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ORIGINAL RESEARCH

Bibliometric and Visual Analysis of Alzheimer's Disease and Herpes Simplex Virus Type 1 Infection Between 1990 and 2024

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Background: Recently, some studies suggested that Herpes simplex virus type 1 (HSV-1) infection is an important environmental factor for Alzheimer's disease(AD). The literature on research about HSV-1 infection and AD is emerging. This study used the bibliometric method to investigate the relationship between HSV-1 infection and AD.

Methods: We searched the Web of Science Core Collection for relevant literature on AD and HSV-1 from 1990 to 2024. Bibliometric and visualization analyses were performed using VOSviewer and CiteSpace.

Results: From 1990 to 2024, the number of publications showed an increasing trend. The United States made the largest contributions in productivity. The University of Manchester was the most productive organization. Professor Ruth F. Itzhaki was the most influential researcher. The Journal of Alzheimer's Disease had published the most articles. Research on the mechanisms by which HSV infection contributes to AD remains a hotspot in the field, and future studies may further focus on antiviral therapeutic strategies targeting HSV-1 infection.

Conclusion: Our analysis provides basic information about research in AD and HSV-1. The current research hotspots in this field mainly include the mechanism of AD caused by HSV-1, and antiviral drugs to treat or prevent AD.

Keywords: Alzheimer's disease, Herpes simplex virus type 1, bibliometric, visualized analysis, VOSviewer, citespace

Introduction

Alzheimer's disease (AD) is a widespread form of cognitive impairment, according to the Alzheimer's Association, the number of AD patients worldwide is projected to reach approximately 14 million by 2060.[1] Since its discovery in 1906, AD has received extensive attention from researchers. However, its pathogenesis is complex, and the exact mechanism has yet to be fully elucidated. The main pathological features of AD involve the formation of amyloid plaques by beta-amyloid (Aβ) and the development of neurofibrillary tangles (NFTs) due to hyperphosphorylated Tau protein. In AD, impaired clearance leads to Aβ accumulation. Aβ oligomers disrupt synaptic plasticity, trigger neuroinflammation,[2,3] and promote Tau hyperphosphorylation, forming NFTs.[4] Ultimately, these processes result in synaptic loss, neuronal death, and cognitive decline. Tau protein hyperphosphorylation leads to the formation of NFTs, disrupting microtubule stability, synaptic function, and neuronal survival, ultimately resulting in cognitive decline.[5–7] This process is one of the core mechanisms of AD pathology and, together with Aβ pathology, drives disease progression.In addition to the previously proposed amyloid hypothesis, it is also believed to be associated with genetic factors, lifestyle, environmental factors, and gut microbiota, among others.[8,9] The apolipoprotein E ε4 allele (APOE-ε4) promotes disease progression by impairing Aβ clearance and exacerbating Tau pathology,[10,11] while mutations in APP,

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PSEN1, and PSEN2 increase Aβ production and deposition.[12] Additionally, environmental factors such as diet and physical activity significantly influence the onset and progression of AD by modulating oxidative stress (OS), inflammation, and Aβ accumulation.[13,14] The exact cause of AD remains unknown. Emerging theories suggest that infections caused by bacteria, viruses, or parasites may play a role in AD pathogenesis.[15–19]

Herpes simplex virus type 1 (HSV-1) is a double-stranded DNA virus belonging to the α-herpesvirus family, primarily transmitted through direct contact with infected saliva or herpetic fluid, and characterized by its ability to establish latent infections and undergo reactivation.[20] According to 2020 global estimates, the prevalence of HSV-1 infection among individuals aged 15–49 years was approximately 66.6% (3.7356 billion people).[21] Primary HSV-1 infection typically occurs during childhood and may present as oral herpes or remain asymptomatic. Following primary infection, the virus establishes a lifelong latency in the sensory neurons of the trigeminal ganglion.[22] Under certain conditions such as psychological stress, physical trauma, or immunosuppression, latent HSV-1 can be reactivated.[23] Emerging evidence suggests that recurrent HSV-1 infections in the central nervous system (CNS) and their cumulative neurotoxic effects may lead to progressive neuronal damage, resembling the pathological changes observed in AD.[24]

Research has shown that HSV-1 can be detected in the brain tissues of both AD patients and normal elderly individuals, with a positive correlation between herpes virus load in the brain and the severity of dementia.[25–27] Reactivation of HSV-1 can induce neuroinflammatory responses and OS, thereby promoting the production and deposition of Aβ.[28,29] Notably, although HSV-1 infection is detectable in normal elderly populations, they do not exhibit clinical symptoms, which may be related to the absence of the AD risk gene APOE-ε4.[30,31] Carriers of the APOE-ε4 allele are more susceptible to HSV-1 induced neuronal damage due to their impaired Aβ clearance capacity, which significantly increases their risk of developing AD. Further studies using human brain tissue models have confirmed that repetitive injury can lead to HSV-1 reactivation and induce the production of AD-related pathological phenotypes.[32] This finding suggests that the APOE-ε4 allele may contribute to the pathogenesis of AD by potentiating the neurotoxic effects of HSV-1 reactivation. In recent years, significant progress has been made in understanding the relationship between AD and HSV-1, resulting in a wealth of literature. However, there remains a paucity of systematic organization and quantitative analysis of research in this field. Conducting such studies will help comprehensively understand the current state of development, identify research hotspots, and provide important references for future research directions.

