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The 100 top-cited articles in the field of Wilson's disease from 1990 to 2022: A bibliometric study

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ABSTRACT

Objectives: To characterize the 100 most-cited articles in the field of Wilson's Disease (WD) to provide a general overview and reveal the historical developments classical studies, and new findings.

Design: WD-related articles were searched on the Web of Science database. The 100 most-cited articles were retrieved and their descriptive statistics were analyzed.

Data extraction and synthesis: The 100 most-cited articles in the field of WD were selected and several parameters, including citation count, citation density, first author, corresponding author, journal, country, institution, and keywords were extracted to assess the overall quality and impact of the articles.

Results: Most of the selected 100 articles were published in the 1990s and 2000s, with the highest number of articles published in 2005. Citations per paper ranged from 100 to 1,631, with a mean number of citations of 199.03. The top 100 articles were published in 38 journals, and the majority were published in the *Journal of Biological Chemistry*. The most prominent research themes were clinical presentations, clinical trials, copper transport mechanisms, and dysregulation of copper metabolism. Prof. Svetlana Lutsenko, Prof. Peter Ferenci, Prof. George J. Brewer, and Prof. Diane W. Cox were among the most influential researchers in this field, while Euro-American countries were the most dominant in terms of research output. Keywords network analysis identified "Transporting ATPase," "*ATP7B*," and "Menkes disease" as the most influential keywords. Moreover, disease management, WD clinical phenotype, *ATP7B* function, and copper metabolism are potential hotspots in future WD research.

Conclusions: This study reveals the most influential articles in the field of WD research. In addition, the major research themes and technological innovations in the field of WD worldwide are presented.

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1. Introduction

Wilson's Disease (WD) is named after Samuel Alexander Kinnier Wilson, a neurologist who first described the condition in 1912. Since the 1910s, numerous studies have investigated the pathomechanisms and treatment options for WD, particularly in recent decades. WD is an inherited disorder that is characterized by abnormal copper metabolism. It is caused by mutations in the ATPase copper transporting beta gene (*ATP7B*). *ATP7B* encodes transmembrane copper-transporting ATPase 2 which regulates copper homeostasis and provides the copper needed for the functional synthesis of ceruloplasmin [1]. The clinical hallmark of WD is the Kaiser-Fleischer (KF) ring, which is present in 90% of patients with neurological symptoms [2]. Currently, drugs that induce negative copper balance, including chelation agents that increase urinary copper excretion and zinc salts that reduce copper absorption in the digestive tract, are the mainstay treatments for WD. Over the years, many studies have been conducted to explore the mechanisms underlying WD development to reveal therapeutic targets and clinical phenotypes. Among them, the article entitled "*Copper induces cell death by targeting lipoylated TCA cycle proteins*" by Prof. Peter Tsvetkov and his colleagues published in *Science* on March 8, 2022, proposed a new form of cell death named cuprotosis [3]. As a treatable genetic disorder closely linked to copper metabolism, WD has attracted the attention of numerous scholars. A timely and comprehensive systematic review of published articles can provide novice researchers with key knowledge on a specific domain. As scientific literature on the topic continues to accumulate, particular emphasis is placed on highly cited papers. The number of citations signifies their significant impact within the field. Thus, analysis of the 100 most-cited papers will help researchers identify influential studies that have shaped the research landscape and provide valuable insights for future investigations.

Creating a strategy that can quickly and effectively evaluate the most influential research in a specific field is still a challenge. Bibliometric analysis is a unique tool for analyzing the quality and characteristics of published articles and describing the trends in a given research topic [4]. Since its discovery in the late 19th century, bibliometric studies have been used to assess and estimate trends in various research fields. Moreover, the availability of Internet access has increased the application of bibliometric tools to assess the value of published articles.

The number of published articles from *in vitro* experiments, animal experiments, and clinical studies has been increasing annually. Therefore, we performed a bibliometric analysis based on data from the Web of Science to analyze the 100 most-cited WD-related publications from 1990 to May 2022. Although this is not the first bibliometric analysis of publications in the field of WD [5], it is the first bibliometric analysis focusing on WD-related studies with high-level impact. It highlights the important milestones in research on WD and reveals the factors influencing their citations. The findings of this study are expected to guide the design of future research.

2. Material and methods

2.1. Search strategy and criteria

Articles published between Jan 1st, 1990, and May 25th, 2022, were identified by searching the Web of Science Core Collection, BIOSIS Citation Index, MEDLINE, and SciELO Citation Index to retrieve the WD-relevant publications on Mar 1st, 2023. The following search terms were used: TS = ("Wilson's Disease" OR "Wilsons Disease" OR "Wilson Disease" OR "hepatolenticular degeneration" OR "ATP7B") AND Publication type = (Article) AND Language = (English). A total of 9605 publications were identified. This number was reduced to 4772 articles after excluding review articles, guidelines, abstracts, editorial materials, meetings, and books. The articles were ranked in descending order based on citation counts. Articles that met the following criteria were included: (1) basic study, animal research, and clinical trials related to WD; (2) studies investigating the epidemiology, diagnosis, treatment, and prognosis of WD. Two investigators independently evaluated papers using predefined inclusion criteria. Any disagreements were resolved through discussion. Finally, the 100 most-cited articles on WD were selected for further analysis (the selection process is shown in Fig. 1).

2.2. Data extraction

The following data were extracted from the studies: citation count, citation density (total citations/article age), first author, corresponding author, journal, country (based on the first authors' affiliation), institution, and keywords, were extracted from the top 100 articles and used to evaluate the quality of the articles. Moreover, a list of the journal impact factors 2022 (IF 2022) was obtained from the Journal Citation Reports 2022.

2.3. Statistical analysis

Descriptive statistics were analyzed using SPSS Statistics 25.0 and R version 3.5.3. The Shapiro-Wilk test was used to test the distribution of individual variables. All data extracted in this study exhibited non-normal distribution, and thus were analyzed using either the Kruskal-Wallis test or Spearman's rank correlation test based on the nature of the article. A $p < 0.05$ was considered to be statistically significant. VOSviewer and Citespace 6.1. R4 were used to analyze the network of the most influential authors and keyword co-occurrence (the unit of analysis was set to "All keywords") to explore the research direction and identify hot spots.

3. Results

3.1. Distribution of citations

The 100 most-cited papers on WD are listed in Table 1, with a total of 19,903 citations. The number of citations per paper ranged from 100 to 1,631 with a median of 142. Notably, two articles were cited over 1000 times. The articles with more than 400 citations were all published in the 1990s. The citation density (citations/article age) ranged from 3.13 to 56.24 with a median value of 7.49. The two most-cited articles were by Peter C Bull [6] (n = 1,631) and Rudolph E Tanzi [7] (n = 1,089), and both investigated the location of the WD gene. Initially, following their publication in 1993, the two articles did not receive frequent citations. However, the number of citations experienced a rapid increase and eventually reached a stable level of approximately 50 per year starting in 1999. Our data suggested that WD-associated articles with high citation density had high citation counts, and a moderately positive correlation (r = 0.678, $P < 0.01$).

3.2. Publication date

The 100 top-cited articles were published between 1990 [8] and 2016 [9] (Fig. 2A). The majority were published in the 1990s (48%) and 2000s (42%), with only 10% of the articles published in the 2010s (Fig. 2B). The largest number of articles published in a single year was recorded in 2005 (n = 10). The mean citation per article was 199.03 overall (245.65 in the 1990s, 160.05 in the 2000s, and 139 in the 2010s). Notably, there were no significant differences among the 3 groups (Fig. 2C). Among the 100 top-cited papers, *Copper Capture in a Thioether-Functionalized Porous Polymer Applied to the Detection of Wilson's Disease* [9], published in 2016, was the most recent paper (citation = 102), while *Cranial MRI in Wilson's disease*, published in 1990, was the earliest paper (citation = 100) [8]. Interestingly, these two articles had similar citation counts. The mean citation density per article was 9.66 (9.13 in the 1990s, 9.10 in the 2000s, and 14.57 in the 2010s).

3.3. Distribution of countries and institutions

The 100 top-cited papers were from 18 countries as determined based on the affiliation of the first authors. The United States of America (USA) was the most productive country, contributing to 43% of the publications, followed by Germany with 10 papers, Canada with 9 papers, and Austria and the United Kingdom (UK), with 6 papers each. Fig. 3a shows that almost all the 100 top-cited papers were from Euro-American countries, with only a few articles originating from Asia and South America. In the co-authorship analysis, 50 countries with more than two publications in the field were analyzed (Fig. 3b). The top 3 countries with the highest connection intensity were Germany (total link strength = 19 times), the USA (13 times), and Australia (10 times).

Moreover, 55 institutions contributed to the 100 top-cited articles. The University of Michigan topped the list with 9 papers, followed by Oregon Health and Science University with 7 papers, and Washington University with 6 papers. The top 4 institutions were all from the USA. Hospital for Sick Children from Canada tied for fourth position with 5 papers, but with higher average citations per paper. Fig. 4A shows that 18 institutions had published at least 2 papers. There was no correlation between the number of articles associated with an institution and the average article citations (r = 0.242, $P > 0.05$). Institution co-authorship analysis results are presented in Fig. 4B, and only institutions with more than two publications are included. Of the 31 institutions that met the threshold, University California, Berkeley (5 times), and University Groningen (5 times) were the institutions with largest total link strength.

