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MAJOR ARTICLE

Association Between Herpes Simplex Virus-1 Infection and Dementia or Alzheimer's Disease: A Systematic Review and Meta-Analysis

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Background: Herpes simplex virus-1 (HSV-1) infects approximately two-thirds of the global population under the age of 50 years. The possible implications of HSV-1 in neurodegenerative diseases, especially dementia and Alzheimer's disease, remain poorly characterized. We conducted a systematic review and meta-analysis to further explore the potential association between HSV-1 infection and dementia or Alzheimer's disease.

Methods: We searched PubMed, Embase (Elsevier/Ovid), Web of Science, Scopus, Global Health, PsycInfo, Cochrane Library, and Clinicaltrials.gov between inception and February 2024 for any studies on the association between HSV-1 infection and dementia and/or Alzheimer's disease. We conducted a random-effects meta-analysis to estimate the cumulative odds-ratio (OR) of developing dementia or Alzheimer's disease across all studies and performed meta-regression to explore sources of heterogeneity.

Results: We identified 2,178 studies and included 11 in the final analysis. HSV-1 infection was associated with an increased risk of developing either dementia or Alzheimer's disease (OR 1.48,

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95% confidence interval [CI] 1.16 to 1.89). Results remained consistent when studies were stratified by adjusted covariates (age, ApoE, cardiovascular disease), study type, and study quality.

Conclusions: HSV-1 infection is associated with an increased risk of developing either dementia or Alzheimer's disease. Further prospective epidemiological and intervention studies are needed to clarify that relationship.

Key Words: herpes simplex virus 1, dementia, Alzheimer's disease

Key Points: Herpes simplex virus (HSV)-1 has long been suspected to be involved in the development of neurodegenerative diseases. Our findings suggest that HSV-1 infection is associated with an increased risk of developing either dementia or Alzheimer's disease.

INTRODUCTION

Over 110,000 Americans die from Alzheimer's disease each year. Alzheimer's disease and its subtypes are the sixth leading cause of mortality in the United States[1,2]. The prevalence of dementia is expected to further increase as the population ages, with the number of dementia cases expected to nearly triple to 152.8 million cases globally by 2050 from an estimated 57.4 million in 2019[3]. Although Alzheimer's disease contributes to more than 80% of all dementia diagnoses, only one-third of all Alzheimer's disease cases can be attributed to modifiable risk factors[4]. That unknown etiology, combined with the lack of effective treatments for Alzheimer's disease, has spurred substantial research in hopes of clarifying its pathogenesis and prevention methods[5]. Specific causes of Alzheimer's disease and dementia have long been postulated and investigated, with increasing evidence from large population-based studies suggesting viral etiologies of dementia and cognitive impairment[6–8].

Potential viral risk factors for dementia, including herpes simplex virus-1 (HSV-1) infection, have been a subject of speculation for decades. HSV-1 is a neuroinvasive and neurotoxic virus capable of entering the brain and remaining latent for the host's lifespan, making it a candidate for increasing dementia risk[9,10].

In 2016, an estimated 67% of the world's population under the age of 50 years was infected with HSV-1[11]. Its wide prevalence necessitates further exploration of its role in neurological diseases. HSV-1 has already been shown to induce characteristic Alzheimer's disease-like changes in neural stem cells, 2-dimenstional neuronal models, and 3-dimensional human brain-like models[12]. Despite findings of HSV-1 latency in human brain tissue and potential associations between HSV-1 antibody seropositivity and an increased Alzheimer's risk, the implications of these findings for clinical practice are still unclear. Randomized controlled treatment trials are currently underway to investigate the role of antiviral treatment of HSV-1 in Alzheimer's disease[13,14]. However, evidence at the population level remains unclear, and there are no established antiviral strategies for reducing the risk of cognitive decline[15].

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Previous systematic reviews exploring the relationship between herpesviruses and dementia found inconsistent results, particularly concerning HSV-1. A review in 2019 found no difference in risk of dementia between those infected with HSV-1 and those without (pooled odds ratio [OR] 1.31, 95% confidence interval [CI] 0.90 to 1.90)[16]. A more recent study in 2023 also found similar results with HSV-1 and risk of Alzheimer's disease (risk ratio [RR] 1.16, 95% CI 0.99 to 1.35) but did note a significant association between any HSV infection and incidence of dementia (pooled RR 2.23, 95% CI 1.18 to 2.29)[17]. Given the conflicting results on HSV-1's role in dementia, we aim to update existing reviews by including studies published in recent years and narrowing our scope to focus on HSV-1 infection specifically. We also performed adjusted analyses to examine the effects of various risk factors of dementia and Alzheimer's disease—including age, ApoE, and cardiovascular disease. We conducted a systematic review and meta-analysis to help elucidate the association between HSV-1 infection, dementia, and Alzheimer's disease.

