Statistics 2017 census, taken on 30 June 2017, which were used as the denominator population and point prevalence date, respectively.

Point prevalence estimation

Patients with confirmed WD from within the above 4 CCGs (study area) who were alive on 30 June 2017 were included in the estimation of point prevalence; WD patients from the study area who were not alive on 30 June 2017 were not included. Point prevalence per million persons was calculated with Poisson 95% CIs. All analyses were performed using Stata 15 statistical software (StataCorp LP, Texas, USA).

Results

Study cohort

A total of 2,086 entries were identified from individual sources during the study period (Fig. 1). After amalgamating patients identified by more than 1 source (2 sources n = 215, 3 sources n = 20 and 4 sources n = 4) and patients who had more than 1 entry in the same source (n = 53), a total of 1,794 patients were included in the study cohort.

Case ascertainment

Of patients included in the study cohort (n = 1,794), 48 (2.7%) were identified to have a Leipzig score of 2 or more. The rest (n = 1,746, 97.3%), unlikely to have WD, were excluded from further interrogation.

Of the 48 patients identified, 19 (39.6%) had a confirmed diagnosis of WD; the rest (n = 29, 60.4%), deemed 'possible' WD, were identified by low serum ceruloplasmin and/or elevated 24-hour urinary copper excretion (Fig. 1). There was no difference in age (at the time of the point prevalence or death, if earlier) between those with confirmed WD (median 30.9 years, IQR 14.6–38.8) and those with 'possible' WD (median 33.0 years, IQR 24.5–46.6; $p = 0.24$). Similarly, there was no difference in the 24-hour urinary copper excretion recorded between the groups (median 3.13 μmol/24 hours, IQR 0.42–4.94 *vs.* median 0.88 μmol/24 hours, IQR 0.71–1.11; $p = 0.12$). However, serum ceruloplasmin level was significantly lower in those with confirmed WD (median 0.08 g/L, IQR 0.03–0.15) compared to those with 'possible' WD (median 0.17 g/L, IQR 0.15–0.18; $p = 0.0005$). Although there were more males in both groups, the 'possible'

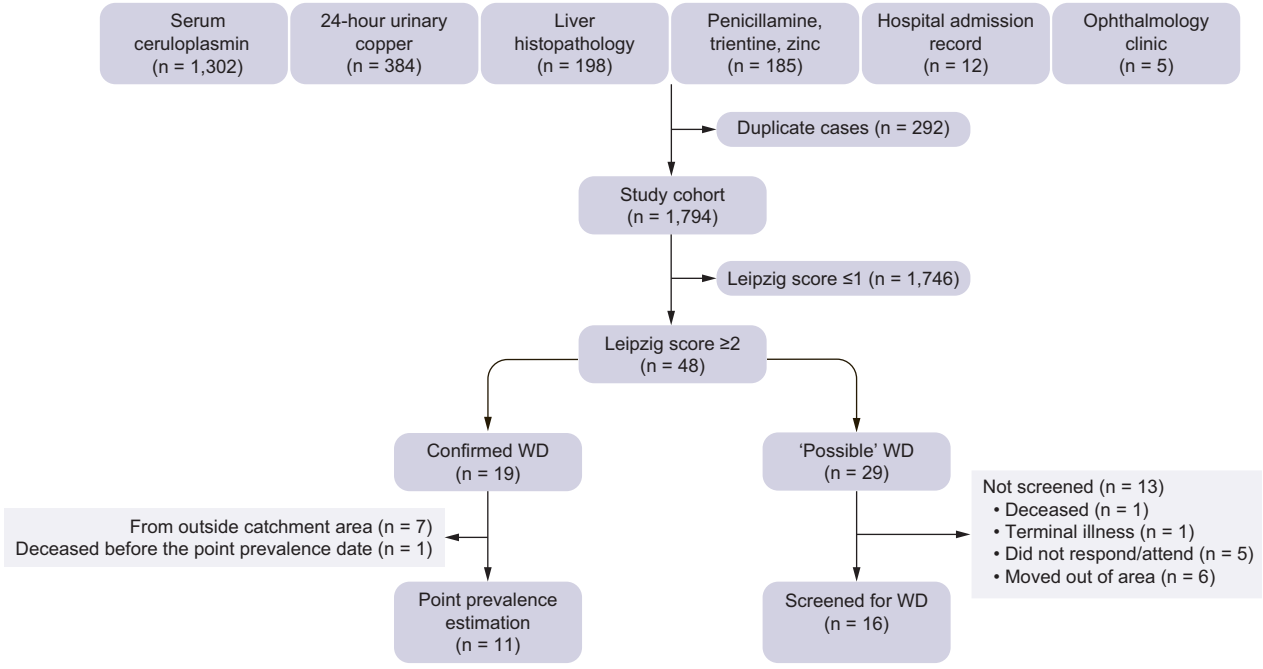

Fig. 1. Study flow diagram. Overview of study population and the study design. The flow chart illustrates the patient flow through the study. WD, Wilson's disease.

WD group had a significantly higher proportion of males than those with confirmed WD (57.9% *vs.* 86.2%; $p = 0.03$).

