

SYSTEMATIC REVIEW

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Viral infections and the risk of neurodegenerative diseases: a comprehensive meta-analysis and systematic review

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BACKGROUND: Viral infections have been implicated in the pathogenesis of neurodegenerative diseases (NDs); however, evidence linking specific viruses to Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS) remains inconclusive. This study conducted a meta-analysis and systematic review to investigate these associations.

METHODS: Thorough searches were conducted across Embase, PubMed, Cochrane Library, Web of Science and Scopus until May 18, 2025, to identify observational studies investigating the relationship between viral infections and the risk of NDs, including AD, PD, and ALS. Meta-analyses were executed using a random-effects model with Stata MP18.0.

RESULTS: A total of 34,417 articles were identified, of which 73 met the eligibility criteria for inclusion in the meta-analysis, and 48 were included in the systematic review. The analysis demonstrated that infections with cytomegalovirus (CMV) (odds ratio [OR] = 1.41; 95% confidence interval [CI]: 1.03, 1.93), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (OR = 1.88; 95% CI: 1.53, 2.32), hepatitis C virus (HCV) (OR = 1.39; 95% CI: 1.14, 1.69), and human herpesvirus (HHV) (OR = 1.24; 95% CI: 1.02, 1.51) were associated with an increased risk of AD. Regarding PD, infections with hepatitis B virus (HBV) (OR = 1.18; 95% CI: 1.04, 1.35) and HCV (OR = 1.29; 95% CI: 1.18, 1.41) were identified as risk factors. Conversely, no significant correlation was found between any viral infection and the risk of ALS.

CONCLUSION: This meta-analysis supports the role of select viral infections in AD and PD pathogenesis. However, no association was found between viral infections and ALS, warranting further large, multicenter, and longitudinal studies to elucidate mechanisms and confirm causality.

Translational Psychiatry (2025)15:388; <https://doi.org/10.1038/s41398-025-03639-2>

INTRODUCTION

Neurodegenerative diseases (NDs) refer to a category of disorders within the nervous system characterized by the progressive loss of neurons, often due to mechanisms that remain poorly understood. These diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS), are clinically defined by the gradual decline in cognitive, motor, and behavioral functions, posing significant global health challenges. AD, being the most prevalent ND and the leading cause of dementia, is distinguished by cognitive and behavioral impairments, typically manifesting as memory loss related to recent events [1]. It is estimated that 6.9 million Americans aged 65 and older currently live with AD [2]. PD, the second most common ND, has a global prevalence of 1.51 cases per 1000 [3], resulting in both motor and non-motor symptoms due to dopaminergic neuronal degeneration. Over the past three decades and into the next, the prevalence of AD and PD is projected to double every 20 to 30 years [4, 5]. ALS, one of the most devastating NDs, involves the degeneration of both upper and lower motor neurons. The prevalence of ALS ranges from 1.57 per 100,000 in Iran to 11.80 per 100,000 in the United States [6]. Despite its relatively low incidence, ALS has a high mortality rate, with an average survival

period of only 3 to 5 years post-diagnosis [7]. Collectively, these diseases impose a substantial socioeconomic burden, necessitating considerable healthcare expenditures and significantly impacting the quality of life for patients and caregivers.

Although numerous studies have focused on these NDs, the etiology remains incompletely understood. In addition to genetic factors — such as APP, PSEN1 and PSEN2 in AD; SNCA, LRRK2 and GBA in PD; C9orf72 and SOD1 in ALS, etc [8–10] — a range of environmental exposures and lifestyle factors have been identified as significant contributors to the onset of NDs. These include air pollution, pesticides, sedentary behavior, and smoking, among others [11–15]. Furthermore, Ijezie et al. have shown that infection with herpes simplex virus type 1 (HSV-1) leads to the induction of Tau oligomerization and hyperphosphorylation, uncovering a novel link between HSV-1 infection and the progression of AD [16]. Beyond these findings, recent experimental evidence indicates that various viruses trigger microglial aging, which causes senescent microglia to display activated behavior, thereby inducing neuroinflammation and contributing to neurodegeneration [17]. However, observational studies investigating this association have yielded conflicting results. For instance, a population-based cohort study in Taiwan suggested that

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Received: 9 April 2025 Revised: 13 August 2025 Accepted: 4 September 2025
Published online: 10 October 2025

individuals with HSV infections might face a 2.74-fold increased risk of developing AD [18]. In contrast, a recent cohort study from United States reported entirely contradictory findings [19]. As a result, the evidence supporting the viral etiology for NDs remains inconclusive, with significant variability across studies. Given the high prevalence of these viral infections globally, even a modest infection-related increase in the risk of NDs could have profound public health implications. Consequently, clarifying the role of viral infections in the development of NDs may offer new avenues for intervention and provide critical insights for prevention and early prediction strategies.