METHODS

Search Strategy and Selection Criteria

This systematic review was conducted according to PRISMA guidelines and was registered in PROSPERO (CRD42024516789)[18,19]. We searched PubMed, Embase (Elsevier/Ovid), Web of Science, Scopus, Global Health, PsycInfo, Cochrane Library, and Clinicaltrials.gov between inception and February 2024, using search terms related to ('Herpes simplex virus 1') AND ('Dementia' OR 'Alzheimer's disease')[20]. We excluded any studies not published in English.

Two authors (F.L. and A.V.) independently screened the titles and abstracts from the database search, followed by a full text review. Covidence, a systematic review tool, was used to organize and screen all studies. All disagreements were resolved with a third author (A.H. or I.L.). We included all randomized control trials, cross-sectional studies, prospective and retrospective cohort studies, case-control studies, and brain specimen-based studies of deceased patients that included a comparison group. Study subjects were required to be at least 18 years of age, and all study settings were considered including inpatient hospital care, outpatient services, and primary care environments. Exposure to HSV-1 was ascertained either through clinical evaluation, laboratory serology tests, medical records, or brain specimen imaging. Controls included all subjects determined to be HSV-1 uninfected through similar diagnostic methodology. The primary outcomes of interest were the diagnoses of either dementia or Alzheimer's disease, as confirmed through clinical diagnosis, neuroimaging, or histopathology findings. Most clinical diagnoses were made according to the criteria of the National Institute of Neurological and Communicative Diseases and Stroke and the Alzheimer's Disease and Related Disorders Association, as well as a battery of neuropsychological exams. These cognitive exams included the Mini Mental State Examination, Stroop Test, Word Learning Test, and Verbal Fluency Task.

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Data extraction

Data extraction was performed by two independent reviewers (F.L. and A.V.) using a standardized extraction table. We extracted several types of data pertaining to each study. For study characteristics, we extracted information regarding authors, publication year, study design, covariates adjusted for, and period of study. For study subject characteristics, we extracted sex, age, ethnicity, socioeconomic status, APOE4 status, antiviral therapy status, and recruitment and sampling methods. For outcomes, we extracted the total number of individuals with a positive HSV-1 infection status, negative HSV-1 infection status, dementia diagnosis, Alzheimer's disease diagnosis, and any combinations of these outcomes. We also extracted the reported effect measure from each study (in the form of a hazard ratio [HR], odds ratio, or risk ratio), the 95% confidence interval for each effect size, their p-value, and whether the effect size was crude or adjusted. If any study looked at both dementia and Alzheimer's disease separately, we considered these as two separate studies in the analyses.

Quality assessment

Two reviewers (F.L. and A.H.) independently assessed the quality of evidence and risk of bias from each study, and all disagreements were resolved through consensus. The quality assessment used criteria from the Newcastle-Ottawa Scale, a framework designed for assessing case-control and cohort studies[21]. For case-control studies, we assessed the quality of the studies' selection criteria, comparability of cases and controls, and definition and ascertainment of exposure. For cohort studies, we assessed the quality of the studies' selection criteria, comparability of cases and controls, and assessment of outcomes. Studies could be awarded a maximum of 4 stars in the selection criteria section, 2 stars in the comparability section, 3 stars in the exposure section (only applicable to case-control studies), and 3 stars in the outcomes section (only applicable to cohort studies. Stars were awarded based on a standardized grading manual provided by the Newcastle-Ottawa Scale[21]. Studies were considered to have low risk of bias if they achieved at least 6 stars out of a maximum of 9 stars.

Data analysis

All statistical analyses were conducted using Stata 18 software (College Station, TX). We conducted a random-effect meta-analysis to estimate the combined effect size for the relationship between HSV-1 and subsequent dementia or Alzheimer's disease. For this study, we combined HRs and ORs after observing that the estimated effect size did not differ between studies reporting HRs vs. ORs. Heterogeneity was tested using Cochrane's Q test to evaluate whether the OR was different among the studies. We also reported I^2 as an estimate of the degree of heterogeneity, with a p-value ≤ 0.05 indicating significant heterogeneity. To explore heterogeneity, we evaluated Galbraith plots, and to evaluate small study effects, we used a funnel plot as well as Egger's test for small study bias. Last, we conducted a trim and fill analysis to further assess small study effects. To explore the potential causes of heterogeneity, we stratified studies by diagnosis type (dementia

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vs. Alzheimer's disease), study design, effect type, crude vs adjusted results, study quality, and whether the study adjusted for age in years, ApoE status, or presence of cardiovascular disease.

RESULTS

Study Selection and Subject Characteristics

After a comprehensive search, a total of 2,178 titles and abstracts were identified from 8 databases. Of those, 172 articles were selected for full-text review by F.L. and A.V., after which 11 studies remained eligible for data extraction (Figure 1). The dates of those studies ranged from 1997 to 2024. Baseline characteristics of each study can be found in Table 1. From those 11 studies, a total of 56,292 individuals were observed, with an overall mean age of 66.1 years.

