iWilson Registry

2024 Annual Data Report

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Orphalan

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PHASTAR, UK providing data management support, extracted the data from the iWilson Registry database, creating tabulated data and listings for use in this report.

Ergomed, UK Contract Research Organisation for clinical study support.

iWilson Registry Scientific Steering Committee

ACKNOWLEDGEMENTS

The iWilson Registry Scientific Steering Committee would like to thank all the Wilson's disease (WD) individuals, their families and supports for attending their clinics and providing data generously to the Registry.

We would extend our sincere gratitude to the iWilson Registry sites for their dedication to enrolling people with WD and submitting their data to the Registry.

Without the hard work from the Investigators and their teams, this Registry would not be possible.

For more information about this report, or the iWD Registry, please visit our website **(www.iwilsonpatientregistry.com)** or contact us: **info@orphalan.com**

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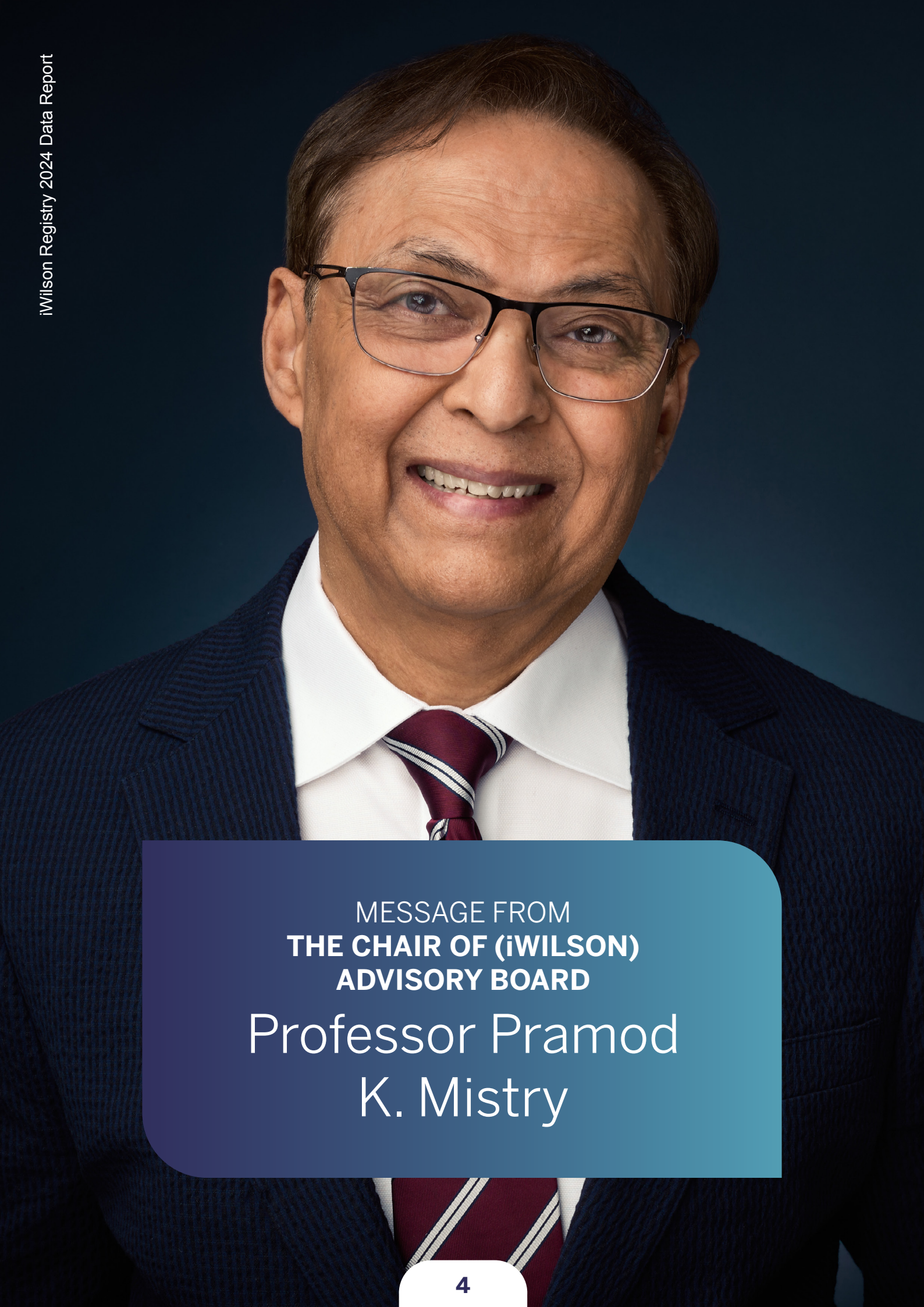


MESSAGE FROM
THE CHAIR OF (iWILSON) ADVISORY BOARD

Professor Pramod K. Mistry

It is with profound pride and purpose that we present this inaugural Annual Report of the International Wilson's Disease (iWD) Registry. In just over two years, the iWD Registry has achieved remarkable momentum—387 individuals enrolled from seven countries, spanning the full spectrum of Wilson's disease phenotypes through lifespan and lived experiences. Behind each datapoint lies a personal story—a journey often marked by diagnostic delay, therapeutic uncertainty, and immense resilience.

The iWD Registry is more than a data repository. It is a beacon of our collective commitment to transform the landscape of Wilson's disease—from enigmatic and misunderstood to measurable, predictable, and ultimately, manageable. In rare diseases, every datapoint matters, and every individual contributes to building a legacy of knowledge that will shape care for generations to come.

With the launch of the iWD Registry—the first truly international effort to capture real-world data in Wilson's disease—we now stand at the threshold of a transformative era in how this complex disorder is understood and managed. Our guiding principles are clear:

- Real-world evidence, especially when gathered across geographies, captures the true breadth of disease experience—something that clinical trials or single-centre studies rarely achieve. By aggregating longitudinal data from diverse healthcare settings, diagnostic practices, and population backgrounds, the iWD Registry provides insights that are biologically and socially grounded. It allows us to uncover regional patterns in presentation, treatment choices, adherence, and outcomes—thereby informing care that is both personalized and globally relevant.
- Phenotypes must give way to Endotypes—moving from symptom clusters to biologically grounded disease subtypes defined by neuropsychiatric signatures, hepatic progression, and individual treatment responses.
- Patient Experience is Core Evidence—not anecdote. This year's data on quality of life highlights that physical and emotional burdens persist even when biochemical control appears adequate. We must continue to listen to patients—not only to assess outcomes, but to define what truly matters in their journey.
- Shared Governance and Transparency are essential. The success of the iWD Registry depends on the integrity of its clinician-industry-patient partnership. With an independent scientific committee at the helm, we aim to uphold the highest standards of data stewardship, ethical oversight, and scientific rigor.

As we look to the future, the iWD Registry holds the promise of shaping not just clinical care, but also regulatory perspectives, health technology assessments, and national policy frameworks. By capturing lived experience and therapeutic outcomes at scale, we create the evidence base needed to support access, equity, and innovation in Wilson's disease. In doing so, we elevate the voice of our community—from patients and families to physicians and policymakers—ensuring that no one is left behind in the pursuit of better outcomes.

Our work is just beginning—but the foundation is strong. I extend deep gratitude to the investigators, data managers, and most importantly, the individuals and families living with Wilson's disease who have entrusted us with their stories. Together, we are not merely documenting the history of this disease—we are reshaping its future.

Professor Pramod K. Mistry, MD, PhD, FAASLD, FRCP, MA (Yale privatum)

Chair, iWilson Registry Advisory Board
Yale University School of Medicine

MESSAGE FROM
PATIENT REPRESENTATIVE, ADVISORY BOARD

Caroline ROATTA

As someone who lives with Wilson's disease and represents the voice of our patient community, it is with great hope and gratitude that I present the first annual report of the International Wilson's Disease (iWD) Registry.

Wilson's disease is more than just a rare genetic condition—it is a lifelong journey filled with uncertainty, misdiagnosis, and often, isolation. The symptoms we face can be invisible, misunderstood, or attributed to something else entirely. The path to diagnosis is rarely straightforward, and the road that follows can be just as challenging. Yet, despite this, we continue to push forward—not just for ourselves, but for our families, our peers, and for future generations who will walk this path after us.

The establishment of the iWD Registry in 2021 marks a turning point in how our disease is understood and addressed. With 387 individuals already enrolled by July 2024, this initiative is not just collecting numbers—it is collecting our stories, our struggles, our resilience. Behind every data point is a person, a life impacted by Wilson's disease.

This report shows promising progress. It reflects not only the diversity of our experiences across countries and continents but also highlights critical gaps in quality of life, particularly in mental and physical well-being, which deserve far more attention than they often receive. That our community experiences lower health scores than the general population is a call to action—for clinicians, researchers, policymakers, and industry partners alike.

The Registry opens doors to future clinical trials, helps inform educational campaigns, and strengthens collaborations between scientists. Most importantly, it ensures that patient experience remain at the heart of everything.

On behalf of the Wilson's disease community, I extend heartfelt thanks to all those contributing to this effort: the clinical teams, the data scientists and the sponsors.

This is just the beginning. With each entry into the Registry, we move one step closer to better care, greater awareness, and, someday, a cure.

Together, we are not only surviving Wilson's disease—we are shaping the future of how it is understood and treated.

Caroline ROATTA

MESSAGE FROM
CHIEF EXECUTIVE OFFICER AT ORPHALAN

Naseem Amin

Orphalan is proud to publish the first Annual Report of the International Wilson's disease (iWD) Patient Registry. This report details the patient data collected at the first visit between the launch of the Registry in June 2022 and the cut-off point for data entry to compile this report in July 2024, representing the first 25 months of enrolment. Wilson's disease is a rare condition which affects the body's ability to metabolise copper, resulting in a range of potentially severe and in some cases, life threatening hepatic, neurological and psychiatric symptoms. These symptoms can negatively impact the quality of life of individuals living with Wilson's disease and result in significant physical and psychological disability and clinical complications. Without optimal treatment and good adherence, Wilson's disease is potentially fatal. For many, juggling burdensome and complex medication regimens with their daily lives can be a significant challenge.

The iWD Registry was designed to serve as a vital resource for people living with Wilson's disease, clinicians, researchers and policymakers. In this first report, we collected data from 387 people living with Wilson's disease across 7 countries, providing valuable insights into the natural history, treatment outcomes and quality of life for those living with WD.

Key highlights from this year's report include:

- Demographic information and disease characteristics
- Description of current treatment approaches
- Clinical assessment and investigations undertaken as part of WD monitoring
- Treatment and outcomes during pregnancy

On behalf of Orphalan and our partners in 16 recruiting centres in Spain, UK, France, Belgium, Germany, Poland and Saudi Arabia, I extend my sincere gratitude to all the people living with Wilson's disease, families, and healthcare providers who have contributed to this Registry. Your participation is crucial in advancing our understanding of Wilson's disease and improving care for all those affected. As we look to the future, we remain committed to leveraging these data to drive research, inform clinical practice and advocate for the needs of the Wilson's disease community across the globe.

Naseem Amin

CEO, Orphalan

This report is written for the benefit of anyone interested in the health, care and outcomes of individuals with Wilson's disease (WD). This includes people with WD, their families and clinical teams, researchers, commissioners and policy makers.

A glossary of scientific and clinical terms can be found on **page 44**

An at-a-glance version of this report can be found at: **www.orphalan.com/annual-data-report-2024**

EXECUTIVE SUMMARY

This is the first annual report of the International Wilson's disease (iWD) Registry, established in 2021, with the first patient enrolled in June 2022.

The iWD is a global Registry for WD with the specific aims and objectives of:

1. Describing the natural history of treated WD and to explore the clinical phenotype, geographic, racial and gender influences on the course of the lives of people living with Wilson's disease.
2. Describing the distribution of age at onset of symptoms and time to diagnosis.
3. Describing the therapies used during the journey of people living with Wilson's disease.
4. For some people living with Wilson's disease, there is progression and increasing severity of their Wilson's disease resulting in the need for liver transplantation. The registry will collect data on the criteria used for liver transplantation and its prevalence.
5. Describe variation in clinical practice, enabling researchers and policymakers to investigate further to identify different models of care.
6. Provide data for healthcare professionals, scientists and industry to assist in the planning of future Independent Ethics Committee/Institutional Review Board (IEC/IRB) approved research projects/clinical trials addressing the unmet needs people living with Wilson's disease.
7. To obtain patient reported quality of life at the point of Registry entry using the SF-12.
8. To facilitate the development of best practice, through real world data generation.

Wilson's disease is a rare genetic disorder that affects the movement of copper in the body. It is characterized by the accumulation of copper in the liver, brain, and other vital organs, leading to liver disease, neurological problems, and psychiatric symptoms. Caused by a defect in the ATP7B gene, which regulates copper transport, Wilson's disease can be difficult to diagnose as many of the symptoms can be non-specific. Whilst the average age of diagnosis in this Registry was 18 years, eleven people (3% of all participants in the Registry) had their diagnosis of Wilson's disease confirmed after the age of 50 with the oldest diagnosis in this cohort from Spain, aged 67 years. This may reflect the difficulties and delays experienced by some people living with Wilson's disease to have their condition confirmed. Approximately 30 people out of each million of the population of any given country will have Wilson's disease. With Wilson's disease requiring lifelong management and treatment, this may impact the quality of life for individuals living with the disease and their families.

The report contains demographic descriptions, symptoms and treatment taken by people living with Wilson's disease who have consented to participate in the iWD Registry. For this report, the iWD Registry enrols people living with Wilson's disease from adult clinics and one paediatric clinic. These participants may enter the Registry at or close to diagnosis or at a point during the maintenance phase of treatment, which may be many years from diagnosis. At the point of data collection (July 2024), 387 individuals had been enrolled into the Registry over a 25-month period.

An abstract on the quality-of-life data collected from the Registry was accepted at an International Scientific Meeting, the European Association for the Study of the Liver, Milan June 5th to 8th 2024 (Appendix 4). Whilst Registry data from people living with Wilson's disease demonstrated general health was perceived to be high, average physical and mental health scores were lower than the reference general population, highlighting a potential area for further investigation. This Registry holds the potential for providing clinical data for future studies and for the identification of suitable participants for future clinician led clinical trials. In addition, future data generation may assist with disease awareness educational programs and through partnerships with patient advocacy groups, future public campaigns involving individuals living with Wilson's disease.

WILSON'S DISEASE

Wilson's disease is an inherited disease caused by a faulty gene ("mutation") on chromosome 13. The gene (called the ATP7B gene) and the protein it codes for (the ATP7B protein) controls the movement of copper within the liver. This movement is necessary to remove the extra copper that we get from our diet from the body and to assist in the distribution of copper to all the organs in the body where copper is necessary for essential chemical reactions in our cells. When the gene is faulty, the protein it codes for might be reduced, absent or dysfunctional and it can cause the build-up of copper in the liver, brain and other major organs. Wilson's disease is characterised by liver involvement (tiredness, jaundice, itchiness, elevations of liver enzymes) and brain involvement (tremors, swallowing and speech disturbances, muscle stiffness, clumsiness, changes in mood and behaviour amongst the most common symptoms). Some unfortunate people living with Wilson's disease may have the diagnosis confirmed with advanced severe liver and brain involvement and need urgent lifesaving interventions.

Globally, it is estimated that 30 individuals out of every million of the population, will have Wilson's disease.

INTRODUCTION

THE INTERNATIONAL WILSON'S DISEASE PATIENT REGISTRY

Established in 2021, this is the first annual report for the iWD Patient Registry.

As of July 2024, 387 individuals with WD have been enrolled from participating centres in the UK, France, Belgium, Spain, Germany, Poland and Saudi Arabia after the first enrolment in June 2022.

The Registry is sponsored by Orphalan S.A., a French biotechnology company which manufactures a medicine (trientine tetrahydrochloride) for the treatment of WD. The overall objective of the Registry is to improve our understanding of Wilson's disease and to identify opportunities for all those involved (people living with Wilson's disease, doctors, researchers, policymakers) to study and find potential solutions for the challenges and difficulties which people living with Wilson's disease face every day.

The Registry is a secure centralised database of consenting people with WD from participating centres, collecting data (for example symptoms reported by the individual with Wilson's disease to their doctor, results of their medical investigations) from each clinic visit. As the data is collected over time, the Registry will have the capacity to reflect the natural history (experience or "patient journey") of an individual living with Wilson's disease. The data is entered by the local Wilson's disease research team into the electronic database with oversight and support provided by a CRO (Contract Research Organisation). This is an active database, collecting information from routinely scheduled clinic visits at approximately 6-month intervals. The database is password protected and complies with all local data protection regulations.

As the iWD Patient Registry collects information in real time, the objective, following the initial (baseline) visit is to document the natural history of people living with and receiving treatment for Wilson's disease over time; (note: baseline visit refers to the first clinic appointment since being enrolled in the Registry).

The governance and control of the information collected in the Registry is managed by an independent scientific advisory board (committee of experts) in Wilson's disease (hepatologists, neurologists, paediatric hepatologists and patient representative). This committee monitors progress of the Registry, provides scientific advice and reviews requests for data from investigators. If approved by the scientific committee, the release of data, with the potential of sharing of data with patient support groups, clinicians and research scientists may lead to improvements and advances in the understanding of Wilson's disease.

OVERVIEW OF WILSON'S DISEASE

Copper, an essential mineral, is naturally occurring in many foods and is needed for metabolic (chemical) processes (such as enzyme reactions) throughout the body. As a healthy diet contains more copper than the body needs, most of the excess dietary copper is removed from the liver in the bile to the gut and eliminated from the body in the faeces.

