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Genome-wide association study in Alzheimer's disease: a bibliometric and visualization analysis

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Background: Thousands of research studies concerning genome-wide association studies (GWAS) in Alzheimer's disease (AD) have been published in the last decades. However, a comprehensive understanding of the current research status and future development trends of GWAS in AD have not been clearly shown. In this study, we tried to gain a systematic overview of GWAS in AD by bibliometric and visualization analysis.

Methods: The literature search terms are: ("genome-wide analysis" or "genome-wide association study" or "whole-genome analysis") AND ("Alzheimer's Disease" or "Alzheimer Disease"). Relevant publications were extracted from the Web of Science Core Collection (WoSCC) database. Collected data were further analyzed using VOSviewer, CiteSpace and R package Bibliometrix. The countries, institutions, authors and scholar collaborations were investigated. The co-citation analysis of publications was visualized. In addition, research hotspots and fronts were examined.

Results: A total of 1,350 publications with 59,818 citations were identified. The number of publications and citations presented a significant rising trend since 2013. The United States was the leading country with an overwhelming number of publications (775) and citations (42,237). The University of Washington and Harvard University were the most prolific institutions with 101 publications each. Bennett DA was the most influential researcher with the highest local H-index. *Neurobiology of Aging* was the journal with the highest number of publications. A β , tau, immunity, microglia and DNA methylation were research hotspots. Disease and causal variants were research fronts.

Conclusion: The most frequently studied AD pathogenesis and research hotspots are (1) A β and tau, (2) immunity and microglia, with *TREM2* as a potential immunotherapy target, and (3) DNA methylation. The research fronts are (1) looking for genetic similarities between AD and other neurological diseases and syndromes, and (2) searching for causal variants of AD. These hotspots suggest noteworthy directions for future studies on AD pathogenesis and genetics, in which basic research regarding immunity is promising for clinical conversion. The current under-researched directions are (1) GWAS in AD biomarkers based on large sample sizes, (2) studies of causal variants of AD, and (3) GWAS in AD based on non-European populations, which need to be strengthened in the future.

KEYWORDS

Alzheimer's disease, genome-wide association study, bibliometric, CiteSpace, VOSviewer

Introduction

Alzheimer's disease (AD) is the most common cause of dementia, with tremendous economic and social burden. About 6.7 million Americans living with AD in 2023 are 65 years and older, and as the aging population increases, the prevalence of dementia is predicted to increase to 131.5 million in 2050 (Anonymous, 2023, p. 1598–1695). With memory and cognitive decline, AD can have a significant negative impact on the patient and family (Hsiao et al., 2018). However, there is still no satisfactory treatment for diagnosed AD (Golde, 2022). Therefore, identifying risk factors and susceptible populations for AD is crucial for targeted interventions.

AD is a genetically complex disorder with an apparent hereditary predisposition, and the heritability factors account for 58–79% of the risk of late-onset AD, and up to 92–100% of the risk of early-onset AD (Sims et al., 2020; Ayodele et al., 2021). Therefore, identifying genetic characteristics not only is essential for fundamentally understanding AD etiology, but also provides with the possibility of early intervention for susceptible populations. Linkage studies have long established *APP*, *PSEN1* and *PSEN2* to cause early-onset AD, while early-onset form only accounts for less than 5% of all AD cases (Ikram and Decarli, 2012). The discovery of *APOEε4* in 1993 denoted the first gene to increase susceptibility for the more common late-onset AD, and *APOEε4* remained the only robustly replicated gene for late-onset AD for almost two decades (Bertram et al., 2010; Serrano-Pozo et al., 2021). However, finding more AD risk variants was difficult due to the limitations of research technology at that time.

In recent years, technological advances have given rise to genome-wide association studies (GWAS) in AD (Andrews et al., 2020). By using high-throughput genotyping and next-generation sequencing, GWAS has made it possible to uncover more AD risk variants (Xiao et al., 2022). GWAS has increased statistical power by adding clinically or pathologically diagnosed cases and controls, and has facilitated the discovery of DNA sequence variations across the human genome (Andrews et al., 2020). By GWAS, single nucleotide polymorphisms (SNPs) that are highly associated with the disease can be identified (Gibson, 2010). Progress in GWAS and global cooperation of genome projects started a new era of exploring AD genetic characteristics and helped us to predict AD occurrence better. Since the first GWAS in AD emerged in 2007, GWAS has facilitated the exploration of the genetic architecture underlying amyloid- β (A β) and tau, and implicated a host of genetic variants associated with A β and tau biological processing (Khani et al., 2022). Meanwhile, a large number of genes involved in physiopathologic processes including cholesterol metabolism (*APOE*, *CLU*, *ABCA7* and *SORL1*), immune response (*CR1*, *CD33*, *MS4A*, *CLU*, *ABCA7* and *EPHA1*), endocytosis (*BINI*, *PICALM*, *CD2AP*, *EPHA1* and *SORL1*) have been proven to be associated with the risk of AD (Ikram and Decarli, 2012; Karch and Goate, 2015). However, among these gene-indicated mechanisms, which are most critical in the AD process remains unknown. In addition, research interests were constantly changing with the development of the discipline. Branches of GWAS such as single-cell genomics, transcriptomics, metabolomics, epigenomics, and the exploration of gene-disease causation have been applied to the genetic exploration of AD. However, the current cutting-edge research directions have not yet been revealed. Therefore, a comprehensive literature analysis of GWAS for the AD field is necessary.

Bibliometrics is a reliable means for literature analysis. It allows quantitative description for publications of a specific field using mathematical and statistical methods, and enables visualization of bibliometric statistics by CiteSpace, VOSviewer and R software. It helps researchers identify research trends, hotspots and critical cooperation networks that collectively guide academic decisions (Ma and Ho, 2016; Chen, 2017). In this study, we drew a whole picture of GWAS in AD from the first publication to 2022 in a bibliometric way, to provide hints for future explorations in this field.