The results of the quality assessment can be found in Table 2. Most studies had a low risk of bias whereas one study (Kobayashi, 2013) was considered to have a moderate risk of bias, due to the study's lack of covariate matching between cohorts and significant differences in age, gender, and education levels between groups.

The overall pooled OR of developing either dementia or Alzheimer's disease among those infected with HSV-1 was 1.48 (95% CI 1.16 to 1.89) (Figure 2). HSV-1 infection was associated with an increased risk of developing Alzheimer's disease alone (OR 1.44, 95% CI 1.07 to 1.94), although there was heterogeneity ($p<0.01$, $I^2=75.0\%$). HSV-1 infection was not associated with a significantly increased risk of developing dementia alone (OR 1.56, 95% CI 0.98 to 2.49), although there was heterogeneity ($p<0.01$, $I^2=91.3\%$). The results remained consistent when stratified by study type, effect type, effect adjustment, and study quality: case control study, (OR 1.62, 95% CI 1.18 to 2.23); cohort study, (OR 1.44, 95% CI 1.04 to 1.99); odds ratio (OR 1.62, 95% CI 1.18 to 2.23); hazard ratio (OR 1.44, 95% CI 1.04 to 1.99); crude effect size (OR 1.53, 95% CI 0.88 to 2.64); adjusted effect size (OR 1.47, 95% CI 1.12 to 1.93); lower quality study (OR 1.79, 95% CI 1.21 to 2.67); higher quality study (OR 1.43, 95% CI 1.08 to 1.90). Heterogeneity remained consistent when studies were stratified by study design, effect type, adjusted effect size, and higher quality studies. Interestingly, no significant heterogeneity was present in studies reporting crude effect sizes ($p=0.51$, $I^2=0\%$) and lower quality studies ($p=0.57$, $I^2=0\%$).

When stratified by whether the study had adjusted for certain covariates (age, ApoE status, cardiovascular disease), we found that, among studies that did not adjust for age, HSV-1 infection was associated with an increased risk of developing dementia or Alzheimer's disease (OR 1.70, 95% CI 1.19 to 2.42). Among studies that adjusted for age, HSV-1 infection was associated with an increased risk of dementia or Alzheimer's disease (OR 1.48, 95% CI 1.16 to 1.93). However, heterogeneity was present in these studies ($p<0.01$, $I^2=94.7\%$), and absent in the studies without age adjustment. Among studies that did not adjust for ApoE status, HSV-1 infection was associated with an increased risk of dementia or Alzheimer's disease (OR 1.54, 95% CI 1.11 to 2.15). There

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was significant heterogeneity among these studies ($p<0.01$, $I^2=94.8\%$) (Figure 3). Among studies that adjusted for ApoE status, HSV-1 infection was also associated with an increased risk of dementia or Alzheimer's disease (OR 1.27, 95% CI 1.02 to 1.58). There was no significant heterogeneity in the studies that adjusted for ApoE status. Finally, among studies that did not adjust for cardiovascular disease, HSV-1 infection was not associated with a significantly increased risk of dementia or Alzheimer's disease (OR 1.31, 95% CI 0.98 to 1.74). However, among studies that did adjust for cardiovascular disease, HSV-1 infection was associated with an increased risk of dementia or Alzheimer's disease (OR 1.75, 95% CI 1.16 to 2.64). Adjusting for cardiovascular disease presence did not explain the study heterogeneity.

We also performed meta-regression to evaluate the dual effects of adjusting for various covariates. When assessing the effects of diagnosis and age-adjustment, we found that studies which adjusted for age had a lower but still significant effect size, without significant heterogeneity (p=0.46), compared to studies without age-adjustment. Compared to studies without ApoE status adjustment, studies that adjusted for ApoE status had a lower but still significant effect size, without significant heterogeneity (p=0.33) (Figure 4). Finally, compared to studies that did not adjust for cardiovascular disease, studies that adjusted for cardiovascular disease had a larger effect size without significant heterogeneity (p=0.25).

The results of the meta-regression can be found in Table 3. Compared to studies that did not adjust for age (OR 0.50, 95% CI 0.27 to 0.93) or ApoE status (OR 0.55, 95% CI 0.34 to 0.92), adjustment for each of these factors significantly decreased the effect size. In contrast, adjustment for cardiovascular disease significantly increased the effect size (OR 2.20, 95% CI 1.34 to 3.61).

After constructing the funnel plot (Figure 5), several studies did not fall within the pseudo-95% confidence interval. The Egger's test to evaluate publication bias was nonsignificant (p=0.599). A trim-and-fill analysis found no changes in the estimated effect size (OR=1.48, 95% CI: 1.16, 1.89). Finally, the Galbraith plot (Supplementary Figure 1) demonstrated the presence of outliers.