Individuals with Wilson's disease are unable to eliminate this excess copper and copper builds up primarily in the liver followed by other other organs. This starts after birth but continues gradually after birth as the amount of copper in the diet increases. Without appropriate treatment, the increased levels of copper in the tissues and organs, including the liver and brain, may cause a range of potentially severe liver, neurological and psychiatric symptoms.

With over 900 mutations identified of the ATP7B gene, not all are associated with symptoms of Wilson's disease in making the diagnosis complex. A detailed history and examination focusing on the liver, brain and behavioural and emotional symptoms should prompt the healthcare professional to request tests to screen for Wilson's disease. These can include, but are not limited to, blood levels of caeruloplasmin (typically very low in WD), the amount of copper in the urine collected over a 24-hour period (Urinary Copper Excretion or UCE), haemoglobin, liver enzymes, eye examination to look for copper deposits in the cornea (these copper rings are known as Keyser Fleischer rings), testing for the genetic mutation, magnetic resonance imaging (MRI) of the brain, and for some people, it is necessary to perform a liver biopsy to confirm the diagnosis.

Clinical presentation

Hepatic

Scarring of the liver (cirrhosis) which prevents normal functioning. Liver failure can occur slowly over years (chronic), or suddenly (acute).

Neurological

Tremors, speech difficulties, migraine headaches, insomnia, and even seizures can occur

Psychiatric

Psychiatric symptoms might include depression and personality changes.

Other

The kidneys and bones can also be affected in Wilson's disease, potentially causing kidney stones or arthritis, respectively. Dark rings around the iris of the eye or cataracts may occur in some people.

Treatment of Wilson's disease

Treatment for all individuals with a confirmed diagnosis of Wilson's disease includes chelators and inhibitors of copper absorption. Chelators are medicines which bind to copper and form a copper-chelator complex which is then removed from the body in the urine. Copper chelators include d-Penicillamine, trientine dihydrochloride and trientine tetrahydrochloride. Zinc salts are used to block the absorption of copper in the diet from the intestine.

The goal of lifelong medical therapy is to control the amount of excessive copper in the body combined with a low copper diet. Wilson's disease medications need to be taken daily, multiple times a day and all medicines need to be taken separately from meals to be effective. Poor compliance with these instructions to take their medicines may expose people living with Wilson's disease to an increased risk of experiencing worsening of their disease including the onset of new symptoms.

In this first Annual Report, data, where available, from the baseline visit from the 387 individuals enrolled to the Registry between June 1st, 2022, and July 15th, 2024, are summarised and presented in tables and figures. Where appropriate, statistical tests have been used to describe and compare data between groups (countries, age, disease phenotype).

SUMMARY OF KEY DATA

The data shown below are obtained from the first hospital appointment (baseline visit) once a person with Wilson's disease provided consent to the iWD Registry during the reporting period. Data may be incomplete at the time of database lock and the denominator used to calculate the percentages and averages throughout the report may differ for each variable presented. For the summary table below, denominators are shown in the footnote.

	Study Period (June 2022 -July 2024)
People with WD enrolled	**387**
Median Age (range) in years at enrolment[a]	**34 (12, 86)**
Median Age (range) in years at WD diagnosis[b]	**18 (0, 67)**
Median Age (range) in years at first symptoms[c]	**19 (3, 60)**
Females (%)	**50.13**
Genetic data entered[d]	**279**
Total number of liver transplants in reporting period	**1**
Age (mean) at liver transplantation in years	**46**
Total deaths in reporting period	**3**
Age (mean) at death in years	**44.67**

Data are incomplete:
[a]data obtained from 381 records
[b]data obtained from 370 records
[c]data obtained from 220 records
[d]data obtained from 382 records

ANNUAL REPORT DATA FROM INTERNATIONAL WILSON'S DISEASE (iWD) REGISTRY

1. RECRUITMENT

The protocol for this Registry was approved in 2021, followed by activities necessary to open sites to recruitment including for regulatory submissions to local human research ethics committees, initially for sites in Belgium, Poland, Spain, United Kingdom and Germany and in the second phase, France (2023) and Saudi Arabia (2024). The first site to enrol a patient into the Registry was the University of Leuven, Belgium (site 3201) with a progressive roll out to other centres and countries. All the participating sites are shown in Figure 1.1. The initiation dates for each site are listed and described in Table 1.1. The net accumulative enrolment over time is shown in Figure 1.2.

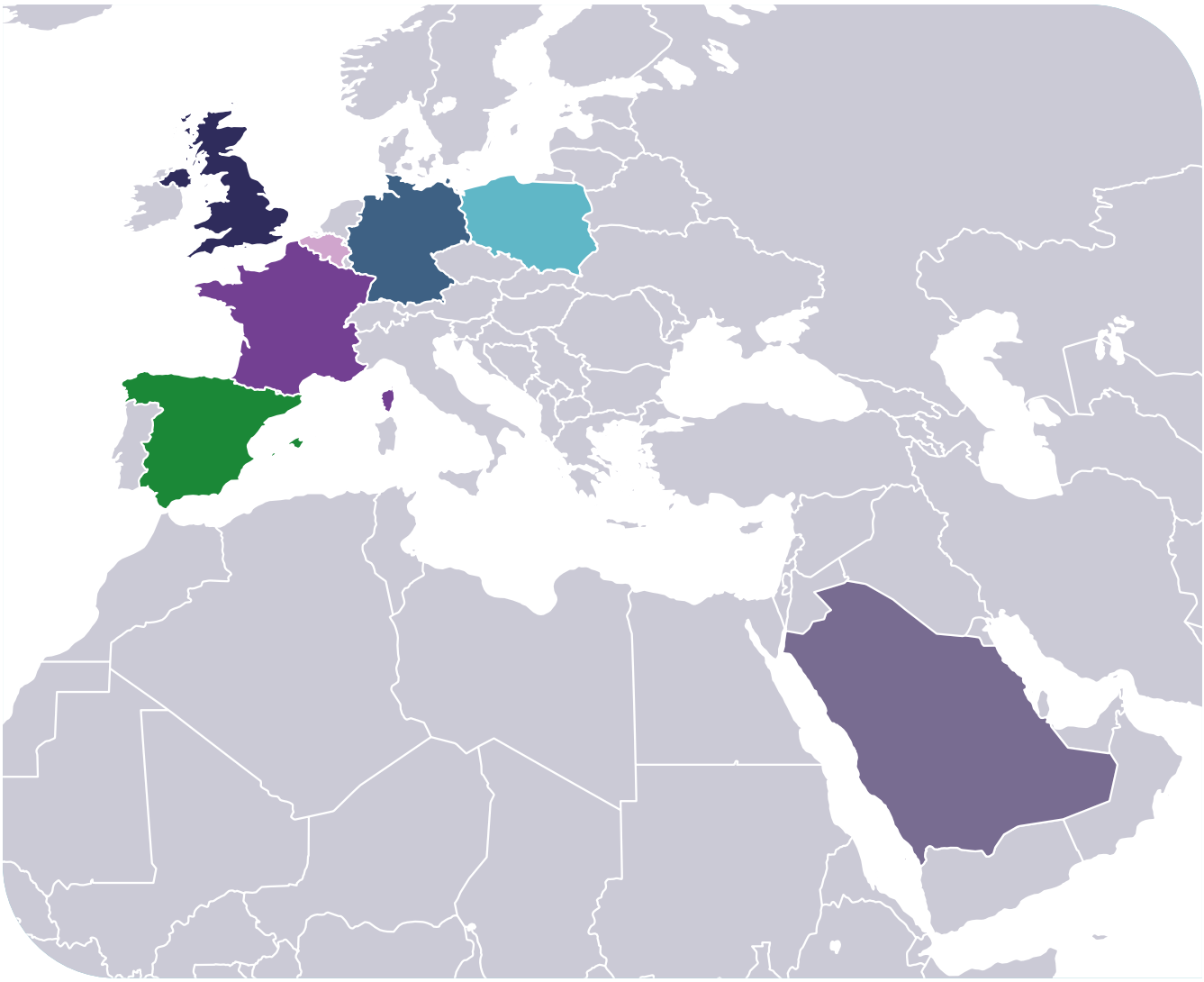


Figure 1.1 Map of countries actively contributing data to the iWilson Registry

Country /Site ID	First Patient Enrolled (date)	Enrolled 2022 (June – Dec)	Enrolled 2023 Jan – Dec)	Enrolled 2024 Jan – July)	Total
Belgium / 3201	2022-10-06	6	9	0	**15**
France / 3301	2023-04-28	N/A	27	3	**30**
France / 3302	2023-05-03	N/A	30	0	**30**
Spain / 3401	2023-01-17	N/A	14	0	**14**
Spain / 3402	2022-10-04	22	8	0	**30**
Spain / 3403	2022-08-31	8	19	3	**30**
Spain / 3404	2023-03-01	N/A	12	1	**13**
United Kingdom / 4401	2023-01-19	N/A	18	0	**18**
United Kingdom / 4402	2022-12-06	2	28	0	**30**
Poland / 4801	2022-07-14	26	18	6	**50**
Poland / 4802	2022-06-29	11	1	5	**17**
Germany / 4901	2022-12-07	5	28	0	**33**
Germany / 4902	2022-09-29	9	7	0	**16**
Germany / 4903	2022-12-21	1	9	0	**10**
Germany / 4904	2022-09-21	11	7	9	**27**
Saudi Arabia / 9601	2024-01-16	N/A	0	24	**24**
ALL Countries	-	101	235	51	**387**

Table 1.1 Table summarising enrolment activity per site by chronological year following first patient enrolment

This figure shows the cumulative enrollment of people living with Wilson's disease to the iWilson Registry by month (June 2022 through to July 2024)

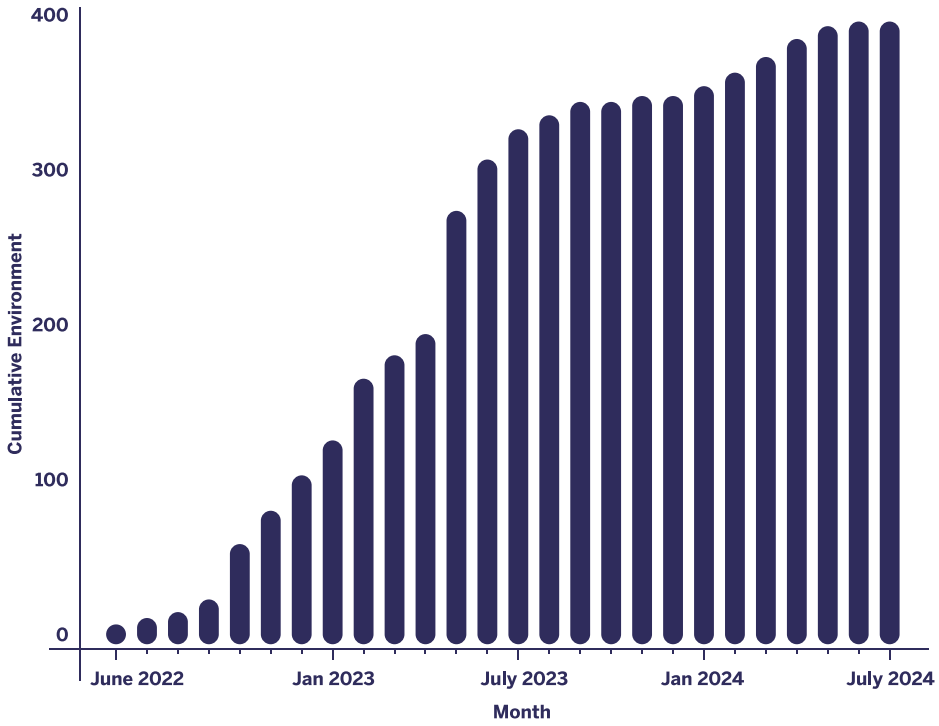
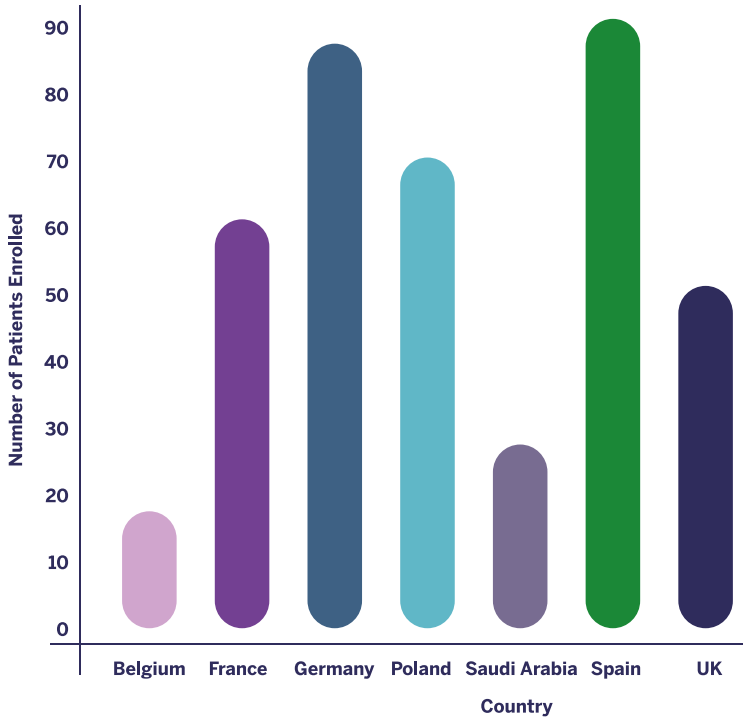


Figure 1.2 Cumulative enrollment by month

During the reporting period, a total of 16 hospitals from seven countries contributed data to this report. There is 1 centre in Belgium, 2 in France, 4 in Germany, 2 in Poland, 1 in Saudi Arabia, 4 in Spain and 2 in the United Kingdom. All centres are adult WD clinics with one exception, a paediatric hospital (The Children's Memorial Health Institute) in Poland.

This figure shows the number of people living with Wilson's disease enrolled in the iWilson Registry by country.



*Footnote: Caps for recruiting people living with Wilson's disease is set and negotiated locally for each site and will be reviewed in 2026
Belgium has 1 site with a cap of 20 / Spain has 4 sites each with a cap of 30
France has 2 sites each with a cap of 30 / Germany has 4 sites each with a cap of 30
United Kingdom has 2 sites each with a cap of 30 / Poland has 2 sites each with a cap of 50
Saudi Arabia has 1 site with a cap of 30

Figure 1.3 Enrollment by country

2. DEMOGRAPHICS

Ethnicity and race

Data on ethnicity was not collected as part of the Registry, however we report data on race, collected from 229 respondents. Most people living with Wilson's disease identified themselves as white (214), with 10 identifying as Asian and 5 documented as "other". 158 people living with Wilson's disease did not provide data for this question on race.

The average (median) age of people living with Wilson's disease at the time of first study visit was 34 years. The median, interquartile range and range of ages of individuals living with Wilson's disease by country are shown in Figure 2.1. The two countries with the lowest median age (under 30 years of age) are Poland (with a Children's Hospital as one of the recruiting centres) and Saudia Arabia.

This figure shows the age distribution at the time of entry in the Registry, by country. The median age is represented by the bold lines inside the boxes.

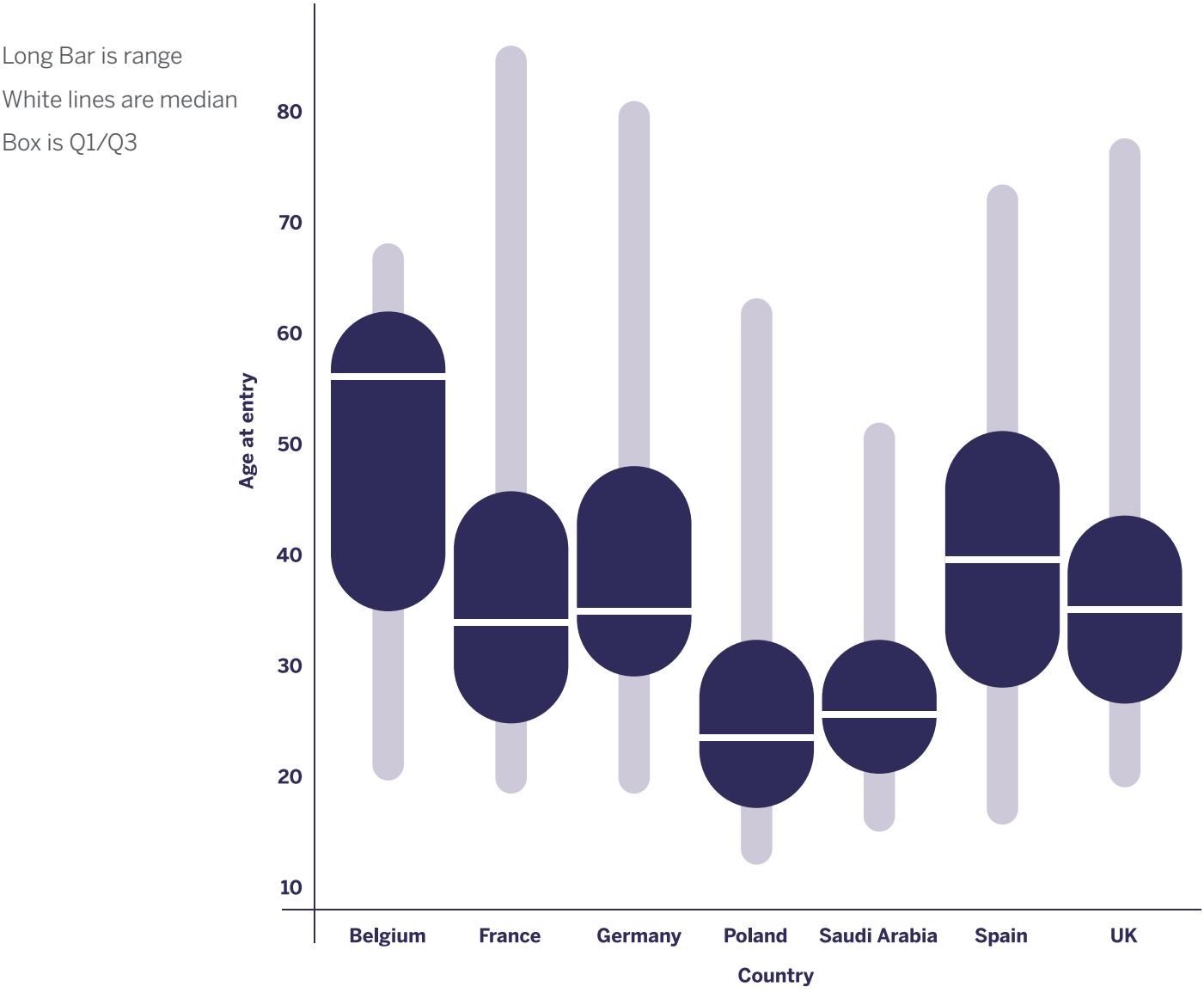


Figure 2.1 Age at entry

This figure shows the proportion of paediatric (<18 years) and adult individuals living with Wilson's disease in the Registry, by country. Eligibility for people living with Wilson's disease to participate in the iWD Registry is adults and children/adolescents aged > 12 years of age. The figure shows the proportion of young adults aged less than 18 years enrolled into the Registry. Most of the participating centres are based within adult hospitals and this explains why most participants in the Registry are adults living with Wilson's disease.