Methods

Data source and search strategies

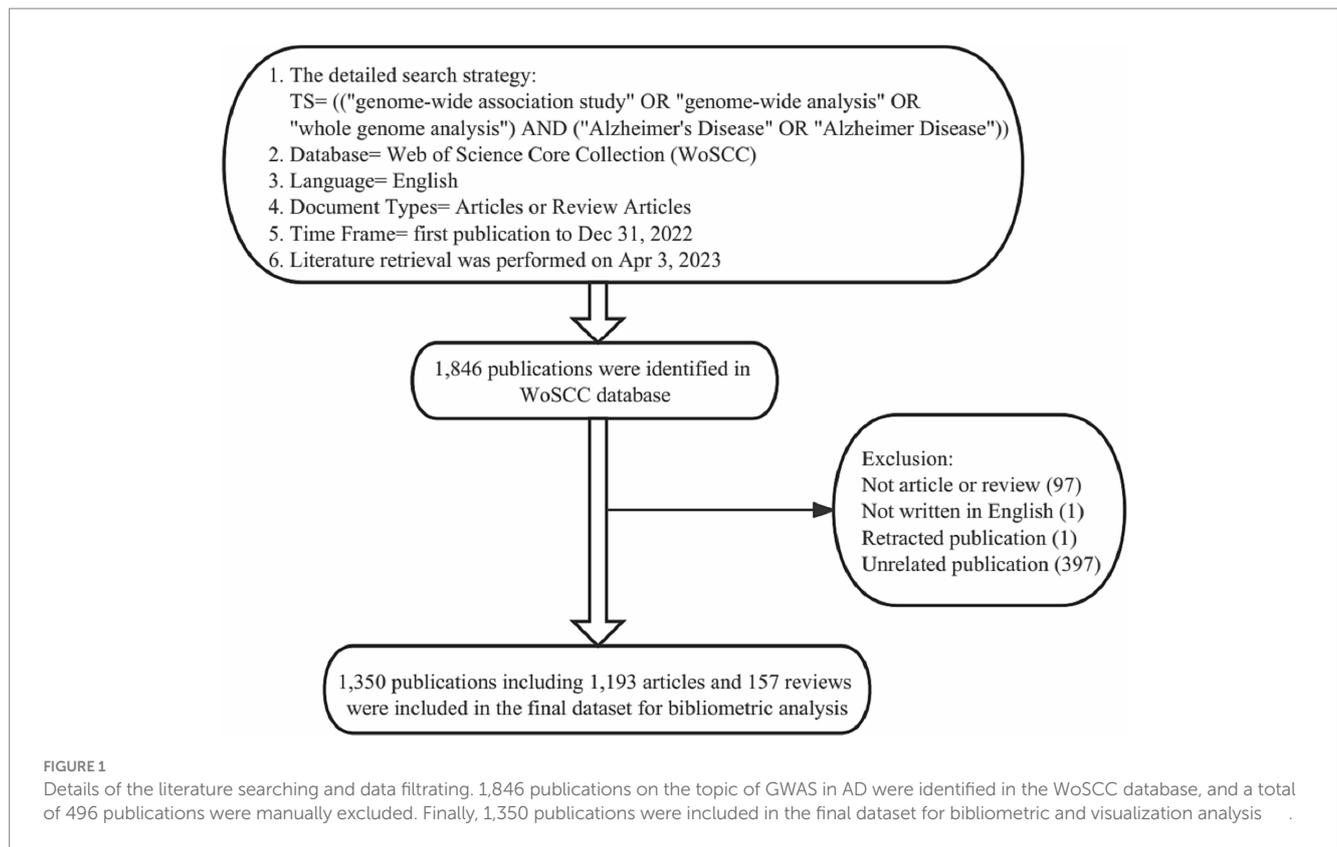
A comprehensive search was performed within the Web of Science Core Collection (WoSCC) database (Clarivate Analytics, Philadelphia, PA, United States) using the following search strategy: TS= (“genome-wide analysis” or “genome-wide association study” or “whole-genome analysis”) AND (“Alzheimer's Disease” or “Alzheimer Disease”), document type= (article or review), and language= English. The time frame was limited from January 1, 2007 to December 31, 2022. All data searches and retrievals were completed in a single day on April 3, 2023, to minimize the bias led by database updates (Figure 1).

Data extraction and screening

All bibliographical information of publications, including publication year, title, author's names, affiliations, nationalities, abstracts, keywords, journal names and citation numbers, were recorded and then converted to text format. Subsequently, the data was imported into Microsoft Excel 2019 (Microsoft Corporation). Non-English publications and duplicate publications were removed. Then two researchers (Junyao Zhang and Yinuo Wang) independently examined and manually excluded the publications unrelated to the topic, 1,221 publications were agreed to meet the inclusion criteria. Then, the third researcher (Yingying Zhang) examined the parts where the other two researchers disagreed (234 publications) and made a final assessment to reach a consensus among researchers. In the end, 1,350 publications (including 1,193 articles and 157 reviews) were included in the final dataset (Figure 1).

Bibliometric analysis

The final dataset was imported into bibliometric software. VOSviewer (version 1.6.18) was used for co-authorship analysis of countries, institutions and researchers, and also used for keyword co-occurrence analysis. CiteSpace (version 5.8.R3) was used for publication co-citation analysis, knowledge base analysis, knowledge flow analysis and burst keyword analysis. R package Bibliometrix (version 4.2.1) was used for the authors' local H-index analysis. In addition, the Microsoft Excel 2019 (Microsoft Corporation) software was used to present global trends of annual publications and citations. SCImago Graphica (version beta 1.0.21) was used for geographic visualization in country co-authorship analysis.



Results

Analysis of global publication output and citation trend

All the 1,350 publications (including 1,193 articles and 157 reviews) were cited 59,818 times from the first publication in 2007 to the end of 2022. The trend of annual publication and citation numbers was generally on the rise. The annual publication number increased rapidly after 2013 and peaked in 2021 with 187 publications. The average number of citations per year increased and maintained at a high level after 2013 (Figure 2).

Distribution of countries and regions

Seventy countries and regions participated in the publication of GWAS in AD. When ranked by the number of publications, the United States was the most productive country with 775 publications cited 42,237 times, followed by China with 309 publications cited 7,259 times, and the United Kingdom with 302 publications cited 25,311 times. The map indicating the contributions of countries or regions in this field is shown in Figure 3A. The top 10 countries with the most significant number of publications are listed in Table 1.

A country co-authorship map is shown in Figure 3B. The United States was the most active country and extensively cooperated with the United Kingdom, China and other countries. European countries also worked closely with each other and contributed a lot in the field of GWAS in AD.

Analysis of the most productive institutions

Overall, a total of 1,819 institutions performed GWAS in AD. As presented in Table 2, both the University of Washington and Harvard University topped the list with 101 publications each, closely followed by Columbia University with 92 publications. Harvard University was the research institution with the highest total citations (6,851 citations), while the University of Washington and Boston University followed with a total citation of 5,817 and 4,715, respectively.

An institution co-authorship map is shown in Figure 4A. Institutions in the United States, like Harvard University, the University of Washington, Columbia University, Rush University and the University of Miami were most active in collaborating with other institutions.

According to the overlay map generated by VOSviewer, the Mayo Clinic, the University of Pittsburgh, the University of Toronto, the University of Miami and the University of California Los Angeles started working on GWAS in AD the earliest. Columbia University, Harvard University, Rush University, the University of Washington, the University of Cambridge and King's College London published the most between 2016 and 2017. Research by Stanford University, the University of Oxford and Duke University were the institutions published the most after 2018 (Figure 4B).