DISCUSSION

We conducted a systematic review and meta-analysis of the relationship between HSV-1 infection and dementia or Alzheimer's disease. We found that HSV-1 infection was associated with a significantly increased risk of developing either dementia or Alzheimer's disease. The results were consistent when stratifying studies by study design, diagnosis type, type of effect size reported (crude of adjusted effect sizes), study quality, and adjustment for age, ApoE status, or cardiovascular disease. Results of the funnel plot suggested a presence of publication bias; however, the Egger's test was nonsignificant, indicating an absence of small-study bias, and the trim-and-fill analysis showed no changes in estimated effect size. The Galbraith plot suggested that outliers were present and contributed to the observed heterogeneity.

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Our findings extend prior studies on HSV-1 infection and dementia. In 2019, Warren-Gash et al conducted a systematic review and meta-analysis and found no significant difference in the detection of HSV-1 in the brains of dementia patients and controls in 17 case-control studies (pooled OR 1.31 [95% CI 0.90–1.90])[22]. However, the authors noted that those studies were at high risk of bias, and that 14 of 17 studies had under 100 participants. In studies with lower or no risk of bias, there still was no association between HSV-1 and rates of cognitive decline in patients. Similarly, in a meta-analysis conducted in 2023 of 19 studies, Elhalag et al found no significant difference in Alzheimer's disease risk between those infected with HSV-1 and controls (RR 1.16 [95% CI 0.99–1.35])[23]. However, their review only included two studies with HSV-1-specific results. In contrast, a 2015 study by Steel and Eslick found significant associations between HSV-1 and Alzheimer's disease (pooled OR 1.38 [95% CI 1.03–1.84])[24]. More recently, a systematic review and meta-analysis performed in 2025 by Ji et al also found significant associations between HSV-1 and Alzheimer's disease (pooled OR 1.46 [95% CI 1.14–1.86])[25]. Those studies reported similar effect sizes to those presented in our study. Of note, a retrospective cohort study using a large, electronic database was published after the dates of our search and supports our findings[26]. In that study, Araya et al found that a history of HSV-1 infection was associated with an increased risk of developing dementia (OR 2.16 [95% CI 1.76–2.66]).

Several hypotheses surrounding the mechanism of the potential role of HSV-1 infection in dementia and Alzheimer's disease have been proposed. The progressive neuronal cell death in Alzheimer's disease is typically associated with abnormal accumulation of amyloid-beta peptide (Aβ) plaques and neurofibrillary tangles of tau protein[27]. As such, most of the research surrounding Alzheimer's disease is focused on finding an etiology for those accumulations and/or preventing and reducing them. In their "Antimicrobial Protection Hypothesis," Moir et al suggested that Aβ plays a role in the innate immune system as a protective antimicrobial peptide, citing several studies that provide evidence of its activity against several pathogens, including HSV-1, influenza A, and *C. albicans*[28–31]. They hypothesized that Aβ accumulates as a defense mechanism against infection, which leads to not only neurofibrillary tangles but also chronic inflammation and microglia activation. Those factors synergistically cause neurodegeneration and eventually lead to dementia. Given that HSV-1 is known to infect the central nervous system, particularly the hippocampus, it seems reasonable to infer that its presence can cause increased immune activity and Aβ proliferation. Our study also examined the statistical effects of adjusting for cardiovascular disease status. Cardiovascular disease is known to accentuate any neurological dysfunction caused by Aβ and tau tangles, primarily by decreasing the clearance of their accumulation and increasing the susceptibility of the brain to microvascular injury[32,33]. There is an increasing amount of research suggesting that not only are cardiovascular diseases linked to dementia, but that the risk factors for those diseases themselves can also act as independent risk factors[34]. Many of these risk factors—including hypertension, diabetes mellitus, hypercholesterolemia, and smoking—are ubiquitous yet preventable, highlighting another avenue in the multifaceted approach to dementia and Alzheimer's disease[35].

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From a neuroanatomical viewpoint, the relatively high vulnerability of the hippocampus to HSV-1 infection has also been suspected to play a role in the virus's connection to dementia. The hippocampus plays a critical role in memory and learning and has been shown to undergo characteristic changes in the brains of not only Alzheimer's disease and dementia patients, but those with depression, schizophrenia, and mild cognitive impairment[36]. This region of the brain contains an abundance of receptors necessary for HSV-1's entry into cells and less antiviral immune activity, creating an advantageous environment for the virus[37]. HSV-1 has also been shown to induce neuronal apoptosis in the brains of those with herpes simplex encephalitis[38]. The ability to modulate neuronal survival as well as take advantage of several host signaling pathways lends to its ability to propagate through the central nervous system[39]. Another important aspect of HSV-1 is its tendency to activate several inflammatory processes and induce expression of IL-1β, TNF-α, IL-6, IL-8, and other proinflammatory molecules[40]. This inflammatory state, combined with the immune-activated state mentioned above, could very well contribute to the progressive neurodegeneration seen in dementia and Alzheimer's disease.