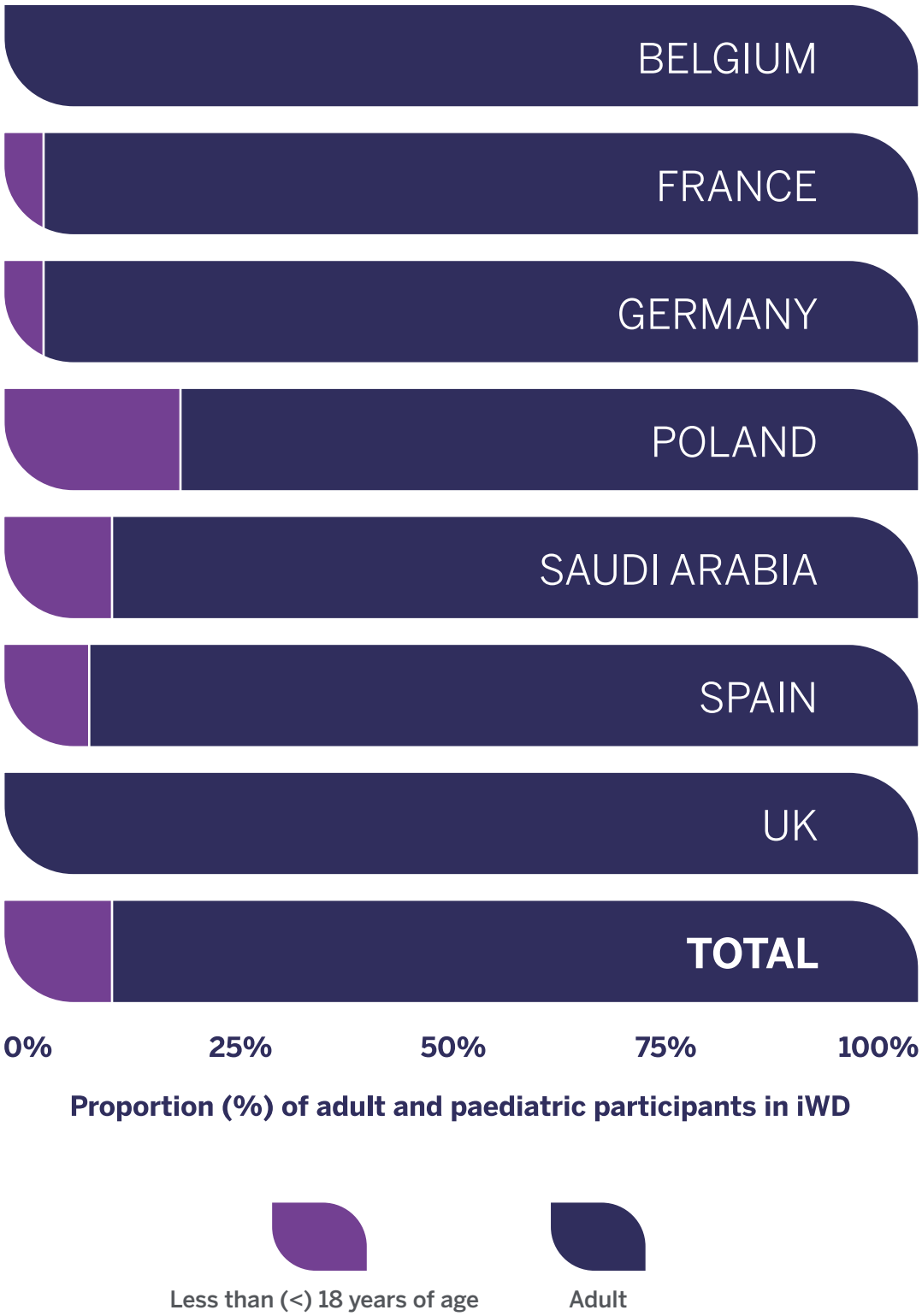


Figure 2.2 Registry population; children and adults

3. DIAGNOSIS

Wilson's disease primarily affects liver and the brain. People living with Wilson's disease will most commonly have either liver related symptoms or liver biochemistry abnormalities on blood testing, neurological symptoms or both. Figure 3.1 shows the symptoms described by people living with Wilson's disease at the baseline visit in the Registry, by country. Except for the United Kingdom, hepatic symptoms were the most commonly reported (58%) which may be reflective of the referral patterns to the sites participating in the Registry. Hepatic symptoms include documented complaints from people living with Wilson's disease as well as abnormalities of liver enzymes detected from blood testing. Of all the countries, the United Kingdom cohort had the greatest proportion (48%) of pre-symptomatic people living with Wilson's disease.

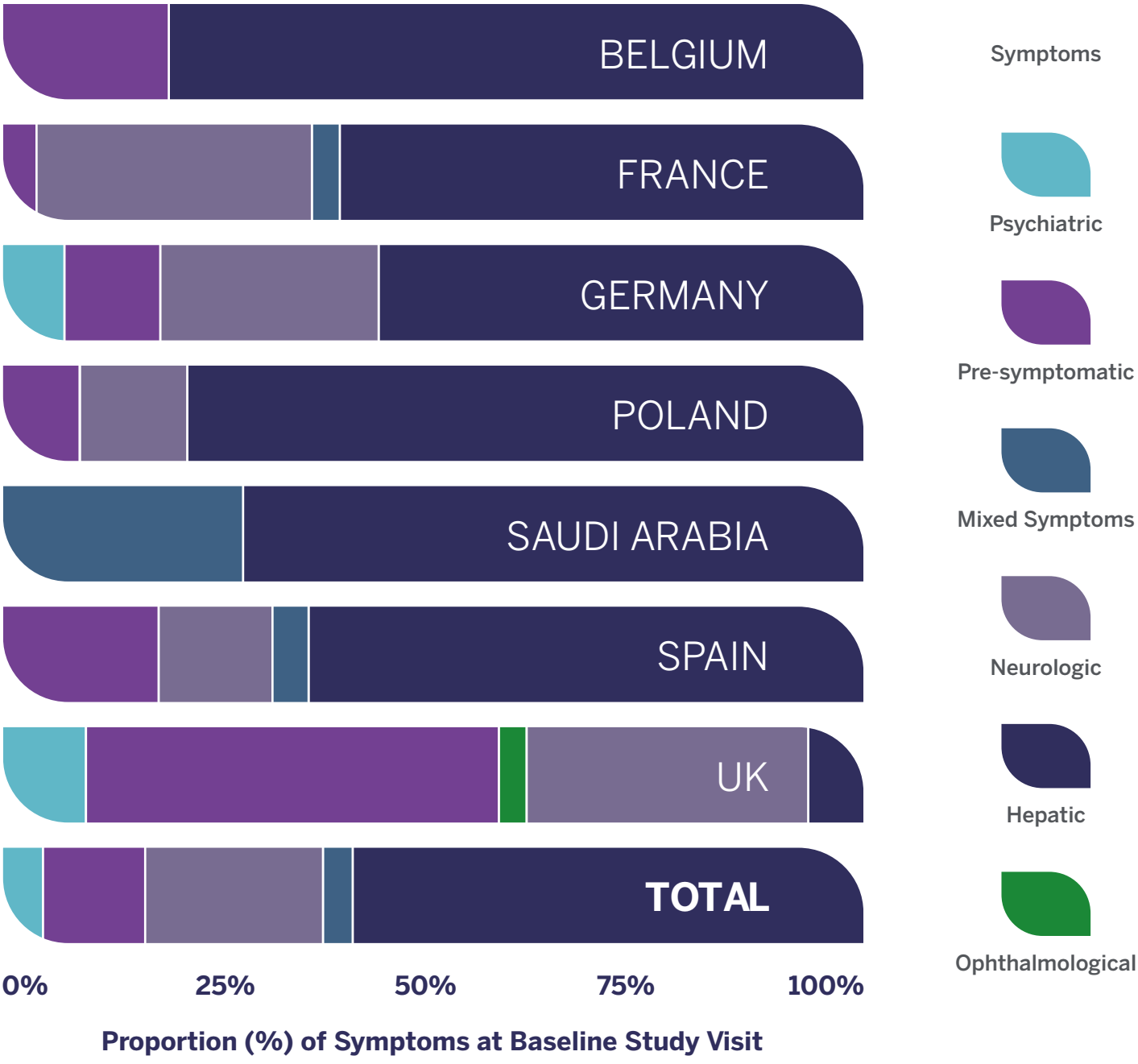


Figure 3.1 Symptoms experienced by people living with Wilson's disease at baseline visit by country

OVERALL SYMPTOMS AT BASELINE

Overall, 58% of people living with Wilson's disease had hepatic symptoms at baseline visit; 21% had neurological symptoms, 15 % did not have any symptoms of Wilson's disease and 4% had mixed symptoms. Only a small proportion of people living with Wilson's disease at the baseline visit were experiencing psychiatric symptoms (2%).

This figure shows the symptoms at baseline visit as a proportion of the total number of individuals for whom data was entered (n = 360).

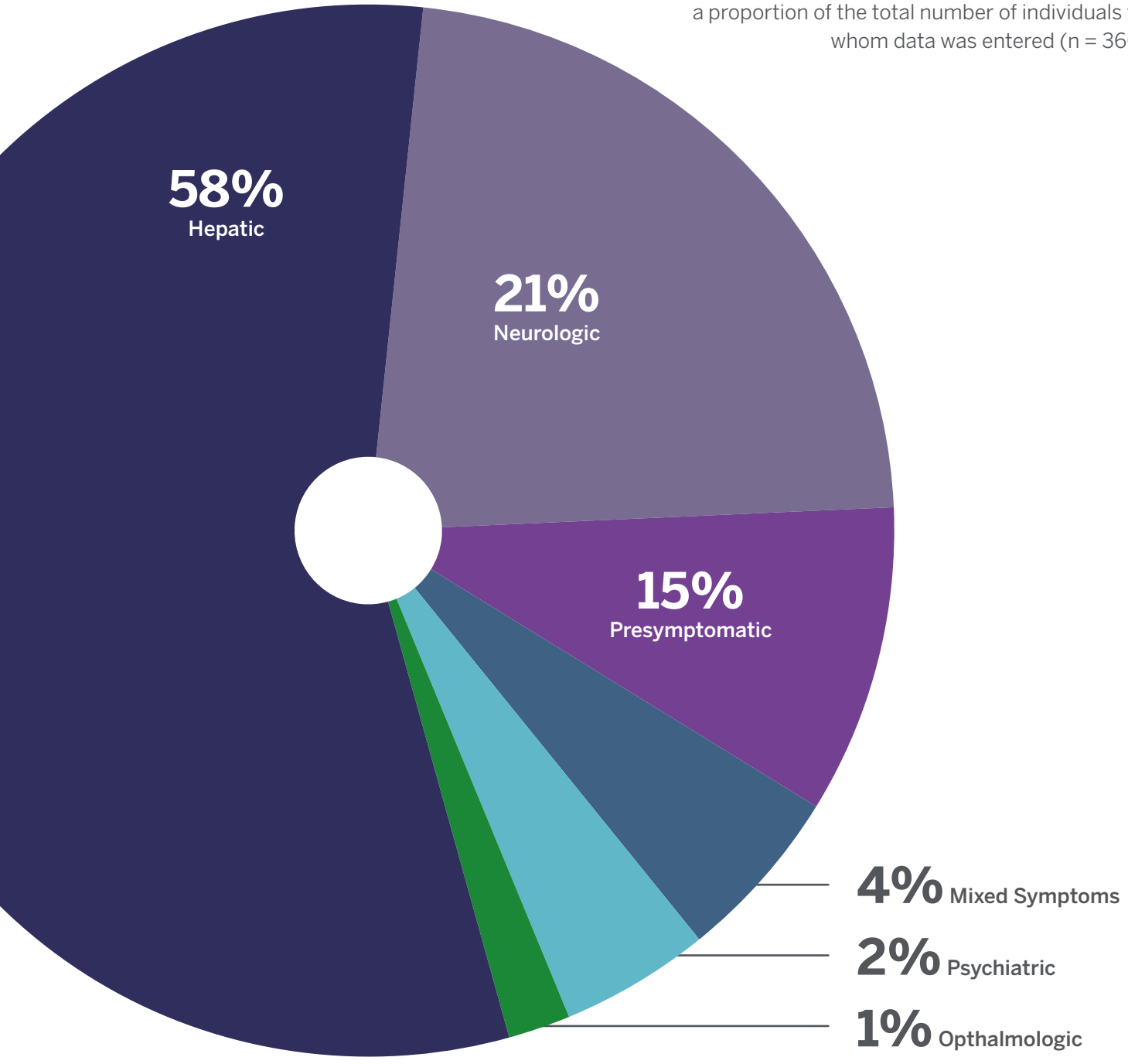


Figure 3.2 Overall symptoms at baseline

These pie charts show the proportion of symptoms which were characterised as hepatic, neurologic, mixed, pre-symptomatic and psychiatric, reported by people living with Wilson's disease at baseline visit, by country

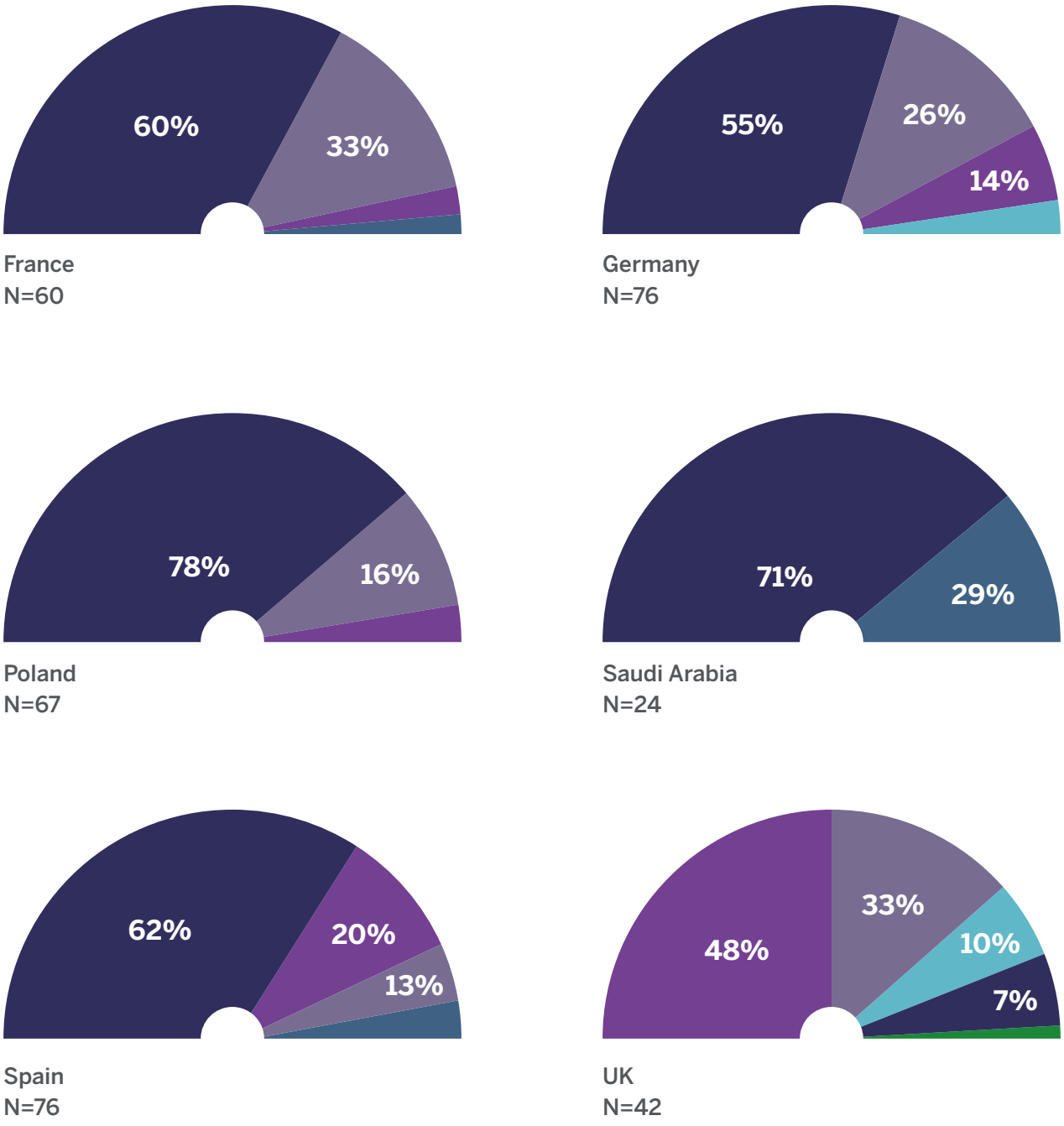


Figure 3.2.1 Symptoms at baseline study visit by country

SYMPTOM ONSET AND TIMING OF DIAGNOSIS

Symptom Onset and Timing of Diagnosis

People living with Wilson's disease may first experience symptoms of WD at any age, although the majority are diagnosed between the ages of 5 and 35 years. As the early symptoms may be either subtle (neuropsychiatric) or absent (presymptomatic with liver involvement), there may be a gap between the onset of symptoms and when the diagnosis of Wilson's disease is confirmed. Data from the iWD Registry confirms that most symptoms are reported by people living with Wilson's disease in their late teens.