Analysis of the most influential researchers

Local H-index refers to h publications cited at least h times for each paper in a certain field. It is an important index to comprehensively measure the quantity and quality of a researcher's

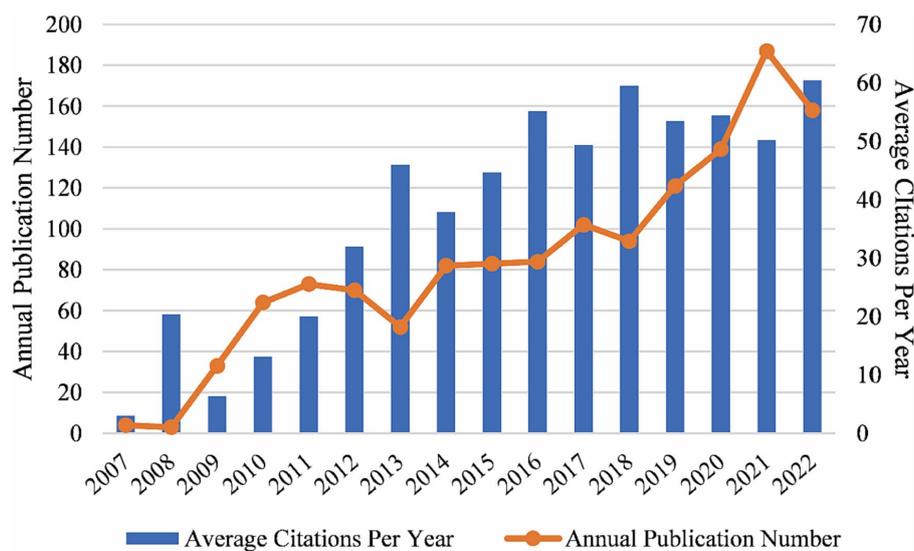


FIGURE 2

Global trends of annual publications and citations on the topic of GWAS in AD from the first publication to 2022, generated by Excel. From 2007 to the end of 2022, the number of publications and citations in this field was generally on the rise.

output. To investigate the most influential researchers, the researchers with the highest H-index were shown. As demonstrated in Figure 5A, Bennett DA, Farrer LA, Mayeux R and De Jager PL were the most influential researchers with high-quality publications in this field.

As indicated by the researcher co-authorship map, Bennett DA, De Jager PL and Saykin AJ were critical researchers and cooperated extensively with others. Researchers from China were in the red cluster, with strong collaborative relationships established with each other, while little collaboration between Chinese researchers and researchers in other countries was observed. And Yu JT and Tan L were influential researchers in this cluster (Figure 5B).

Representative publications and knowledge bases

According to the publication co-citation analysis in Figure 6A, Bertram et al. (2007), Harold et al. (2009), Lambert et al. (2009), Seshadri et al. (2010), Hollingworth et al. (2011), Naj et al. (2011), Guerreiro et al. (2013), and Lambert et al. (2013) were early publications in the field, cited numerous times, these publications could be regarded as roots of the area. Recent work including Jun (2016), Sims et al. (2017), Marioni (2018), Jansen et al. (2019), and Kunkle et al. (2019) were also cited a lot, although it has only been a short time since their publication. The top 10 most-cited publications are listed in Table 3.

In the knowledge base map, articles co-cited by another article had a close academic relationship and were therefore grouped into the same cluster. Tags that represent the knowledge base of the cluster were extracted from the titles of the publications. As demonstrated in Figure 6B, 11 crucial tags were extracted (after removing tags without academic meaning), including #polygenic risk scores, #risk variant, #TREM2, #meta-analysis, #PICALM, #eQTLs, #brain expression, #snRNA-seq, #linkage analysis, #microglia and #Mendelian randomization.

Analysis of prolific journals and knowledge flow

As demonstrated in Table 4, *Neurobiology of Aging* had 105 publications and 2,910 total citations, followed by *J Alzheimer's Disease* with 95 publications cited 1,561 times, *Plos One* with 49 publications cited 2,277 times, and *Alzheimer's & Dementia* with 47 publications cited 1,805 times. Although *Nature Genetics* only had 22 publications, it received an overwhelming 11,327 citations.

To display the evolutionary relationship between citing and cited journals, the knowledge flow overlay map was generated (Chen, 2017). The dots on the left part of the map constitute the citing journals, and the dots on the right include the cited journal. Labels extracted from journal names are linked by lines pointing from the cited journals to the citing journals. As shown in Figure 7, the wide yellow line and the wide pink line were core citation paths, indicating publications in journals of basic science (molecular, biology and genetics) were mainly cited by publications in journals related to basic science (molecular, biology, immunology) and clinical medicine (medicine, medical clinical).

Analysis of essential keywords and hotspots

A co-occurring keyword network based on 4,077 extracted keywords was generated to show the most frequently mentioned keywords. The keywords displayed on the map were divided into four clusters. GWAS terms were in the green cluster, and the pathogenesis of AD (#A β , #tau, #DNA methylation, #microglia, #gene expression, #inflammation) belonged to the red cluster. #genetic association, #protein, #SNP and #population were assigned to the blue cluster. While the most often mentioned genes, including #PICALM, #CLU, #CD33 and #ABCA7, were shown in the yellow cluster (Figure 8A).