The objective of this systematic review and meta-analysis is to comprehensively investigate the association between viral infections and the risk of AD, PD, as well as ALS.

METHODS

As our previous studies, this systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Supplementary Table 1) [20–22]. The protocol for this study was registered with PROSPERO, registration number: CRD42024629593.

Search strategy and information sources

Two reviewers (R-YL and K-FY) independently conducted searches in the PubMed, EMBASE, Cochrane Library, Web of Science and Scopus databases to identify observational studies from their inception to May 18, 2025. Moreover, the search terms such as “neurodegenerative disease”, “degenerative neurologic disease”, “Alzheimer’s disease”, “Parkinson disease”, “amyotrophic lateral sclerosis”, and “virus” were used. Additionally, a “snowball” search was carried out to identify additional studies by checking the references of narrative reviews, systematic reviews, or original research papers included in the study when necessary. Full details of the search strategy are provided in Supplementary Appendix 1.

Inclusion and exclusion criteria

All studies fulfilling the subsequent criteria were encompassed in this analysis: 1) case-control or cohort studies that investigated the impact of viral infections on the risk of AD, PD and ALS in contrast to control group (individuals who showed no evidence of the studied viral infections, but not required to be free of non-viral conditions commonly present in age-matched populations, such as hypertension or diabetes); 2) odds ratios (ORs), relative risks (RRs), and hazard ratios (HRs) with 95% confidence intervals (CIs) should be offered or could be calculated in the included studies; 3) in the event that the data of the same subjects had been published multiple times, the most recent and comprehensive study was selected; 4) articles written in English. We defined viral infection as follows: 1) detection and isolation of viral DNA or RNA in bodily fluids; 2) detection of virus-specific antibodies; and 3) a documented history of prior viral infection. Articles were disqualified based on the following criteria: 1) animal or cell experiments; 2) editorials, letters, notes or commentary lacking original material, etc.; 3) data lines with fewer than 5 cases or controls with or without the outcome [23].

Data extraction

Data were independently extracted by two reviewers through the utilization of a standardized data extraction form. The following data were extracted from each study: the specific viral infection investigated (e.g., HSV-1, Epstein-Barr Virus [EBV], Human Immunodeficiency Virus [HIV], etc.), the last name of the first author, the publication year, the country, the study design, the number of individuals in the NDs group and control group, the study period, the effect size (ORs, RRs, HRs with 95% CIs). We also made a record of the diagnostic criteria used for both NDs (AD, PD, ALS) and viral infections, as well as the confounding factors included in the

adjusted estimates. It is worth noting that when studies had multiple adjusted regression models, we extracted only those values that reflected the maximum degree of adjustment for known risk factors and potential confounders.

Risk of bias and quality assessment

Two investigators (R-YL and K-FY) independently evaluated the risk of bias, and any discrepancies were resolved through a reassessment of the original articles by a third author (S-YH). The research evaluation was carried out by employing the Newcastle-Ottawa Scale (NOS), which encompassed three significant elements, namely participant selection, comparability of groups, and appraisal of the exposures or outcomes. Each domain was assigned a maximum score of 4, 2, and 3 respectively [24]. The possible maximum total score for each study was 9. The final quality evaluation outcomes were as follows: 0–3, low quality; 4–6, moderate quality; 7–9, high quality.

Statistical analyses

We performed a meta-analysis of studies that presented viral infection data for the NDs in comparison with control groups. A random effects model, along with an inverse variance method, was employed to calculate the pooled ORs with the 95% CIs for the association between specific viral infection and NDs across studies with the number of included studies being at least three. A forest plot was generated to visualize the results. Between-study heterogeneity was assessed using Cochran’s Q test and the I^2 statistic, where $I^2 < 25\%$ indicated low heterogeneity, 25–50% indicated low to moderate heterogeneity, 50–75% indicated moderate to substantial heterogeneity, and $> 75\%$ suggested substantial heterogeneity [25]. To evaluate the robustness of the initial analysis, sensitivity analyses entailed excluding studies one by one and were performed using the metanint command. Meanwhile, we carried out subgroup analyses to investigate potential sources of heterogeneity based on factors such as study design and whether confounding variables were adjusted or not. These analyses were performed only for outcomes with at least five studies reporting significant associations. Publication bias was evaluated by funnel plot asymmetry, Egger’s test and Begg’s test. All analyses were conducted using STATA Version 18.0, unless otherwise specified, and $p < 0.05$ was regarded as statistically significant.