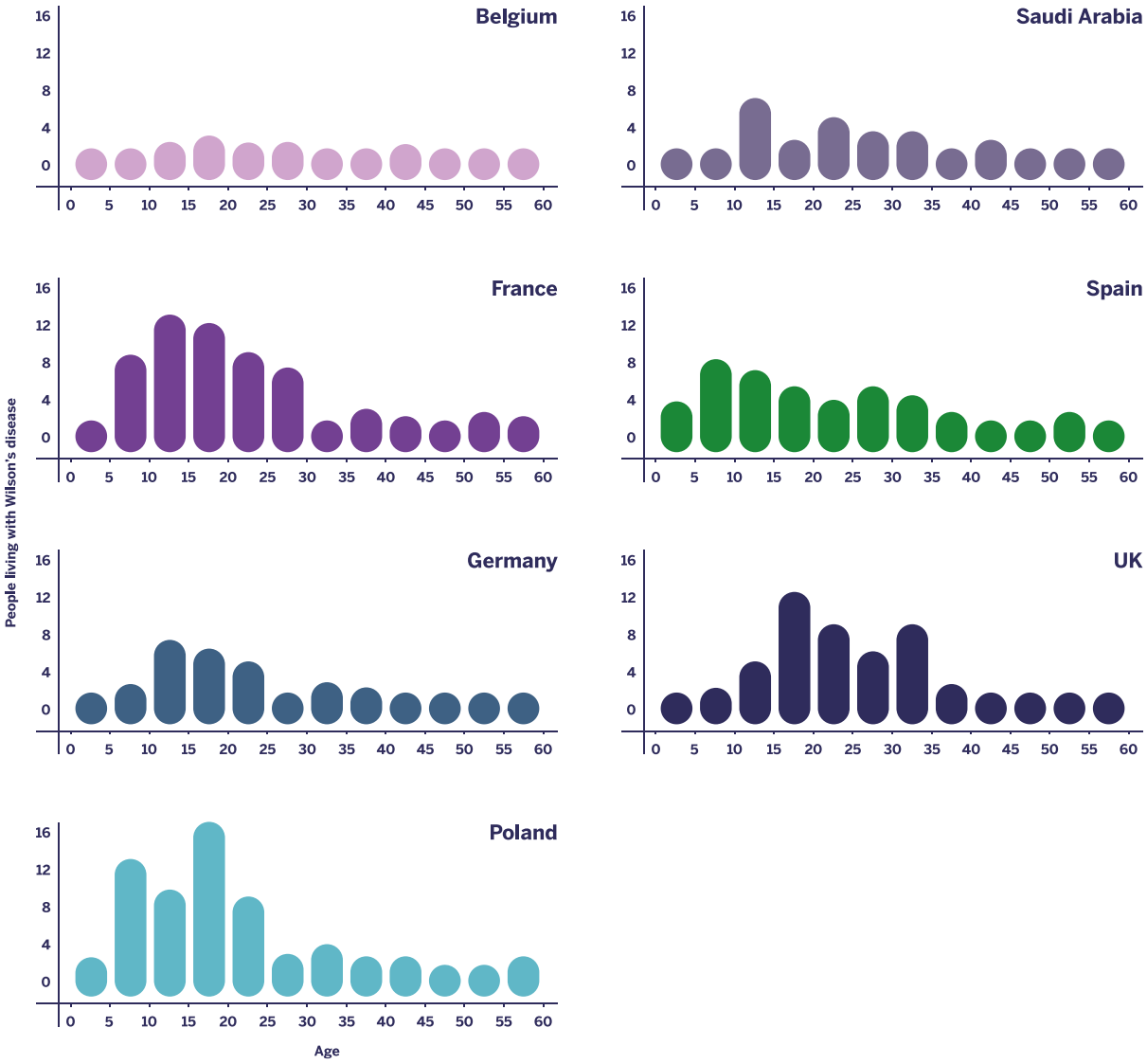


Figure 3.3.1 Age at time of first Wilson's disease symptom appearance, by country

This figure shows the distribution by age, when people living with Wilson's disease first experienced symptoms, by country

The median age at which symptoms first appeared and when people living with Wilson's disease received their diagnosis in the Registry is 19 and 18 years respectively. A possible explanation for this unexpected finding is the discrepancies in the number of participants for which data was available (whilst this report summarises data from 387 people enrolled in the Registry, only 370 and 220 responses were recorded for age at diagnosis and onset of symptoms respectively). In addition, some individuals may have been asymptomatic or pre-symptomatic at the time of diagnosis, with symptoms appearing later.

Across the countries, the median time between onset of symptoms and initial diagnosis of Wilson's disease is 1 year (see Fig. 3.4.3)

Time between symptoms start and initial diagnosis (years)	Belgium	France	Spain	UK	Poland	Germany	Saudi Arabia
Mean	0.5	0.1	-0.5	0.7	-1.9	0.3	0.9
Median	0.5	0.0	1	1	0	1	1

Figure 3.4.3 Mean and Median time between start of symptoms and initial diagnosis (years) by country

Note: negative numbers are indicative of where individuals were either asymptomatic or pre-symptomatic at the time of diagnosis and symptoms developed after diagnosis. Where there are less than 12 months between start of symptoms and initial diagnosis, this is recorded as a fraction of the year (e.g. 0.1)

The following box and whisker plots show the age distribution at which symptoms first appeared in people living with Wilson's disease, by country (note denominators for this measurement are much smaller compared with denominator for age at diagnosis). The median age for first WD symptoms to appear across most of the regions falls in the late teenage years.

Long Bar is range

White lines are median

Box is Q1/Q3

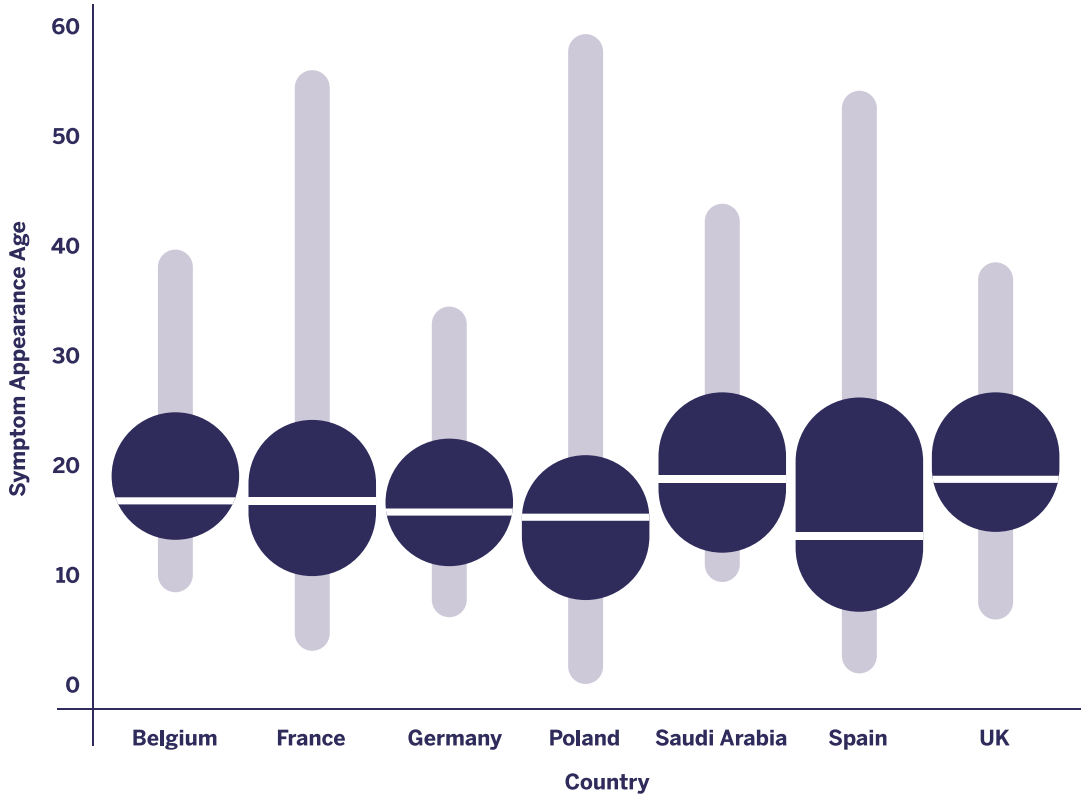


Figure 3.2 Age at Appearance of Initial WD Symptoms

IDENTIFYING (DIAGNOSING) PEOPLE LIVING WITH WILSON'S DISEASE AFTER THE AGE OF 30

Making a timely diagnosis of Wilson's disease is important as treatment can start to regain control of copper levels in the body, reduce the risk of the disease advancing whilst improving the chances of better health for people living with Wilson's disease. The reasons for a diagnosis in later years may be different from one individual to another and the data presented here are purely numerical. No data on either the severity of the disease or type of symptoms can be linked to the age of diagnosis.

The table below details the proportion of people living with Wilson's disease in the Registry who had "late" diagnoses" i.e., diagnosed after 30, 40 and 50 years of age, by country.

Belgium has the highest proportion (27%) of people living with Wilson's disease in the Registry with the age at diagnosis confirmed after the age of 30 years; two of who were diagnosed between 40 and 50 years and two between 50 and 60 years.

Eleven people (3% of all participants in the Registry) had their diagnosis of Wilson's disease confirmed after the age of 50, with the oldest diagnosis in this cohort from Spain, aged 67 years.

	Age>30	Age>40	Age>50	Max Age
Belgium	4 (26.67%)	2 (13.33%)	2 (13.33%)	58
France	8 (13.33%)	4 (6.67%)	3 (5%)	61
Germany	14 (18.18%)	2 (2.6%)	-	50
Poland	14 (20.9%)	6 (8.96%)	1 (1.49%)	60
Saudi Arabia	2 (9.09%)	1 (4.55%)	-	45
Spain	14 (17.07%)	6 (7.32%)	4 (4.88%)	67
UK	9 (19.15%)	2 (4.26%)	1 (2.13%)	51

% is the proportion of individuals enrolled by country

Table 3.3 Time of Wilson's disease diagnosis each decade from 30 years, by country.

This figure shows the distribution by age, at which people living with Wilson's disease in each country were diagnosed with Wilson's disease.

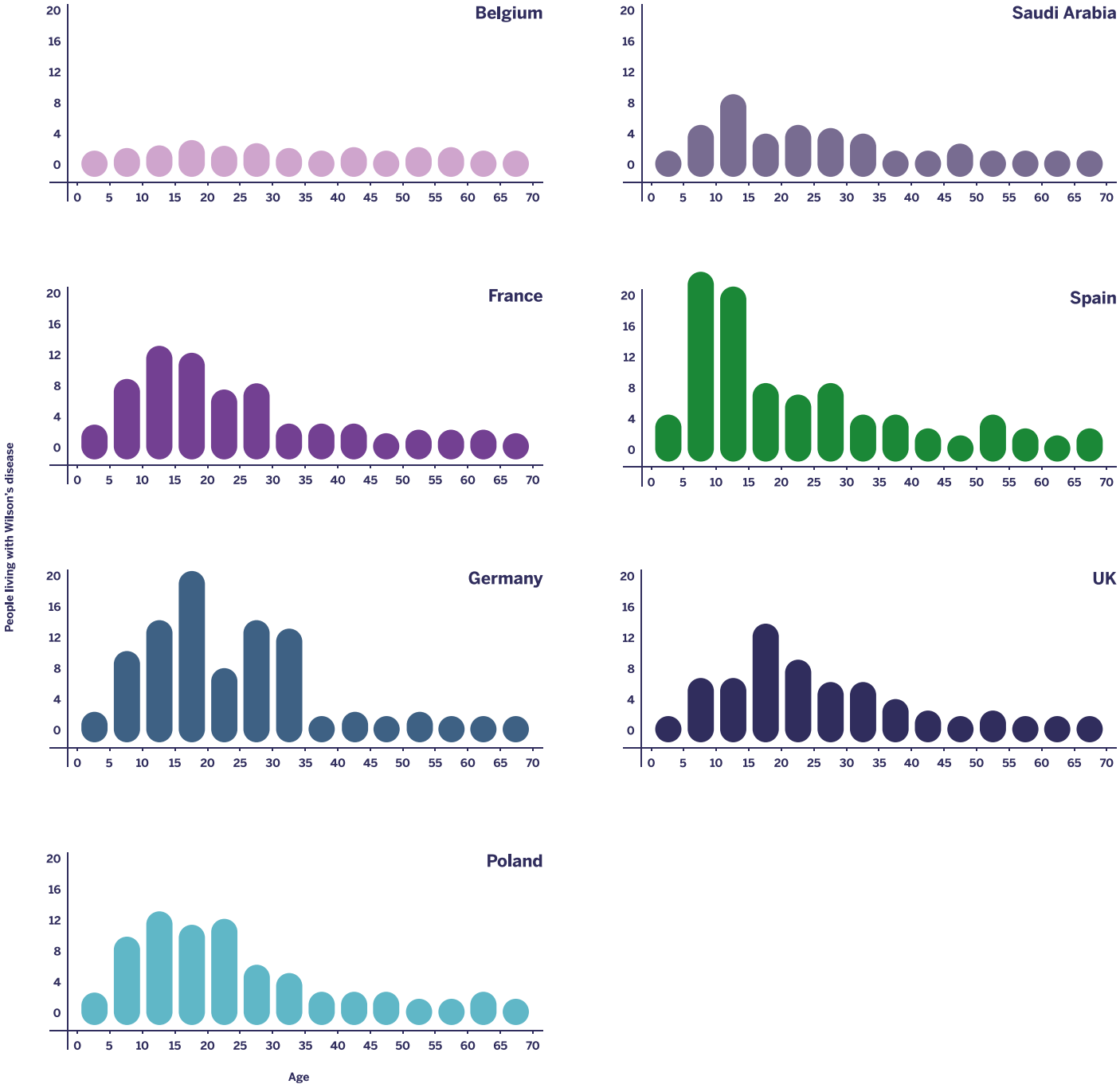


Figure 3.4 Age at diagnosis, by country

The following box and whisker plots show the distribution of age at diagnosis of WD in people living with Wilson's disease by country.

People living with Wilson's disease appear to be diagnosed at an earlier age in Spain (mean age at diagnosis is approximately 18) compared with Belgium, where the mean age at diagnosis was approximately 26 years of age. Comparing the medians, with the exception of Belgium, people living with Wilson's disease were diagnosed during adolescence and teenage years (data may be representative of people enrolled in the Registry rather than geographic factors).