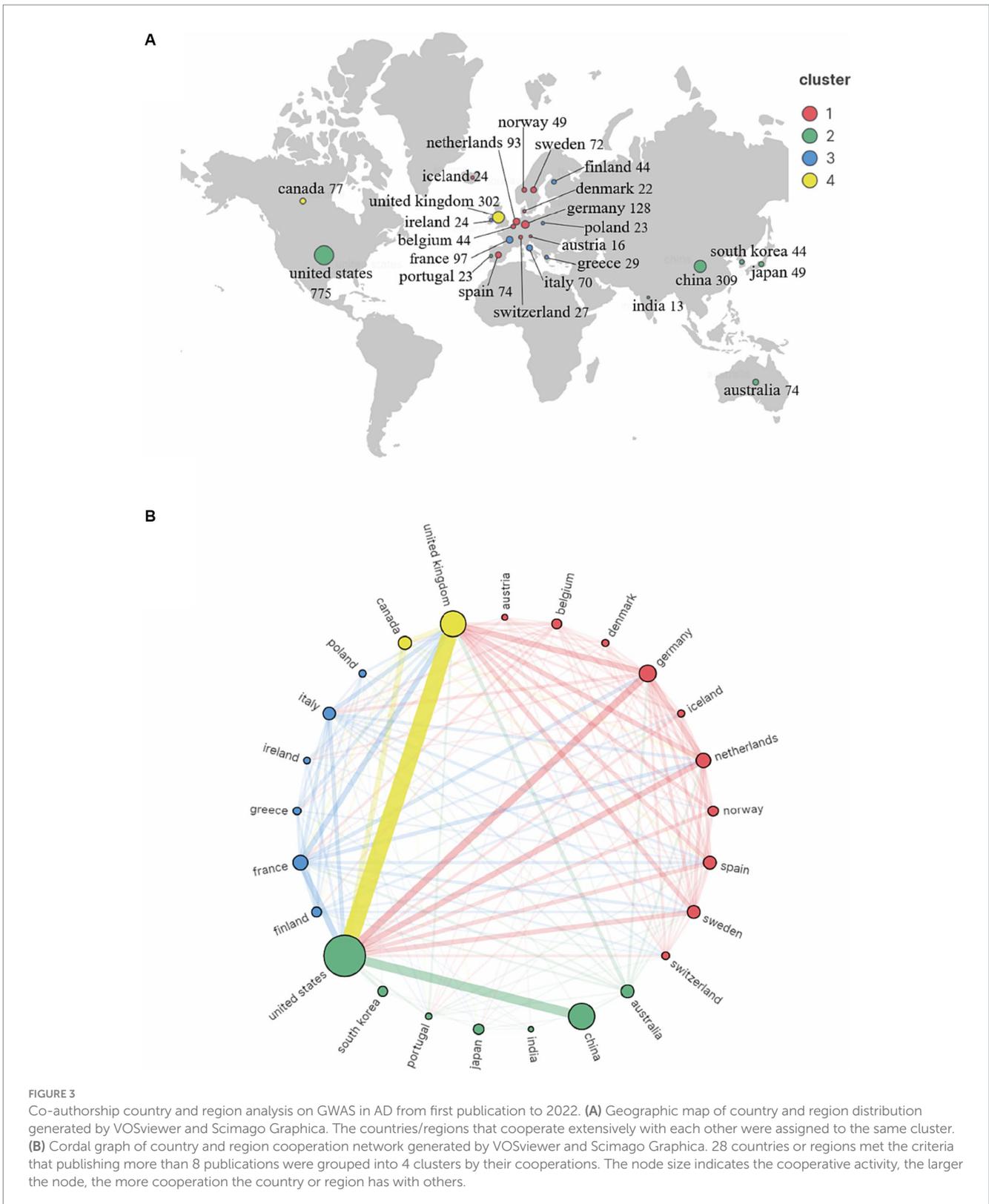


FIGURE 3 Co-authorship country and region analysis on GWAS in AD from first publication to 2022. **(A)** Geographic map of country and region distribution generated by VOSviewer and Scimago Graphica. The countries/regions that cooperate extensively with each other were assigned to the same cluster. **(B)** Cordal graph of country and region cooperation network generated by VOSviewer and Scimago Graphica. 28 countries or regions met the criteria that publishing more than 8 publications were grouped into 4 clusters by their cooperations. The node size indicates the cooperative activity, the larger the node, the more cooperation the country or region has with others.

To visualize the dynamics of frontier topics in the field, the burst analysis of keywords from 2007 to 2022 was performed. The whole segments stand for the time span of each keyword, while the red segments represent sudden increases in the frequency of the keyword occurrence during this period. The burst strength is a statistical value

calculated from the keyword occurrence frequency over time. The top 20 keywords with the strongest bursts are shown in Figure 8B. The keywords #genetic association, #APOE, #late-onset AD, #susceptibility gene, #identifies variant, #CLU, #PICALM, #common variant, #CD2AP, #EPHA1, #CD33 had burst time before 2016. The keywords

TABLE 1 List of top 10 countries/regions.

Country/Region	Publications	Citations	Total Link Strength*
The United States	775	42,237	981
China	309	7,259	207
The United Kingdom	302	25,311	810
Germany	128	15,730	509
France	97	14,893	473
Netherlands	93	12,780	485
Canada	77	12,992	272
Spain	74	11,550	347
Australia	74	4,839	261
Sweden	72	8,481	356

*Total link strength indicates the cooperative activity of the country or region.

TABLE 2 List of top 10 institutions.

Institution	Publications	Citations	Total link strength*
Harvard University	101	6,851	582
The University of Washington	101	5,817	685
Columbia University	92	4,127	606
Boston University	80	4,715	588
The University of Pennsylvania	79	4,303	590
Rush University	71	4,595	535
The University of Miami	67	4,364	509
Indiana University School of Medicine	67	2,752	348
The Mayo Clinic	64	4,550	390
Qingdao University	62	869	84

*Total link strength indicates the cooperative activity of the institution.

#Mendelian randomization, #A β , #UK Biobank, #meta-analysis, #causal association, #causal effect, #disease, #microglia and #sensitivity analysis has become popular since 2020 till now, suggesting the present research fever of the field.

Discussion

Research trend and current profile of GWAS in AD

We investigated 1,350 publications, including original articles and reviews on GWAS in the AD field between 2007 and 2022. Since several small GWAS opened the new era of AD research in 2007, the number of annual publications of GWAS in AD has been generally on the rise, indicating it is an academic concern. There were not many citations in the first few years, while the average citations per year increased and maintained at a high level after 2013 (Figure 2), which suggests that a growing number of high-quality, influential studies

emerged. In 2013, a large-scale GWAS was conducted by the International Genomics of Alzheimer's Project with 11 new AD-associated loci identified, it has been the most-cited publication till now (Lambert et al., 2013). The sample size of GWAS kept expanding in recent years. In 2021, a meta-analysis study including 1,126,563 individuals identified 38 susceptibility loci for the late-onset form of AD, which was the largest GWAS for clinically diagnosed AD to date (Wightman et al., 2021). So far, around 70 loci implicating the risk for AD have been identified by GWAS, providing strong evidence for the genetic pathogenesis of AD.

Then, we got an overview of GWAS in AD by demonstrating the main contributors and their cooperation networks. The highest number of studies was generated by the United States (775), followed by China (309) and the United Kingdom (302). When ranked by total citations, the United States had an overwhelming 42,237 citations, and the United Kingdom ranked second with 25,311 citations. Although China had many publications, the total citations were not high (7,259) (Table 1). The top ten institutions included nine in the United States and one in China (Table 2). The most influential researchers were Bennett DA, Farrer LA, Mayeux R, De Jager PL, Schellenberg GD, Peterson RC, Haines JL and Younkin SG from the United States, Hardy J from the United Kingdom, and Amouyel P from France (Figure 5A). From the results above, it can be found that the United States was the country that had made a remarkable contribution in this field. China has also explored much, but the research quality needs further improvement. The cooperation analysis indicates that researchers in the United States collaborated extensively with researchers in other countries. While researchers from China preferred to establish cooperative relations with domestic rather than international counterparts (Figure 5B). According to Table 4, *Neurobiology of Aging* was the journal that published the most research in this field, and *Nature Genetics* was the authority of this field with the largest number of citations.