Bibliometrics as an interdisciplinary research methodology, employs mathematical and statistical approaches to quantitatively analyze knowledge carriers, thereby elucidating the relationships among disciplines, research fields, scientific publications, and authors.[33,34] This methodology has been extensively applied in both domestic and international contexts, demonstrating its effectiveness in analyzing the current research status and predicting future development trends across various disciplines.[35] Among the most widely utilized visualization tools in bibliometric analysis are CiteSpace and VOSviewer, which have been extensively employed in scientific mapping and knowledge domain visualization.[36–38]

In this study, we utilized VOSviewer v1.6.18, developed by the Centre for Science and Technology Studies at Leiden University in the Netherlands,[38] and CiteSpace R6.4.R1, developed by Professor Chao-Mei Chen,[39] to systematically analyze research on AD and HSV-1. Our objective is to elucidate the current knowledge structure and identify potential future research trajectories in this field.

Materials and Methods

Literature Data Sources and Inclusion

The Web of Science Core Collection (WoSCC), recognized as a premier digital repository for scientific literature, has gained widespread acceptance among researchers and is widely regarded as the most reliable database for conducting bibliometric analyses.[40,41] On June 1, 2024, we gathered bibliographic data from the WoSCC database using the search string: TS= ["Alzheimer's disease"] AND TS= ["HSV-1" OR "Herpes simplex virus type 1"] to select SCI-E documents published from 1990–01-01 to 2024–06-01, including original research articles and reviews, written in English. However, it should be noted that data retrieved from the database may contain certain limitations, particularly regarding thematic relevance and accuracy. To mitigate potential biases arising from data quality issues and ensure the validity of subsequent

analyses, we implemented a two-stage screening process: we utilized the advanced filtering functions of WoSCC for initial data purification, followed by manual removal of documents with insufficient thematic relevance. The retrieved documents' full records and cited references were saved as a "TXT" file, suitable for VOSviewer and CiteSpace software.

Data Analysis and Visualization

Use "thesaurus_terms.txt" in VOSviewer to create thesaurus files to disambiguation, such as merged "AD" and "Alzheimer's disease", "HSV-1" and "Herpes simplex virus type 1", "amyloid beta" and "Aβ", "apolipoprotein e4" and "APOE-ε4", "wozniak, matthew a" and "wozniak, ma", "harvard med sch" and "harvard univ" in term analysis. The VOSviewer software is utilized to analyze information from articles regarding authors, source journals, institutions, countries, and cited literature. In the visual network graph, the color of an element indicates the cluster it belongs to. The size of a node represents the frequency of occurrence of a particular knowledge unit, and the strength of the links between nodes represents the relevance of the units. Use keyword bursts in CiteSpace software to study changes in research hot spots in the field. The burst detection analysis was conducted with a minimum duration of 1 year to identify statistically significant keyword bursts. The blue line denotes the time axis, while the red segment on the blue time axis indicates burst detection, showing the start year, end year, and burst duration.

Results

General Data

A total of 333 relevant publications focusing on the relationship between AD and HSV-1 were identified in the WoSCC database spanning the period from 1990 to 2024. Following the application of rigorous inclusion criteria, which restricted the search to peer-reviewed original research articles and review articles published in English while excluding irrelevant documents and noise words, 287 qualified publications were ultimately retrieved, comprising 215 original research articles and 72 comprehensive reviews. Statistical analysis revealed a significant upward trend in publication output over the study period, as illustrated in Figure 1.

Top Contributing Countries/ Regions

Publications were collected from 49 countries and regions. The United States was the most productive country, with 90 articles published, representing 31.36% of the total productivity. Subsequent leading contributors included England (53, 18.47%), Italy (40, 13.94%), China (31, 10.80%), and Spain (23, 8.01%), collectively representing a substantial portion of the global research output (Figure 2).

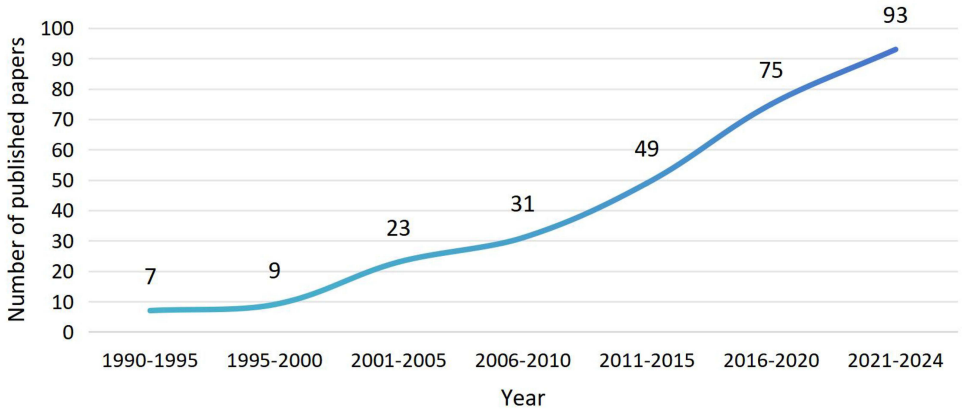

Figure 1 Trends of the number of published articles on HSV-1 and AD from 1990 to 2024.