RESULTS

Study selection

Among the 34,417 articles initially identified from five databases and additional articles identified from citation tracking, 104 unique articles were included in our study. Collectively, these articles reported 204 independent analytical studies (defined as separate analyses for distinct virus-disease pairs or disease entities). Specifically, 73 articles contributed 117 studies to the meta-analysis, 48 articles contributed 87 studies to the systematic review, with 17 articles overlapping between the two analyses. Some articles go beyond investigating the relationship between a single virus and a specific disease; instead, they explore the associations between viral infections and two or even all three major NDs: AD, PD, and ALS [26–29], thus directly accounting for the numerical discrepancy. Figure 1 shows the PRISMA flow diagram of the study selection process.

Study characteristics and study quality assessment

Study and participant characteristics are presented in Supplementary Table 2–4. All included 204 independent analytical studies were designed as case-control study or cohort study. Sixty-eight articles of 104 were published after the year 2000, and 58.6% were published in the last 10 years. And many of the studies were conducted in the United States (18.26%) or China

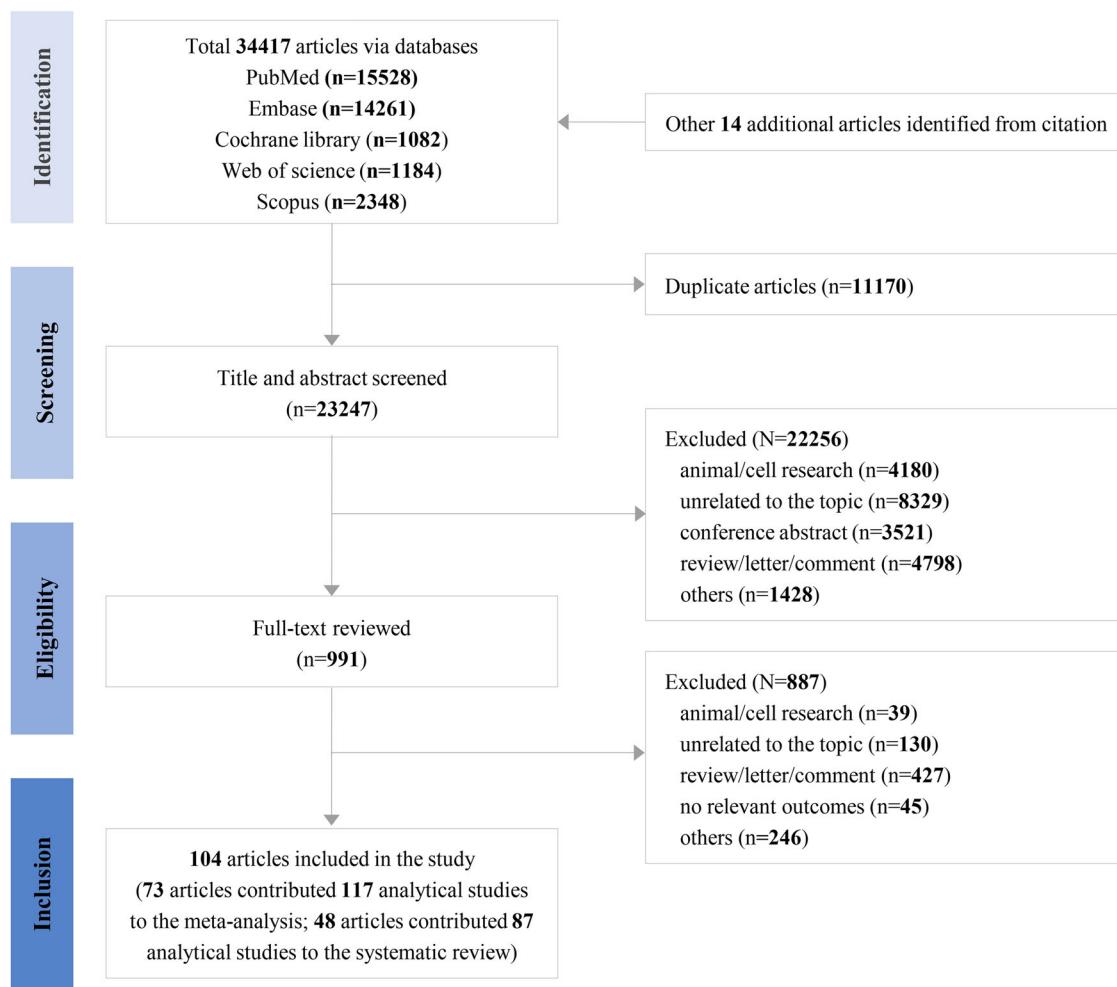


Fig. 1 Search flow diagram for included studies in the meta-analysis. N, n: Number of study.