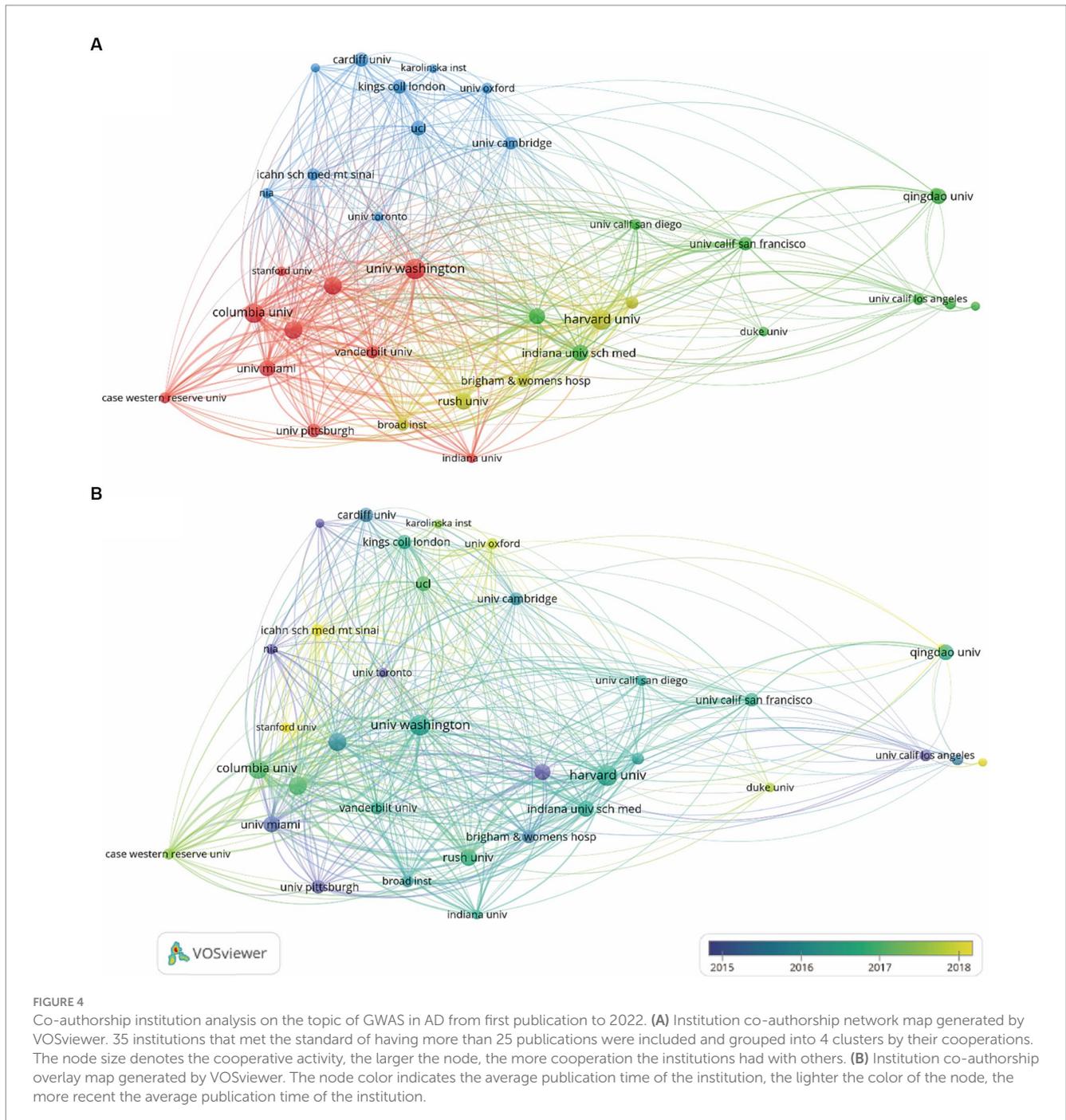
As indicated in Figure 6B, after clustering the co-cited publications, the knowledge base map was generated by extracting words from publication titles. The knowledge bases included #polygenic risk scores, #risk variant, #TREM2, #meta-analysis, #PICALM, #eQTLs, #snRNA-seq, #linkage analysis, #microglia and #Mendelian randomization, which were important words or phrases that summarize the basic concepts underlying the field, including research objects and methods of GWAS in AD.

Knowledge flow analysis is an intuitive way to show the developmental trajectory of research. The cited literature was published earlier, and the citing literature was published later. As Figure 7 demonstrates, the studies were mainly published in journals of basic research (molecular, biology, and genetics) in earlier times. Later studies were published in both journals of basic research (molecular, biology, immunology) and journals of clinical medicine (medicine, medical clinical), reflecting a shift in the research focus from bench to practice over the years.

Research hotspots of AD pathogenesis

A β and tau: pathological biomarkers and the genetic basis

Our keyword analysis revealed that #A β and #tau were frequently mentioned keywords in this field. Extracellular plaques that consist of



A β and intracellular neurofibrillary tangles (NFT) with over-phosphorylated tau protein are the basic pathological features of AD, and are recognized as major players in disease progression (Sierksma et al., 2020).

A β was the most well-studied pathological feature, as indicated by Figure 8A. It had a research fever in recent years (a citation burst from 2020 to 2022, Figure 8B), indicating its core position in AD genetic studies. In A β pathology, altered amyloid precursor protein (APP) metabolism with the overproduction of A β peptides is the primary cause of amyloidosis, and APOE ϵ 4 and ABCA7 were identified to be most strongly associated with A β production (Apostolova et al., 2018). Of all the APOE protein isoforms, APOE ϵ 4 has the strongest

effect on stimulating neuronal A β production by enhancing APP transcription (Huang Y. W. A. et al., 2017). ABCA7 loss of function facilitates the process of APP protein cleaving, leading to rapid accumulation of cortical A β at the early stage of AD (Sakae et al., 2016). Moreover, several GWAS-defined genes linked to endocytosis (BIN1, CD2AP and PICALM) and endosomes (FERMT2 and SORL1) can also modulate APP metabolism and A β production (Dourlen et al., 2019). The dysregulated clearance pathway is another cause of A β accumulation. In normal conditions, LRP1 receptor in neurons is shown to uptake A β -APOE complexes. But when the APOE ϵ 4 variant takes place, the clearance rate is lower. At the same time, PICALM regulates A β clearance across the blood-brain barrier by