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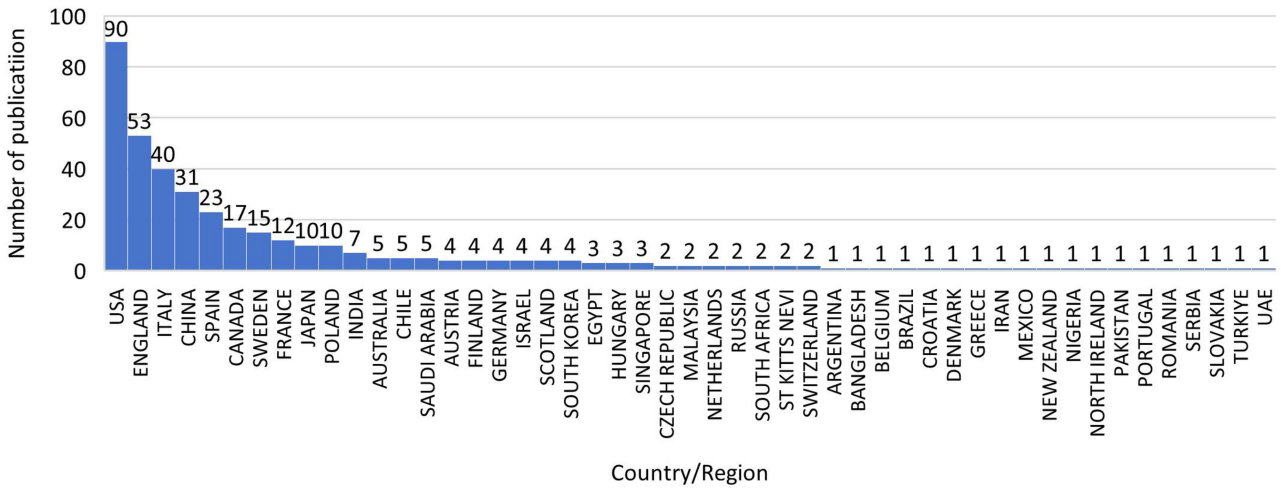

Figure 2 The country/regions where the article was published and the number of publications on HSV-1 and AD.

Top Productive Institutions

A total of 458 institutions have contributed to research on AD and HSV-1, with the University of Manchester emerging as the most productive institution (n=31), followed by the University of Autonoma Madrid. Furthermore, the University of Manchester demonstrated the highest citation impact, indicating the significant influence and recognition of its research contributions in this field (Figure 3).

Top Contributing and Co-Cited Journals

Between 1990 and 2024, 153 journals published articles about HSV-1 and AD. The Journal of Alzheimer's Disease emerged as the most prolific publisher with 38 articles, followed by Neurobiology of Aging with 11 articles (Table 1). In the research field under investigation, the majority of articles are published in Q1 and Q2 journals. These journals in the Q1 and Q2 zones have demonstrated outstanding performance in many dimensions, such as the impact factor, citation frequency, and academic reputation. It can be seen that most articles in this field possess a high academic standard. Citation analysis identified the Journal of Virology as the most frequently cited source (n=986 citations), followed by the Journal of Alzheimer's Disease (Table 2). Figure 4 presents the density visualization of the journal co-citation network,

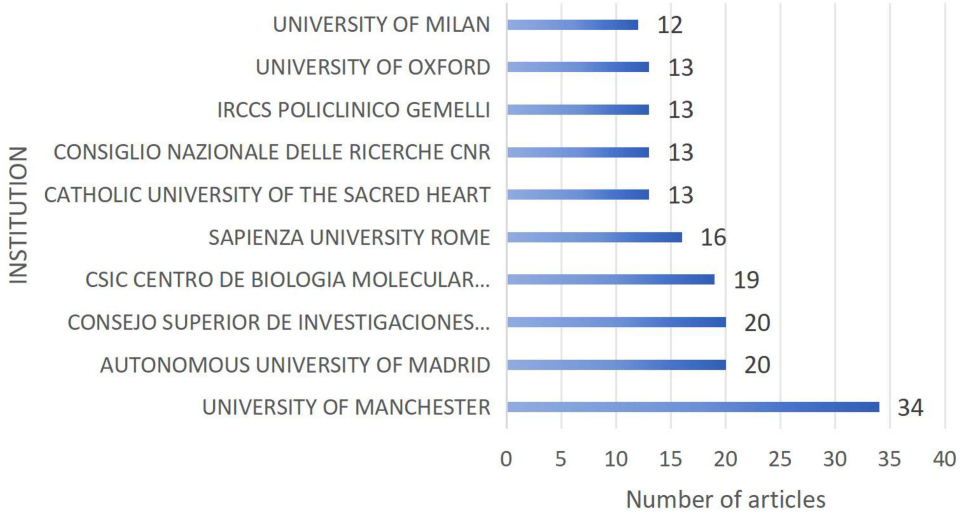

Figure 3 The top 10 productive institutions on HSV-1 and AD.

