INPLASY

Association between Herpesviruses and Alzheimer's disease: A Meta-Analysis Based on Case-Control Studies

INPLASY202520051
doi: 10.37766/inplasy2025.2.0051
Received: 9 February 2025
Published: 9 February 2025

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Data analysis.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202520051

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 9 February 2025 and was last updated on 9 February 2025.

INTRODUCTION

Review question / Objective This systematic meta-analysis was aimed to evaluate the relationship between Herpesviruses infection and the risk of developing AD.

Condition being studied Alzheimer's disease (AD) is the most common cause of primary senile dementia, a highly age-related central nervous system degenerative disease characterized by progressive cognitive impairment and memory impairment.The incidence rate of AD is 5.3% among people aged 65 to 74 years old, and 34.6% among people aged 85 years and above.Emerging evidence underscores the roles of herpes virus, such as herpes simplex virus type 1 (HSV-1) and human cytomegalovirus (HCMV), in the pathogenesis of AD.Although a number of studies have revealed the relationship between HSV-1 infection and the incidence of AD, the correlation between the infection of HSV-1 and the risk of developing AD remains controversial. For instance, a population-based cohort study conducted by Meghan J. Murphy revealed a correlation between HSV-1 infection and mild cognitive impairments, yet refuted a direct association with the risk of developing AD. Similarly, the research results on the association between HCMV infection and AD risk are also debatable.To address the inconsistent results among previous studies, we conducted this meta-analysis to separately evaluate the correlation between HSV-1 and HCMV infections and the incidence rate of AD.

METHODS

Search strategy Databases including CNKI, PubMed, Web of Science, Embase, and Cochrane Library were searched for studies comparing the Herpesviruses positivity between AD patients and controls. We found that among all existing case-control studies, HSV-1 and HCMV subtypes of herpesviruses had the highest number of studies on their association with AD. Therefore, we chose these two viruses for a more in-depth retrieval and study.The retrieval time is from the establishment

of the database to February 2025. There was no limitation to language. Additionally, a manual search of the reference list of important articles was conducted.Keywords used in English include 'Alzheimer Disease', 'Herpesvirus 1, Human' and 'Cytomegalovirus'.

Participant or population The following inclusion criteria were used for further screening: (1) study type: Case-control experiment; (2) subjects: Alzheimer's patient; healthy control; (3) content: investigated the relationship between HSV-1, HCMV infection and the risk of AD; (4) diagnostic criteria: clinically and/or histologically, the experimental group was diagnosed as AD patients, while the control group did not have any symptom of neurodegenerative disease.
The exclusion criteria were set as follows:(1) irrelevant; (2) not a case-control experiment; (3) unable to obtain full-text studies; (4) repeatedly published or identical studies; (5) studies that cannot calculate the odds ratio (OR) of HSV-1, HCMV infection due to lack of test data or vague description; (6) review, Meta-analysis and others; (7) duplicated data.

Intervention Clinically and/or histologically, the experimental group was diagnosed as AD patients.

Comparator The control group did not have any symptom of neurodegenerative disease.

Study designs to be included Case-control studies.

Eligibility criteria The following inclusion criteria were used for further screening: (1) study type: Case-control experiment; (2) subjects: Alzheimer's patient; healthy control; (3) content: investigated the relationship between HSV-1, HCMV infection and the risk of AD; (4) diagnostic criteria: clinically and/or histologically, the experimental group was diagnosed as AD patients, while the control group did not have any symptom of neurodegenerative disease.
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Main outcome(s) Odds ratio (OR) with 95% confidence intervals was used to estimate the degree of the association between HSV-1, HCMV infection and AD. The effect size (OR value 1) indicates that the factor is a risk factor.

Quality assessment / Risk of bias analysis New Castle-Ottawa Quality Assessment Scale (NOS) was used to evaluate the quality of the literature. The NOS conducts a comprehensive evaluation from three aspects of the study: selection, comparability, and exposure.The NOS scale has a total score of 9 points including three categorical criteria: low (0 ~ 3 points), medium (4 ~ 6 points) and high (7 ~ 9 points). Two authors independently assessed the quality. Any discrepancies were solved via discussion.

Strategy of data synthesis Odds ratio (OR) with 95% confidence intervals was used to estimate the degree of the association between HSV-1, HCMV infection and AD. The effect size (OR value 1) indicates that the factor is a risk factor. Cochran's Q and I2 statistics were used to determine study heterogeneity. If I20.1 for Cochran's Q, it suggests that homogeneity exists among the studies, and then the fixed-effects model is used for analysis; I2≥50% or the p value<0.1 for Cochran's Q suggests that there is heterogeneity among the studies, the random-effects model would be used for the analysis. In case of high heterogeneity, subgroup analysis and sensitivity analysis were carried out to analyze the source of heterogeneity. All the Funnel plot and Begg and Egger tests were depicted to analyze the publication bias of the included studies. The Forest plot and the Funnel plot were made by Review Manager 5.3 software. Potential publication bias is suggested when the funnel plot is asymmetric. Begg and Egger tests were carried out to identify the publication bias using Stata 17 software where the P-value< 0.05 was considered statistically significant publication bias.

Subgroup analysis Conduct a subgroup analysis of literature before and after 2010 based on the years of the collected literature.

Sensitivity analysis Remove one article in a meta-analysis sequence and conduct articles. By on the remaining in the merged observing the changes whether the results, evaluate results have original meta-analysis changes due to undergone significant studies. the influence of certain

Country(ies) involved China.

Keywords Alzheimer's disease; HSV-1; HCMV; Meta-analysis.

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