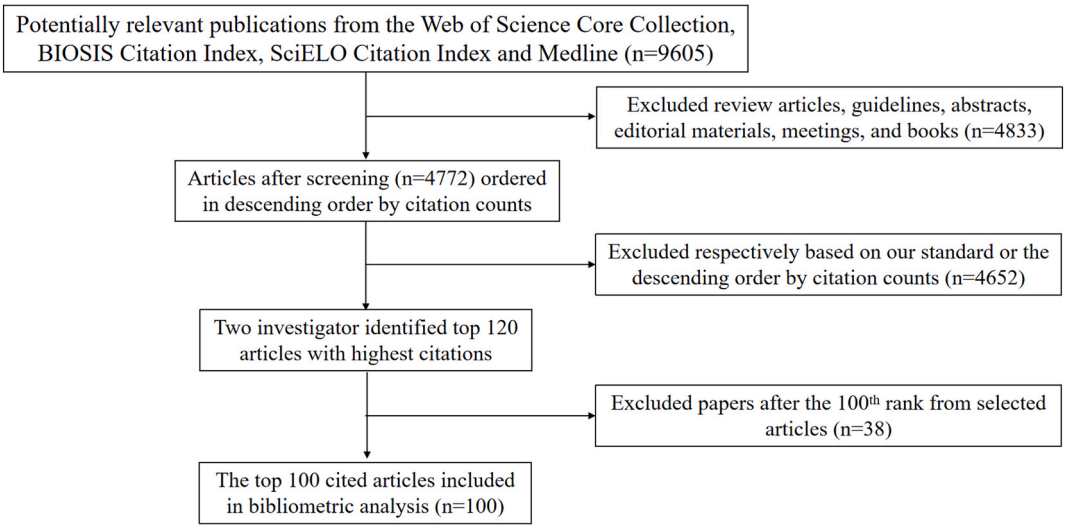

Fig. 1. Flowchart illustrating the data extraction process.

Table 1
List of the 100 most-cited articles.

Title	Journal	IF	Publication Year	First Author	Corresponding Author	Country	Institutions	Citations	Citation Density
The Wilson disease gene is a putative copper transporting P-type ATPase similar to the Menkes gene	Nature Genetics	38.33	1993	Peter C. Bull	Diane W. Cox	Canada	Hospital for Sick Children	1631	56.24
The Wilson disease gene is a copper transporting ATPase with homology to the Menkes disease gene	Nature Genetics	38.33	1993	Rudolph E. Tanzi	Conrad T. Gilliam	USA	Harvard Medical School	1091	37.62
Metal ion chaperone function of the soluble Cu (I) receptor Atx1.	Science	47.728	1997	Robert A. Pufahl	Thomas V·O'Halloran	USA	Northwestern University	589	23.56
The Wilson disease gene: spectrum of mutations and their consequences	Nature Genetics	38.33	1995	Gordon R. Thomas	Diane W. Cox	Canada	Hospital for Sick Children	465	17.22
Isolation and characterization of a human liver cDNA as a candidate gene for Wilson disease	Biochemical and Biophysical Research Communications	3.575	1993	Yukitoshi Yamaguchi	Jonathan D. Gitlin	USA	Washington University	450	15.52
Mapping, cloning and genetic characterization of the region containing the Wilson disease gene	Nature Genetics	38.33	1993	Konstantin Petrukhin	Conrad T. Gilliam	USA	Columbia University	431	14.86
The Menkes/Wilson disease gene homologue in yeast provides copper to a ceruloplasmin-like oxidase required for iron uptake.	Proceedings of the National Academy of Sciences of the United States of America	11.205	1995	Daniel S. Yuan	Richard D. Klausner	USA	National Institutes of Health	389	14.41
CopA: An *Escherichia coli* Cu(I)-translocating P-type ATPase	Proceedings of the National Academy of Sciences of the United States of America	11.205	2000	Christopher Rensing	Barry P. Rosen	USA	Wayne State University	379	17.23
Liver cell death and anemia in Wilson disease involve acid sphingomyelinase and ceramide	Nature Medicine	53.44	2007	Philipp A. Lang	Erich Gulbins; Florian Lang	Germany	Institute of Physiology University of Tübingen	370	24.67
Clinical presentation, diagnosis and long-term outcome of Wilson's disease: a cohort study	Gut	23.059	2007	Uta Merle	Uta Merle	Germany	University Hospital Heidelberg	356	23.73
The LEC rat has a deletion in the copper transporting ATPase gene homologous to the Wilson disease gene.	Nature Genetics	38.33	1994	Jingshi Wu	Diane W. Cox	Canada	Hospital for Sick Children	350	12.50
Structural basis for copper transfer by the metallochaperone for the Menkes/Wilson disease proteins	Nature Structural & Molecular Biology (Nature structural biology)	15.369	2000	Amy K. Wernimont	Amy C. Rosenzweig	USA	Northwestern University	335	15.23
Spontaneous hepatic copper accumulation in Long-Evans Cinnamon rats with hereditary hepatitis. A model of Wilson's disease	The Journal of Clinical Investigation	14.808	1991	Yu Li	Yu Li	Japan	Hokkaido University School of Medicine	317	10.23
Characterization of the Wilson disease gene encoding a P-type copper transporting ATPase: genomic organization, alternative splicing, and structure/function predictions.	Human Molecular Genetics	6.15	1994	Konstantin Petrukhin	Conrad T. Gilliam	USA	Columbia University	293	10.46
Wilson's disease in patients presenting with liver disease: a diagnostic challenge.	Gastroenterology	22.682	1997	Petra Steindl	Petra Steindl	Austria	University of Vienna	275	11.00
Biochemical characterization of the Wilson disease protein and functional expression in the yeast *Saccharomyces cerevisiae*.	The Journal of Biological Chemistry	5.157	1997	Irene H Hung	Jonathan D. Gitlin	USA	Washington University	273	10.92

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Table 1 (*continued*)

Title	Journal	IF	Publication Year	First Author	Corresponding Author	Country	Institutions	Citations	Citation Density
Identification and analysis of mutations in the Wilson disease gene (ATP7B): population frequencies, genotype-phenotype correlation, and functional analyses.	American journal of human genetics	11.025	1997	Anjali B. Shah	Konstantin Petrukhin	USA	Columbia University	268	10.72
Wilson's disease in children: 37-year experience and revised king's score for liver transplantation	Liver Transplantation	5.799	2005	Anil Dhawan	Anil Dhawan	United Kingdom	King's College Hospital	241	14.18
Crystal structure of a copper-transporting PIB-type ATPase	Nature	49.962	2011	Pontus Gourdon	Poul Nissen	Denmark	Aarhus University	236	21.45
Interaction of the copper chaperone HAH1 with the Wilson disease protein is essential for copper homeostasis	Proceedings of the National Academy of Sciences of the United States of America	11.205	1999	Iqbal Hamza	Jonathan D. Gitlin	USA	Washington University	224	9.74
Hepatic failure and liver cell damage in acute Wilson's disease involve CD95 (APO-1/Fas) mediated apoptosis.	Nature Medicine	53.44	1998	Susanne Strand	Peter R. Galle	Germany	University Hospital Heidelberg	213	8.88
Copper-induced apical trafficking of ATP7B in polarized hepatoma cells provides a mechanism for biliary copper excretion	Gastroenterology	22.682	2000	Han Roelofsen	Han Roelofsen	Netherlands	University Hospital Groningen	210	9.55
N-terminal domains of human copper-transporting adenosine triphosphatases (the Wilson's and Menkes disease proteins) bind copper selectively in vivo and *in vitro* with stoichiometry of one copper per metal-binding repeat.	The Journal of Biological Chemistry	5.157	1997	Svetlana Lutsenko	Svetlana Lutsenko	USA	Oregon Health and Science University	207	8.28
Treatment of Wilson disease with ammonium tetrathiomolybdate - IV. Comparison of tetrathiomolybdate and trientine in a double-blind study of treatment of the neurologic presentation of Wilson disease	JAMA Neurology (Archieves of Neurology)	18.302	2006	George J. Brewer	George J. Brewer	USA	University of Michigan	205	12.81
Increased p53 mutation load in nontumorous human liver of Wilson disease and hemochromatosis: Oxyradical overload diseases	Proceedings of the National Academy of Sciences of the United States of America	11.205	2000	Perwez S. Hussain	Curtis C. Harris	USA	National Institutes of Health	200	9.09
A genetic study of Wilson's disease in the United Kingdom	Brain	13.501	2013	Alison J. Coffey	Oliver Bandmann	United Kingdom	Wellcome Trust Sanger Institute	198	22.00
Liver transplantation for Wilson's disease: indications and outcome.	Hepatology	17.425	1994	Micheal L. Schilsky	Micheal L. Schilsky	USA	Albert Einstein College of Medicine	196	7.00
In vivo reduction of amyloid-beta by a mutant copper transporter	Proceedings of the National Academy of Sciences of the United States of America	11.205	2003	Amie L Phinney	David Westaway	Canada	University of Toronto	183	9.63
Hepatocyte-specific localization and copper-dependent trafficking of the Wilson's disease protein in the liver	American Journal of Physiology-Gastroentestinal and Lver Physiology	4.052	1999	Mark Schaefer	Jonathan D. Gitlin	USA	Washington University	182	7.91
Treatment of Wilson's disease with zinc: XV long-term follow-up studies.	The Journal of Laboratory and Clinical Medicine	2.795	1998	George J. Brewer	George J. Brewer	USA	University of Michigan	180	7.50

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Table 1 (*continued*)