(16.35%), followed by the United Kingdom (8.65%), Korea (8.65%) and Sweden (7.69%). Among these reported viral infections, HSV-1, HSV type 2 (HSV-2), varicella-zoster virus (VZV), cytomegalovirus (CMV), measles virus (MeV), hepatitis B virus (HBV), hepatitis C virus (HCV), Influenza virus (IFV), mumps virus (MuV) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were reported in three or more studies, which was sufficient for meta-analysis. Other viruses, such as EBV, dengue virus (DENV) and human T-lymphotropic virus 1 (HTLV-1), which did not meet this criterion, were only included in the systematic review. Furthermore, by consulting the International Committee on Taxonomy of Viruses (ICTV) and the Genetic Sequence Database (GenBank), we have recorded the classification and genome of 28 viruses (Supplementary Table 5).

The NOS scale was employed to evaluate the quality of the involved records. The detailed quality evaluation results are shown in Supplementary Table 6. We found most included records were of high or moderate quality. In the meta-analysis, 37 (72.55%) for AD and 20 (80.00%) for PD had a NOS score of ≥ 7 , while in the systematic review, 13 (65.00%) for AD, 15 (78.95%) for PD, and 6 (50.00%) for ALS had such a score (Fig. 2).

Relationship between virus infection and AD

Meta-analysis. Among the 64 articles on AD, 15 types of viruses were involved, with 35 case-control studies and 29 cohort studies. Meta-analysis was feasible only for studies on HSV-1, HSV-2, VZV, CMV, SARS-CoV-2, HCV and three types of mixed infections (co-infection of HSV-1 and CMV, HSV [referring to HSV-1, HSV-2, or

both], as well as human herpesvirus [HHV]), with the results presented in Fig. 3. According to our meta-analysis, we identified an association between the viruses and the altered risk of AD, specifically with SARS-CoV-2 ($OR = 1.88$, 95% CI: 1.53, 2.32; $I^2 = 81.0\%$), CMV ($OR = 1.41$, 95% CI: 1.03, 1.93; $I^2 = 50.6\%$), HCV ($OR = 1.39$, 95% CI: 1.14, 1.69; $I^2 = 51.5\%$), and HHV ($OR = 1.24$, 95% CI: 1.02, 1.51; $I^2 = 81.4\%$). As evidenced by the high I^2 values, heterogeneity between studies was substantial, particularly for SARS-CoV-2 and HHV ($I^2 > 75\%$). And no clear association between other viruses and the onset of AD was confirmed.

Systematic review. The other 9 types of viruses were systematically reviewed. Two cohort studies conducted in Taiwan, China, have shown that DENV, with an HR of 1.16 (95% CI: 1.01, 1.32), and human papillomavirus (HPV), with an HR of 1.48 (95% CI: 1.32, 1.67), are associated with an increased risk of AD [30, 31]. However, no further studies have yet been conducted to validate these findings. Additionally, IFV, poliovirus (PV), HBV, EBV, Human Herpes virus 6 (HHV-6), MeV, and rubella virus (RuV) were not associated with the risk of developing AD in less than 3 studies.

Publication bias and sensitivity analysis. Publication bias was assessed using funnel plots, Egger's test and Begg's test, and no significant publication bias was found in the quantitative studies on these viruses (Supplementary Figure 1). Sensitivity analysis, performed using the leave-one-out method, showed that the overall estimates remained consistent across most studies (Supplementary Figure 3). For studies reporting on CMV and

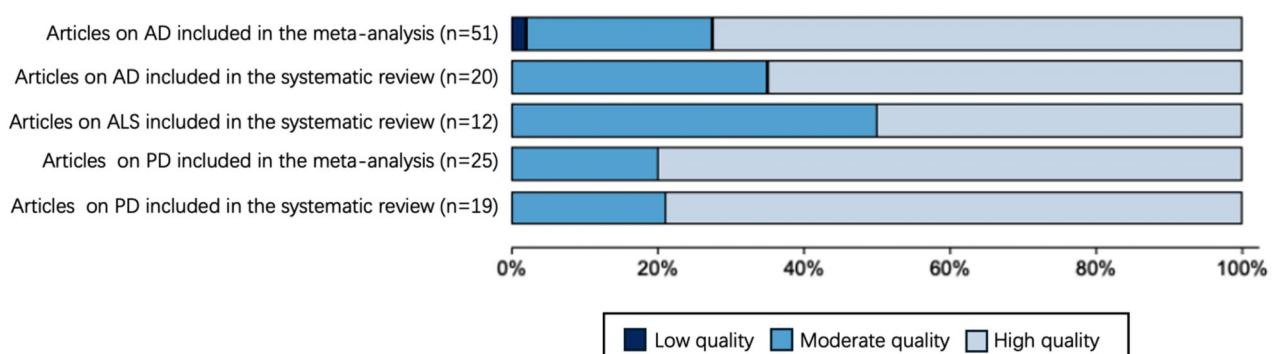


Fig. 2 Proportion of NOS scores for records included in the systematic review and meta-analysis. NOS scores were divided into 3 groups high risk of bias (0 ~ 3), moderate risk of bias (4 ~ 6), low risk of bias (7 ~ 9). NOS, Newcastle-Ottawa Scale; n, Number of study.