Screening clinic outcome

Of the 29 patients identified as 'possible' WD and warranting further investigation, 16 (55.2%) attended screening clinic and investigations. Of the rest, 6 had moved out of the region, 5 did not respond to repeated invitations, 1 was terminally ill, and 1 had died (Fig. 1).

None of the patients who underwent screening had WD-related symptoms or signs. WD screening investigations were within normal parameters in 6 patients. The others (n = 10) had a serum ceruloplasmin level <0.2 g/L (range 0.155–0.194) but otherwise normal WD screening investigations, resulting in a new Leipzig score of 1 and making a WD diagnosis unlikely.

Patients with Wilson's disease

Of the 19 patients with WD, 11 (57.9%) were males; the median age at diagnosis was 18.5 years (IQR 13.9–22.4). The majority (n = 12, 63.2%) were of European origin; 5 (26.3%) were of South Asian origin; and ethnic origin was not known in the rest.

Fifteen (78.9%) patients had hepatic, 10 (52.6%) had neuropsychiatric, 5 (26.3%) had ophthalmic, and 1 (5.3%) had renal manifestations of WD. Most patients (n = 11, 57.9%) were on zinc as a monotherapy or in combination with D-penicillamine or trientine; 9 (47.4%) were on trientine and 4 (21.1%) were on D-penicillamine. One (5.3%) patient had undergone liver transplantation and 1 (5.3%) had died from non-WD-related causes. Demographic and clinical details of individual patients are summarised in Table 1 and the details of Leipzig score at diagnosis are summarised in Table S1.

Prevalence of Wilson's disease

Of the 19 patients with WD, 12 (63.2%) were from within the catchment area. However, 1 patient had died prior to the date of point prevalence calculation, thus only 11 patients were included in estimation. The total population of all 4 CCGs, derived from the Office for National Statistics 2017 census taken on 30 June 2017, was 709,738 (males 354,331 and females 355,407).

The overall clinical point prevalence was 15.5/million (95% CI 7.7–27.7). The prevalence in males was 16.9/million (95% CI 6.2–36.9) and in females 14.1/million (95% CI 4.6–32.8).

Discussion

This is the first UK clinical prevalence study of WD. To our knowledge, it is also the first study to ascertain cases using clinical criteria in a systematic approach from multiple data sources, which afforded the unique opportunity to not only find existing cases, but also evaluate potential cases of WD. The estimated overall clinical prevalence of 15.5/million is markedly lower than the estimated UK genetic prevalence of 142/million.

Most clinical prevalence studies have solely relied on insurance records or medical registries.[16-20] A few studies have attempted to estimate prevalence through population screening for Kayser-Fleischer rings or ceruloplasmin,[21-23] but none have combined multiple clinical parameters and medical records to identify patients with WD, as in this study. Although insurance records are an easier way of estimating prevalence, case ascertainment using clinical parameters is more appropriate for a country such as the UK where medical insurance is only held by a minority of the population. Further, the latter, as shown in this study, is also able to identify those who warrant additional investigations. This is critical for a disease such as WD which has a

Table 1. Summary of patients with Wilson's disease.

	Age[†]	Sex	Ethnic origin	Clinical manifestation/s	*ATP7B* gene mutation	Current medication	Outcome
1	20	M	South Asian	Hepatic; neuropsychiatric		Trientine	Alive
2	47	F	European	Neuropsychiatric		Trientine	Dead
3	17	F	NK	Neuropsychiatric		Zinc	Alive
4	13	M	European	Hepatic; neuropsychiatric; ophthalmic	p.Gln111*; p.Gly869Arg	Trientine	Alive
5	24	M	European	Neuropsychiatric		D-penicillamine	Alive
6	10	F	South Asian	Hepatic; ophthalmic	p.Ala1003Val; p.Asn1270Ser	Zinc	Alive
7	3	M	European	Hepatic	p.Thr977Met; p.His1069Gln	Zinc	Alive
8	25	F	European	Hepatic; ophthalmic		Trientine	Alive
9	14	F	European	Hepatic; neuropsychiatric; ophthalmic; renal		D-penicillamine, Zinc	Alive
10	19	M	European	Hepatic	p.Trp779*; p.Val945fs	D-penicillamine, Zinc	Alive
11	17	F	European	Hepatic	p.Ala874Val; p.His1069Gln	Trientine, Zinc	Alive
12	12	M	South Asian	Hepatic	p.Val1216Met; p.Asn1270Ser	D-penicillamine, Zinc	Alive
13	3	M	South Asian	Hepatic	p.Val1216Met; p.Asn1270Ser	Zinc	Alive
14	18	M	NK	Neuropsychiatric		Zinc	Alive
15	30	F	European	Hepatic		NA	Alive (liver transplantation)
16	20	M	South Asian	Hepatic; neuropsychiatric	p.Ala1003Val; p.Asn1270Ser	Trientine	Alive
17	22	M	European	Hepatic; neuropsychiatric; ophthalmic		Trientine, Zinc	Alive
18	22	M	European	Hepatic; neuropsychiatric		Trientine, Zinc	Alive
19	20	F	European	Hepatic		Trientine	Alive

F, female; M, male; NA, not applicable; NK, not known.
* Indicates a translation termination (stop) codon.
† Age at the time of diagnosis of Wilson's disease.

poorly streamlined diagnostic pathway, lack of diagnostic test(s) and unpredictable clinical presentation and intensity.