Title	Journal	IF	Publication Year	First Author	Corresponding Author	Country	Institutions	Citations	Citation Density
Functional expression of the Wilson disease protein reveals mislocalization and impaired copper-dependent trafficking of the common H1069Q mutation.	Proceedings of the National Academy of Sciences of the United States of America	11.205	1998	Aimee S. Payne	Jonathan D. Gitlin	USA	Washington University	175	7.29
High copper selectively alters lipid metabolism and cell cycle machinery in the mouse model of Wilson disease	The Journal of Biological Chemistry	5.157	2007	Dominik Huster	Svetlana Lutsenko	USA	Oregon Health and Science University	165	11.00
Initial therapy of patients with Wilson's disease with tetrathiomolybdate	JAMA Neurology (Archieves of Neurology)	18.302	1991	George J. Brewer	George J. Brewer	USA	University of Michigan	165	5.32
Wilson disease - Description of 282 patients evaluated over 3 decades	Medicine	1.889	2007	Arun B. Taly	Arun B. Taly	India	National Institute of Mental Health and Neurosciences	164	10.93
Late-onset Wilson's disease	Gastroenterology	22.682	2007	Peter Ferenci	Peter Ferenci	Austria	Medical University of Vienna	161	10.73
Oxidant injury to hepatic mitochondria in patients with Wilson's disease and Bedlington terriers with copper toxicosis.	Gastroenterology	22.682	1994	Ronald J. Sokol	Ronald J. Sokol	USA	University of Colorado School of Medicine	160	5.71
Null mutation of the murine ATP7B (Wilson disease) gene results in intracellular copper accumulation and late-onset hepatic nodular transformation	Human Molecular Genetics	6.15	1999	Olesia I. Bulakova	Conrad T. Gilliam	USA	Columbia University	156	6.78
Near-infrared fluorescent sensor for in vivo copper imaging in a murine Wilson disease model	Proceedings of the National Academy of Sciences of the United States of America	11.205	2012	Tasuku Hirayama	Christopher J. Chang	USA	University of California	154	15.40
Diagnosis of Wilson's disease: an experience over three decades	Gut	23.059	2000	Pual J. Gow	Richard A. Smallwood	Ausralia	Austin and Repatriation Medical Centre	153	6.95
The toxic milk mouse is a murine model of Wilson disease.	Human Molecular Genetics	6.15	1996	Michael B. Theophilos	Julian F. B. Mercer	Ausralia	Royal Children's Hospital	151	5.81
Screening for Wilson disease in acute liver failure: A comparison of currently available diagnostic tests	Hepatology	17.425	2008	Jessica D. Korman	Michael L. Schilsky	USA	Montefiore Medical Center	149	10.64
The copper toxicosis gene product Murr1 directly interacts with the Wilson disease protein	The Journal of Biological Chemistry	5.157	2003	Ting Y. Tao	Jonathan D. Gitlin	USA	Washington University	149	7.84
Wilson's disease: cranial MRI observations and clinical correlation	Neuroradiology	2.804	2006	Shashank Sinha	Shashank Sinha	India	National Institute of Mental Health and Neurosciences	147	9.19
Consequences of copper accumulation in the livers of the Atp7b (−/−) (Wilson disease gene) knockout mice	American Journal of Pathology	4.307	2006	Dominik Huster	Svetlana Lutsenko	USA	Oregon Health and Science University	146	9.13
Cranial MR imaging in Wilson's disease.	American Journal of Roentgenology	3.959	1996	Aleah D. King	Aleah D. King	United Kingdom	Middlesex Hospital	145	5.58
Molecular pathology and haplotype analysis of Wilson disease in Mediterranean populations	American Journal of Human Genetics	11.025	1995	Annalena Figus	Mario Pirastu	Italy	Istituto di Medicina Interna	145	5.37
Neurological manifestations in Wilson's disease: Report of 119 cases	Moverment Disorders	10.338	2006	Alexandre Machado	Alexandre Machado	Brazil	University of São Paulo	144	9.00

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Table 1 (*continued*)

Title	Journal	IF	Publication Year	First Author	Corresponding Author	Country	Institutions	Citations	Citation Density
Diagnostic value of quantitative hepatic copper determination in patients with Wilson's disease	Clinical Gastroenterology and Hepatology	11.382	2005	Peter Ferenci	Peter Ferenci	Austria	Medical University of Vienna	144	8.47
Abnormal deposition of collagen around hepatocytes in Wilson's disease is associated with hepatocyte specific expression of lysyl oxidase and lysyl oxidase like protein-2	Journal of Hepatology	25.083	2005	Zehava Vadasz	Gera Neufeld	Israel	Israel Institute of Technology	143	8.41
Treatment of Wilson disease with ammonium tetrathiomolybdate - III. Initial therapy in a total of 55 neurologically affected patients and follow-up with zinc therapy	JAMA Neurology (Archieves of Neurology)	18.302	2003	George J. Brewer	George J. Brewer	USA	University of Michigan	142	7.47
Functional characterization of missense mutations in ATP7B: Wilson disease mutation or normal variant	American journal of human genetics	11.025	1998	John R. Forbes	Diane W. Cox	Canada	University of Alberta	142	5.92
Wilson Disease Protein ATP7B Utilizes Lysosomal Exocytosis to Maintain Copper Homeostasis	Developmental Cell	12.27	2014	Elena V. Polishchuk	Roman S. Polishchuk	Italy	Telethon Institute of Genetics and Medicine	141	17.63
Characterization of the interaction between the Wilson and Menkes disease proteins and the cytoplasmic copper chaperone, HAH1p	The Journal of Biological Chemistry	5.157	1999	Dmitri Larin	Conrad T. Gilliam	USA	Columbia University	140	6.09
Restoration of holoceruloplasmin synthesis in LEC rat after infusion of recombinant adenovirus bearing WND cDNA	The Journal of Biological Chemistry	5.157	1998	Kunihiko Terada	Toshihiro Sugiyama	Japan	Akita University School of Medicine	137	5.71
Copper-dependent trafficking of Wilson disease mutant ATP7B proteins	Human Molecular Genetics	6.15	2000	John R. Forbes	Diane W. Cox	Canada	University of Alberta	135	6.14
Role of the copper-binding domain in the copper transport function of ATP7B, the P-type ATPase defective in Wilson disease	The Journal of Biological Chemistry	5.157	1999	John R. Forbes	Diane W. Cox	Canada	University of Alberta	133	5.78
The copper-transporting ATPases, Menkes and Wilson disease proteins, have distinct roles in adult and developing cerebellum	The Journal of Biological Chemistry	5.157	2005	Natalie Barnes	Svetlana Lutsenko	USA	Oregon Health and Science University	132	7.76
Value of urinary copper excretion after penicillamine challenge in the diagnosis of Wilson's disease	Hepatology	17.425	1992	Claudia Martins Da Costa	Giorgina Mieli-Verga	United Kingdom	King's College Hospital	132	4.40
Molecular characterization of Wilson disease in the Sardinian population - Evidence of a founder effect	Human Mutation	4.878	1999	Georgios Loudianos	Georgios Loudianos	Italy	Ospedale Regionale per Le Microcitemie	131	5.70
Structure of human Wilson protein domains 5 and 6 and their interplay with domain 4 and the copper chaperone HAM in copper uptake	Proceedings of the National Academy of Sciences of the United States of America	11.205	2006	David Achila	David L. Huffman	USA	Western Michigan University	130	8.13
XIAP is a copper binding protein dereaulated in Wilson's disease and other copper toxicosis disorders	Molecular Cell	17.97	2006	Arjmand R. Mufti	Colin S. Duckett	USA	University of Michigan	129	8.06
High prevalence of the H1069Q mutation in East German patients with Wilson disease: rapid detection of mutations by limited	Journal of Hepatology	25.083	2001	Karel Caca	Karel Caca	Germany	University of Leipzig	129	6.14

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Table 1 (*continued*)

Title	Journal	IF	Publication Year	First Author	Corresponding Author	Country	Institutions	Citations	Citation Density
sequencing and phenotype-genotype analysis									
Expression, purification, and metal binding properties of the N-terminal domain from the wilson disease putative copper-transporting ATPase (ATP7B).	The Journal of Biological Chemistry	5.157	1997	Michael DiDonato	Biswajit Sarkar	Canada	Hospital for Sick Children	129	5.16
Wilson disease in septuagenarian siblings: Raising the bar for diagnosis	Hepatology	17.425	2005	Aftab Ala	Michael Schilsky	USA	The Mount Sinai Medical Center	127	7.47
The Lys (1010)-Lys (1325) fragment of the Wilson's disease protein binds nucleotides and interacts with the N-terminal domain of this protein in a copper-dependent manner	The Journal of Biological Chemistry	5.157	2001	Ruslan Tsivkovskii	Svetlana Lutsenko	USA	Oregon Health and Science University	127	6.05
Hepatic iron deprivation prevents spontaneous development of fulminant hepatitis and liver cancer in Long-Evans Cinnamon rats	The Journal of Clinical Investigation	14.808	1996	Junji Kato	Yoshiro Niitsu	Japan	Sapporo Medical University School of Medicine	127	4.88
Metallochaperone Atox1 transfers copper to the NH2-terminal domain of the Wilson's disease protein and regulates its catalytic activity	The Journal of Biological Chemistry	5.157	2002	Joel M Walker	Svetlana Lutsenko	USA	Oregon Health and Science University	125	6.25
Albumin dialysis: effective removal of copper in a patient with fulminant Wilson disease and successful bridging to liver transplantation: a new possibility for the elimination of protein-bound toxins	Journal of Hepatology	25.083	1999	Bernhard Kreymann	Bernhard Kreymann	Germany	Technical University of Munich	124	5.39
Treatment of Wilson disease with ammonium tetrathiomolybdate. II. Initial therapy in 33 neurologically affected patients and follow-up with zinc therapy	JAMA Neurology (Archieves of Neurology)	18.302	1996	George J. Brewer	George J. Brewer	USA	University of Michigan	122	4.69
Treatment of Wilson's disease with ammonium tetrathiomolybdate. I. Initial therapy in 17 neurologically affected patients	JAMA Neurology (Archieves of Neurology)	18.302	1994	George J. Brewer	George J. Brewer	USA	University of Michigan	122	4.36
Haplotype and mutation analysis in Japanese patients with Wilson disease.	American journal of human genetics	11.025	1997	Manoj S. Nanji	Diane W. Cox	Canada	Hospital for Sick Children	120	4.80
Liver transplantation for Wilson's disease: The burden of neurological and psychiatric disorders	Liver Transplantation	5.799	2005	Valentina Medici	Stefano Fagiuoli	Italy	University of Padua	119	7.00
Treatment of Wilson's disease with zinc: X. Intestinal metallothionein induction	The Journal of Laboratory and Clinical Medicine	2.795	1992	Yuzbasiyan-Gurkan Vilma	George J. Brewer	USA	University of Michigan	119	3.97
Clinical differentiation of fulminant Wilsonian hepatitis from other causes of hepatic failure	Gastroenterology	22.682	1991	David H. Berman	David H. Van Thiel	USA	University of Pittsburgh	119	3.84
Wilson's disease: the problem of delayed diagnosis	Journal of Neurology, Neurosurgery, and Psychiatry	10.283	1992	Janice M. Walshe	Janice M. Walshe	United Kingdom	Addenbrooke's Hospital	118	3.93
Neurological and neuropsychiatric spectrum of Wilson's disease: a prospective study of 45 cases.	Journal of Neurology	4.849	1991	Walter Oder	Walter Oder	Austria	Neurologische Universitätsklinik	117	3.77