HCV, excluding some studies rendered the pooled results of the remaining studies statistically insignificant, suggesting that the findings lack robustness.

Relationship between virus infection and PD

Meta-analysis. The research on the viral etiology of PD includes 18 viruses, of which 8 have a sufficient number of studies to perform meta-analysis (Fig. 4). The results indicate that HBV and HCV are associated with an increased risk of PD, with OR of 1.18 (95% CI: 1.04, 1.35; $I^2 = 75.4\%$) and 1.29 (95% CI: 1.18, 1.41; $I^2 = 47.8\%$), respectively. The meta-analysis related to HBV and PD demonstrated considerable heterogeneity. In contrast, other viruses, such as HSV, VZV, MeV, IFV, CMV and MuV, show no significant association with the development of PD.

Systematic review. For viruses that could not be quantitatively synthesized, a systematic review was conducted. SARS-CoV-2 has been shown in two cohort studies to increase the risk of developing PD [29, 32]. Borna Disease Virus (BDV), Ljungan virus, DENV, and Japanese Encephalitis Virus (JEV) have each been confirmed to be associated with an increased risk of PD, although each virus is supported by only a single clinical study [33–36]. Additionally, no studies have confirmed an association between HSV-1, EBV, HHV-6, RuV, or HIV and the incidence of PD.

Publication bias and sensitivity analysis. We did not find any publication bias in any studies, and the symmetrical nature of the funnel plot was further supported by the p-value from Egger's test and Begg's test (Supplementary Figure 2). Sensitivity analysis showed that the meta-analysis results for HCV were robust, with consistent pooled estimates regardless of the exclusion of any individual study, whereas the results for HBV showed slightly weaker robustness (Supplementary Figure 4).

Relationship between virus infection and ALS

Meta-analysis. Due to the limited number of studies, we could not perform a meta-analysis on the viral etiology of ALS.

Systematic review. We identified twelve case-control studies investigating the viral etiology of ALS, encompassing nineteen different viruses (Supplementary Table 3). However, only one virus, enterovirus (EV), has been confirmed to increase the risk of ALS. Berger et al. and Vandenberghe et al. found that EV nucleotide sequences were more frequently detected in the cerebrospinal fluid (CSF) of ALS patients compared to the control group [37, 38]. Other viruses, such as VZV, HHV-6 and MeV, have not yet been confirmed to be associated with ALS in existing clinical studies.

Subgroup analyses. We performed subgroup analyses based on the study design and confounding adjustments, with the aim of

exploring the potential source of heterogeneity. And subgroup analysis of the association between AD and CMV, stratified by adjustment status, demonstrated a slight reduction in heterogeneity, with statistical significance preserved in the adjusted group (Supplementary Table 7). However, we were unable to identify the source of heterogeneity in the association between PD and HBV. These results are largely due to the limited number of studies included in the analysis.

DISCUSSION

To investigate the potential viral etiology of NDs, we performed a meta-analysis of existing literature. A total of 104 articles examined the infection rates of 28 different viral species in patients with NDs, specifically in AD, PD, or ALS, compared to controls. Through comprehensive quantitative synthesis, HCV infection emerged as a risk factor for both AD and PD. Furthermore, infections with CMV, SARS-CoV-2 and HHV were associated with an elevated risk of AD, while HBV infection was linked to the onset of PD. In contrast, no significant association was established between viral infections and the development of ALS.

To evaluate the strength of evidence, viral infections were categorized according to predefined criteria: infections with effect sizes (ORs or HRs) ≥ 1.3 were designated as Class I evidence, indicating strong pathogenic factors, while those with smaller effect sizes were classified as Class II evidence, representing weaker pathogenic factors [21]. According to this classification, CMV (OR = 1.41), HCV (OR = 1.39), and SARS-CoV-2 (OR = 1.88) infections were identified as Class I evidence for the onset of AD. In contrast, HHV co-infections (OR = 1.24) were categorized as Class II evidence. Regarding PD, both HBV (OR = 1.18) and HCV (OR = 1.29) infections were classified as Class II evidence, suggesting a moderate association with disease pathogenesis.

The meta-analysis did not reveal significant evidence of publication bias; however, substantial heterogeneity was detected in certain analyses. Despite performing subgroup analyses to account for confounding adjustments and variations in viral infection detection methodologies, the underlying sources of heterogeneity remained unresolved. Potential contributors to this heterogeneity may include variables such as age, sex, and ethnicity. Due to insufficient data availability in some included studies, stratified analyses of these variables were not feasible. Sensitivity analyses indicated that the meta-analytic associations for HBV in PD and CMV/HCV in AD exhibited limited robustness, as the sequential exclusion of individual studies led to a loss of statistical significance in the pooled estimates. These findings underscore the necessity for cautious interpretation of these associations and highlight critical gaps in the current evidence that warrant targeted investigation in future research.

