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.

https://doi.org/10.1016/j.jhepr.2021.100329
Estimating the clinical prevalence of Wilson’s disease in the UK

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JHEP Reports 2021. https://doi.org/10.1016/j.jhepr.2021.100329

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 21 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 practices could be adopted nationally.

Lay summary: Our study estimates the clinical prevalence of Wilson’s disease in the UK, a rare genetic disorder of copper metabolism, to be markedly lower than the estimated UK genetic prevalence. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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 has 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.5,9 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 predictions10 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.

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 approach used in this study may be cost-effective, and similar practises could be adopted nationally.

Keywords: Wilson’s disease; Copper metabolism disorder; Clinical prevalence; Multiple sources of case ascertainment.

Received 23 March 2021; received in revised form 20 May 2021; accepted 28 June 2021; available online 7 July 2021
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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\(^1\)\(^-\)\(^1\(^5\) 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\(^1\(^5\) and our laboratory reference range, a serum ceruloplasmin level of <0.2 g/L and a 24-hour urinary copper excretion of >0.95 \(\mu\text{mol/day}\) (>0.64 \(\mu\text{mol/day}\) 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 \(\mu\text{mol/24 hours}\), IQR 0.42–4.94 vs. median 0.88 \(\mu\text{mol/24 hours}\), 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’
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. A few studies have attempted to estimate prevalence through population screening for Kayser-Fleischer rings or ceruloplasmin, 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...
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. A previous Western European population-based clinical studies. The clinical prevalence in the Republic of Ireland in 2011 was 9.0/million. 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. A previous Western European population-based clinical studies. The clinical prevalence in the Republic of Ireland in 2011 was 9.0/million.

Interestingly, a number of previous studies have indicated a significant difference in clinical prevalence between males and females. Although this may be due to underdiagnosis, a time lag in the disease presentation in females has also been described. A Polish study which looked specifically at gender differences in 627 consecutive patients presenting to a tertiary centre observed a significant male predominance. 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 CGGs, 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. 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. 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. 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.

### 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            | Hepatic; neuropsychiatric |                     | Trientine         | Alive   |
| 2    | 47  | F            | European Neuropsychiatric |                     | Trientine         | Dead    |
| 3    | 17  | F            | NK                       | Trientine           | Zinc              | Alive   |
| 4    | 13  | M            | European Hepatic; ophthalmic; | p.Gln111*; p.Gly869Arg | Trientine         | Alive   |
| 5    | 24  | M            | European Neuropsychiatric |                     | D-penicillamine    | Alive   |
| 6    | 10  | F            | South Asian Hepatic      | p.Ala1003Val; p.Asn1270Ser | Zinc              | Alive   |
| 7    | 3   | M            | European Hepatic         | p.Thr977Met; p.His1069Gln | Zinc              | Alive   |
| 8    | 25  | F            | European Hepatic         | p.Gln111*; p.Gly869Arg | Trientine         | Alive   |
| 9    | 14  | F            | European Hepatic         | p.Gln111*; p.Gly869Arg | D-penicillamine, Zinc | Alive   |
| 10   | 19  | M            | European Hepatic         | p.Thr779*; 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            | European Hepatic         |                      | Zinc              | Alive   |
| 15   | 30  | F            | European Hepatic         |                      | NA                | Alive (liver transplantation) |
| 16   | 20  | M            | South Asian Hepatic      | p.Ala1003Val; p.Asn1270Ser | Trientine         | Alive   |
| 17   | 22  | M            | European Hepatic         | p.Ala1003Val; p.Asn1270Ser | Trientine, Zinc | Alive   |
| 18   | 22  | M            | European Hepatic         |                      | 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.
1 Age at the time of diagnosis of Wilson’s disease.
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**
The study was funded partly through an investigator-initiated research grant (PW and ADA) from Orphalan UK.

**Conflict of interest**
The authors declare no conflicts of interest that pertain to this work. Please refer to the accompanying ICEMJE 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.

**Acknowledgements**
We thank Irena Wales (Department of Gastroenterology and Hepatology, Nottingham University Hospitals NHS Trust) for the administrative assistance of organising the Wilson’s disease screening clinics, Karim Premji (Department of Pathology, Nottingham University Hospitals NHS Trust) for the assistance in extracting laboratory data, National Congenital Anomaly and Rare Disease Registration Service (NCARDRS) for sharing data on admissions to Nottingham University Hospitals NHS Trust with disorders of copper metabolism (ICD-10 E 83.0) as part of their national case confirmation exercise of all suspected cases of Wilson’s disease in England and NIHR Nottingham Biomedical Research Centre for the provision of infrastructure and personnel support for the Wilson’s disease screening clinics.

**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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