Table 1 The Top 5 Journals With the Highest Number of Published Articles

Rank	Journal	Document
1	Journal of alzheimer's disease	38
2	Neurobiology of aging	11
3	Frontiers in aging neuroscience	9
4	PLoS one	9
5	Alzheimers & dementia	8

Table 2 The Top 5 Journals With the Highest Number of Citations

Rank	Journal	Citations
1	The Journal of Virology	986
2	Journal of alzheimer's disease	913
3	PLoS one	438
4	Neurobiology of Aging	596
5	Proceedings of the National Academy of Sciences of the United States of America	544

highlighting the Journal of Alzheimer's Disease and the Journal of Virology as the most influential knowledge sources in this research domain.

Top Contributing and Co-Cited Authors

A total of 1233 authors contributed to the research, with 12 authors having more than 10 articles in the field. The primary research foci of these prolific authors encompass virology, infectious diseases, and neurodegenerative disorders (ND), reflecting the interdisciplinary nature of this research field. Figure 5a presents the scientific collaboration network among researchers investigating the HSV-1 and AD relationship. The network visualization specifically highlights collaborative patterns among 36 highly productive authors, each having contributed a minimum of 5 publications to this research area. Figure 5b further presents the co-citation network of authors across a series of publications. Based on the information in

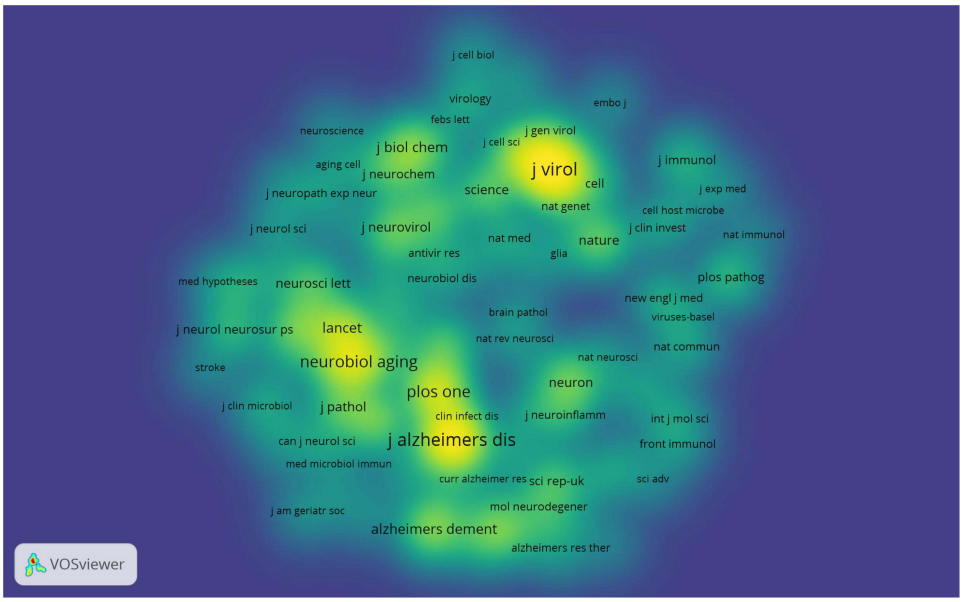

Figure 4 The density visualization of the journal co-citation network. The nodes represent journals and the closer it is to yellow, the more co-citations of journals.

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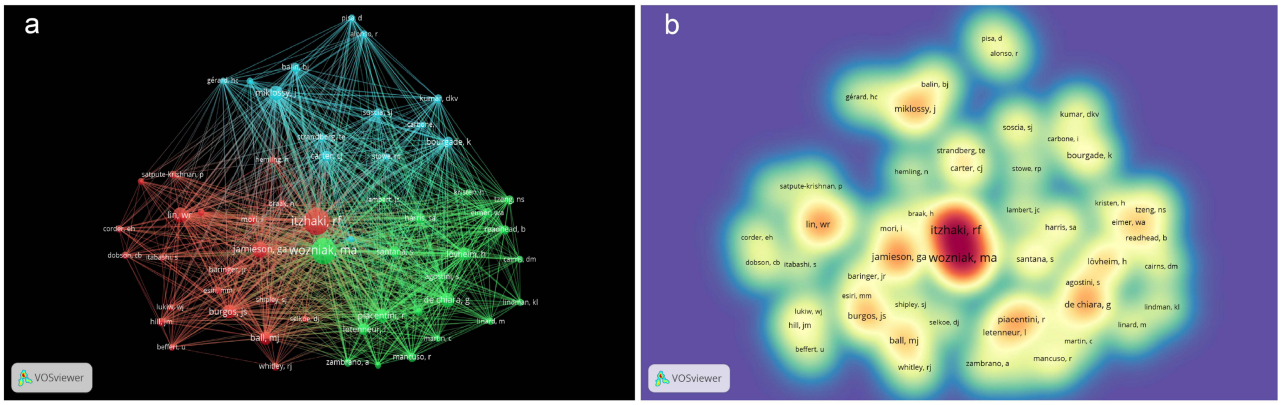