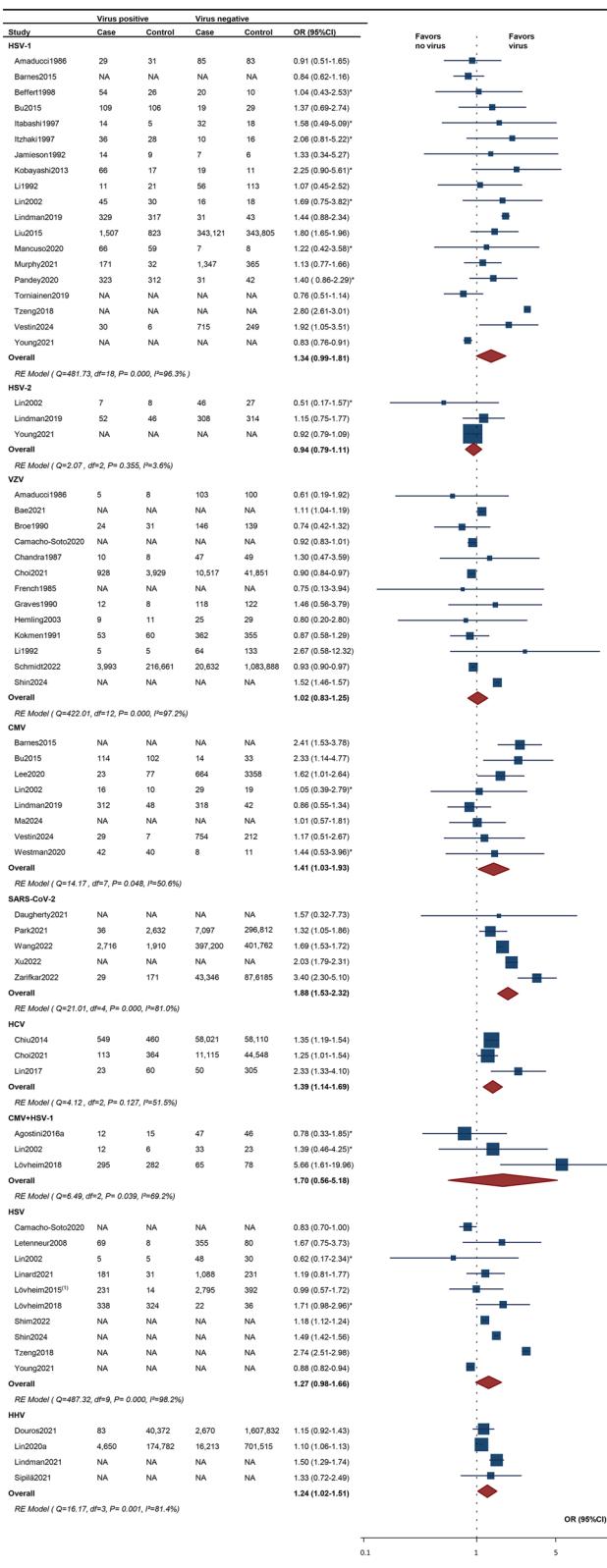


Fig. 3 Meta-analysis of studies exploring the association between viral infections and AD. OR: odds ratio; CI: confidence interval; HSV-1/2: Herpes Simplex Virus Type 1/2; VZV: Varicella-Zoster Virus; CMV: Cytomegalovirus; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; HCV: Hepatitis C Virus; HHV: Human Herpesvirus. *Calculated by the author.

Mechanisms and mediation

Association between viral infections and AD. In our research, SARS-CoV-2, CMV, HHV and HCV were identified as risk factors contributing to the development of AD. Numerous studies have consistently corroborated that SARS-CoV-2 elevates the risk of AD, and Mendelian randomization analysis by Baranova et al. further confirms that severe COVID-19 exacerbates this risk, potentially through mechanisms like cytokine release, neuroinflammation, oxidative stress, and ferroptosis [29, 39–42]. A recent study suggests that SARS-CoV-2 infection may be associated with increased β-amyloid pathology in the brains of older adults, thereby potentially affecting long-term neurological health and increasing the risk of AD [43]. Although a previous meta-analysis did not establish a link between CMV infection and AD [44], our analysis, excluding studies with very small sample sizes, indicated that CMV may indeed elevate the risk of developing AD [45, 46]. The underlying mechanism may involve CMV-induced inflammatory responses, leading to cerebral tissue damage and an increased risk of moderate to severe dementia [47]. Beyond CMV, a broader spectrum of HHV (including VZV, HSV, EBV, among others) has also been shown to be associated with AD. HSV-1, the most prevalent HHV, is not directly associated with AD in our study, however, its reactivation is acknowledged as a pathogenic factor in the development of AD [48, 49].