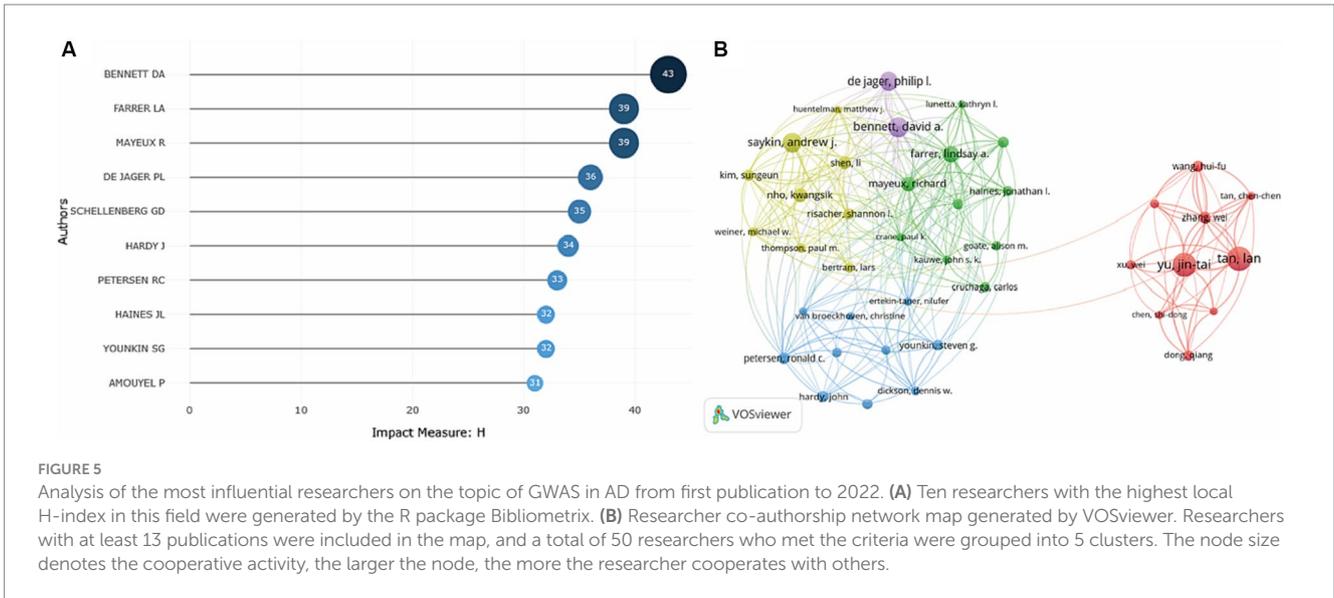


FIGURE 5 Analysis of the most influential researchers on the topic of GWAS in AD from first publication to 2022. **(A)** Ten researchers with the highest local H-index in this field were generated by the R package Bibliometrix. **(B)** Researcher co-authorship network map generated by VOSviewer. Researchers with at least 13 publications were included in the map, and a total of 50 researchers who met the criteria were grouped into 5 clusters. The node size denotes the cooperative activity, the larger the node, the more the researcher cooperates with others.

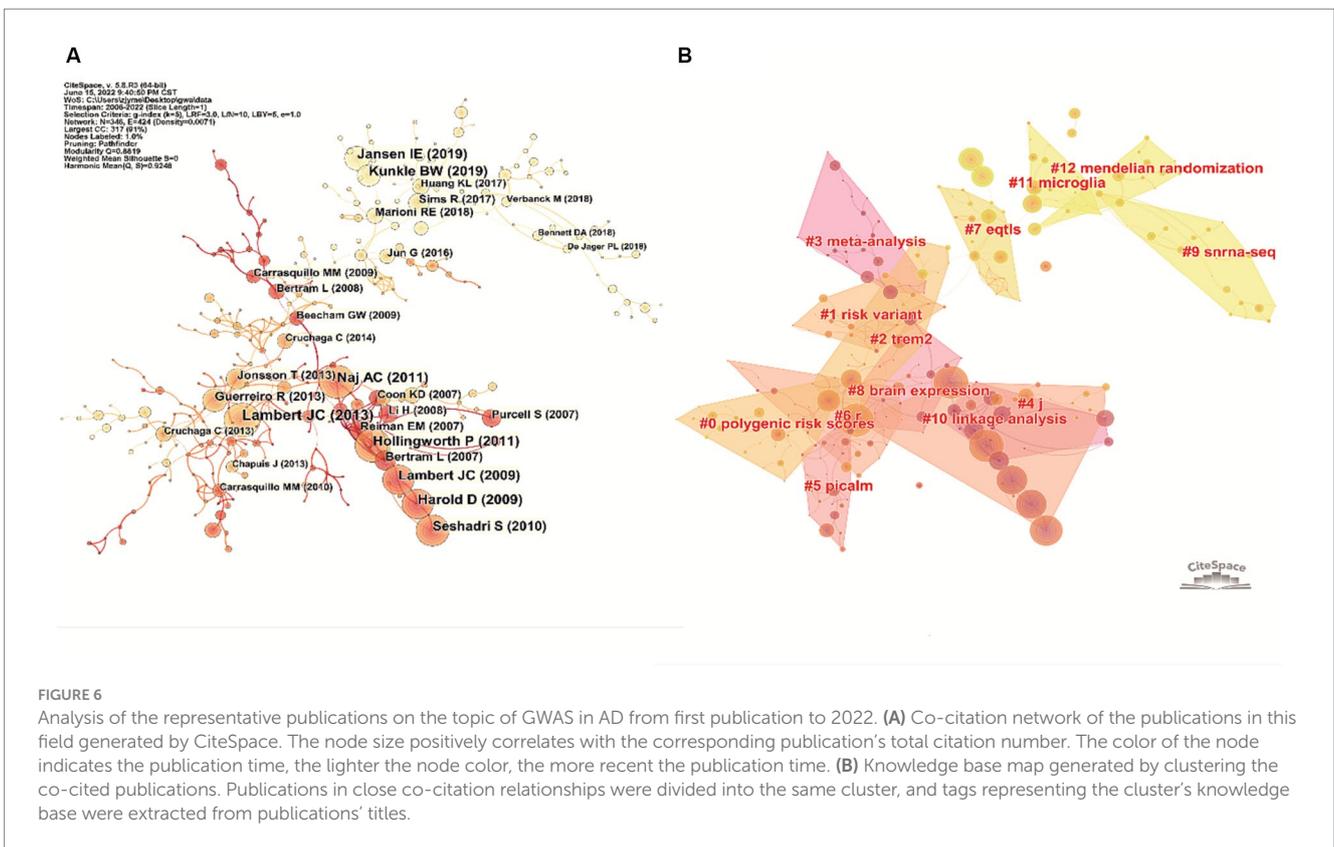


FIGURE 6 Analysis of the representative publications on the topic of GWAS in AD from first publication to 2022. **(A)** Co-citation network of the publications in this field generated by CiteSpace. The node size positively correlates with the corresponding publication's total citation number. The color of the node indicates the publication time, the lighter the node color, the more recent the publication time. **(B)** Knowledge base map generated by clustering the co-cited publications. Publications in close co-citation relationships were divided into the same cluster, and tags representing the cluster's knowledge base were extracted from publications' titles.

internalization and transcytosis, and the variants of *PICALM* disrupt the mechanism (Zhao et al., 2015).

Tau is another essential feature of AD progression. The prevalent notion is that pathological tau is integral for $A\beta$ to exert neurotoxicity (Frost, 2023). A recent study has strongly suggested that tau protein is also an early indicator of preclinical AD, that aggregations of tau protein seem to precede the deposition of $A\beta$ by approximately a decade, and that the location of pathogenic tau, but not $A\beta$, can predict the degeneration of the brain areas in the following 2 years (La Joie et al., 2020). Thus, uncovering the genetic factor associated with

tau pathology is particularly important for intervening in the disease process in the preclinical stage. *BIN1*, the first tau-related AD risk gene, has been the focus of tau pathology. Compiling GWAS evidence indicated that variants in *BIN1* increase AD risk (Kingwell, 2013; Franzmeier et al., 2019), and its variants have been proven to be associated with only tau loads but not $A\beta$ loads in AD brains (Chapuis et al., 2013). Several mechanism studies have reported the protective role of *BIN1*. A study using transgenic mice concludes that *BIN1* overexpression prevents both tau mislocalization and somatic inclusion in the hippocampus and directly binds tau to rescue

TABLE 3 List of 10 most-cited publications.