Figure 5 The co-occurrence map of authors on HSV-1 and AD. (**a**) Author production co-occurrence network in HSV-1 and AD-related fields. The nodes represent authors and the larger the size of the node, the more citations of authors. The links between nodes represent the co-cited relationship between authors. The thickness of links represents the frequency of the co-cited relationship between authors.(**b**) The density map of co-cited authors on HSV-1 and AD. The nodes represent authors and the higher the author's weight, the closer it is to red.

Table 3, which lists the top five authors by the number of publications, it can be concluded that Ruth Itzhaki is the most influential authority in this field. Her seminal research contributions have primarily focused on elucidating the etiological mechanisms and pathogenic processes underlying AD, with particular emphasis on its association with viral infections. Professor Itzhaki not only leads in publication output but also dominates citation metrics, highlighting her outstanding contributions and academic standing in this field.

Co-Citation Analysis of References

A total of 14007 references were cited in the field of HSV-1 and AD, Table 4 illustrates the top 10 most co-cited references. The most frequently co-cited article, "The risk of herpes simplex virus type 1 and Alzheimer's disease in the brain", was published in The Lancet (IF=98.4, Q1), one of the world's most prestigious medical journals, underscoring its exceptional academic impact. The article concludes that the co-occurrence of HSV-1 cerebral infection and APOE-ε4 allele carriage constitutes a significant risk factor for AD development, providing crucial insights into the disease's etiopathogenesis.

Table 3 The Top 5 Authors With the Highest Number of Published Articles

Rank	Author	Document	Affiliation
1	Ruth F. Itzhaki	32	University of Oxford/University of Manchester
2	Wozniak,MA	15	University of Manchester
3	Giovanni De Chiara	14	Sapienza University Rome
4	Palamara, Anna Teresa	13	Sapienza University Rome
5	Roberta Mancuso	13	Regis University/University of Milan

Table 4 The Top 10 Papers With the Highest Number of Citations

Rank	Title	First Author	Citations	Journal
1	Herpes simplex virus type 1 in brain and risk of Alzheimer's disease.	Ruth F. Itzhaki	153	The Lancet
2	Herpes simplex virus type 1 DNA is located within Alzheimer's disease amyloid plaques	Wozniak,MA	111	Journal of Pathology
3	Herpes simplex virus infection causes cellular beta-amyloid accumulation and secretase upregulation	Wozniak,MA	110	Neuroscience Letters

(*Continued*)

Table 4 (Continued).

Rank	Title	First Author	Citations	Journal
4	Latent herpes simplex virus type I in normal and Alzheimer's disease brains	Gordon. Jamieson	98	Journal of Medical Virology
5	Seropositivity to herpes simplex virus antibodies and risk of Alzheimer's disease: a population-based cohort study	Letenneur l	83	PLoS one
6	Alzheimer's disease-specific tau phosphorylation is induced by herpes simplex virus type 1	Wozniak,MA	67	Journal of Alzheimer's Disease
7	Productive herpes simplex virus in brain of elderly normal subjects and Alzheimer's disease patients	Wozniak, MA	66	Journal of Medical Virology
8	Limbic Predilection in Alzheimer Dementia: Is Reactivated Herpesvirus Involved?	Ball MJ	65	Canadian Journal of Neurological Sciences
9	Herpes simplex virus type I DNA is present in specific regions of brain from aged people with and without senile dementia of the Alzheimer type.	Gordon.Jamieson	62	Journal of Pathology
10	Multiscale Analysis of Independent Alzheimer's Cohorts Finds Disruption of Molecular, Genetic, and Clinical Networks by Human Herpesvirus	Ben Readhead	61	Neuron

Analysis of Keywords

Keywords are a crucial component of academic papers, succinctly encapsulating the topic's essence and aiding the reader in comprehending the main content of the paper. Analyzing keywords can identify research hotspots,[42] we use "keyword co-occurrence" in VOSviewer and "keyword burst" in CiteSpace to implement keyword clustering analysis and observe research hotspot changes. Then, 22 out of 1515 keywords with a frequency of 15 or more were extracted and analyzed by VOSviewer software. The top 10 most frequently used keywords included "herpes simplex virus type 1", "Alzheimer's disease", "brain", "infection", "amyloid", "apoe", "risk", "central nervous system", and "neurodegenerative disease". The network visualization of keyword co-occurrence is shown in Figure 6a. The 22 core keywords were classified into four clusters. Cluster 1 (red color) focuses on how HSV-1 infection influences the accumulation of Aβ and tau proteins, thereby promoting the pathological progression of AD. Cluster 2 (green color) focuses on the epidemiological and biological associations between HSV-1 infection and AD. Cluster 3 (blue color) focuses on the interaction between the APOE gene and HSV-1 infection, as well as their combined impact on AD. Cluster 4 (yellow color) focuses on the infection of the central nervous system by HSV-1 and other pathogens, as well as their relationship with Mild Cognitive Impairment (MCI) and AD.