Association between viral infections and PD. Our meta-analysis substantiates that both HBV and HCV serve as risk factors for PD. HBV, a hepatotropic DNA virus, is implicated in acute and chronic liver infections, frequently resulting in persistent inflammation, hepatic damage, and immune dysregulation [50]. Despite this, there is a scarcity of research exploring the link between HBV and PD within the current body of literature. It is hypothesized that chronic HBV infection may have systemic repercussions, including the induction of oxidative stress and neuroinflammation, both of which are recognized contributors to neurodegenerative processes [51]. These mechanisms may play a role in the pathogenesis of NDs. Nevertheless, further studies are essential to elucidate the specific pathways involved and to establish a causal relationship. Regarding HCV, our findings align with two previous meta-analyses that have also confirmed HCV as a risk factor for PD [52, 53]. HCV is a small RNA virus belonging to the Flaviviridae family and the Hepacivirus genus. HCV has the potential to damage neural cells and impair brain function, with documented HCV-induced dopaminergic neuronal toxicity observed in both in vivo and in vitro studies [54, 55]. The potential mechanisms may involve the upregulation of pro-inflammatory mediators, such as TNF-α, IL-6 and IL-1β, alongside the downregulation of the anti-inflammatory factor TIMP-1. This imbalance could contribute to neuroinflammation, a critical element in the pathogenesis of PD [56, 57]. Lin et al. reported a reduced incidence of PD in patients with chronic HCV infection who underwent interferon-based antiviral therapy [58]. These observations may support the hypothesis that HCV serves as a risk factor for neurodegeneration, potentially accelerating the onset of PD and exacerbating the progression of AD.

Association between viral infections and ALS. Due to the limited number of studies available, a quantitative analysis of the relationship between viruses and ALS was not conducted. Two previous studies have suggested that EV may elevate the risk of developing ALS [37, 38]. Research indicates that EV infection can activate microglia and astrocytes, resulting in neuroinflammation and neuronal damage, which are closely linked to the pathological mechanisms of ALS [59]. Furthermore, EV infection may disrupt intracellular protein homeostasis, leading to the accumulation of misfolded proteins. This disruption is associated with the