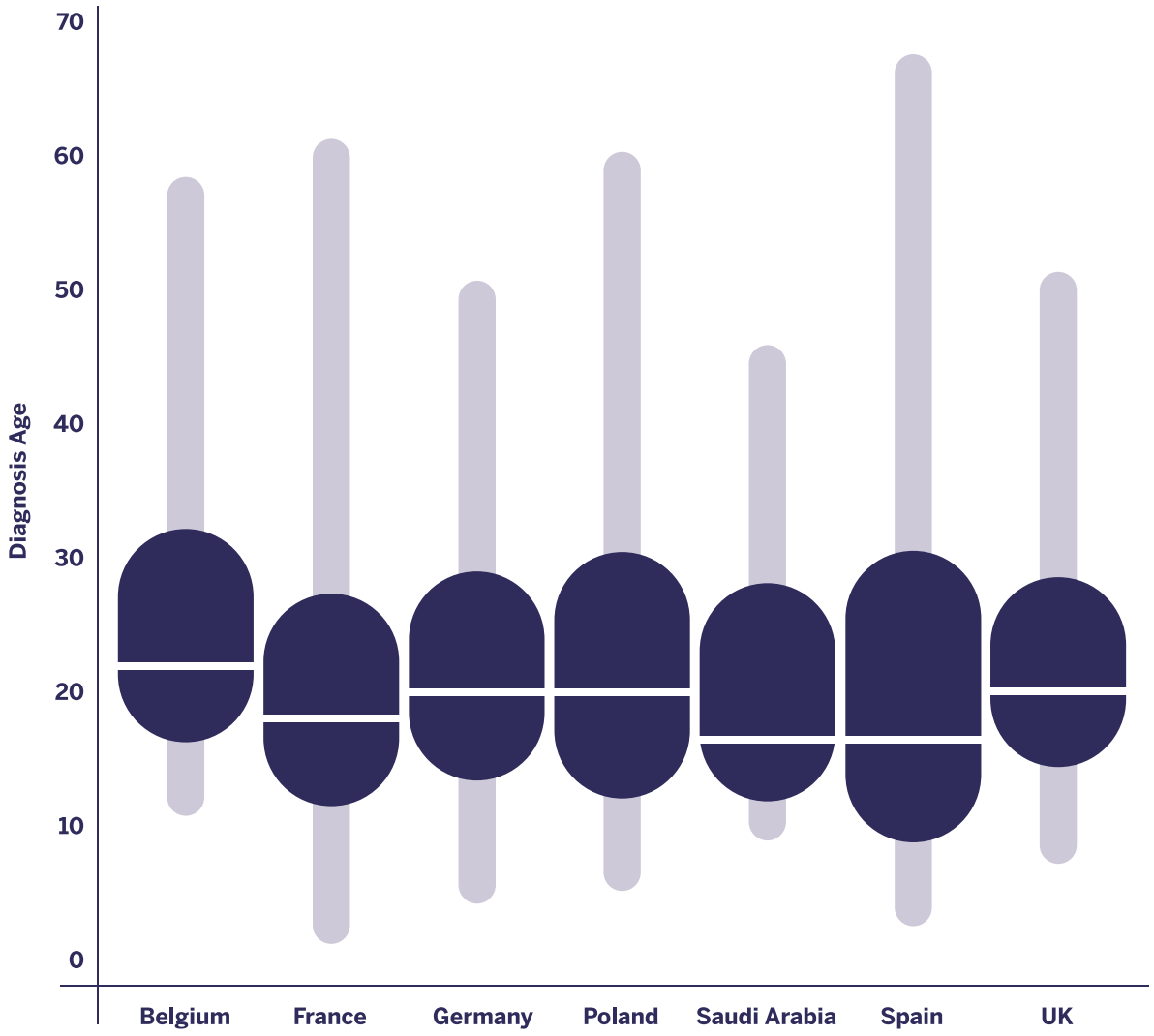
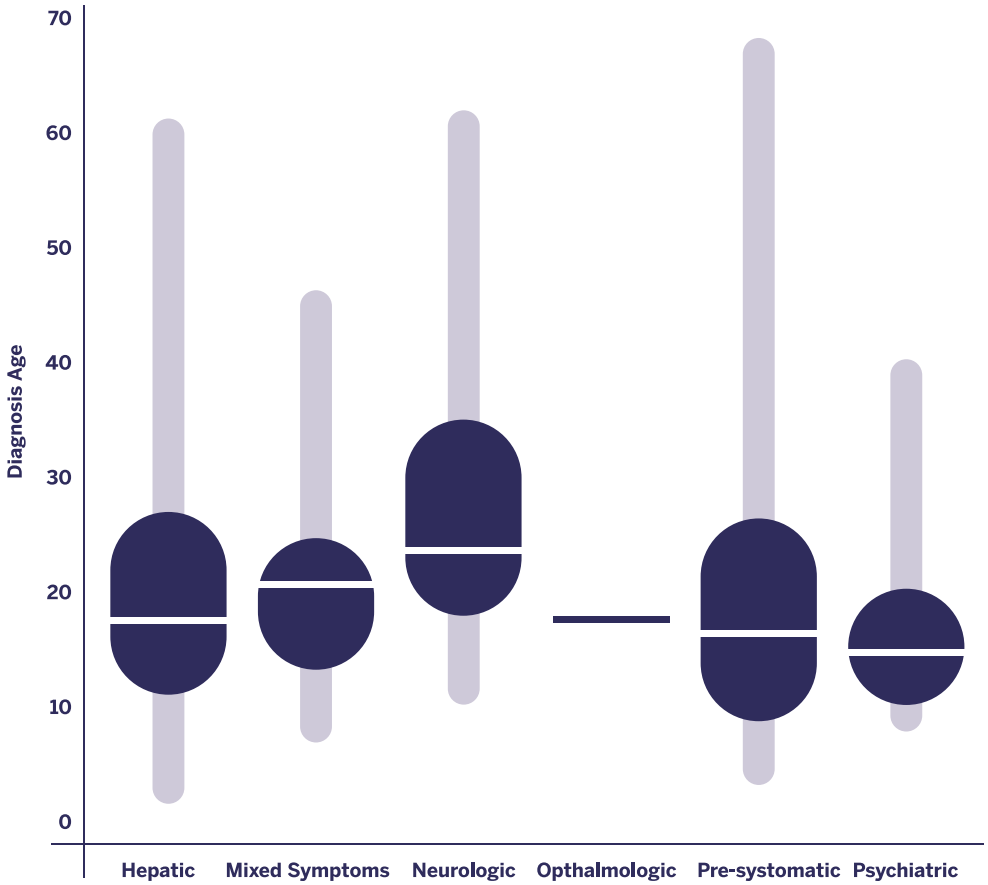


Figure 3.4.1 Age at diagnosis by country – box and whisker plots

AGE AT DIAGNOSIS GROUPED BY SYMPTOMS OF WILSON'S DISEASE AT BASELINE VISIT

This box and whisker plot shows the distribution of age at diagnosis according to the various symptoms people living with Wilson's disease reported. The table summarises the mean and median ages of diagnosis associated with the nature of symptoms reported. Overall, the mean age of diagnosis for hepatic presentation appears to be earlier than for neurological presentation, which is what one would expect. The mean age of diagnosis for people living with Wilson's disease presenting with psychiatric symptoms is during adolescence at 16 years of age.



	Mean	Median	N
Hepatic	18.58	16	203
Mixed Sumptoms	19.15	19	13
Neurologic	25.27	22	27
Opthalmologic	16.00	16	1
Presymptomatic	19.46	18	50
Psychiatric	16.00	13	7

Figure 3.4.2 Box and whisker plots of age at diagnosis by classification of Wilson's disease symptoms

LEIPZIG SCORES AT DIAGNOSIS

The Leipzig or Ferenci Score is a diagnostic tool developed to assess the likelihood of confirming Wilson's disease (WD) in an individual. It integrates clinical, laboratory, and imaging findings to improve diagnostic accuracy, especially in people who have either atypical presentations (symptoms) or inconclusive test results.

The components of the Leipzig Score are:

1. Points based on the presence or absence of specific features:

- Kayser-Fleischer rings (copper deposits in the eye)
- Neurological symptoms (severity graded)

2. Laboratory testing with points assigned based upon established criteria

- Serum ceruloplasmin levels
- Coombs-negative haemolytic anemia
- 24-hour urinary copper excretion
- Liver biopsy

3. Genetic testing with points assigned based upon established criteria

If the total Leipzig Score is greater than or equal to 4, the diagnosis of Wilson's disease is very likely.

This figure shows the distribution of Leipzig scores at diagnosis in all people living with Wilson's disease where this data was provided.

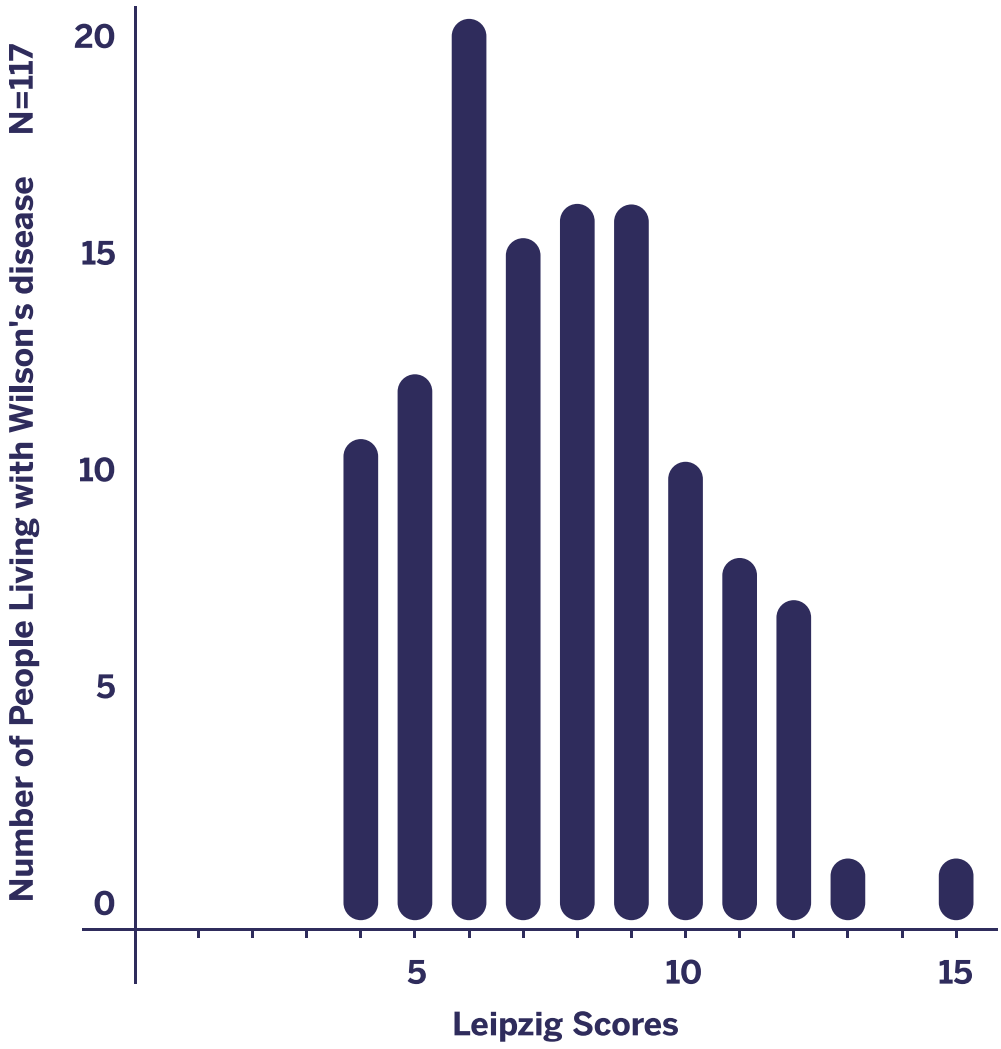


Figure 3.6 Distribution of Leipzig score at diagnosis

SELF REPORTED HEALTH STATUS BY PEOPLE LIVING WITH WILSON'S DISEASE

4. SHORT FORM SURVEY TO EVALUATE OVERALL HEALTH STATUS

At the first baseline visit, all individuals living with Wilson's disease were provided with a health-related quality of life questionnaire to complete. The Short Form Survey (SF-12) contains 12 questions and is a validated multipurpose indicator of health status. Figure 4.1 shows the responses provided by people living with Wilson's disease when asked about their health, according to country. This data was taken from the first Question of the 12-Item Short Form Survey (SF-12) questionnaire : "In general, would you say your health is...." [options are as follows: Excellent, Very Good, Good, Fair and Poor].

Many people living with Wilson's disease across the countries perceived their health to range from good to excellent. In Saudi Arabia, a greater proportion of people living with Wilson's disease described their health as excellent compared to the other countries. Almost 50% of people living with Wilson's disease in Saudi Arabia describe their health as being excellent.

Whilst only a very small proportion of people living with Wilson's disease perceived their health to be poor across the countries, it is noteworthy that no individuals living with Wilson's disease either in France or Belgium, reported their health as poor.

The United Kingdom had the highest proportion of people living with Wilson's disease (compared with other countries) reporting their health as poor.

A scientific abstract and poster presentation summarising SF-12 questionnaire data completed by people living with Wilson disease was presented at the European Association Study of the Liver Meeting in Milan in 2024 (refer to poster appendix 3)

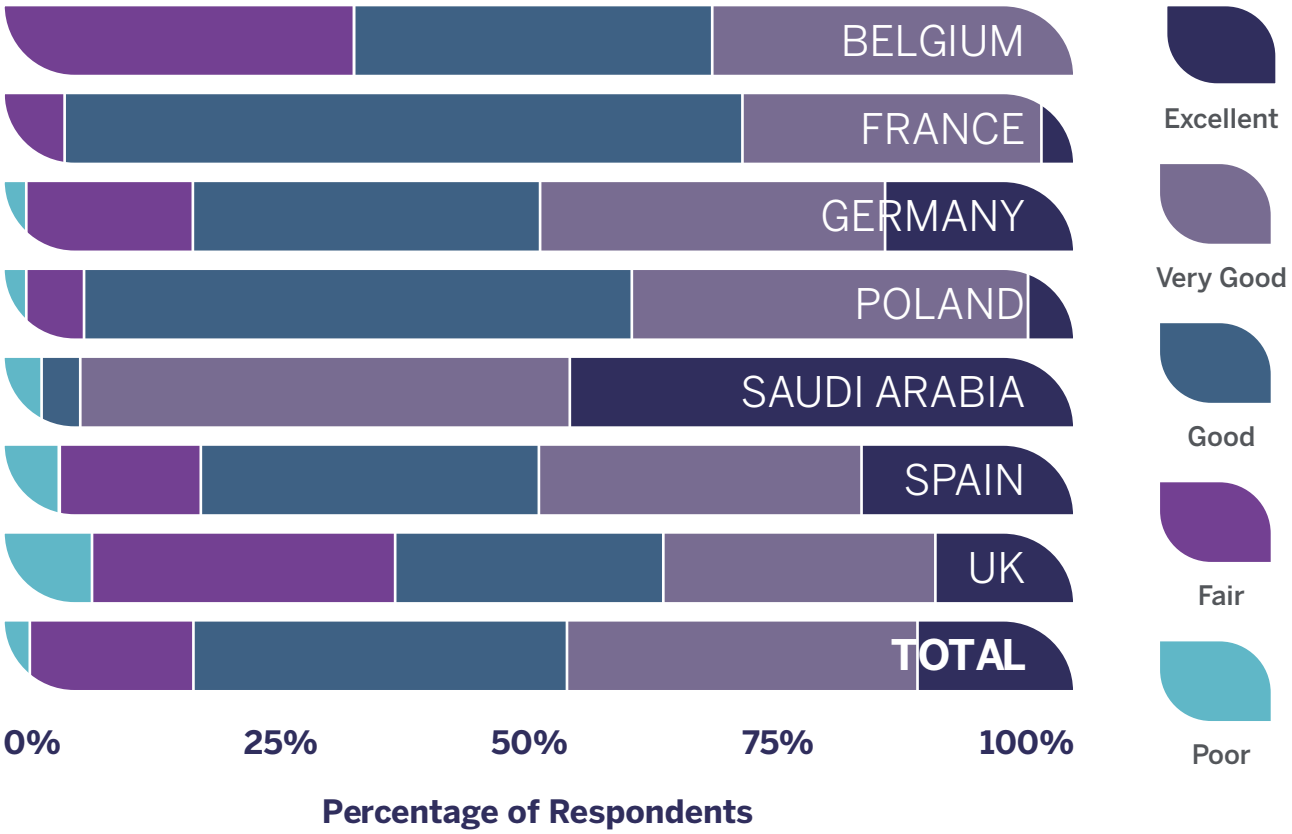


Figure 4.1 Self-Reported Perception of health by people living with Wilson's disease

5. LIVER ENZYME LEVELS OBSERVED IN PEOPLE LIVING WITH WILSON'S DISEASE.

Liver enzyme values at at entry into the Registry, 37% of 356 people living with Wilson's disease had ALT levels greater than the upper limit of normal. For AST, data from 335 people living with Wilson's disease, showed that 27% had levels greater than the upper limit of normal.

The table below shows the liver enzyme levels (AST and ALT) at the baseline visit, by country. They are grouped into normal and abnormal values. Abnormal values are defined according to local laboratory reference ranges as being above the upper limit of normal (ULN). Abnormal levels of ALT were seen in 27% (Spain) to 43% (UK, Poland) of people living with Wilson's disease and were more commonly seen compared with AST levels.

ALT/SGPT	Belgium	France	Spain	UK	Poland	Germany	Saudi Arabia	Total
n	15	60	80	46	61	71	23	**356**
Normal	9 (60%)	40 (67%)	58 (73%)	26 (57%)	35 (57%)	43 (61%)	14 (61%)	**225** (63%)
Abnormal	6 (40%)	20 (33%)	22 (27%)	20 (43%)	26 (43%)	28 (39%)	9 (39%)	**131** (37%)

AST/SGOT								
n	15	60	79	28	59	71	23	**335**
Normal	10 (67%)	39 (65%)	66 (84%)	18 (64%)	46 (78%)	50 (70%)	17 (74%)	**246** (73%)
Abnormal	5 (33%)	21 (35%)	13 (16%)	10 (36%)	13 (22%)	21 (30%)	6 (26%)	**89** (27%)

The Nazer Score

The Nazer score is a prognostic scoring system which can be used to identify individuals living with Wilson's disease that have a high likelihood of death and will require liver transplantation. The score has three components: total serum bilirubin, serum aspartate aminotransferase and INR. A score greater than or equal to 7 indicates the person living with Wilson's disease is unlikely to survive without liver transplantation.

Nazer Score	Belgium N = 11	France N = 21	Spain N = 0	UK N = 14	Poland N = 1	Germany N = 38	Saudi Arabia N = 0
Mean	1.3	1.0	-	1.0	1.0	1.2	-
Median	2.0	1.0	-	1.0	1.0	1.0	-

Nazer scores at baseline visit, by country

This figure shows the distribution of Nazer scores in people living with Wilson's disease at their baseline visit. The data provided are the mean, median and minimum and maximum values.

The maximum score is 3 and the minimum score is 0 at baseline visit. This indicates that at baseline visit, the people living with Wilson's disease appeared to be well controlled and the outlook (prognosis) in terms of liver health, is excellent in those individuals where Nazer score was reported (N=85). As expected due to the nature of this cohort, no single person living with Wilson's disease presented with a Nazer score of greater than 3.