Figure 6b mainly shows the temporal trend of keyword co-occurrence, from the evolution of keywords, the research trajectory has shifted from direct links between HSV-1 infection and AD pathology (eg, NFTs, amyloid precursor protein(APP)) to broader mechanisms (eg, neuroinflammation, blood-brain barrier(BBB) dysfunction) and epidemiological connections (eg, infection, risk factors). The scope has expanded from HSV-1 alone to its interactions with other viruses and its role in neurodegenerative diseases. This reflects a deeper understanding of HSV-1-AD relationships, emphasizing multifactorial and multi-mechanistic interactions in disease pathogenesis. Future research hotspots are likely to focus on antiviral therapy, therapeutic targets, and multifactorial mechanisms of action.

Figure 6c illustrates the temporal evolution of research priorities in HSV-1 and AD. It highlights the top 25 most cited keywords. Among these, "mild cognitive impairment" was the most frequently mentioned keyword (n=9.32), followed by "risk" (n=6.86) and "polymerase chain reaction" (n=6.45). Presently, the commonly used keywords include "HSV-1", "risk" and "cytomegalovirus infection". Based on Figure 6c, we can speculate that the changes in research hotspots can be divided into three phases. The initial phase of research primarily focuses on utilizing PCR technology to detect the presence of viruses such as HSV-1 in brain tissue, exploring their potential association with neurological diseases. Preliminary studies suggest that HSV-1 infection may be linked to ND such as dementia (1991–2005). In the second phase, research has progressively delved into the molecular mechanisms, with a particular focus on how HSV-1 infection