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Table 1 (*continued*)

Title	Journal	IF	Publication Year	First Author	Corresponding Author	Country	Institutions	Citations	Citation Density
Re-evaluation of the Diagnostic Criteria for Wilson Disease in Children With Mild Liver Disease	Hepatology	17.425	2010	Emanuele Nicastro	Raffaele Iorio	Italy	University Federico II	116	9.67
Mutation analysis of the ATP7B gene and genotype/phenotype correlation in 227 patients with Wilson disease	Molecular Genetics and Metabolism	4.797	2005	Slavka Vrabelova	Libor Kozak	Czech Republic	University Hospital Brno	116	6.82
Effects of long-term treatment in Wilson's disease with D-penicillamine and zinc sulphate	Journal of Neurology	4.849	1996	Anna Czlonkowska	Anna Czlonkowska	Poland	Institute of Psychiatry and Neurology	114	4.38
Efficacy and Safety of Oral Chelators in Treatment of Patients With Wilson Disease	Clinical Gastroenterology and Hepatology	11.382	2013	Karl H. Weiss	Roderick H. J. Houwen; Peter Ferenci; Wolfgang Stremmel	Germany	University Hospital Heidelberg	113	12.56
Rescue of ATP7B function in hepatocyte-like cells from Wilson's disease induced pluripotent stem cells using gene therapy or the chaperone drug curcumin	Human Molecular Genetics	6.15	2011	Shiqiang Zhang	Duanqing Pei; Miguel A. Esteban	China	Chinese Academy of Sciences	112	10.18
Liver mitochondrial membrane crosslinking and destruction in a rat model of Wilson disease	The Journal of Clinical Investigation	14.808	2011	Hans Zischka	Hans Zischka	Germany	German Research Center for Environmental Health	112	10.18
Copper inhibits the water and glycerol permeability of aquaporin-3	The Journal of Biological Chemistry	5.157	2004	Marina Zelenina	Anita Aperia	Sweden	Karolinska Institutet	112	6.22
Treatment of Wilson's disease with zinc. XVII: Treatment during pregnancy	Hepatology	17.425	2000	George J. Brewer	George J. Brewer	USA	University of Michigan	112	5.09
NH2-terminal signals in ATP7B Cu-ATPase mediate its Cu-dependent anterograde traffic in polarized hepatic cells	American Journal of Physiology-Gastroentestinal and Lver Physiology	4.052	2005	Guo, Yan	Alun L. Hubbard	USA	Johns Hopkins University School of Medicine	111	6.53
Distinct Wilson's disease mutations in ATP7B are associated with enhanced binding to COMMD1 and reduced stability of ATP7B	Gastroenterology	22.682	2007	Prim de Bie	Leo W. J. Klomp	Netherlands	University Medical Center	110	7.33
Localization of the Wilson's disease protein product to mitochondria	Proceedings of the National Academy of Sciences of the United States of America	11.205	1998	Svetlana Lutsenko	Svetlana Lutsenko	USA	Oregon Health and Science University	109	4.54
Defective cellular localization of mutant ATP7B in Wilson's disease patients and hepatoma cell lines	Gastroenterology	22.682	2003	Dominik Huster	Karel Caca	Germany	University of Leipzig	107	5.63
Chelation treatment of neurological Wilson's disease	the Quarterly Journal of Medicine	3.21	1993	Janice M. Walshe	Janice M. Walshe	United Kingdom	Addenbrooke's Hospital	107	3.69
Zinc Monotherapy Is Not as Effective as Chelating Agents in Treatment of Wilson Disease	Gastroenterology	22.682	2011	Karl H. Weiss	Peter Ferenci; Wolfgang Stremmel	Germany	University Hospital Heidelberg	106	9.64
Intrahepatic transplantation of normal hepatocytes prevents Wilson's disease in Long-Evans cinnamon rats	Gastroenterology	22.682	1996	Yukinori Yoshida	Katsuhiro Ogawa	Japan	Asahikawa Medical College	106	4.08
Frameshift and nonsense mutations in the gene for ATPase7B are associated with severe impairment of copper metabolism and with	Clinical Genetics	4.438	2005	Grazyna Gromadzka	Grazyna Gromadzka	Poland	Institute of Psychiatry and Neurology	105	6.18

(*continued on next page*)

Table 1 (*continued*)

Title	Journal	IF	Publication Year	First Author	Corresponding Author	Country	Institutions	Citations	Citation Density
an early clinical manifestation of Wilson's disease									
The H1069Q mutation in ATP7B is associated with late and neurologic presentation in Wilson disease: results of a meta-analysis	Journal of Hepatology	25.083	2004	Janneke M. Stapelbroek	Roderick H. J. Houwen	Netherlands	University Medical Center	105	5.83
The impact of apolipoprotein E genotypes on age at onset of symptoms and phenotypic expression in Wilson's disease	Brain	13.501	2000	Natalia Schiefermeier-Mach	Harald Kollegger	Austria	University of Vienna	105	4.77
Copper Capture in a Thioether-Functionalized Porous Polymer Applied to the Detection of Wilson's Disease	Journal of the American Chemical Society	15.419	2016	Sumin Lee	Christopher J. Chang	USA	University of California	102	17.00
Plasma copper and antioxidant status in Wilson's disease	Pediatric Research	3.756	1995	Hiromi Ogihara	Touru Ogihara	Japan	Osaka Medical College	102	3.78
Cu(I) binding and transfer by the N terminus of the Wilson disease protein	The Journal of Biological Chemistry	5.157	2007	Liliya A. Yatsunyk	Amy C. Rosenzweig	USA	Northwestern University	100	6.67
MR imaging of the brain in Wilson disease of childhood: Findings before and after treatment with clinical correlation	American Journal of Neuroradiology	3.825	2006	Taek Joon Kim	In-Ok Kim	South Korea	Seoul National University Bundang Hospital	100	6.25
Sonographic detection of basal ganglia lesions in asymptomatic and symptomatic Wilson disease	Neurology	9.91	2005	Ulrich Walter	Ulrich Walter	Germany	University of Rostock	100	5.88
Cranial MRI in Wilson's disease.	Neuroradiology	2.804	1990	Lucas Prayer	Lucas Prayer	Austria	University of Vienna	100	3.13

IF： impact factor, USA： United States of America.

3.4. Distribution of authors

The VOSviewer tool was employed to conduct a network analysis on the co-authorship of highly cited articles to identify the influential authors and collaborative co-authorship among the 100 most-cited articles. The analysis revealed that 583 authors participated in at least 1 article. Prof. Peter Ferenci was the most influential author with 9 articles and 78 total link strengths. Although Prof. Svetlana Lutsenko had the most significant number of documents, her influence was somewhat inferior in terms of the total link strength (Table 2). Further analysis revealed that 85 authors contributed to at least two articles. Fig. 5A shows the overlay visualization of influential authors and Fig. 5B presents the network visualization of data in Fig. 5A. In total, 11 clusters of authors were identified, with 4 clusters having 10 or more authors. The most prominent cluster was that led by Prof. George J. Brewer and included 14 other authors. The names of the most productive first or corresponding authors (who authored two or more papers) are listed in Table 3. Prof. George J. Brewer, from the Department of Human Genetics at the University of Michigan Medical School, was ranked first in both first authorship and corresponding authorship. The main focus of his research revolved around evaluating drugs used in clinical trials for WD. This included long-term follow-ups studies on the use of zinc as a treatment for WD and the effectiveness and side effects of tetrathiomolybdate and trientine in the management of WD. Prof. Diane W. Cox, affiliated to the Hospital for Sick Children, University of Alberta, published seven articles as the corresponding author. Her research focused on unraveling the copper transport mechanism and conducting functional characterizations of *ATP7B* mutations, and their consequences. Additionally, Prof. Diane W. Cox identified the gene responsible for WD. Prof. Svetlana Lutsenko from Oregon Health and Science University performed functional mechanistic studies on *ATP7B*, primarily in *ATP7B* regulated copper transport.