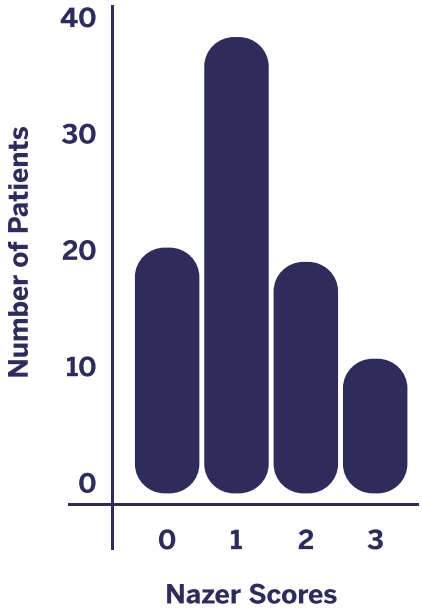


Figure 5.1 Nazer scores

6. HEPATIC IMAGING

Medical imaging of the liver is performed to describe the appearance of the liver including structure (presence of fat, fibrosis, scarring) and relationships to blood vessels and surrounding organs with advanced technologies such as MRI (magnetic resonance imaging). The primary role of the ultrasound is to detect changes in liver tissue as a result of liver disease and to screen for complications such as abnormal growth (tumours). The progression of liver disease is from normal to fatty change, fibrosis and progressive scarring which can ultimately progress to cirrhosis. A Liver Ultrasound scan is a simple non-invasive scan of the liver where pictures are taken, by bouncing high frequency sound waves off the liver and allows doctors to look at the images of the liver and its blood vessels. It is a useful and simple tool available in most clinics.

Vibration controlled transient elastography (TE) is a specialised form of ultrasound-guided assessment of tissue elastic properties designed to measure the stiffness of the liver. Liver stiffness is determined by the level of fibrosis and also impacted by tissue injury (called inflammation) in the liver. A higher stiffness score, in general represents more advanced liver disease which is confirmed by other complementary investigations.

A Liver MRI is also a non-invasive test which uses a powerful magnetic field to produce more detailed images of the liver and detect specific abnormalities which can be associated with Wilson's disease.

From the table, the commonest form of liver imaging used to evaluate liver health of people living with Wilson's disease at the baseline visit was ultrasound. Of interest, in Saudi Arabia, liver MRI was used with almost equal frequency to liver ultrasound.

This table shows the different modalities of liver imaging performed to evaluate people living with Wilson's disease at baseline by country.

At the baseline visit, 140 people with Wilson's disease had a liver ultrasound assessment performed and of these, 31 had evidence of cirrhosis on liver ultrasound.

At the baseline visit, 32 people had a liver MRI performed and of these only one person had evidence of liver cirrhosis

28 people had a liver transient elastography assessment performed at the baseline visit. Two common measures from the TE include an assessment of fat content in the liver (CAP score in decibels per metre) and stiffness (pressure measurement in kilopascals). The CAP score can go up and down over time and shows how much a person's liver is affected by fat build-up. Normal livers can show some fatty change and a score above 238 dB/m indicates abnormally elevated levels of fat in the liver. At the baseline visit, 6 people living with Wilson's disease had a CAP score of 290-400 dB/m (maximum CAP score is 400 dB/m). A CAP score of greater than 290 dB/m indicates that more than two thirds of the liver is affected by fatty change.

A total of 27 people had a liver stiffness assessment at baseline with liver elastography, and the median score was 5.90 kPa (Range 3.6- 29.8 kPa). The liver stiffness is measured in kilopascals (kPa) and normal results are usually between 2 and 7 kPa. The result may be higher than the normal range in people with liver disease.

Of note, 18 people with Wilson's disease underwent liver biopsy at the baseline visit and of these 5 people had evidence of cirrhosis.

	Transient Elastography	Liver Ultrasound	Liver MRI
Belgium	3	9	1
France	6	31	1
Germany	4	10	0
Poland	0	30	4
Saudi Arabia	0	21	18
Spain	13	23	0
UK	2	29	8
Total	28	140	32

Table 6.1 Use of hepatic imaging by country

7. NEUROLOGICAL SYMPTOMS

Documentation of whether neurological symptoms were experienced by people living with Wilson's disease at the baseline visit was limited, with only 137/387 (35%) responses. Approximately half of these people living with Wilson's disease reported experiencing neurological symptoms.

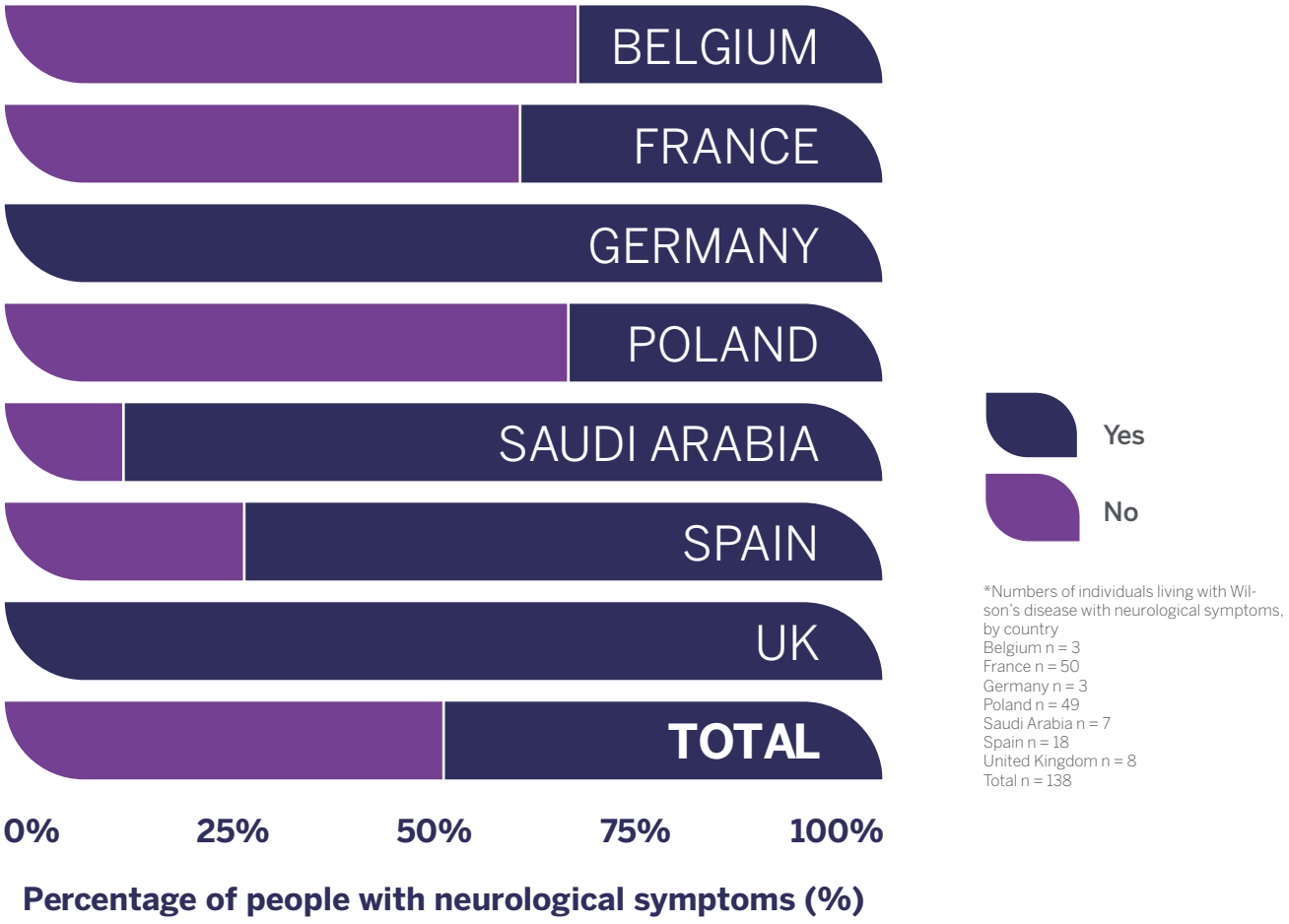


Figure 7.1 Reporting of neurological symptoms, by respondents enrolled from country.

8. NEUROPSYCHIATRIC ASSESSMENT BY COUNTRY

Wilson's disease may be associated with a high prevalence of neuropsychiatric symptoms. Studies indicate that up to two-thirds of people living with Wilson's disease eventually develop psychiatric features. Data from the baseline visit of people living with Wilson's disease was extremely limited with only 18/387 (5%) response rate with 13/387 (3%) recorded as experiencing neuropsychiatric symptoms.

This table shows the responses to the questions on neuropsychiatric assessment at baseline visit, by country.

Note – The zeros seen in the Spain and Poland columns are indicative of the fact that no response was provided to these questions in the Registry Electronic Data Capture/ Case Report Form – i.e. they did not undergo the assessments

General Questions	France N = 11	Spain N = 1	UK N = 2	Poland N = 1	Germany N = 2	Saudi Arabia N = 1	Overall N = 18
Any Psychological and/or neuropsychological symptoms?	9 (82%)	-	2 (100%)	-	1 (50%)	1 (50%)	**13** (72.2%)
Psychiatric Consultation?	1 (9.1%)	-	1 (50%)	-	-	-	**2** (11.1%)
Psychological Assessment?	8 (73%)	-	1 (50%)	-	-	-	**9** (50%)
Neuropsychological assessment?	1 (9.1%)	-	-	-	2 (100%)	1 (50%)	**4** (22.2%)

Table 8.1 Neuropsychiatric assessment at baseline

Whilst 15/387 people living with Wilson's disease received a neuropsychiatric or psychological assessment at their baseline visit (Table 8.1), only 9 had psychiatric symptoms documented, with anxiety and depression the most commonly reported symptoms (Table 8.1.1). These data are very limited with only a fraction of subjects from France (8) and United Kingdom (1) contributing.

	France N = 8	UK N = 1	Overall N = 9
Addictions	2 (25%)	-	**2** (22.2%)
Anxiety	5 (63%)	1 (100%)	**6** 66.7%)
Depression	5 (63%)	1 (100%)	**6** (66.7%)
Suicidal thoughts	1 (13%)	-	**1** (11.1%)
Psychosis/Delirium	-	-	**-**
Other Psychological Symptoms	-	-	**-**

Table 8.1.1 Psychiatric symptoms reported at baseline visit.

9. OPHTHALMOLOGICAL ASSESSMENT

A formal ophthalmological assessment using a slit lamp examination is normally used to look for KF rings at WD diagnosis, although new techniques such as "optical coherence tomography" (OCT) are being evaluated for this purpose. The presence of neurological symptoms plus KF rings are highly suggestive of Wilson's disease.

KF rings may disappear or reduce in size and intensity and is increasingly being used as an indicator of effective treatment and may be useful to monitor adherence to treatment in people living with Wilson's disease. Evaluation of KF rings over time is not formally recommended by current guidelines. Data from the Registry are limited to 63 eye examinations. The data show that 28/63 (44%) of people living with Wilson's disease had visible KF rings.

Characteristic	France N = 1	Spain N = 6	UK N = 34	Poland N = 11	Germany N = 3	Saudi Arabia N = 7	Overall N = 63
Is Kayser-Fleischer ring present?	2 (100%)	3 (50%)	12 (35%)	6 (55%)	-	5 (71%)	**28** (44.4%)

Table 9.1 Ophthalmological assessment at baseline visit, by country.

10. PREGNANCY IN WILSON DISEASE

Monitoring pregnancy in Wilson's disease is important for the health and well-being of both the mother and unborn child. Women with WD who are pregnant are therefore closely monitored throughout their pregnancy to ensure proper foetal development and early detection of any potential problems related to WD or its treatment. It is important that the pregnant woman's blood copper levels are also closely monitored throughout the pregnancy.

The pregnant woman's WD medication is carefully managed and dose adjustments may be necessary to ensure that the foetus, which needs copper for proper growth and brain development, does not become deficient in copper.

This table shows the different treatments for Wilson disease taken by women living with Wilson's disease who were pregnant at baseline visit, by country.

Treatment	France N = 8	Germany N = 3	Poland N = 3	Overall N = 7
Trientine Dihydrochloride	1 (100%)	1 (33%)	-	**2** (28.6%)
Zinc Sulphate	-	-	3 (100%)	**3** (42.9%)
Trientine Tetrahydrochloride	-	1 (33%)	-	**1** (14.3%)
No Treatment	-	1 (33%)	-	**1** (14.3%)

Table 10.1 Treatment taken for Wilson disease during active pregnancy

Based on the limited data in the Registry to date on pregnancy outcomes in women with Wilson's disease, the overall proportion of live births (from a total of 46 pregnancies) is 73.9 %. The overall proportion of miscarriages/spontaneous abortion is 23.9%.

The data from each of the countries should be interpreted with caution because of the small sample sizes.

This table shows the type of Wilson disease treatment taken during a previous pregnancy with outcomes of that pregnancy, by country.

Treatment	France N = 16	Germany N = 4	Poland N = 3	Spain N = 20	UK N = 3	Overall N = 46
Trientine Dihydrochloride	-	-	-	3 (15%)	-	**3** (6.5%)
Zinc Acetate	6 (38%)	-	-	6 (30%)	1 (33%)	**13** (28.3%)
Zinc Sulphate	-	-	2 (67%)	3 (15%)	2 (67%)	**7** (15.2%)
Trientine Tetrahydrochloride	7 (44%)	-	-	-	-	**7** (15.2%)
No Treatment	3 (19%)	4 (100%)	1 (33%)	8 (40%)	-	**16** (34.8%)
Outcome						
Induced Abortion	-	-	-	1 (5.0%)	-	**1** (2.2%)
Live Birth	8 (50%)	3 (75%)	2 (67%)	18 (90%)	3 (100%)	**34** (73.9%)
Miscarriage / spontaneous abortion	8 (50%)	1 (25%)	1 (33%)	1 (5.0%)	-	**11** (23.9%)

Table 10.1.1 Previous pregnancies; Treatment taken for Wilson disease and outcomes

11. TREATMENT FOR WILSON'S DISEASE

Treatment for individuals with a confirmed diagnosis of Wilson's disease includes chelators and inhibitors of copper absorption. Chelators are medicines which bind to copper and form a copper-chelator complex which is then removed from the body in the urine. Examples of chelator medicines are trientine and d-Penicillamine (DPA).

There are two salts of trientine: trientine dihydrochloride and trientine tetrahydrochloride; both of these medications act by chelation or binding of copper, causing its increased urinary excretion, and are known to potentially reduce copper absorption in the intestine as well, suggesting a dual mechanism of action.

Zinc salts are used to block the absorption of dietary copper in the intestine, by inducing a protein called metallothionein in the enterocytes (cells in our intestines). This protein preferentially binds copper, blocking its absorption and facilitating removal of copper in the faeces.

Trientine salts, zinc salts and D-penicillamine are all approved treatments for Wilson's disease and are all available in the countries contributing data to the iWilson Registry. At WD diagnosis, current guidelines recommend the use of chelators as first choice whenever symptoms are present. Zinc salts are often prescribed in pre-symptomatic people living with Wilson's disease or during the maintenance phase of the disease.

From the Registry data, DPA appears to be the most common treatment used overall, (41.7% across the countries) followed by trientine tetrahydrochloride (16.2%) and then zinc sulphate (4.7%). This zinc salt is almost exclusively used in Poland.

In the UK, most of the people living with Wilson's disease in the Registry were treated with DPA; with some trientine and very little zinc use.

Zinc salts are the most common treatment in Poland with almost 70% of people living with Wilson's disease prescribed zinc sulphate.

Treatment with trientine (trientine dihydrochloride and trientine tetrahydrochloride), is recommended as a second-line therapy. It's highest use is in France (52%) and Germany (48%) respectively.

Treatment	Belgium N = 13	France N = 58	Spain N = 85	UK N = 48	Poland N = 60	Germany N = 77	Saudi Arabia N = 17	Overall
d-Penicillamine	9 (69%)	22 (38%)	37 (44%)	21 (44%)	18 (30%)	36 (47%)	6 (35%)	**149** (41.6%)
Trientine	-	-	12 (14%)	5 (10%)	-	4 (5.2%)	8 (47%)	**29** (8.1%)
Trientine Dihydrochloride	-	9 (16%)	1 (1.2%)	8 (17%)	-	11 (14%)	1 (5.9%)	**30** (8.5%)
Trientine Tetrahydrochloride	3 (23%)	21 (36%)	3 (3.5%)	7 (15%)	-	22 (29%)	2 (12%)	**58** (16.2%)
Zinc	-	-	12 (14%)	2 (4.2%)	-	-	3 (18%)	**17** (4.7%)
Zinc Acetate	1 (7.7%)	6 (10%)	18 (21%)	3 (6.3%)	1 (1.7%)	4 (5.2%)	-	**33** (9.2%)
Zinc Citrate	-	-	1 (1.2%)	-	-	-	-	**1** (0.3%)
Zinc Gluconate	-	-	-	-	-	-	7 (41%)	**7** (2.0%)
Zinc Sulfate	-	-	2 (2.4%)	2 (4.2%)	41 (68%)	-	-	**45** (12.6%)

Table 11.1 Wilson's disease treatment taken by people living with Wilson's disease at baseline visit, by country (data as entered by local teams).

The pie charts below show the overall proportions of WD therapies (DPA, trientine, zinc salts), by country documented in 369/387 (95%) of people living with Wilson's disease participating in the Registry. All listed therapies are approved and available in each of the participating countries.