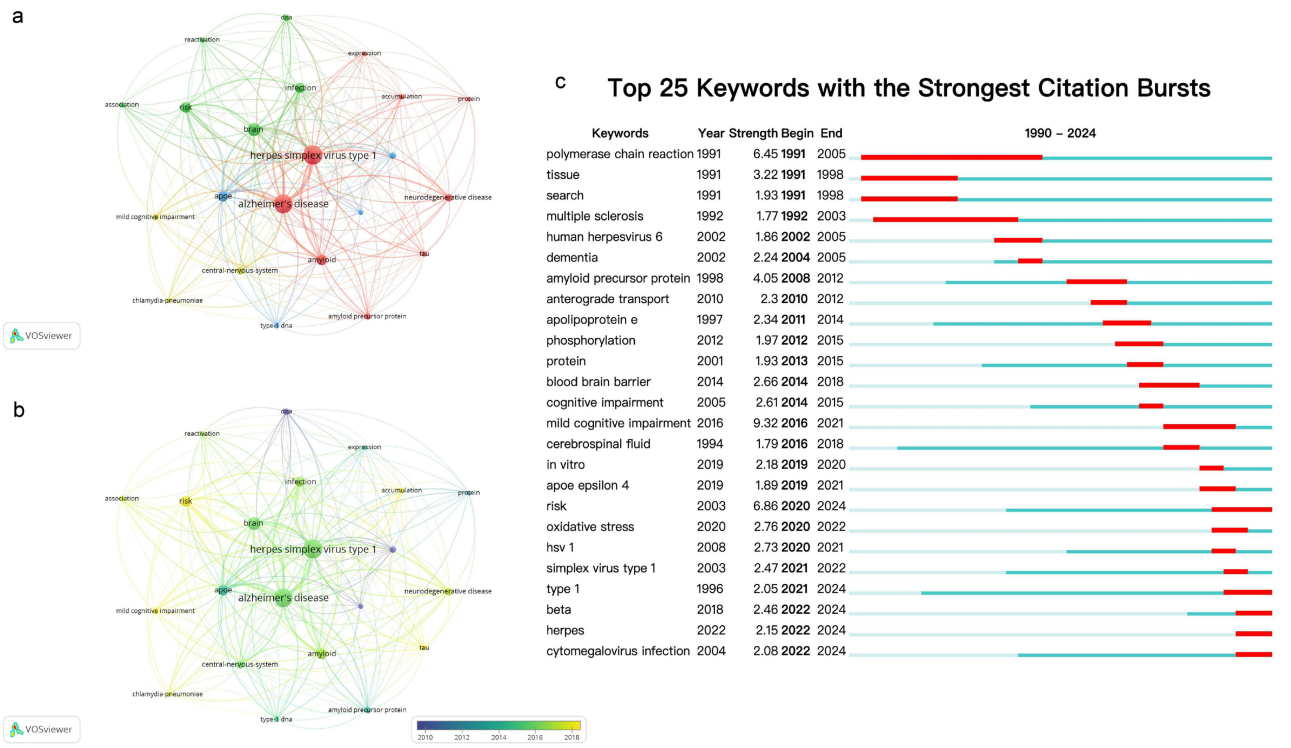

Figure 6 The analysis of keywords in the field of HSV-1 and AD. (**a**) A network visualization map of co-occurring keywords. The color of an element indicates the cluster it belongs to. The larger the size of the node, the higher the frequency of the keyword. The links between keywords represent a co-occurrence relationship. (**b**) Time sequence chart of keyword clusters. The closer the color of the node is to yellow, the later the occurrence of keywords. (**c**) The top 25 keywords with the strongest citation bursts from 1983 to 2024. The blue line denotes the time axis, while the red segment on the blue time axis indicates burst detection, showing the start year, end year, and burst duration.

influences the pathophysiological processes associated with AD. Studies have encompassed the metabolism of APP, phosphorylation processes, the impact of the APOE-ε4 gene, and dysfunction of the BBB. MCI, as a precursor stage to AD, has also garnered significant attention in these investigations (2005–2020). After 2020, the research focuses on HSV-1 infection as a risk factor for AD, particularly examining how it exacerbates the pathological progression of AD through mechanisms such as inducing OS and inflammatory responses. The relationship between the accumulation of Aβ and HSV-1 infection has also been a subject of interest. Furthermore, the potential links between other viral infections and AD have begun to be explored, broadening the scope of understanding in the field.

Discussion

AD is a widely recognized age-related ND,[43] characterized by typical pathological features including amyloid plaques formed by Aβ deposition and NFTs induced by hyperphosphorylation of microtubule-associated protein Tau.[44] Studies have shown that AD is a combination of genetic, lifestyle, and environmental factors,[45] but the exact cause has not yet been elucidated. HSV-1 is a widely prevalent virus with a global infection rate of 60%-90%, making it one of the most common viruses in humans.[46] This virus is characterized by latent infection and periodic reactivation, and its infection can lead to a variety of clinical manifestations, ranging from mild mucocutaneous lesions to severe neurological diseases.[47] In recent years, growing evidence suggests that HSV-1 infection may be an important environmental risk factor for AD. This study analyzed 287 articles on AD and HSV-1 in WoSCC. The VOSviewer software and CiteSpace software are utilized to investigate the knowledge structure, research hotspots, and emerging trends in this field through a comprehensive analysis of various aspects including countries, institutions, journals, authors, and keywords.

We conducted cluster analysis and temporal co-occurrence analysis on high-frequency keywords. Recent hot keywords include MCI, APOE-ε4, OS, Aβ, tau protein, cytomegalovirus infection, and accumulation, among others. Through bibliometric analysis, we systematically organized the evolution of keywords in research related to AD and

HSV-1 infection. The analysis shows that research hotspots have shifted from early virus detection to molecular mechanisms and finally to the role of HSV-1 infection as a risk factor for AD. This evolution reflects the scientific community's deepening understanding of the relationship between HSV-1 and AD, from initial verification of viral presence to exploration of molecular mechanisms, and finally to comprehensive assessment of disease risk. This paper discusses some of the recent research hotspots in the field, providing researchers with additional directions for future studies.

HSV-1 infection promotes Aβ accumulation and tau phosphorylation, which are key pathological features of AD. Interestingly, Aβ is considered a natural antimicrobial peptide that can trap and neutralize pathogens by forming fibrillar structures, suggesting a protective role in the central nervous system.[48,49] However, excessive Aβ accumulation due to high viral load may lead to plaque formation, neuroinflammation, and neuronal damage, ultimately contributing to AD pathogenesis. Studies show that HSV-1 disrupts the BBB to enter the CNS, triggering pathological changes.[50–53] HSV-1 stimulates glial cells to produce cytokines, upregulates APP expression, induces Aβ generation,[54,55] and impairs Aβ clearance by inhibiting autophagy and lysosomal function, promoting plaque formation.[56–58] Additionally, HSV-1 triggers tau phosphorylation, leading to NFTs.[59] Phosphorylated tau spreads via extracellular vesicles (EVs), exacerbating neurodegeneration.[60,61] These changes align with core AD features, supporting HSV-1's role in AD development. Repeated reactivation of HSV-1 may lead to excessive production of reactive oxygen species (ROS),[62] thereby inducing OS.[63] ROS upregulate ɣ-secretase and BACE-1, increasing Aβ production and impairing its clearance.[64–66] Simultaneously, protein oxidative damage caused by OS promotes tau self-aggregation, accelerating the formation of NFTs.[67,68] Furthermore, the CNS is particularly vulnerable to OS,[69,70] leading to impaired neuronal function and reduced survival rates, ultimately potentially contributing to AD.[71,72]