3.5. Analysis of journals and reference

The 100 top-cited articles were published in 38 journals, with the majority published in the *Journal of Biological Chemistry* (n = 13), followed by *Gastroenterology* (n = 9) and *Proceedings of the National Academy of Sciences of the United States of America* (*PNAS*) (n = 9). *Nature Genetics* ranked first in the mean citation per paper, with an average citation of 794 per paper. The journals containing two or more articles are displayed in Fig. 6. According to the IF 2022 list, the IF of 38 journals ranged from 1.871 to 87.241, with 36 articles having an IF of less than 10. Thirty-five articles had an IF ranging between 10 and 20, and 29 publications had an IF of higher than 20.

A subject knowledge base of the 100 most-cited articles can be created by analyzing the reference with high citation frequency and centrality presented by the cited reference network (Fig. 7). As shown in Table 4, the articles *Biochemical characterization of the Wilson disease protein and functional expression in the yeast Saccharomyces cerevisiae* [10] and *Wilson disease* [11] were the most cited with 7 citations each. A reference with high centrality often indicates a significant breakthrough in the research field. The article published in 1999 by Prof. Valeria C. Culotta and her colleagues, which identified and elucidated the function of two copper chaperones, holds the highest centrality among the articles analyzed [12].

Contribution of keywords; Furthermore, we performed network analysis to identify hot-spot keywords among the 100 most-cited articles. The relevance score was considered strong when a noun phrase predominantly appeared in conjunction with a limited number of other noun phrases, and conversely, it was deemed weak when it had frequent associations with a wide range of other noun phrases. Keywords with high relevance had a significant meaning, which enables the researchers to focus first on the keywords that mean the most to their research line. Fig. 8a illustrates the overlay visualization of influential keywords, and Fig. 8b demonstrates the density

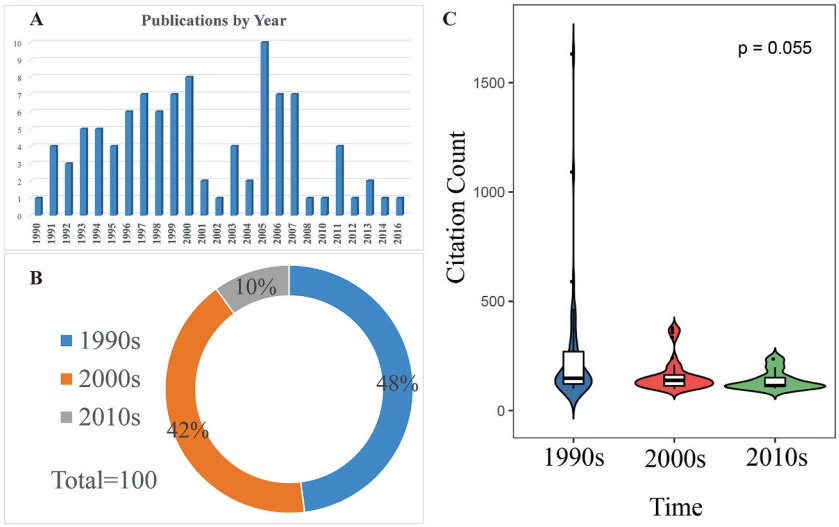

Fig. 2. (A) Number of publications according to the year of publication. (B) Time distribution of top 100 most-cited publications in WD. Most articles were published in the 1990s (48%, n = 48) and 200s (42%, n = 42). (C) There was no significant difference in number of publications among three groups (P > 0.05).

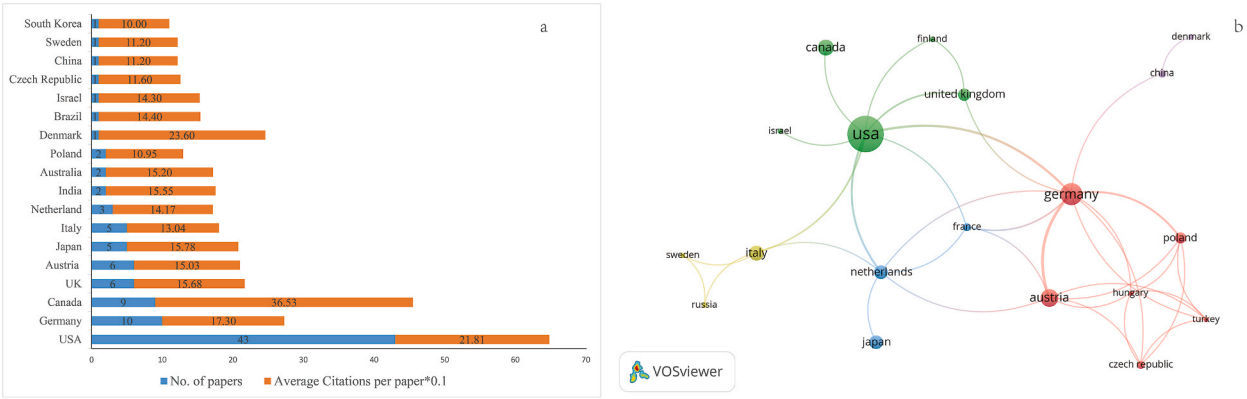

Fig. 3. (a) Countries of the top 100 most-cited articles. (b) Network map of co-authorship between countries with more than two publications. Note: USA: United States of America, UK: United Kingdom.

visualization of data in Fig. 8a. The nodes represent the analyzed elements, and their importance is reflected by their size, which corresponds to the frequency of keyword occurrences. Larger spheres indicate higher frequencies of keyword occurrence. Among the 303 keywords analyzed, "transporting ATPase," (n = 13) "ATP7B," (n = 12), and "Menkes disease" (n = 11) were the most frequent keywords. A keyword network analysis of the articles published in the last 5 years in the WD field revealed that "Management," "clinical presentation," "magnetic resonance imaging (MRI)," "KF ring," "copper metabolism," "CTR1," "pediatrics," and "spectrum" had a high frequency in recently 2 years, whereas "copper," (n = 286) "diagnosis," (n = 255) "ATP7B," (n = 195) "liver disease," (n = 138) and "children" (n = 112) were the most influential keywords in the recent 5 years (Fig. 8c and d). Keyword burst and timeline visualization are often used to identify research trends and hot spots and results are displayed using CiteSpace. Fig. 9 shows that the top three keywords with the highest burst strength were "transporting ATPase", "Menkes disease", and "candidate gene", which were also the earliest keywords to show burst. The keywords exhibiting a high burst strength in recent years included "mutations", "penicillamine therapy" and "long term treatment". The keywords timeline view displayed the evolution trend of the research. Notably, 6 clusters were generated as shown in Fig. Supplementary 1. The length of the horizontal line indicates the time range of a single cluster, with recent studies being closer to the right. Data shown in the figure demonstrated that keywords such as "distinct", "copper transporter", and "penicillamine therapy" were closer to the right on the picture, suggesting that topics associated with these keywords were the focus of recent studies on WD.

4. Discussion

Although the availability of a large number of studies on WD has promoted the development of this field, it has increased the difficulty of distinguishing between valuable studies and less significant others. Thus, we performed a bibliometric study of the 100 most-cited WD-related articles to identify those with a high impact in this field.

Bibliometric analysis of the most cited publications in WD is beneficial for several reasons. First, it provides valuable details about scientific progress, including key topics, authors, institutions, journals, and trends in research. Second, it shows how research in the

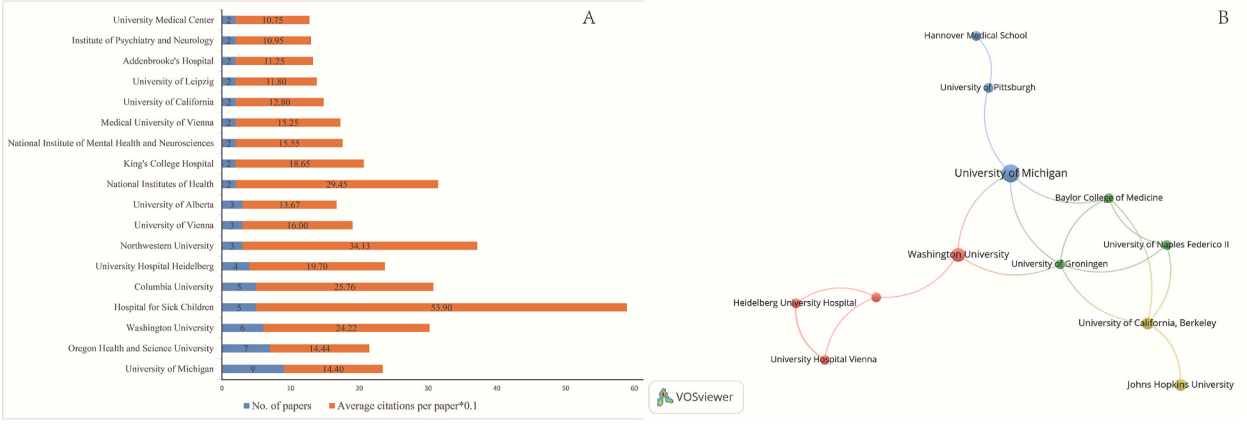

Fig. 4. (A) Institutions with at least 2 articles in the top 100 most-cited articles. (B) Network map of co-authorship between institutions with more than two publications.

Table 2
Authors with the strongest occurrence among top-100 cite articles (analysis by VOSviewer, threshold set 1).