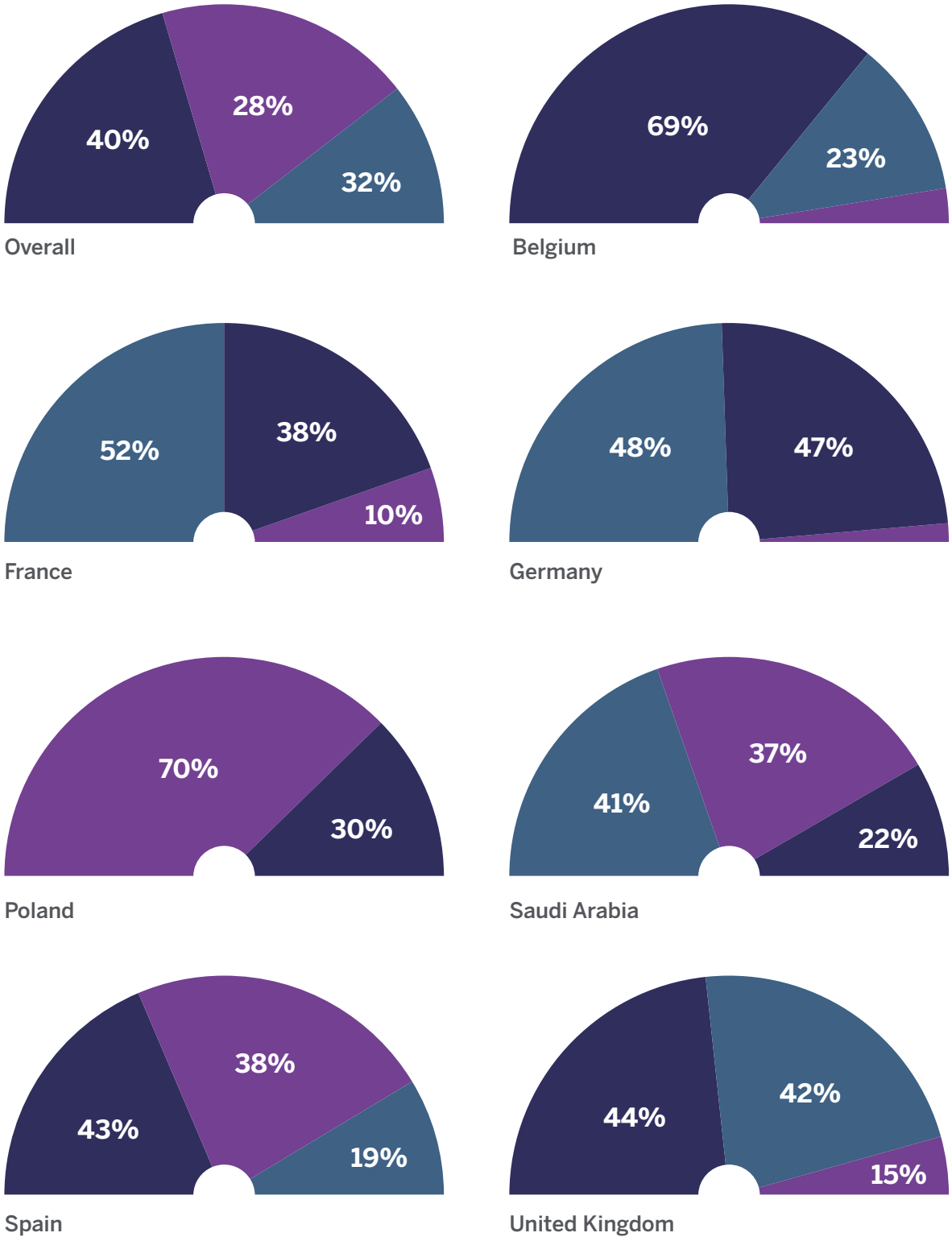


Figure 11.1.1 Breakdown of current Wilson disease treatment in the Registry – Overall and by country

Physician assessment of treatment adherence

At the baseline visit, physicians making a clinical assessment of people living with Wilson's disease were asked to determine whether they considered the individual was taking their medicines regularly and correctly (adherent to treatment). The majority of people living with Wilson's disease were perceived by their treating doctor to be adherent to their Wilson's disease medications. The doctors were not requested to quantify this assessment with clinical evidence.

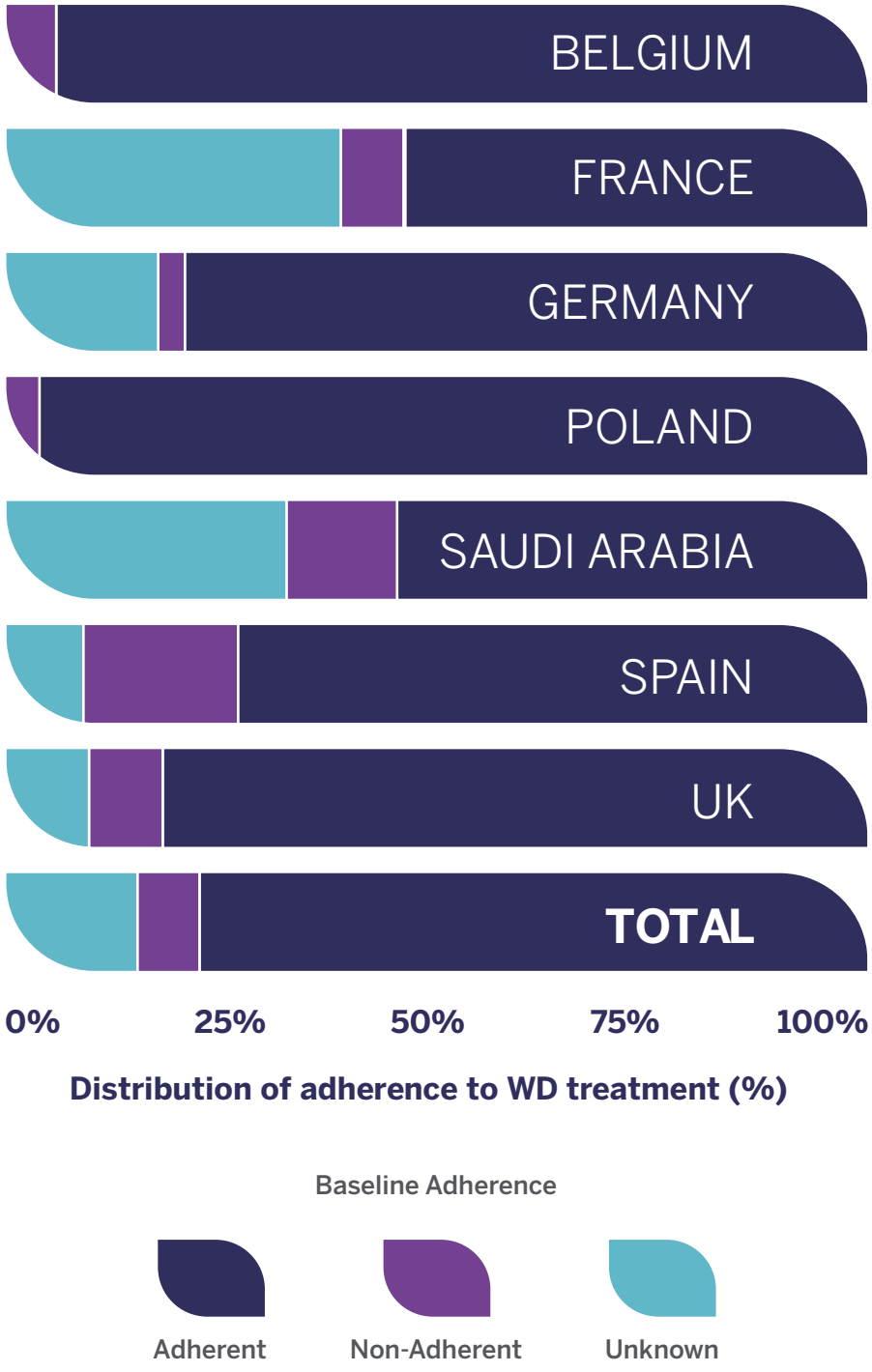


Figure 3.5 Adherence to treatment of people living with Wilson's disease, as per physician assessment at baseline visit, by country.

12. LIVER TRANSPLANTATION IN WILSON DISEASE

During the period of data collection for this annual report (June 2022 to July 2024), there was one person living with Wilson's disease who received a liver transplant with the indications for this surgical intervention listed in the table below.

Indicator	Country of Patient
Acute Hepatic Decompensation	Belgium
Decompensated Cirrhosis CHILD C13, MELD 29	France
HCC on a background of Wilsons and chronic HBV infection	UK

Table 12.1 Indication for liver transplant by country

Wilson's disease history and treatment in individuals who underwent liver transplant

Of the three people living with Wilson's disease who received a liver transplant, two (from Belgium and France) had liver transplants prior to entry in the Registry (in 2015 and 2016 respectively). These two people living with Wilson's disease were subsequently excluded from the Registry as they were not receiving any WD treatment post liver transplant. These two individuals will not be included in subsequent reports.

The person living with Wilson's disease from the UK underwent liver transplant during the reporting period for this annual report (July 2022 to July 2024).

Individual summaries of the treatment course of these three people living with Wilson's disease prior to their liver transplant. Two of these individuals were diagnosed after 30 years; 39 and 53 years respectively and thus can be considered as late diagnoses.

- The UK individual living with Wilson's disease was diagnosed in 2016 at the age of 39. They received treatment with D-penicillamine (DPA) from 2017 to 2018. Trientine dihydrochloride was initiated in 2018 because of DPA induced nephrotic syndrome and continued until 2023, when a decision was made to perform liver transplantation for Wilson's disease complicated by HCC (hepatocellular carcinoma) and chronic Hepatitis B (HBV) infection.
- The French individual living with Wilson's disease was diagnosed with severe liver disease in September 2016 at the age of 53 and began treatment with d-Penicillamine (DPA) in the same month. Within a month, in October 2016, they received a liver transplant for decompensated cirrhosis (CHILD C13, MELD 29).
- The Belgian individual living with Wilson's disease was diagnosed in 1996 at the age of 20 and began treatment with D-penicillamine (DPA) from 1996 to 2000. Zinc therapy was then subsequently added in combination with DPA up until 2005, when the patient was treated with Zinc salts monotherapy until 2010 when DPA was re-started for progressive liver disease. In July 2015 liver transplantation was performed for acute hepatic decompensation.

13. DEATHS

For the period of data collection for this annual report (June 2022 to July 2024), there were 3 deaths reported with the causes listed in the table below.

One individual living with Wilson's disease from Spain died at the age of 56. The Wilson disease treatment they were taking at the time of death was zinc acetate. They were experiencing hepatic symptoms at baseline visit and died because of progressive severe (end stage) acute on chronic liver failure.

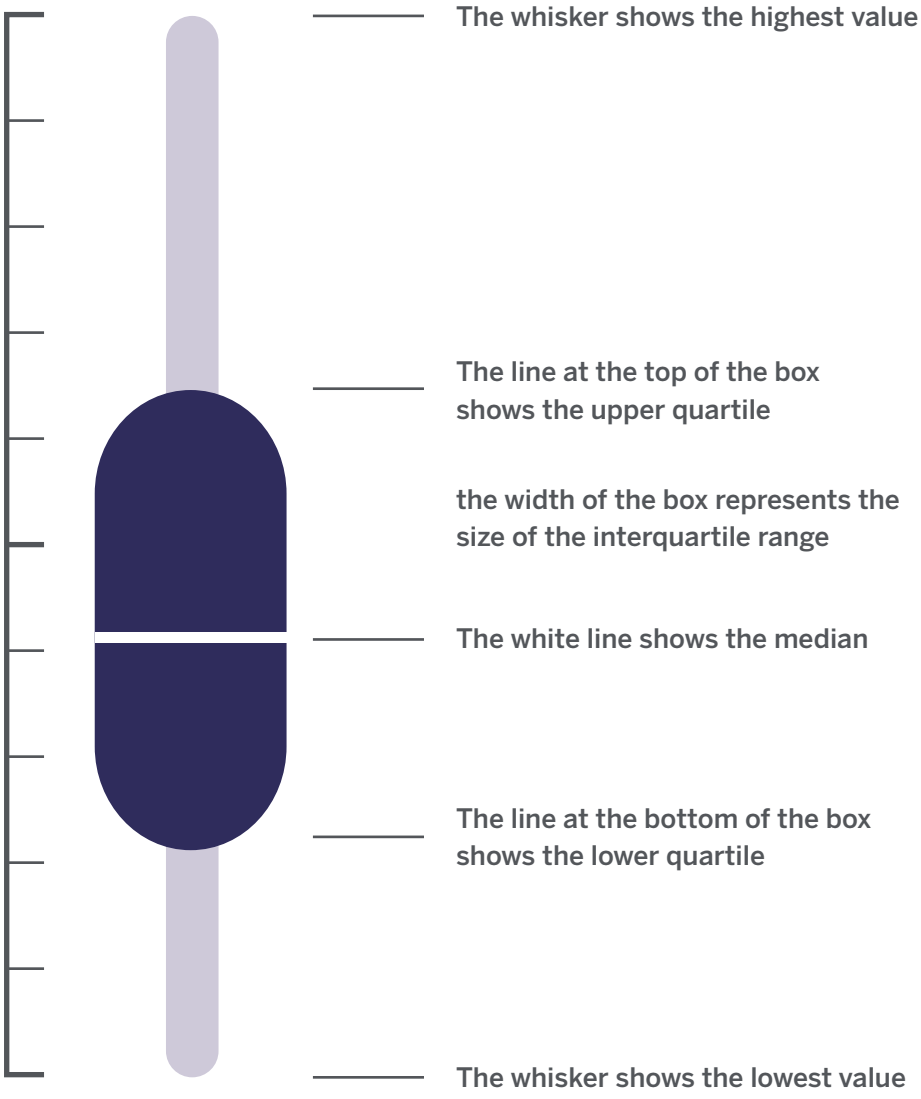
One individual living with Wilson's disease from the United Kingdom died at the age of 44. They were taking trientine tetrahydrochloride at the time of death. They were experiencing hepatic symptoms at baseline visit and died because of progressive severe (end stage) acute on chronic liver failure secondary to Wilson's disease and alcohol related liver disease. The individual was abstinent at the time of death and had previously refused to be placed on a liver transplant list.

One individual living with Wilson's disease from Poland died at the age of 30. They were taking zinc salts at the time of death and were experiencing neurological symptoms at baseline. The reported cause of death was suicide.

Casue of death	Age
End stage liver failure	56
Decompensated liver failure and alcohol-related hepatic cirrhosis	44
Suicide	30

Table 12.1 Reported cause and age at death

14. GUIDE TO GRAPHS USED IN THIS REPORT



- These plots are called "box and whisker plots". When all the data for an area of interest (for example age) is examined, the data can be visualised using a box and whisker plot.
- The 'box' shows the middle half of the data from the first quartile to the third quartile. The length of the box is determined by the degree of variability (more varied data will result in a longer box).
- The bold horizontal line within the box represents the median.
- The 'whiskers' above and below the box show the highest and lowest values for the dataset of interest (for example age).
- The position of the box relative to the whiskers shows the distribution of the data; if it favours either the higher or lower whisker, the data is described as "skewed". If a box is positioned close to the lower whisker, more of the data of interest (for example age) were recorded at the low end of the scale.

GLOSSARY OF TERMS

Word/Phrase	Meaning
Adherence	Refers to whether individuals take their medications as prescribed by their doctor.
Alcohol Associated hepatic cirrhosis	Refers to scarring of the liver as a result of alcohol consumption. In cirrhosis the liver is severely damaged and can be potentially life-threatening if not treated.
ALT	Liver enzyme, Alanine Transaminase
AST	Liver enzyme, Aspartate Aminotransferase
Cataract	A cataract is a clouding of the lens in the eye which can make a person's vision foggy.
Child-Pugh score	Refers to a scoring system which is used to assess the outlook (prognosis) of chronic liver disease, mainly scarring of the liver (cirrhosis) – it gives an indication of how well a person's liver is functioning and estimates the severity of liver disease.
Decompensated liver failure	This refers to a complication of advanced liver disease where there is an acute deterioration in liver function where the liver is no longer able to function properly and is a medical emergency which can be fatal if not treated. This may be a new development (acute liver failure; ALF) or a deterioration in liver health (acute on chronic liver failure; ACLF).
Transient Elastography	This is a type of ultrasound-guided imaging which measures stiffness (related to inflammation) of the liver. It can help doctors to understand how much scarring (fibrosis) is in the liver and tailor treatment.
HBV	This refers to Hepatitis B virus which can chronically infect the liver and cause scarring and long-term damage to the liver.
HCC	This refers to Hepatocellular Carcinoma, which is a type of liver cancer, where a tumour grows on the liver.
Hepatic Imaging	This refers to the different scans which are used to diagnose and monitor liver health over time in Wilson's disease.
IQR (interquartile range)	The IQR is a measure of spread or distribution of the data in the middle of all the numbers in a dataset. It shows the difference between the upper (Q3) and lower (Q1) quartiles. IQR = Q3 minus Q1.
iWD	International Wilson's Disease Registry.
Leipzig score	This is a scoring system which is used to help diagnose Wilson's disease. It has several components which include clinical, laboratory and imaging findings which are used to calculate a total score telling us the likelihood of a person having a diagnosis of Wilson's disease. A higher score suggests a higher likelihood of the person having Wilson's disease.
Liver MRI	This is a non-invasive diagnostic test that uses a powerful magnetic field to produce detailed images of the liver (MRI; magnetic resonance imaging).