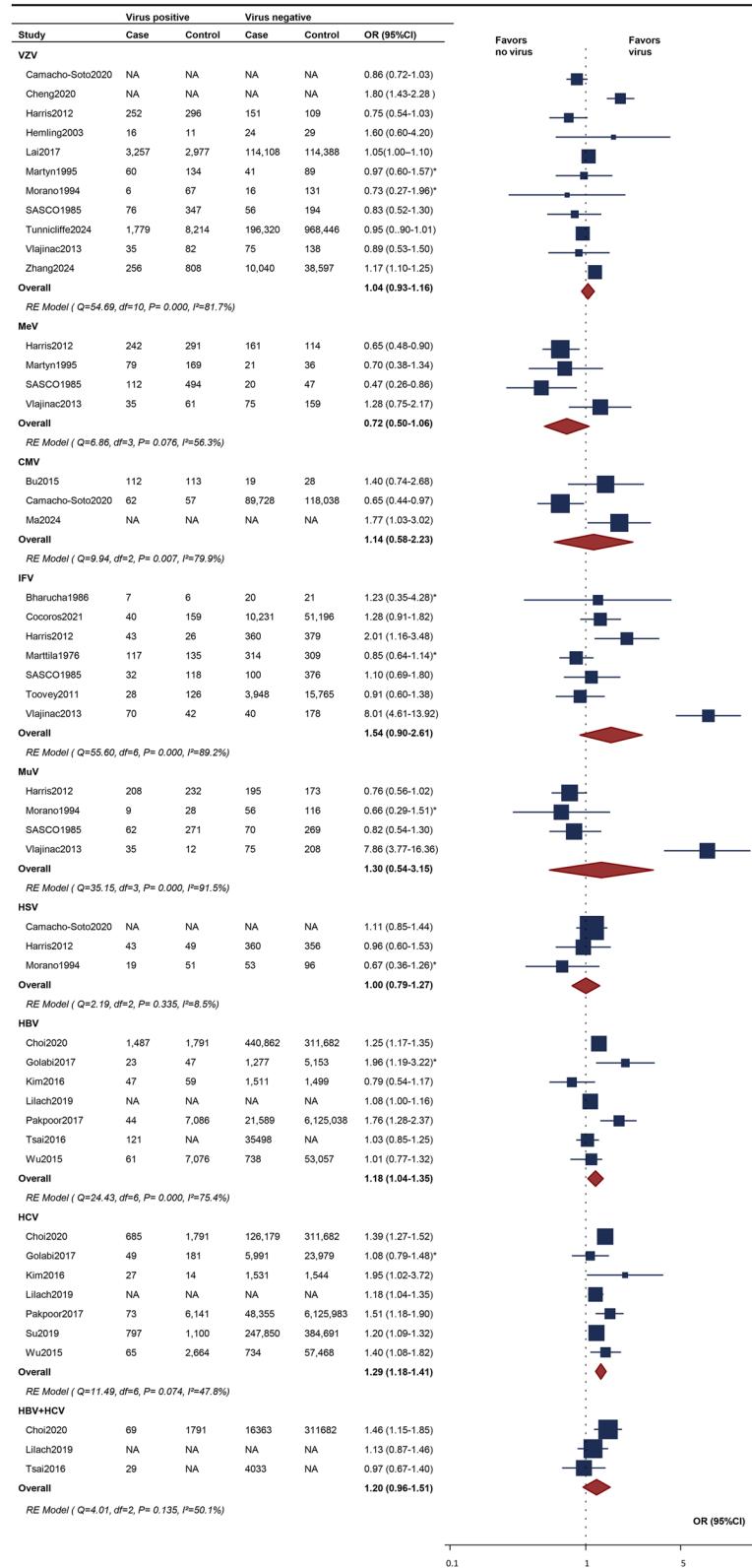


Fig. 4 Meta-analysis of studies exploring the association between viral infections and PD. OR: odds ratio; CI: confidence interval; VZV: Varicella-Zoster Virus; MeV: Measles Virus; CMV: Cytomegalovirus; IFV: Influenza virus; MuV: Mumps virus; HSV: Herpes Simplex Virus; HBV/HCV: Hepatitis B/C Virus. *Calculated by the author.

abnormal aggregation of proteins such as TDP-43 and SOD1 in ALS [60]. Nonetheless, further research is required to elucidate the precise pathophysiological relationship between EV and the risk of ALS.

Limitations. When interpreting the results, it is essential to consider the limitations inherent in the meta-analysis, as these may impact the validity and generalizability of the findings. Firstly, as with any review of observational studies, the observed associations should not be construed as evidence of causation. Secondly, the limitations include the exclusion of non-English studies, insufficient information on participant characteristics, and a relatively small number of disease controls. Thirdly, the search terms for viral exposures (infect*, pathogenicity, virus*, viral*) were defined as broad conceptual categories. Although this approach was intended to enhance sensitivity, it might have failed to capture all virus-specific diseases, potentially leading to the omission of relevant studies. Finally, the diverse methodologies, follow-up durations, and study populations across the included studies contribute to significant heterogeneity in the results. In light of these challenges, future research with larger sample sizes and enhanced methodological rigor is necessary to establish the precise causal relationship between viral infections and NDs.

Despite these limitations, it is important to recognize that the meta-analysis offers valuable insights into the potential association between viral infections and NDs. Although the findings are not definitive, they reveal a consistent pattern that merits further investigation and can serve as a foundation for subsequent research.

CONCLUSIONS

In conclusion, this study presents a thorough evaluation of the role of viral infections in the pathogenesis of AD, PD, and ALS. Unlike previous research, this work constitutes the first meta-analysis to systematically investigate a broad spectrum of pertinent viruses. The results underscore potential associations with viruses such as CMV, SARS-CoV-2, HBV, and HCV. Despite certain limitations, this study provides valuable insights and reference data for future research on the role of viral infections in the etiology of these NDs, thereby establishing a foundation for further investigations in this domain.

DATA AVAILABILITY

The data and analytic code that support the findings of this study are available from the corresponding author upon reasonable request.

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ACKNOWLEDGEMENTS

This study was supported by the National Key Research and Development Program of China (Grant no. 2022YFC2703101), the 1·3·5 project for disciplines of excellence—Clinical Research Fund, West China Hospital, Sichuan University (Grant no. 2023HXFH032), and the Science and Technology Bureau Fund of Sichuan Province (Grant no. 2023YFS0269 and Grant no. 2022NSFSC0749). The authors would like to thank the participants in the included studies and all the researchers of them.

AUTHOR CONTRIBUTIONS

Y-PC designed and supervised the project. R-YL selected the database for meta-analysis and wrote the first draft. K-FY and S-YH selected the articles and extracted and cross-checked the data. W-MS, Q-QD, X-JW, TC, SC, J-RL and BC contributed to the statistical analysis. RY-L and Y-PC wrote, revised and discussed the final edition. All authors read and approved the final version of the manuscript.

COMPETING INTERESTS

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.

CONSENT FOR PUBLICATION

All the authors have consented to publication.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1038/s41398-025-03639-2>.

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