Rank	Authors	Documents	Total link strength
1	Peter Ferenci	9	78
3	Svetlana Lutsenko	13	77
2	George J. Brewer	9	61
4	Wolfgang Stremmel	5	47
12	Conrad T. Gilliam	6	47
5	Karen J. Kluin	7	45
6	Barbara Ross	5	45
7	Diane W. Cox	10	44
8	Konstantin Petrukhin	5	44
9	Igor Chernov	4	40
10	Robert D. Dick	6	39
11	Giorgina Mieli-Verga	3	37
13	Harald Hefter	2	36
14	Uta Merle	4	36
15	Christopher J. Chang	3	31

field has evolved over time and the existing gaps [13]. Third, it provides reference data to guide the design of future studies in the WD field. Moreover, reviewers, funding agencies, and journal editors might utilize the information produced by bibliometric analysis when reviewing and evaluating studies and funding proposals [14]. Last, it could provide critical quantitative information about the classic studies in the field of WD, and recent advances thereby improving our understanding of WD [14].

4.1. Citation analysis

Assessing the quality of a research paper solely through subjective peer review is often a contentious matter. However, it is widely acknowledged that articles with a higher citation count possess a greater potential to influence the research community, and hence affect clinical practice [15,16]. Despite the ongoing debate surrounding this issue, the citation count remains a reasonably reliable metric for evaluating the impact of scholarly work [17]. To enhance research quality, it is advisable for researchers to read highly cited articles in their field prior to starting their investigation. The most-cited articles (so-called "citation classic") can provide important information about scientific progress and research trends in a specific field.

In the early stages of research in the field of WD, citations predominantly revolved around studies concerning clinical manifestations. Over time, however, there has been a noticeable shift towards exploring mechanisms and therapeutic interventions. Notably, the identification of "copper-induced cell death" has facilitated deep investigations into the underlying mechanisms and treatment strategies for WD. The top 2 most cited articles in our study, with high citation counts and citation densities, laid the foundation upon which other studies in the field of WD. These two articles identified the WD gene, opening a new door for the next phase of WD research. Among the 100 most-cited articles, only two papers did not include WD-related terms. Nevertheless, they are still widely

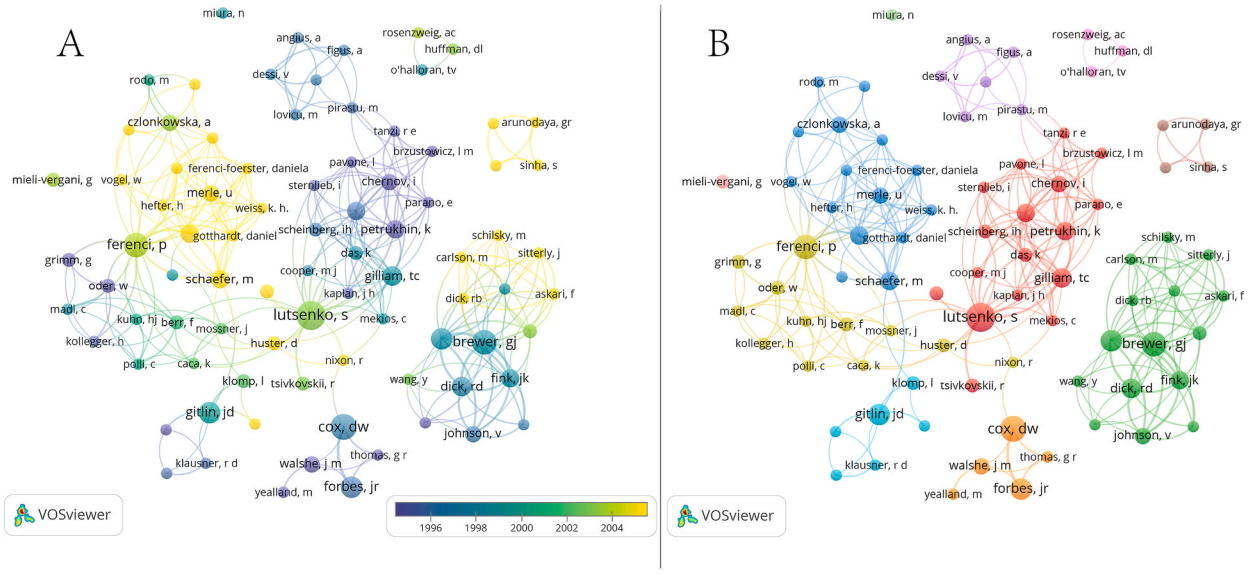

Fig. 5. Network plot of influential authors in WD research among the top 100 most-cited articles. (A) Overlay visualization, (B) Network visualization of (A). Note: see Table Supplementary 1 for the full names of the abbreviations.

Table 3
List of first/corresponidng authors with frequent articles.

Frequent Authors	First Author	Corresponding Author
	No. of articles	No. of articles
George J. Brewer	7	8
Svetlana Lutsenko	2	7
Diane W. Cox	0	7
Jonathan D. Gitlin	0	6
Peter Ferenci	2	4
Conrad T. Gilliam	0	5
Micheal L. Schilsky	1	3
Janice M. Walshe	2	2
Karel Caca	1	2
Konstantin Petrukhin	2	1
Dominik Huster	3	0
John R. Forbes	3	0
Amy C. Rosenzweig	0	2
Roderick H. J. Houwen	0	2
Christopher J. Chang	0	2
Karl H. Weiss	2	0

No.: Number.

cited because of their relevance to the function of *ATP7B* and can help researchers to gain a deeper understanding of the roles of *ATP7B*. This observation implies that well-designed preclinical studies pave the way for the successful implementation of subsequent translation studies. It is worth noting that as data from these studies are incorporated into professional textbooks, a phenomenon known as "obliteration by incorporation" [18,19] may occur, resulting in a decline in citation density. However, it is crucial to acknowledge the significant historical importance of these older articles despite the potential bias towards their increased citation likelihood [20]. To mitigate this bias, we conducted an analysis of the citation density among the 100 most-cited articles. The results showed a correlation between citation count and citation density, suggesting a growing trend in WD-related research.

Since review articles and guidelines are more likely to be cited compared with original articles, we excluded these types of publications from our citation analysis to avoid this bias.

There is still a certain gap in citation count between the WD field and other popular fields. Researchers should strive to improve the quality of their research and increase the number of excellent publications despite WD being a relatively rare disease.

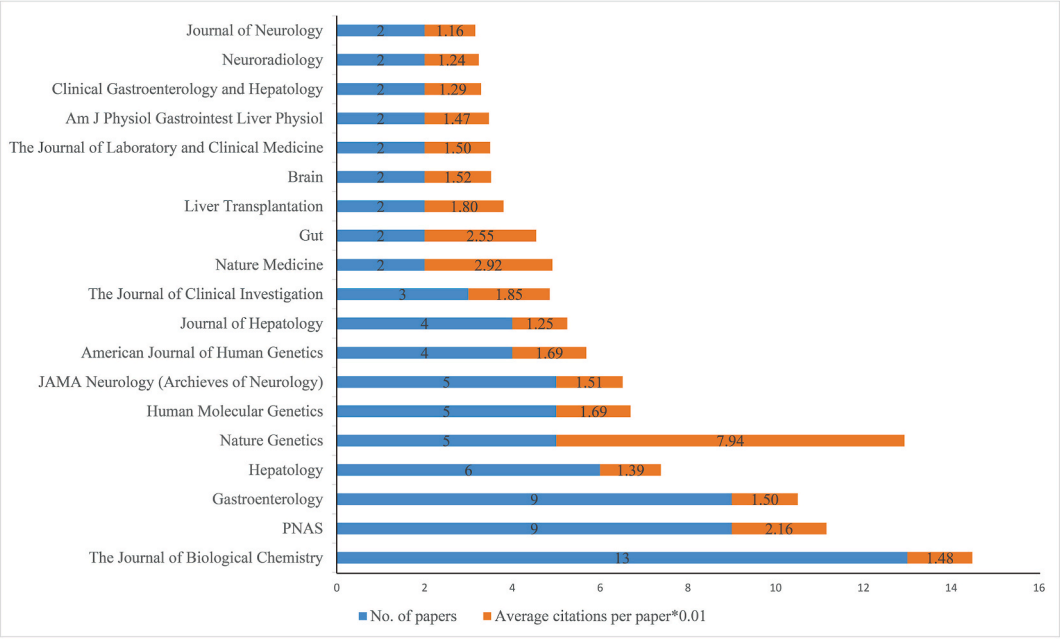

Fig. 6. Journals with at least 2 publications in the top 100 most-cited articles. Note: PNAS: Proceedings of the National Academy of Sciences of the United States of America.