Author/Year	Title
Lambert et al. (2013)	Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease
Harold et al. (2009)	Genome-wide association study identifies variants at <i>CLU</i> and <i>PICALM</i> associated with Alzheimer's disease
Guerreiro et al. (2013) and Guerreiro et al. (2013)	<i>TREM2</i> variants in Alzheimer's disease
Lambert et al. (2009)	Genome-wide association study identifies variants at <i>CLU</i> and <i>CR1</i> associated with Alzheimer's disease
Hollingsworth et al. (2011)	Common variants at <i>ABCA7</i> , <i>MS4A6A/MS4A4E</i> , <i>EPHA1</i> , <i>CD33</i> and <i>CD2AP</i> are associated with Alzheimer's disease
Naj et al. (2011)	Common variants at <i>MS4A4/MS4A6E</i> , <i>CD2AP</i> , <i>CD33</i> and <i>EPHA1</i> are associated with late-onset Alzheimer's disease
Kunkle et al. (2019)	Genetic meta-analysis of diagnosed Alzheimer's disease identifies new risk loci and implicates A β , tau, immunity and lipid processing
Jansen et al. (2019)	Genome-wide meta-analysis identifies new loci and functional pathways influencing Alzheimer's disease risk
Seshadri et al. (2010) and Seshadri et al. (2010)	Genome-wide analysis of genetic loci associated with Alzheimer disease
Bertram et al. (2007)	Systematic meta-analysis of Alzheimer's disease genetic association studies: the AlzGene database

TABLE 4 List of top 10 journals.

Journals	Publications	Citations
Neurobiology of Aging	105	2,910
J Alzheimer's Disease	95	1,561
Plos One	49	2,277
Alzheimer's and Dementia	47	1,805
Molecular Psychiatry	43	2,267
Translational Psychiatry	30	652
Scientific Reports	28	306
Molecular Neurobiology	27	628
Nature Genetics	22	11,327
Human Molecular Genetics	22	1,151

long-term memory deficits (Sartori et al., 2019). Lower *BIN1* levels promote tau propagation by efficiently increasing endocytosis and endosomal trafficking (Calafate et al., 2016). However, there are opposite opinions that loss of forebrain *BIN1* mitigates tau pathology in the hippocampus and entorhinal/piriform cortex of the tauopathy mice, thus attenuating synapse loss, neuronal death, neuroinflammation and brain atrophy (Ponnusamy et al., 2023). Other genes were also reported to affect tau pathology. *APOE ϵ 4* increases tau phosphorylation and aggregation (Therriault et al., 2020), and *PTK2B* acts as a tau toxicity suppressor (Brody et al., 2022). Although an increasing number of functional studies demonstrated that GWAS-identified AD risk genes are associated with tau pathology, the tau-related genetic profile is less uncovered compared to A β .

In recent years, GWAS based on neuroimaging or cerebrospinal fluid (CSF) A β and tau levels has been conducted. Although in its initial stage, it has identified vital genes associated with A β and tau (Li et al., 2022). Ramanan et al. conducted the first neuroimaging GWAS by integrating positron emission tomography (PET) phenotypes with genetic data, confirming the association of *APOE* and *BCHE* with A β burden (Ramanan et al., 2014). In the latest GWAS of tau-PET, the *APOE* dysfunction is emphasized, and novel loci regulating *VNN2* and *EYA4* are identified (Guo Y. et al., 2022). At present, the sample sizes are relatively small, and large-scale GWAS in AD biomarkers is still lacking.

Immunity and microglia: from genetic implications to clinical conversion

In the field of GWAS in AD, #immunity and #microglia were recurring keywords, suggesting the hotspots of AD mechanism (Figure 8A). It has been reported that the enhancer sequences for the immune process are regions where AD risk loci are preferentially enriched (Gjoneska et al., 2015). Over the years, plenty of GWAS-defined genes participating in the immune process (*APOE*, *TREM2*, *CD33*, *CLU*, *CR1*, *ABCA7*, *EPHA1*, *MS4As*, *INPP5D*, *SPI1*, *PLCG2*, *ABI3*, *HLA-DR15*, etc.) have been reported to be associated to AD (Lambert et al., 2009; Seshadri et al., 2010; Hollingsworth et al., 2011; Reitz et al., 2013; Tan et al., 2013; Deming et al., 2017; Huang K. L. et al., 2017; Sims et al., 2017; Kunkle et al., 2019). Among these genes, *TREM2*, *CD33* and *CLU* were the most studied ones according to Figure 8A. This evidence suggests that immunity is a vital part of AD pathogenesis.

As the most important cells of brain immune surveillance and neuronal support (Chen and Holtzman, 2022), microglia were also the research focus and have become increasingly popular with a citation burst after 2021 in the field (Figures 8A,B). Microglia protects the brain by phagocytosis, A β degradation and anti-inflammatory cytokines secretion under homeostatic conditions, while microglial excessive activation and phenotype conversion in AD brains leads to the release of pro-inflammatory cytokines and complement (Leng and Edison, 2021). Nott et al. identify that common non-coding variants associated with AD risk are enriched in microglial enhancers (Nott et al., 2019). Many AD risk genes involved in immune response and phagocytic function are highly expressed by microglia (Efthymiou and Goate, 2017), suggesting that microglia is the gathering spot of immune function.

The triggering receptor expressed on myeloid cell 2 (*TREM2*) is a microglial receptor encoded by *TREM2*. It is pivotal for maintaining the microglial cell number and function (Zheng et al., 2016). *TREM2* R47H variant has been identified as a risk factor for AD as early as 2013 (Guerreiro et al., 2013), while mechanism studies have implicated that the unwanted mutations in *TREM2* can lead to the reduced protective s*TREM2* release, diminished microglial viability, and subsequent increased A β burden and neuroinflammation (Carmona et al., 2018; Zhao et al., 2018). In contrast to the protective role of *TREM2*, evidence suggests that *CD33* inhibits microglial phagocytosis

reduced tau pathology (Zhu et al., 2022). The other gene, *CLU*, also regulates A β in several dimensions. Its protein product clusterin interferes with A β aggregation by binding with oligomers, regulating A β microglial uptake, and modulating A β transport through the blood–brain barrier. However, whether clusterin–A β aggregation is more toxic than aggregates containing A β alone is controversial, and whether clusterin can promote A β clearance is still unknown (Foster et al., 2019). Although GWAS have suggested that *CR1* and *CLU* are strongly associated with AD, the biological or pathological functions of *CR1* and *CLU* in the pathogenesis of AD are far from clear.

The accumulating genetic evidence by GWAS emphasizes the preponderant role of immunity and microglia in the pathogenesis of AD, which has aroused researchers' interest in mechanism studies concerning AD and immunity. Therefore, we can speculate that immunotherapies may become a promising research direction after the failure of AD therapies targeting A β and tau.