The strengths of this study include a large sample size from several countries and the high quality of evidence of the included studies. In addition to focusing on HSV-1 infection only, the sub analyses were stratified by various covariates and study-level variables showed consistent results with our main analysis. However, some important limitations should be noted. First, many of the studies used different methods to identify and/or diagnose dementia or Alzheimer's disease. Some studies used data from medical records, while others had a healthcare provider evaluate subjects using certain specific criteria. Furthermore, in some studies that used patient interviews to diagnose outcomes, there were several different diagnostic criteria used. Second, as many of the studies were retrospective in design, we are unable to infer causation in our conclusions. Our review lacked prospective, long-term randomized controlled trials that offer reduced risk of bias and the potential to demonstrate causality. Third, many of the studies did not provide information regarding the use of anti-herpetic medications, which has been shown to reduce the risk of developing dementia and Alzheimer's disease[41]. Finally, there was a general lack of information regarding dementia severity, leaving us unable to perform analyses stratified by dementia severity. Future studies that address this limitation could provide a more nuanced view of the associations seen in our results.

Importantly, several of the meta-regressions had significant levels of heterogeneity between studies. We found that studies that did not adjust for ApoE status are contributing the most to the heterogeneity. Given the well-established role of the ApoE allele in the pathogenesis of Alzheimer's disease and dementia, it is possible that there is some level of confounding in the results from those studies. At the same time, studies that adjusted for age are also significantly contributing to the observed heterogeneity, in spite of age playing the largest role in Alzheimer's disease and dementia development. We hypothesize that the cohort study conducted by Torniainen-Holm et al is a significant source of the heterogeneity, as its results suggested a somewhat protective effect of HSV-1 infection against dementia or Alzheimer's disease. However,

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their results showed that HSV-1 infection was associated with poorer cognitive performance in certain assessments[42]. This discrepancy could be explained by the reliance on diagnostic codes in the subjects' medical records, which could lead to misdiagnosis and misclassification of dementia or Alzheimer's disease. However, the heterogeneity in our results is likely due to a combination of several factors that are inherent to relying on observational studies—many of which were retrospective in nature.

Our review adds to the growing body of evidence surrounding microbial etiologies of dementia and Alzheimer's disease. As one of the most common human viral infections, clarification of the role of HSV-1 infection in neurodegenerative diseases could have widespread implications for the prevention of dementia and Alzheimer's disease. Further research is necessary to explore the biological mechanisms behind these associations and avenues for treatment and prevention. Future directions might include prospective studies evaluating anti-herpetic medications or preventive vaccines and their effects on the incidence of dementia or Alzheimer's disease.

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Conflicts of Interest: The authors have no conflicts of interest to declare.

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Patient Consent Statement: This study does not include factors necessitating patient consent.

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Table 1. Baseline Characteristics of Included Studies

Author, Year	Country	Study Design	No. of Subjects	Mean Age (years)
Beffert, 1998	Canada	Case Control	110	75.6
Bu, 2015	China	Case Control	263	69.5
Itabashi, 1997	Japan	Case Control	69	75.1
Kobayashi, 2013	Japan	Case Control	119	75.3
Lindman, 2019	Sweden	Case Control	720	61.2
Lovheim, 2015	Sweden	Cohort	3,432	62.7
Mekli, 2022	United Kingdom	Case Control	9,431	67.0
Murphy, 2021	Netherlands	Cohort	1,915	71.3
Torniainen-Holm, 2019	Finland	Cohort	5,783	53.0
Tzeng, 2018	Taiwan	Cohort	33,448	68.1
Vestin, 2024	Sweden	Cohort	1,002	70.2

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Table 2. Quality Assessment Results. A total of 4 stars can be awarded in the Selection category, 2 in Comparability, and 3 in Exposure or Outcome, for a total of 9 possible stars.

Author, Year	Selection	Comparability	Exposure (case-control)	Outcome (cohort)	Total Stars Awarded
Beffert, 1998	✪✪✪✪		✪✪✪	-	**7**
Bu, 2015	✪✪✪	✪✪	✪✪✪	-	**8**
Itabashi, 1997	✪✪	✪	✪✪✪	-	**6**
Kobayashi, 2013	✪✪		✪✪✪	-	**5**
Lindman, 2019	✪✪✪✪	✪✪	✪✪✪	-	**9**
Lovheim, 2015	✪✪✪✪	✪✪	-	✪✪✪	**9**
Mekli, 2022	✪✪✪	✪	✪✪✪	-	**7**
Murphy, 2021	✪✪✪✪	✪✪	-	✪✪✪	**9**
Torniainen-Holm, 2019	✪✪✪✪	✪✪	-	✪✪	**8**
Tzeng, 2018	✪✪✪	✪✪	-	✪✪✪	**8**
Vestin, 2024	✪✪✪✪	✪✪	-	✪✪✪	**9**