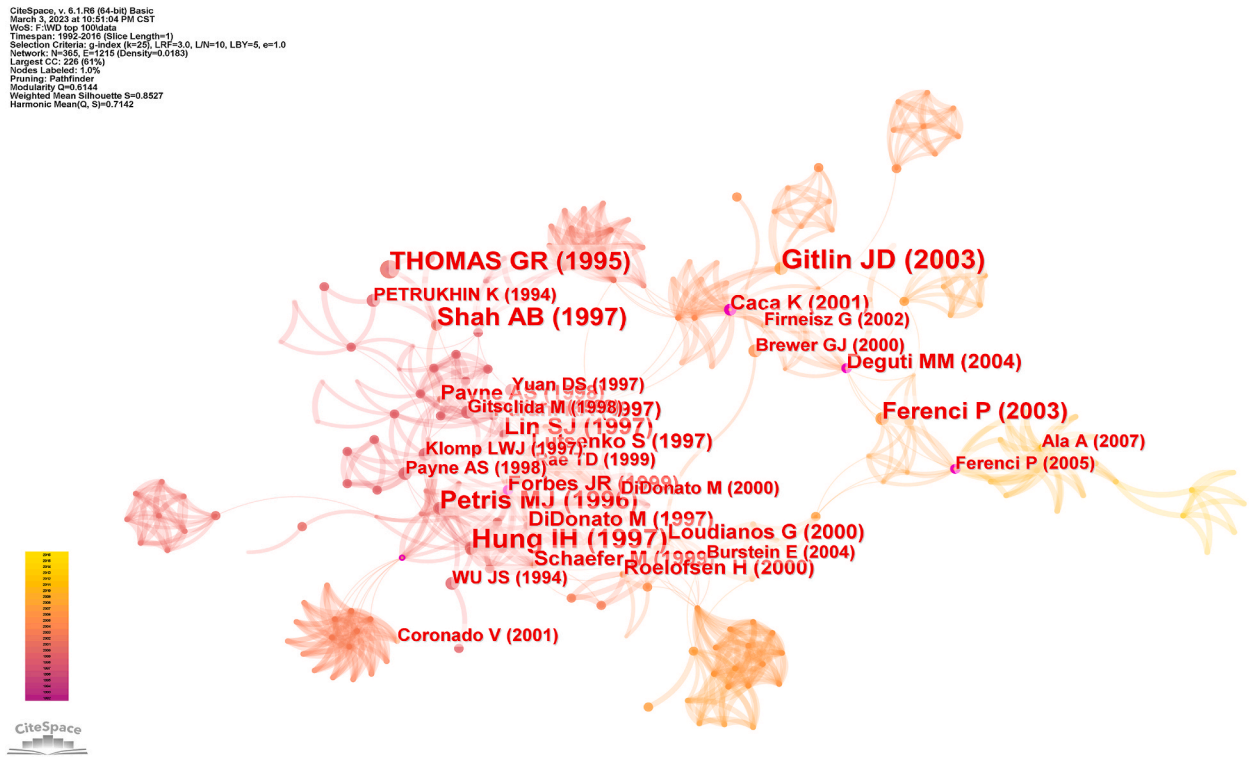

Fig. 7. Co-citation network of reference in WD research among the top 100 most-cited articles.

4.2. Publication date

One of the most remarkable findings of this study was that the publication date influenced the citation count. Across various research disciplines, it is widely observed that the likelihood of an article being cited increases as more time elapses since its publication. Our findings align with this trend, as 90% of the 100 most-cited articles in our analysis were published prior to 2010, and none

Table 4
Top 5 references in terms of citation frequency and centrality.

Rank	Frequency	References	Authors and publication year	Rank	Centrality	References	Authors and publication year
1	7	Biochemical characterization of the Wilson disease protein and functional expression in the yeast *Saccharomyces cerevisiae*.	Irene H. Hung (1997)	1	0.28	Intracellular pathways of copper trafficking in yeast and humans	Valeria C. Culotta (1999)
2	7	Wilson disease	Jonathan D. Gitlin (2003)	2	0.21	High prevalence of the H1069Q mutation in East German patients with Wilson disease: rapid detection of mutations by limited sequencing and phenotype-genotype analysis	Karel Caca (2001)
3	6	Identification and analysis of mutations in the Wilson disease gene (ATP7B): population frequencies, genotype-phenotype correlation, and functional analyses	Anjali B. Shah (1997)	3	0.19	Copper-induced conformational changes in the N-terminal domain of the Wilson disease copper-transporting ATPase	Michael DiDonato (2000)
4	6	The Wilson disease gene: spectrum of mutations and their consequences	Gordon R. Thomas (1995)	4	0.18	Role of the copper-binding domain in the copper transport function of ATP7B, the P-type ATPase defective in Wilson disease	John R. Forbes (1999)
5	6	Ligand-regulated transport of the Menkes copper P-type ATPase efflux pump from the Golgi apparatus to the plasma membrane: a novel mechanism of regulated trafficking	Michael J. Petrisl (1996)	5	0.14	Wilson disease: novel mutations in the ATP7B gene and clinical correlation in Brazilian patients	Marta M. Deguti (2004)

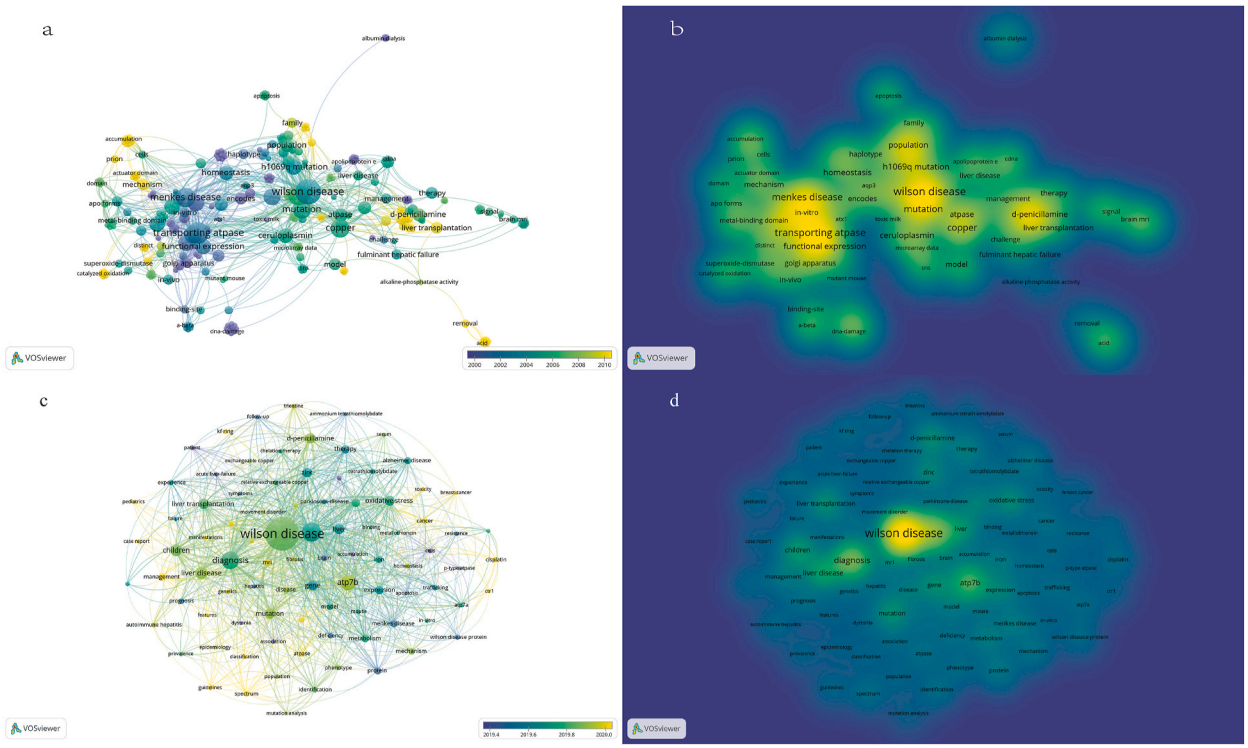

Fig. 8. Network plot of influential keywords in WD research. (a) Overlay visualization among the top 100 most-cited articles, (b) density visualization of (a). (c) Overlay visualization among the latest 5 years articles, (d) density visualization of (c).

were published after 2016. This temporal pattern highlights the importance of recognizing that citation frequency can be influenced by the duration since publication in the field of study. On the same note, the quality and impact of recently published articles will be revealed in the future. For instance, articles published after 2010 have higher citation density, indicating that they have improved quality and their significance is likely to grow in the future. According to the analysis of the keywords in WD-related publications in the last 5 years, topics covered in these articles included copper inspection technique, copper transport mechanism, and WD clinical presentation. However, it is difficult to predict the 20-years impact of an article after its publication [21–23].

Notably, few high-quality recent articles had not accrued sufficient citations to be included in our list, like the article *Copper induces cell death by targeting lipoylated TCA cycle proteins* [3], which reported a new form of cell death, named cuproptosis. These articles are likely to be included shortly, contributing to further WD-related research.

4.3. Distribution of countries and institutions

Analysis of the geographical distribution of these articles indicated that most of the top 100 articles were from Euro-American countries, similar to other research fields. Nearly half of the articles were from the USA. In addition, most of the top 55 academic institutions engaged on WD were from the USA. The most influential author (Prof. Svetlana Lutsenko), the most influential first author (Prof. George J. Brewer), and the most influential corresponding author (Prof. George J. Brewer) were all from the USA. The findings suggest that the USA emerged as the frontrunner in research related to WD. This dominance can be attributed to a variety of factors, which are interconnected and bolster one another.

1 A previous study demonstrated the weak correlation between the per capita gross domestic product (GDP) of a country and its achievement in research [24]. The USA and many other developed countries in Western Europe devote a significant proportion of their GDP to medical research. With sufficient financial support, a robust academic environment, as well as leading research institutions, it is no surprise that these developed countries rank high in the number of publications.
2 Language advantage: native English speakers are more likely to be understood and thus receive more citations. On the same note, their outcomes are more likely to be published in a local journal, especially for American authors [25,26]. When the search on databases was done without language restrictions, we obtained the same 100 top-cited articles, proving that English was the preferred language for worldwide academic communication.
3 The leading countries set the pace in terms of identifying hotspots and thus contribute to the number of publications. Notably, a substantial number of publications in prestigious journals such as *Science*, *Nature,* and *Cell* stem from Euro-American countries, highlighting their significant influence on research.