The APOE-ε4 gene is the most common genetic risk factor for AD. Studies have shown that individuals carrying the APOE-ε4 genotype who are HSV-1 positive have a significantly higher risk of developing AD.[31] Research by Javier S. Burgos revealed that during the latent phase of viral infection, APOE-ε4 mice exhibited significantly higher viral loads in the brain compared to other genotypes.[73] This may be because APOE-ε4 and HSV-1 share the same binding site (heparan sulfate proteoglycan),[74,75] allowing HSV-1 to more easily enter neurons and promote its spread between neurons. By maintaining the balance of lipid metabolism and antioxidant capacity, APOE-ε3 protects neurons from damage caused by HSV-1 infection, resulting in APOE-ε3 carriers typically exhibiting milder disease symptoms and slower disease progression following HSV-1 infection.[15,76] Besides, APOE-ε2 reduces the inflammatory response after HSV-1 infection by enhancing the expression of anti-inflammatory cytokines while suppressing the release of pro-inflammatory cytokines.[25,77] The antioxidant activity of APOE-ε4 is lower than that of APOE-ε3 and APOE-ε2, making neurons of APOE-ε4 carriers more vulnerable to damage during the OS triggered by HSV-1 infection.[76,78] Jose L. Cantero further discovered that the association between HSV-1 infection and Aβ burden is regulated by the APOE-ε4 genotype.[79] These findings highlight the broader impact of APOE genotypes on neurological and infectious diseases, underscoring the importance of further research into their roles in disease pathogenesis.

Co-infection with other viruses also increases the risk of AD. The co-infection of HSV-1 and varicella zoster virus or cytomegalovirus was found to be associated with a greater risk of AD in comparison to HSV-1 infection alone.[80,81] The mechanism may be that the immune system is activated after viral infection, further reactivating latent HSV-1. Moreover, HSV-1 and SARS-CoV-2 co-infection may synergistically promote AD pathogenesis via mechanisms including autophagy dysregulation, OS exacerbation, and protein homeostasis disruption, thereby enhancing AD susceptibility.[82]

Research has shown that the accumulation of HSV-1 infection is closely associated with an increased risk of AD. Some scholars have proposed that decreasing HSV-1 viral load may be an effective strategy for preventing AD in the future.[83,84] For example, antiviral drugs could be used to inhibit HSV-1 replication or reactivation, thereby reducing viral damage to the nervous system.[85–87] Alternatively, immune modulation could enhance the body's ability to clear HSV-1,[88] decreasing viral accumulation in the CNS. Antiviral drugs such as acyclovir for HSV infection can reduce the accumulation of Aβ and P-tau while reducing viral load.[87] Acyclovir has also been shown to prevent HSV-associated neuronal death.[89] Additionally, early intervention in HSV-1 infection, particularly during the MCI stage, may help delay or prevent the onset of AD.[85] The potential value of this strategy has been supported by preliminary studies. However, since HSV-1 performs viral transcription, DNA replication, capsid assembly, and DNA encapsulation in vivo, the

selection of intervention time points will be one of the directions of future research. Further large-scale clinical trials are needed to validate its efficacy and safety.

Research on HSV-1 infection and AD has evolved from initial pathological associations to broader areas, including genetics, viral infection characteristics, multi-virus comparisons, and comprehensive multi-mechanism studies. The research scope has continuously deepened, expanding from single-factor analyses to the interactions of multiple factors and mechanisms, gradually revealing the complex role of HSV-1 infection in AD and other ND. Currently, studies on the mechanisms by which HSV-1 infection contributes to AD remain a hotspot in the field. Future research is likely to focus more on antiviral strategies targeting HSV-1 infection, exploring their potential applications in the prevention and treatment of AD.

Limitations

The current mechanistic research landscape predominantly focuses on HSV-1-mediated AD pathogenesis through secondary pathways, particularly Aβ deposition and tau protein hyperphosphorylation, while direct mechanisms linking HSV-1 infection to AD neuropathology remain substantially underinvestigated. Furthermore, current therapeutic strategies remain predominantly confined to conventional antiviral agents and vaccine development, highlighting the critical need for innovative pharmacological approaches targeting novel molecular pathways in future research endeavors. Methodologically, the present study's scope is constrained by the limited sample size of included publications, necessitating future investigations to expand their analytical framework through comprehensive database integration and multilingual literature inclusion to enhance the generalizability and robustness of findings.

Conclusion

This comprehensive bibliometric analysis examined 287 original research articles focusing on the relationship between HSV-1 and AD, spanning from January 1990 to 2024 (June 1, 2024), retrieved from the WoSCC database. The collected data were systematically analyzed using VOSviewer and Citespace software to construct a detailed knowledge mapping framework. In recent years, there has been a rapid increase in the number of articles on HSV-1 and AD research. While there is currently substantial evidence that HSV-1 is involved in the pathogenesis of AD, the question remains controversial about whether this association is directly pathogenic or indirect, necessitating further mechanistic investigations to elucidate the underlying pathophysiological processes. Importantly, emerging evidence suggests that targeted anti-infective strategies and prophylactic vaccination approaches may represent promising therapeutic avenues for AD intervention, warranting further clinical investigation.

Data Sharing Statement

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

Ethics Approval

This is an observational study and does not involve ethics.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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