Table 3: Meta-Regression to Evaluate the Effect of Covariate Adjustment

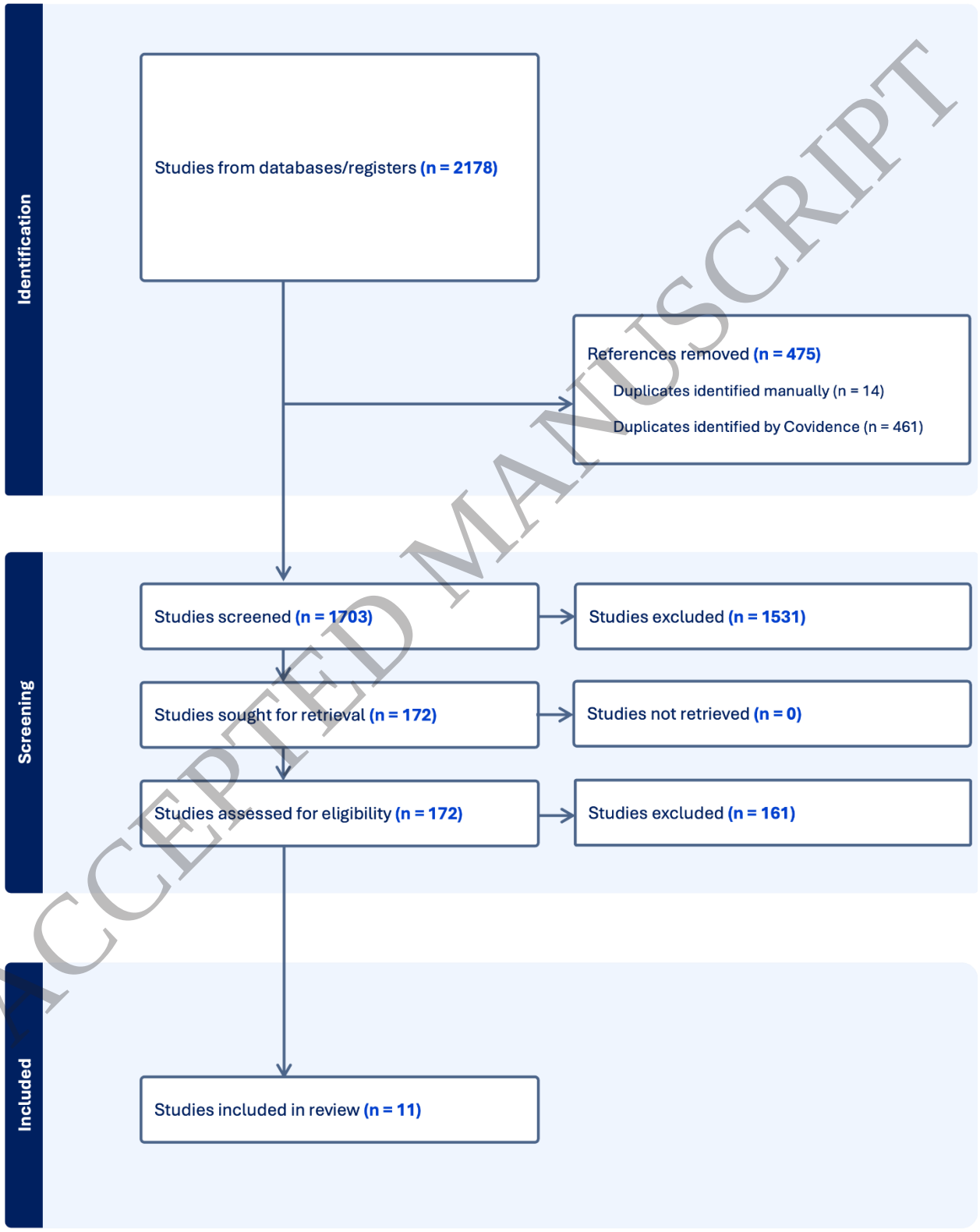
Covariate	**OR (95% CI)**	**p-value**
Age	0.50 (0.27, 0.93)	0.031
ApoE	0.55 (0.34, 0.92)	0.025
Cardiovascular Disease	2.20 (1.34, 3.61)	0.005

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FIGURE CAPTIONS

Figure 1. Study selection flowchart.