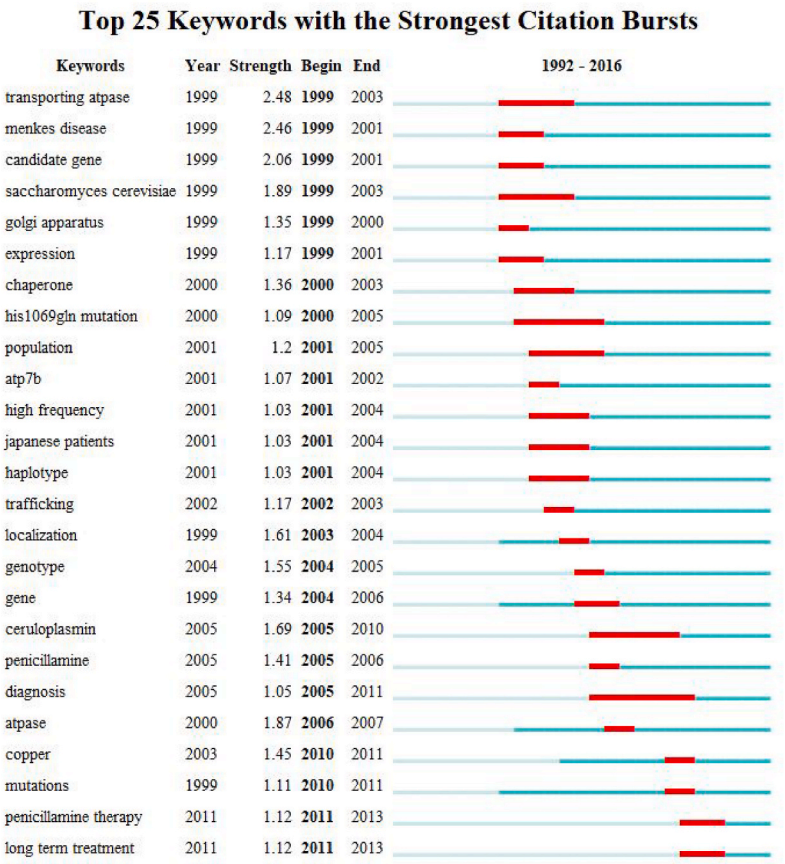

Fig. 9. Top 25 keywords with strongest citation bursts based on Citespace.

4 The USA has a thriving research environment, and this is reflected in the significant number of journals originating from the country. Furthermore, American reviewers exhibit a preference for papers originating from the USA [27].

There were several publications from China, India, Brazil, and Japan suggesting that research on WD is conducted worldwide. Countries and institutes share their scientific accomplishments with the public to allow people to benefit from important findings. Given that, only the first author affiliations were considered, the contribution of Asian countries may be larger than reported. Interestingly, Figs. 3b and 4b show the lack of cooperation between countries and institutions in the research field of WD. The existing cooperation was mainly seen between Western developed countries. Therefore, it is essential to develop strategies to promote global collaboration and enhance the discovery of many unknown aspects of WD.

4.4. Distribution of authors

The majority of authors were both corresponding authors and first authors. Prof. Svetlana Lutsenko took part in the highest number of studies. Her studies were multi-directional, including WD gene expression, copper transport, and the interaction between copper and ATP7B protein. However, Prof. Peter Ferenci had higher cooperation with others, as evidenced by his higher total link strength. As seen in Fig. 5, Prof. George J. Brewer emerged as relatively independent because his research group was predominantly focused on clinical trials rather than mechanistic studies. A few research groups focused on drug trials among the 100 most-cited articles, which might explain why the figure showed no link strength. Furthermore, most of his articles were published in the *Archives of Neurology*, the precursor of *JAMA Neurology*, which mainly published findings from clinical trials. Physicians focused on WD clinical direction might as well design their clinical research based on his publications.

4.5. Analysis of journals and reference

Analysis of article distribution can reveal the top journals in a specific field. Researchers can use this information to select suitable journals to publish their work. The WD-related articles were mainly published in the *Journal of Biological Chemistry*, *PNAS*, *Gastroenterology*, *Hepatology*, *Human Molecular Genetics*, *JAMA Neurology* (used name *Archives of Neurology*), *Nature Genetics*, and *American*

Journal of Human Genetics, and the *Journal of Hepatology*. The distribution of these journals was highly centralized given that 60% of the articles were published in just 9 journals. WD is a hereditary disorder characterized by disruption of copper metabolism primarily impairing liver and brain functions. Articles related to WD were prominently featured in biochemistry, genetics, gastroenterology, and neurology journals. These findings indicate that WD research transcends a single academic field and is truly multidisciplinary in nature. Only 2 publications were published in each of these journals *Cell*, *Nature*, and *Science* and none was published in four major medical journals (BMJ, Lancet, JAMA, and NEJM), which implied that most WD researchers preferred to submit their manuscripts to the most influential journals in their respective fields [28]. However, the review time, rejection rates, page charges, and journal publication frequency may also invariably affect the choice of journals [29,30]. The top five references in terms of citations and centrality were published between 1995 and 2004, and these were related to the pathogenic mechanism of WD. This further demonstrated that basic research is the cornerstone of all translational research.

Distribution of keywords; Keywords provide a summary of the research topic in a given paper, and co-occurrence can indicate the research hotspots for a specific period. The first two most influential keywords, "transporting ATPase" and "ATP7B", exhibited high frequency in recent decades, whereas WD gene location and ATP7B function showed high frequency in the 1990s. The third most influential keyword was "Menkes disease", which together with WD belongs to the class of hereditary human disorders of copper homeostasis. Hence, the pathogenic mechanisms of these two diseases are always explored concurrently. This was also aligned with the researchers' focus on disease identification in the 2000s. Of note, the influential keywords were identified in the most recent 5 years, which showed that researchers tended to focus their research on disease management, WD clinical phenotype, childhood morbidity, the application of MRI in WD, ATP7B gene function, and copper metabolism. The analysis further revealed that research on WD has increased in recent years. Meanwhile, network visualization analysis of keywords in articles published in the past 5 years articles revealed that "copper," "diagnosis," "ATP7B," "liver disease," "gene, mutation," "oxidative stress," "zinc," and "d-penicillamine" were the most influential keywords with high total link strength and occurrence. Combined with the results of the keywords burst and timeline visualization, further investigation into copper metabolism is advocated to identify novel therapies and WD management strategies.

5. Limitations

Although our study provides important findings, several limitations should be acknowledged.

Firstly, bibliometric analysis is more of a "best fit" data set than an "exact science." Moreover, the "best fit" data set relies on interpretation and reiteration to describe the research area while excluding papers of marginal relevance [31]. Therefore, we chose the Web of Science as it is informally considered the most accurate bibliographic source in the world [32].

Secondly, articles were screened and selected based on the citation count. The most recent influential articles were omitted due to insufficient citations owing to their short publication history. Given that the database is constantly updated, the identified top 100 cited articles could change in the future. Hence, it has a bias toward historical articles. Moreover, meetings, books, and reviews were ignored from the analysis, which might cause omission bias.

Thirdly, only articles published in English were collected in this study. The probability of papers being cited varies depending on the language in which they are written. Therefore, we might have overlooked some significant publications that were written in languages other than our own.

In addition, the top 100 articles were published at the beginning of the field, and some of their hypotheses or standards lacked high-quality clinical evidence. In future, researchers should explore the impact and trends of research, instead of the validity or quality of the publication. New analytical strategies, such as calculating citation count in recent years and citation density, which indicate the activeness of an article, should be included in the analysis. It has also been reported that the accurate assessment of an article's true impact and popularity requires a period of at least two decades. The highest citation density tends to appear 3–10 years after publication [33].

6. Conclusions

In conclusion, we identified the 100 top-cited publications in the field of WD research. Our findings contribute to the existing knowledge of WD and reveal discoveries and research trends in this field. The primary outcomes of this study can be summarized as follows: Regarding WD clinical treatment trials, *ATP7B* location and function investigation, and copper transport were the most extensively explored topics. Most publications on WD studies were relatively concentrated on a few journals. The core author groups were formed at the initial stage of the field and author collaborations have been increasing over the years. However, the distribution of geography and institutions was uneven. By promoting communication and collaboration among diverse groups of researchers and investigators, new and efficient management as well as treatment strategies for patients with WD can be developed.

Strengths and limitations of this study

This study used bibliometric data to analyze the characteristics of the 100 most-cited articles in the field of Wilson's Disease (WD) research. This is a novel approach to exploring the scientific literature related to WD research.

We analyzed the characteristics (such as citation count, citation density, first author, corresponding author, journal, country, institution, and keywords) of the 100 top-cited WD articles on basic research, clinical trials, clinical phenotypes, and treatments for WD.

Bibliometric analysis is more of a "best fit" data set than an "exact science." The "best fit" data set is a curated selection of papers that are relevant to the research area. It is created by interpreting and reiterating the finding of other studies, and it excludes papers that are of marginal relevance.

Recent articles that might have significant influence in the field of WD research but have not received sufficient citations were excluded from the analysis, suggesting that this bibliometric analysis has a bias toward historical articles. Moreover, meetings, books, and reviews were not included in the analysis, and this might lead to omission bias.

Author contribution statement

Shan Gao: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data.
Zhenchu Tang, Ziwei Lan: Performed the experiments; Analyzed and interpreted the data; Wrote the paper.
Jing Li: Analyzed and interpreted the data.
Hedong Zhang: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

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Data availability statement

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e17785.

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