DNA methylation is also one of the hotspots

DNA methylation is the most studied epigenetic mechanism of AD, and detecting DNA methylation by epigenomics has become a branch of AD genetic study. The degree of DNA methylation greatly affects gene expression. DNA hypermethylation often downregulates gene expression, while DNA hypomethylation increases gene expression and functional activation (Younesian et al., 2022). In AD pathology, A β related genes such as *APP*, *PSEN1*, and *BACE1* tend to be DNA hypomethylated (Schrötter et al., 2012), directly resulting in A β plaque overload (De Jager et al., 2014). Besides, several genes are found to be hypermethylated in AD, including *ANK1*, *RPL13*, *RHBDF2*, *DUSP22*, *SORL1*, *ABCA7*, *BIN1*, *SLC24A4*, *HLA-DRB5*, *HOXA*, which are mainly related to A β deposition (Lunnon et al., 2014; Yu et al., 2015; Smith et al., 2018; Min et al., 2021; Nabais et al., 2021). Nowadays, research on epigenomics has become a research hotspot, and studies committed to discovering new DNA methylation sites are rising.

Research fronts in GWAS for the AD field

Figure 8B manifested keywords with a citation burst in recent years (with its burst time followed): A β (2020–2022), UK Biobank (2020–2022), meta-analysis (2020–2022), causal association (2020–2022), causal effect (2020–2022), disease (2020–2022), microglia (2021–2022) and sensitivity analysis (2021–2022), and these keywords indicated the research fronts and future trends of the GWAS in AD field.

Disease (2020–2022)

Diseases or syndromes that have similarities to AD have become the research focus in recent years. According to Figure 8A, diseases including Parkinson's disease (PD) and schizophrenia, and syndrome including mild cognitive impairment (MCI), were common keywords in GWAS for the AD field, suggesting that these diseases or syndrome may partially overlap with genetic features of AD, and searching for genetic similarities of these diseases has become a popular research direction.

MCI due to AD is a stage between healthy aging and dementia, and genetic evidence supports the view that its conversion into dementia is primarily due to the AD pathway. Thus, MCI and AD are often studied in one GWAS as two subgroups (Adams et al., 2015). PD

and AD are both neurodegenerative diseases, and although the clinical presentations are different, finding the genetic similarity of these two types of neurodegenerative diseases has become a new research focus. A large multi-center study identifies that Lewy body dementia shares risk genes and pathways with AD and PD (Chia et al., 2021; Guo P. et al., 2022). Recently, Reginal and colleagues observed a significant local genetic correlation between AD and PD in the *PBK* and *SCARA5* genic regions (Reynolds et al., 2023). Meanwhile, Raffaele et al. reported SNPs within *HLA*, *MAPT* and *APOE* regions jointly contributing to increased risk for AD or PD (Ferrari et al., 2017). In addition, schizophrenia is also investigated considering psychotic symptoms are present in approximately 50% of AD individuals (Murray et al., 2014). Several SNPs are reported to show the same effect on schizophrenia and AD with psychotic symptoms, indicating the genetic connectivity between AD and schizophrenia (Alfimova et al., 2019).

Causal association (2020–2022) and causal effect (2020–2022)

GWAS uncovers the association of many genetic loci with traits and diseases. However, even the variants most strongly associated with AD are not necessarily causal (Andrews et al., 2020). In recent years, pinpointing AD causal risk genes has been a trendy topic. The development of fine mapping and gene prioritization enables researchers to determine whether the loci-trait is causal to the phenotype (Broekema et al., 2020). Amlie-Wolf et al. applied fine-mapping approaches in their study and identified candidate causal variants in four genes: *EPHA1*, *CD33*, *BIN1* and *CD2AP* (Amlie-Wolf et al., 2018). Corces et al. nominates multiple AD risk variants that may be causal, including variants in the *MS4A* and *BIN1* loci (Corces et al., 2020). Recent research by Schwartzentruber suggests that *CCDC6*, *TSPAN14*, *NCK2*, *SPRED2*, *BIN1*, *APH1B*, *PTK2B*, *PILRA* and *CASS4* are likely causal genes of AD (Schwartzentruber et al., 2021). Not much research has been done on causal variants of AD so far, and there is still a long way to go.

Other research fronts

UK Biobank (2020–2022) is a biomedical database containing half a million volunteers' genetic and health information (Littlejohns et al., 2020). UK Biobank is the basis of many large-scale GWAS due to its unparalleled resources, significantly prompting AD genetic research. UK Biobank samples are almost entirely from the United Kingdom, which reflects that GWAS are based on specific regions and ethnicities. To some extent, European ancestry is overrepresented in genetic studies, and data based on other regions or ethnicities are relatively scarce, despite African Americans and Hispanic Americans being more likely to develop AD in the same community (Andrews et al., 2023).

As GWAS continues to evolve, some methodologies have also been developed. Mendelian randomization (2020–2022) is a statistical method based on GWAS, which is used to infer causal associations between exposures and disease outcomes using genetic variants. Mendelian randomization can effectively reduce confounding bias due to the advantage of alleles being randomly assigned to offspring. Meanwhile, sensitivity analysis (2021–2022) is a way to assess the reliability of conclusions obtained from Mendelian randomization studies and further enhance the studies' credibility. In recent years, Mendelian randomization and sensitivity analysis have become cutting-edge methods frequently used in AD genetic studies.

Limitations

There are certain limitations to our study. Only references in the WoSCC database and publications written in English were included in our study owing to the nature of bibliometric software. The publications we included in this work were selected by database retrieval as well as manual screening, and therefore have an unavoidable subjective judgment bias. Although we covered a majority of publications, the study cannot fully describe the bibliometric information of the field.

Conclusion

This bibliometric and visualization study demonstrates what GWAS in AD is like, what it tells us, and where it is headed. According to our bibliometric analysis, the most concerned AD pathogenesis and current research hotspots were (1) A β and tau, (2) immunity and microglia, with *TREM2* as a potential immunotherapy target, and (3) DNA methylation. The important pathogenesis implied by genetic studies is valuable for future mechanism studies and clinical conversion. The research fronts were (1) looking for genetic similarities between AD and other neurological diseases and syndromes, and (2) searching for causal variants of AD. Current weaknesses of the discipline are (1) GWAS in AD biomarkers based on relatively large sample sizes are scarce, (2) studies of causal variants of AD are few, and (3) GWAS in AD based on non-European populations are inadequate. It is necessary to pay more attention to these under-researched directions in the future. Our study provides a comprehensive view of GWAS in AD. Researchers new to the field can easily obtain useful information from our research and better investigate the genetic etiology of AD.

Data availability statement

The original contributions presented in the study are included in the article/[Supplementary material](#), further inquiries can be directed to the corresponding author.

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JZ: Conceptualization, Data curation, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing. YW: Data curation, Methodology, Writing – original draft. YZ: Data curation, Methodology, Writing – review & editing. JY: Conceptualization, Funding acquisition, Investigation, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fnagi.2023.1290657/full#supplementary-material>

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