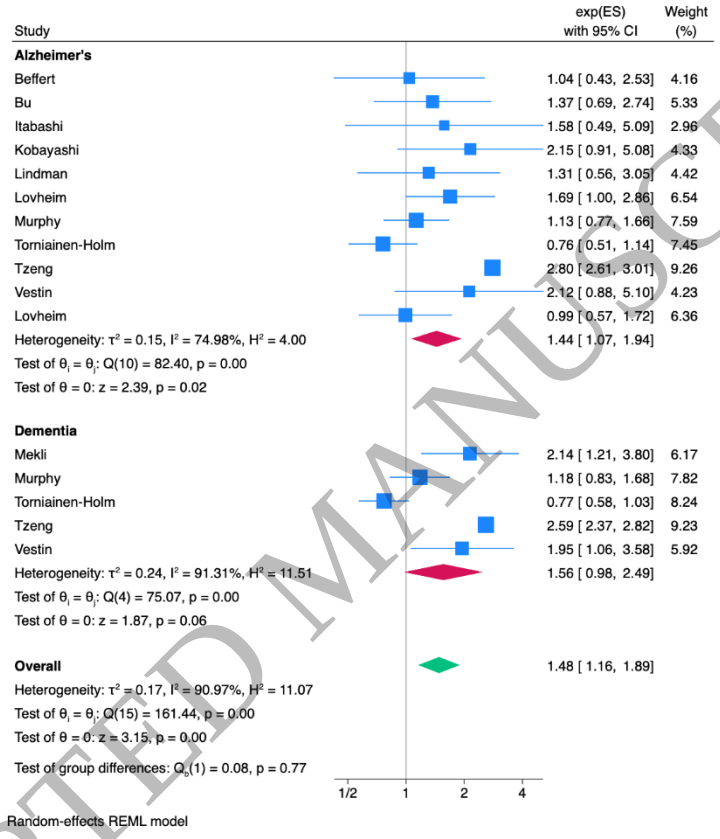


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Alt text: A flowchart detailing each step of the study selection, including the initial search, screening, and final inclusion of studies.

Figure 2. Odds ratios of developing Alzheimer's disease or dementia among patients infected with HSV-1. Abbreviations: ES, effect size (odds ratio); CI, confidence interval; I^2, heterogeneity quantified using the I^2 statistic.

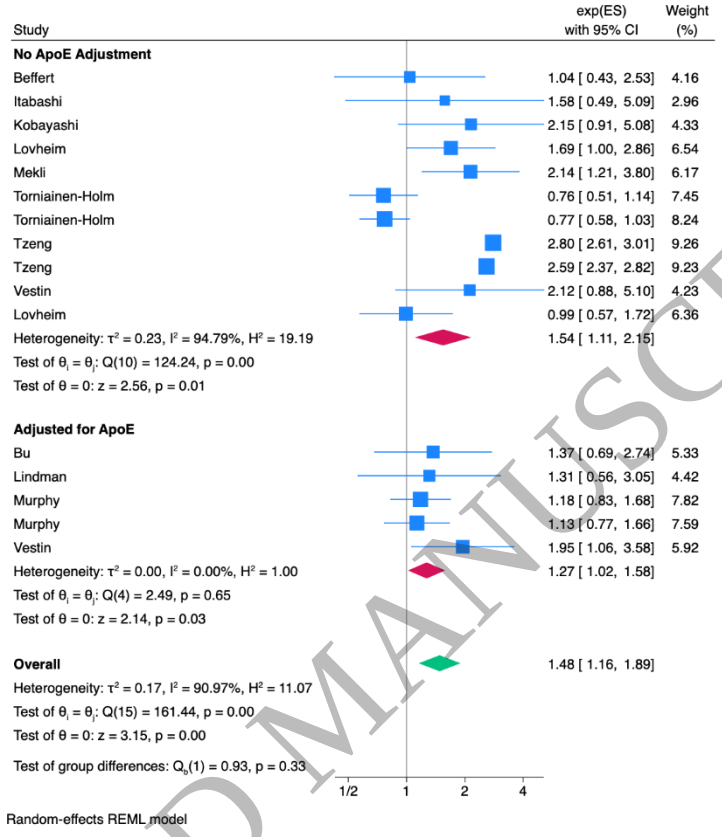


Alt text: Forest plot displaying odds ratios of developing dementia or Alzheimer's disease, stratified by study.

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Figure 3. Odds ratios of developing Alzheimer's disease or dementia among patients infected with HSV-1. Stratified by whether or not the study adjusted their results for subject ApoE status.