GLOSSARY OF TERMS

Word/Phrase	Meaning
Liver Ultrasound	This is a simple non-invasive scan of the liver where pictures are taken by bouncing high-frequency sound waves off the liver and allows doctors to look at the images of the liver and its blood vessels.
Max	This is the maximum value or the highest number in a dataset.
Mean	This is the average value of a set of measurements calculated by adding up all the values and dividing by the number of values.
Median	This is value is the middle number when all the numbers in a dataset are arranged from the smallest to highest.
MELD score	This refers to Model for End Stage Liver Disease (MELD) and is a scoring system to assess the severity of chronic liver disease and the prognosis (outlook) – it also indicates how urgently a patient may need a liver transplant.
Min	This is the minimum value or lowest or smallest number in a dataset.
Nazer score	This is a prognostic scoring system using blood test results which gives a clue about the outlook of Wilson's disease. It is used to identify individuals living with Wilson's disease who have a high likelihood of death and will require liver transplant. A total score of greater than or equal to 7 indicates a patient is unlikely to survive without a liver transplant.
Neurological Assessment	Refers to the tests and physical examination performed to assess the degree of neurological problems as a result of too much copper in the brain.
Neuropsychiatric assessment	Rrefers to the tests and examinations performed to assess the severity of psychiatric and psychological symptoms which people with Wilson's disease may experience as a result of too much copper in the brain.
Ophthalmological assessment	This refers to the tests and examinations performed on the eyes, specifically looking for Kayser-Fleischer rings which are golden to greenish-brown rings of copper due to copper deposits in the cornea. These rings can be seen in about 95% of people with Wilson's disease who have neurological signs and about 65% of people with Wilson's disease who have liver involvement.
Phenotype	This refers to all the visible traits or characteristics of a person (such as eye colour, height etc) which is the result of a person's genes, which they inherit from their parents.
Quartile	When the number of measurements are arranged from smallest to highest and grouped in quarters, Q1, Q2, Q3, Q4 (4 groups). All the measurements in the middle 2 quarters (Q3 minus Q1) is referred to the interquartile range.
SGOT	Liver enzyme, Serum Glutamic-oxaloacetic Transaminase
WD	Wilson's disease.

APPENDIX 1

LIST OF CONTRIBUTING CENTRES

Country	Centre	Centre ID	Investigator team
Belgium	University Hospital Leuven	3201	**David Cassiman** Wouter Meersseman
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Spain	Hospital Universitario Y Politécnico La Fe	3402	**Marina Berenguer** Carmen Vinaixa
Spain	University Hospital Clinic of Barcelona	3403	**Zoe Mariño** Xavier Forns
Spain	Hospital Universitario GC Dr Negrin	3404	**Ildefonso Quinones Morales** Vanessa Ortega Quevedo
UK	Leeds Teaching Hospitals, St James University Hospital	4401	**Joanna Moore** Laura Burke
UK	Royal Free Hospital	4402	**Emmanuel Tsochatzis** Jemima Finkel
Poland	Institute of Psychiatry and Neurology	4801	**Anna Czlonkowska** Tomasz Litwin, Agnieszka Piechal
Poland	The Children's Memorial Health Institute	4802	**Piotr Socha** Wojciech Janczyk
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Germany	Charite-Universitatsmedizin Berlin Hospital	4902	**Frank Tacke** Caroline Zoellner
Germany	Universitatsklinikum Leipzig	4903	**Thomas Berg** Johannes Wiegand

Germany	Hannover Medical School (MHH)	4904	**Heiner Wedemeyer** Katja Deterding
France	Hospices Civils de Lyon	3301	**Eduardo Couchonnal-Bedoya** Alain Lachaux
France	HF Adolphe de Rothschild	3302	**Aurelia Poujois** Alexandre Obadia
Saudi Arabia	King Faisal Specialist Hospital Riyadh	9601	**Saad Alghamdi** Waleed Alhamoudi

APPENDIX 2

INCLUSION CRITERIA FOR iWD

The International Wilson's Disease (iWD) Registry allowed enrolment of all people diagnosed with Wilson's disease (adult and paediatric ≥ 12 years of age) irrespective of current treatment and phase of the disease (either recent diagnosis or maintenance phase).

Inclusion criteria:

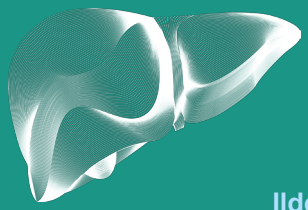
- People with WD aged 12 years and above who are able to provide and have provided written informed consent/assent.
- Written documentation has been obtained in accordance with the relevant country and local privacy requirements, where applicable, including data protection consent for EU sites.
- All people diagnosed with Wilson's disease including pre-symptomatic individuals and individuals with co-morbidities/diagnoses.
- Any treatments prescribed or treatment naïve individuals on no therapy.

Exclusion criteria:

- Refusal of providing informed consent by either the individual or their legally acceptable guardian.
- People with WD post liver transplant.

APPENDIX 3

HEALTH RELATED QUALITY OF LIFE POSTER PRESENTED AT EASL CONGRESS 2024



QUALITY OF LIFE IN ADULT
A STUDY FROM THE INTERNATIO

Claus Niederau[1], Aurelia Poujois[2], George Alex[3], Anil Dhawan[4], Caroline Roatta[5], C.
Ildefonso Quinones Morales[10], Javier Ampuero[11], Emmanouil Tsochatzis[12], Richard Parke
Heiner Wedemeyer[16], Christian Hartmann[17], Thomas Berg[18], David Cassiman

1. Katholische Kliniken Oberhausen, Germany 2. Hospital Fondation Adolphe de Rothschild, Paris, France 3. Royal Children's Hospital, Melbourne, Australia 4. Ki
Hospital Universitario La Fe, Valencia, Spain 10. University Hospital GC Dr Negrin, Spain 11. Hospital Universitario Virgen del Rocío, Spain 12. Royal Free Hospita
Germany 17. University Hospital Dusseldorf, Germany 18. Universitätsklinikum Leipzig, Germany 19. University Hospital, Leuven, Belgium 20. The Children's

Introduction

- Wilson disease (WD) is a prototype inborn error of metabolism manifesting with a wide spectrum of liver disease and neuropsychiatric symptoms
- Multiple therapeutic options are available, however, chronic disease management, may be limited by impaired health related quality of life (HRQoL)
- Due to heterogeneity of WD, real-world generated HRQoL data may provide an opportunity to harness maximal potential of therapies.

Aim

- To describe patient reported HRQoL on enrolment to an international Wilson Disease Registry

Method

- The International Wilson Disease (iWD) registry was established in 2021 (NCT05239858)
- Patients aged ≥18 years at first visit, completed a 12-Item Short-Form Health Survey (SF-12), a validated multipurpose indicator of general health status
- Data were analysed using SPSS v29 and composite scores for Physical Health (PCS) and Mental Health (MCS) were calculated

Results

- Between 29/06/2022 and 30/11/2023, 334 subjects were enrolled, of whom 322 met age eligibility criteria; SF-12 was completed by 314/322 (97.5%)
- Distribution (N) by country is shown in Figure 1 Germany (76), Belgium (15), Spain (83), Poland (44), UK (47), and France (57)
- Of the respondents, 50.6% (163) were female, mean (SD) age of 39.1 (14.6) years; distribution shown in Figure 2
- Clinical phenotypes (Figure 3) were reported in 298 and WD therapy was documented in 318 and shown in Figure 4
- The majority (222/314; 71%) rated their general health as either good or very good, with only 10/314 (3%) reporting this as poor
- Mean (SD) scores for this cohort are shown in Figure 5; PCS 42.8 (4.6) and MCS 45.8 (5.5); no differences seen by gender, class of therapy or country (Figure 6)
- MCS but not PCS was significantly lower with psychiatric phenotype

Figure 1

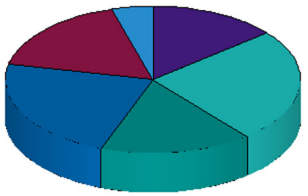


Figure 2

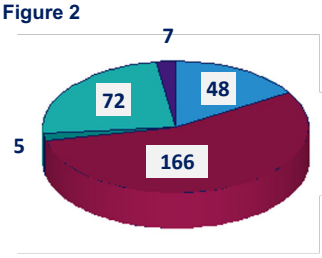


Figure 3

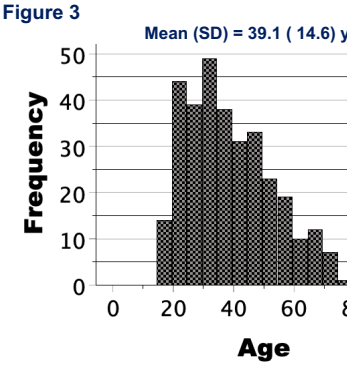
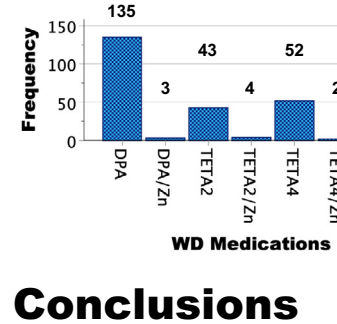


Figure 4



Conclusions

- In a European cross-sec
- However, mean physica
- These data highlight are

References

1. Balijepalli C et al. Quality of Life in Wilson's Disease: A Systematic Literature Review. *JHEOR* 2021
2. Camarata MA et al. The effect of mental health, neurological disease and liver disease on quality of life in patients with Wilson disease. *J Acad Consult Liaison Psychiatry* 2021
3. Carta MG et al. Bipolar disorders and Wilson's disease. *BMC Psychiatry* 2012

TS WITH WILSON DISEASE: NAL WILSON DISEASE REGISTRY

WD EU-ORPH-MEDA-24015 | May 2024

EASL CONGRESS Milan, Italy 5–8 June 2024

Omar Kamlin[6], Timothy Jenkins[6], Pramod Mistry[7], Zoe Marino[8], Marina Berenguer[9], er[13], Joanna Moore[13], Eduardo Couchonnal-Bedoya[14], Alexandre Obadia[2], Frank Tacke[15], [19], Piotr Socha[20], Ana Czlonkowska[21], Saad Alghamdi[22], Waleed AlHamoudi[22]

ngs College London, UK 5. Bernard Papin Institute, France 6. Orphalan SA, Paris, France 7. Yale University, New Haven, USA 8. Hospital Clinic Barcelona, Spain 9. l, London, UK 13. Leeds Teaching Hospitals, UK 14. CHU de Lyon, France 15. Charité - Universitätsmedizin Berlin, Germany 16. Medizinische Hochschule Hannover, s Memorial Health Institute, Warsaw, Poland 21. Institute of Psychiatry and Neurology, Warsaw, Poland 22. King Faisal Specialist Hospital, Riyadh, Saudi Arabia

Orphalan Innovation for Orphan Diseases

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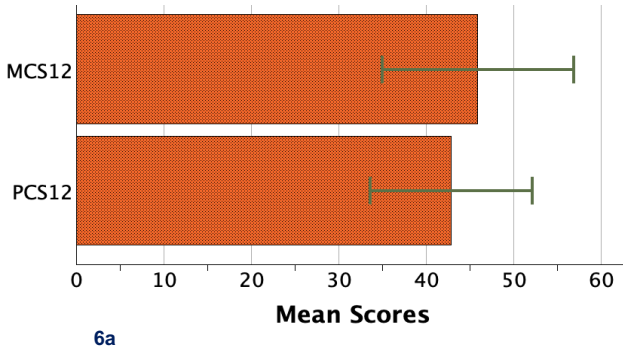
Figure 5



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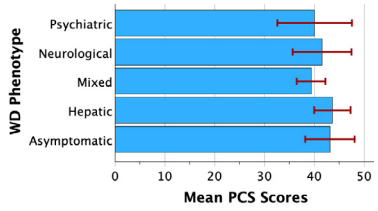

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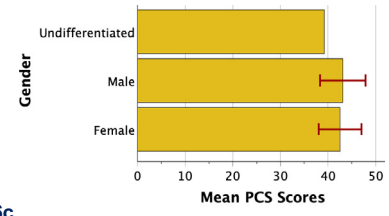

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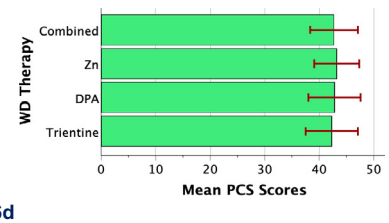

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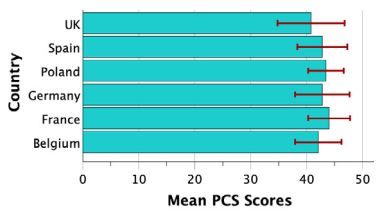

Figure 6:
Effect of Phenotype, Gender, WD therapy, country of residence on Physical and Mental Health QoL

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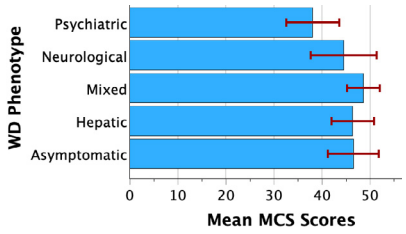

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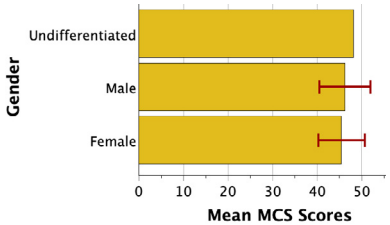

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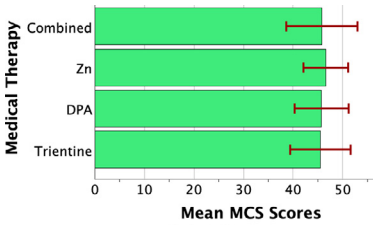

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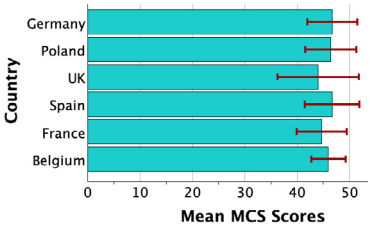
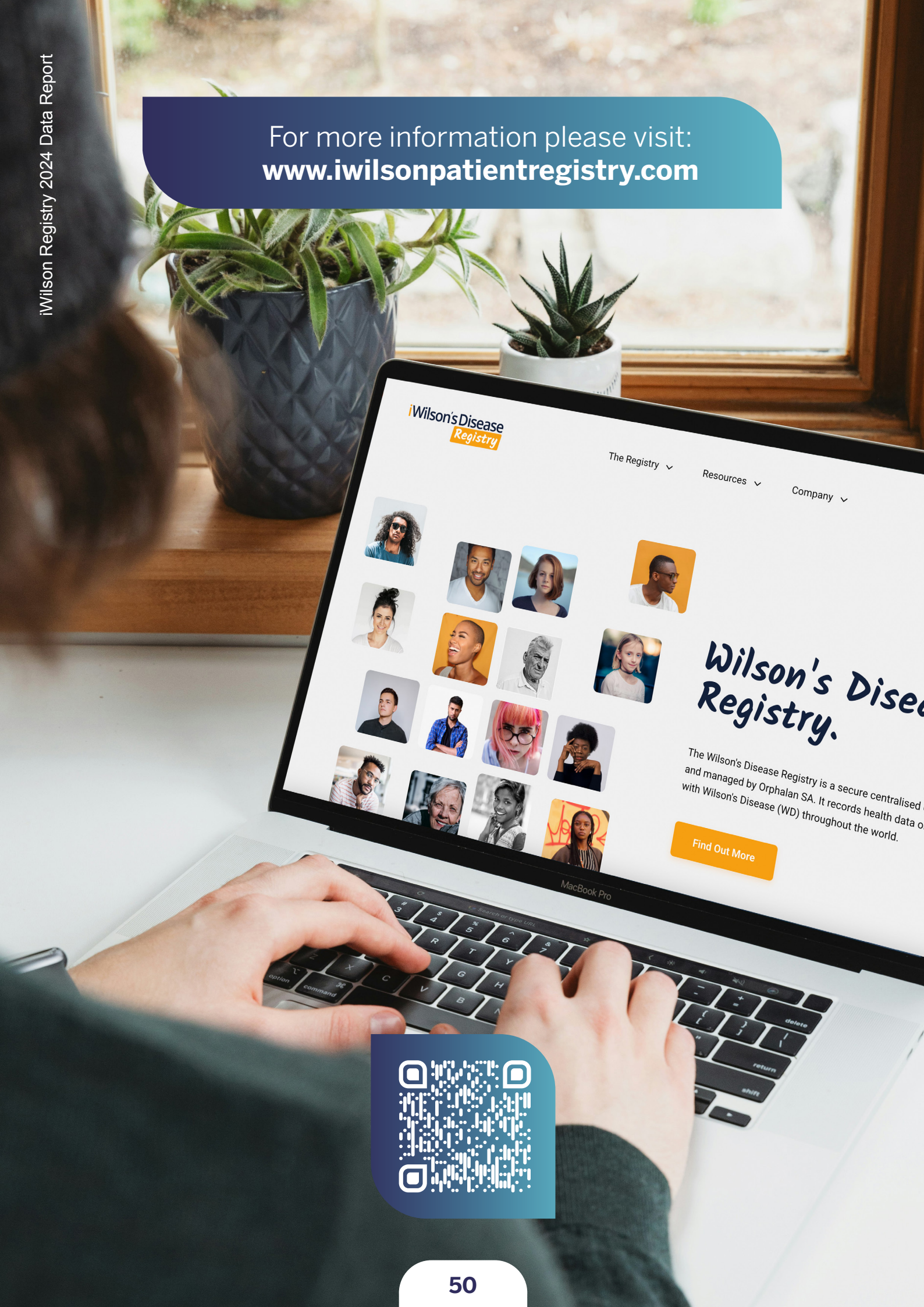


ctional survey of adults with Wilson Disease, self-reported general health was high
l and mental health scores were lower than US general population reference values
eas for improvement in HRQoL ; further research is needed to address these data gaps in Wilson Disease


For more information please visit:
www.iwilsonpatientregistry.com
iWilson's Disease Registry
The Registry
Resources
Company
Wilson's Disease Registry.
The Wilson's Disease Registry is a secure centralised
and managed by Orphalan SA. It records health data o
with Wilson's Disease (WD) throughout the world.
Find Out More
MacBook Pro

APPENDIX 4

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