The marked difference between the clinical prevalence of this study and the previous UK genetic prevalence study is unsurprising. Previous studies have also demonstrated discordance between genetic and clinical prevalence within the same population. A French study that involved whole gene sequencing of 697 indiscriminate individuals estimated the genetic prevalence of pathogenic or likely pathogenic variants to be 115.8/million,[24] which was significantly higher than the clinical prevalence of 15/million estimated using the French National Health Insurance information system, a year earlier.[17] Similar significant differences have also been seen in other counties.[18,25] Several reasons are likely to contribute to this difference including the presence of more than 600 pathogenic or likely pathogenic variants in *ATP7B,*[10] difference in the severity of certain variants *e.g.* truncating variants that lead to a significant decrease in the protein *vs.* missense changes, and also the combination of variants in either homozygous or compound-heterozygous states,[26] new classification criteria for assessing pathogenicity of variants,[27] variation in penetrance of certain variants,[11] the potential for epigenetic mechanisms of gene expression regulation causing clinical disease[28] and the likeliness of undiagnosed cases being missed in clinical prevalence studies.[29]

The usually quoted clinical prevalence estimate of 30/million, published in 1984, was based on epidemiological data from the United States, East Germany and Japan.[30] However, the reported clinical prevalence from individual countries and territories are either markedly higher or lower. While a substantially higher prevalence is seen in some isolated populations,[31-33] the prevalence reported in this study (15.5/million) is comparable to previous Western European population-based clinical studies. The clinical prevalence, based on 58 million health scheme beneficiaries in France was estimated to be 15/million[17] while the clinical prevalence in the Republic of Ireland in 2011 was 9.0/million.[34]

Interestingly, a number of previous studies have indicated a significant difference in clinical prevalence between males and females.[16-18] Although this may be due to underdiagnosis, a time lag in the disease presentation in females has also been described.[18] A Polish study which looked specifically at gender differences in 627 consecutive patients presenting to a tertiary centre observed a significant male predominance.[35] However, such significant gender difference was not evidenced in this study.

Our study has its strengths and limitations. Firstly, this study covers a population in a predictable and a nationally consistent way that is defined by NHS CCGs, and thus the results are generalisable to the UK population. The process of case ascertainment used in this study may be a cost-effective method of identifying patients with WD, and similar practises could be adopted in other NHS hospitals and even nationally. Similar methods could also be used for other rare diseases. However, it is important to highlight that the process of systematic review and curation of large and complex data is labour intensive, which can be overcome with the use of validated algorithms and machine learning.[36,37] On the other hand, patients with WD who have not had any WD-related investigations, including those whose symptoms have not been recognised as being associated with WD and those who are too young to have developed features, are unavoidably missed, which is a major limitation. For example, in a South Korean study, 32% of patients who had WD had been treated for psychiatric symptoms previously, without a diagnosis of WD being considered.[18] Further, although the use of multiple sources of case ascertainment would have mitigated the impact of limited diagnostic accuracy of the individual sources used in this study to identify patients with WD (*e.g.*, serum ceruloplasmin level <0.2 g/L), there is no single diagnostic test or a universal diagnostic value, which is an important limitation.[38] In addition, though entirely a theoretical possibility, patients with WD solely managed by General Practitioners and patients who self-medicate, for example using over the counter zinc

preparations, are also not captured by this study. Therefore, until and unless universal screening with a highly specific/sensitive test for WD becomes part of day-to-day clinical practice (*e.g.*, part of newborn blood spot screening programmes), clinical prevalence estimations will not evince the true the prevalence.

In conclusion, this is the first UK population-based clinical prevalence study of WD. The prevalence found in this study is lower than the previous UK population-based genetic study, but comparable to Western European population-based clinical studies. Similar case ascertainment methods can be implemented nationally for WD and other rare diseases.

Abbreviations

CCG, clinical commissioning group; WD, Wilson's disease.

Financial support

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

PW - data collection, data curation, analysis, writing of manuscript; JH–data curation and review & editing of manuscript; ESN–data collection and review & editing of manuscript; PK–data collection and review & editing of manuscript; EAW–data collection, administration and review & editing of manuscript; JE–data collection and review & editing of manuscript; GPA–data collection and review & editing of manuscript; GJ–data collection and review & editing of manuscript; FP–data analysis, methodology, supervision, and review & editing of manuscript; ADA–conception and design of the study, methodology, data collection, review of results, study supervision and administration and writing of manuscript.

Data availability statement

Owing to the nature of this research, participants of this study were not individually consented for their data to be shared publicly. However, fully anonymised data that support the findings of this study are available from the corresponding author upon reasonable request and an appropriate institutional collaboration agreement.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2021.100329.

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Author names in bold designate shared co-first authorship

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