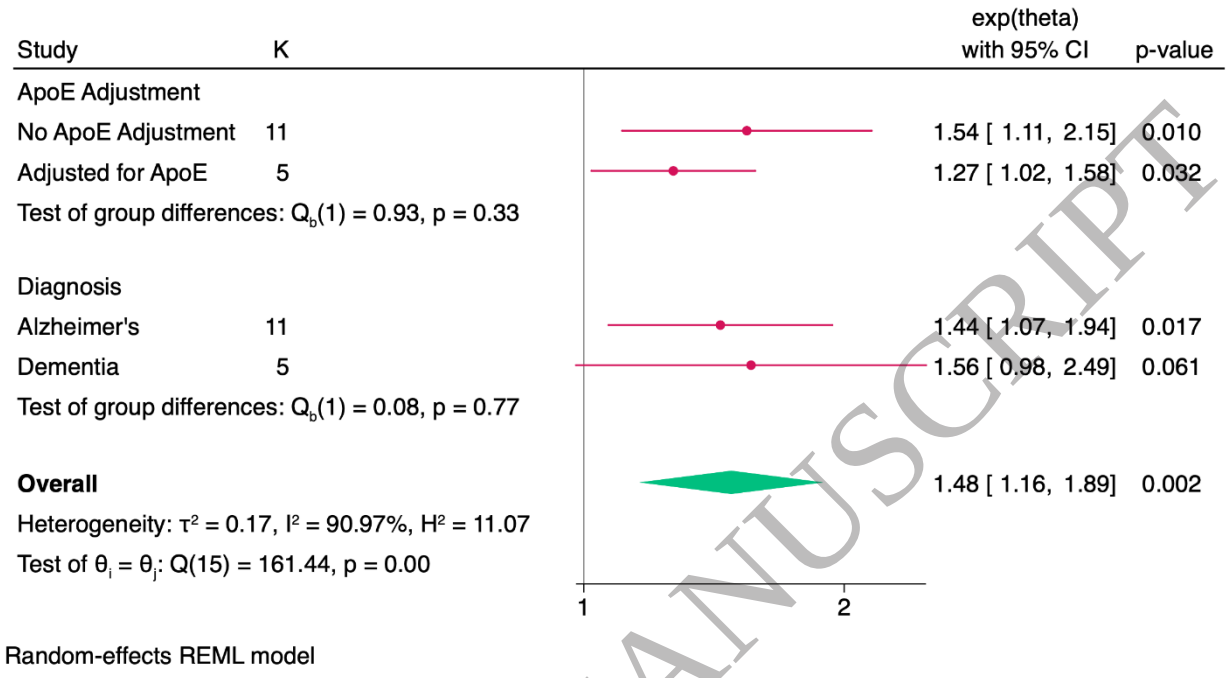


Alt text: Forest plot displaying odds ratios of developing dementia or Alzheimer's disease, stratified by adjustment for ApoE status.

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Figure 4. Forest plots stratified by ApoE status adjustment and diagnosis.

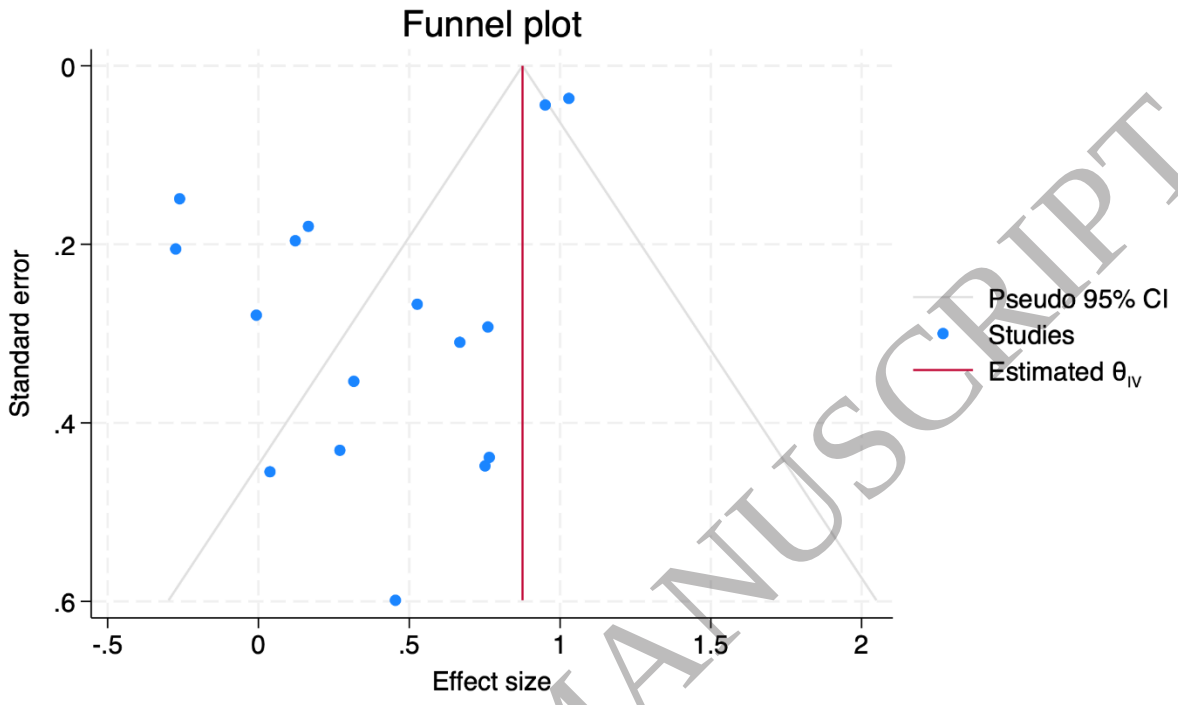


Alt text: Forest plot analyzing the effect that adjusting for ApoE status has on effect sizes.

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Figure 5. Funnel plot assessing publication bias.



Alt text: A funnel plot with studies represented by blue points. Points lying outside of the 95% confidence interval indicate the presence of publication bias.

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