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Herpes simplex virus infection and the risk of dementia: a systematic review and meta-analysis

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Aim: The authors aimed to perform a meta-analysis to evaluate the association between herpes simplex virus (HSV) infection and the risk of developing dementia.

Methods: The authors searched the following databases: PubMed, Scopus, Cochrane Library, and Web of Science. The authors included any randomized control trials and controlled observational studies that investigated the prevalence of dementia in HSV-infected patients and HSV-free control group. Also, if the studies measured the levels of HSV antibodies and incidence of these antibodies in patients with dementia compared with a healthy control group.

Results: After a comprehensive literature search, 19 studies were included in the meta-analysis with 342 535 patients included in the analysis. The pooled analysis showed a statistically significant association between Alzheimer's disease (AD), mild cognitive impairment (MCI), and increased levels of IgG titer group [mean difference (MD) = 0.99, 95% confidence interval (CI) = 0.36–1.63, P-value = 0.002], (MD = 0.80, 95% CI = 0.26–1.35, P-value = 0.004), respectively. Additionally, the generic inverse variance showed a statistically significant association between the HSV group and increased incidence of dementia compared with the no HSV control group [risk ratio (RR) = 2.23, 95% CI = 1.18–2.29, P-value <0.00001]. Moreover, this analysis showed no statistically significant difference between the AD group and the control group in anti-HSV IgM titer n (%) outcome (RR = 1.35, 95% CI = 0.91–2.01, P-value = 0.14), respectively.

Conclusion: This study revealed that AD and MCI patients have increased levels of IgG antibodies titer against HSV infection. The study showed a significant association between HSV infection and increased incidence of dementia. Thus, regular follow-up of HSV patients' IgG titer levels could be useful in the prevention of dementia in these patients.

Keywords: AD, dementia, HSV, MCI, meta-analysis

Introduction

Dementia is described by the World Health Organization and Alzheimer's Disease International as 'a syndrome that results from a brain disease – mostly chronic or progressive in nature – in which there is multiple higher cortical functions disturbance, including memory, thinking, comprehension, orientation, calculation, language, learning capacity, and judgment'[1]. According to statistics from the World Health Organization, dementia is the main cause of dependency and disability among older people globally and the largest contributor to disease burden in advanced market economies[1]. Currently, 5% of adults over 65 years have dementia, and that

HIGHLIGHTS

- We aimed to perform a meta-analysis to evaluate the association between herpes simplex virus (HSV) infection and the risk of developing dementia.
- The pooled analysis showed a statistically significant association between Alzheimer's disease (AD), mild cognitive impairment (MCI), and increased levels of IgG titer, respectively. Additionally, the generic inverse variance showed a statistically significant association between HSV group and increased incidence of dementia compared with no HSV control group.
- Our study revealed that AD and MCI patients have increased levels of IgG antibodies titer against HSV infection. The study showed a significant association between HSV infection and increased incidence of dementia. Thus, regular follow-up of HSV patients IgG titer levels could be useful in prevention of dementia in these patients.

number rises to nearly 50% for those over 90[1]. More than 90% of dementia cases present after the age of 65, making aging the most significant risk factor for dementia. The incidence and prevalence of dementia continue to rise progressively over the world as the average population age rises[2]. According to the World Alzheimer Report, a thorough meta-analysis of population-based studies,

there are currently 46.8 million dementia sufferers worldwide, and that number is predicted to rise to 131.5 million by the year 2050[3]. By 2030, it is expected that the total cost of dementia-related medical expenses and lost wages, which is currently $81 billion (USD) annually, will reach $2 trillion[3]. An intervention that delayed dementia onset by 5 years in the USA alone would save Medicare costs by $283 billion in the year 2050[4].

Alzheimer's disease (AD), vascular dementia (VaD), frontotemporal dementia and associated syndromes, Lewy body dementias, and prion disorders are the most prevalent dementia subtypes[2]. Up to 80% of dementia diagnoses are due to AD, which is by far the most frequent cause of dementia[5]. Between 2000 and 2014, there was an 89% increase in mortality attributed to AD[6]. The estimated yearly cost of healthcare linked to AD, including direct and indirect costs, is close to $500 billion[7].

Mild cognitive impairment (MCI) is subjective and objective deterioration in cognition and function that does not fulfill the criteria for a diagnosis of dementia but is higher than what would be expected given an individual's age and level of education[8–10]. Thus, it represents the preclinical, transitional stage between healthy aging and dementia[11]. Around 10–15% of those with amnestic MCI develop AD annually, as opposed to 1–2% of the population of healthy older adults[8,12]. Histopathologically, AD is distinguished by two features, the presence of intracellular neurofibrillary tangles (NFT), consisting of hyperphosphorylated aggregates of the microtubule-associated protein tau, and extracellular amyloid plaques, consisting of an amyloid beta (Aβ) protein core[13]; however, both MCI and AD pathogenesis show early cognitive changes[14]. Researchers and physicians consider MCI as a 'window' in which it may be feasible to intervene and prevent the progression to dementia[11].

Herpes simplex virus (HSV) type 1 and type 2 are human neurotropic, host-adapted viruses that can cause both lytic and latent infections[15], and infect a relatively large portion of the human population with rates of seropositivity for HSV-1 and HSV-2 being in the order of 67% and 11%, respectively[16,17]. Although the precise causes of dementia are not known, immunity and inflammation have been suggested as potential development pathways for this illness[18]. HSV-1 is a potential pathogen for raising the risk of dementia since it is a neuroinvasive and neurotoxic virus that can reach the brain through peripheral nerves[19,20]. Moir *et al.* explained HSV-1's potential role in dementia development by triggering an innate immunological response that causes Aβ formation[18], which results in Aβ accumulation causing neuroinflammation. Chronic inflammation causes brain cell destruction (neurodegeneration), which may eventually cause dementia. However, some recent studies found that HSV could be a substantial risk factor for AD[21–24]; additionally, they discovered that using antiherpetic drugs cut the risk by roughly 90%[24], other studies did not detect a link between HSV infection and an elevated risk of dementia[25].

Due to this conflict in results, we aimed to perform a meta-analysis to evaluate the association between HSV infection and the risk of developing dementia.

Methods

The Cochrane Handbook of Systematic Reviews[26], the PRISMA (Preferred Reporting Items of Systematic Reviews and Meta-Analyses) 2020 Update, the MOOSE Guidelines, and the standards for PRISMA were all followed when conducting this review. A PRISMA 2020 Checklist completed form was submitted[27,28].

Search strategy

We searched four databases: PubMed, Scopus, Web of Scopus, and Cochrane Library from inception to 11 September 2022, using MeSH terms to form the following search strategy: (Human Herpes Simplex Virus) AND ("Dementia" OR "Alzheimer's disease" OR "Mild cognitive impairment"). As a secondary check, two authors manually searched the references of the included studies.

Study selection

Our inclusion criteria were: (1) any randomized control trials and (2) controlled observational studies as cross-sectional, prospective, or retrospective cohort and case–control studies that investigated the prevalence of dementia in HSV-infected patients and HSV-free control group. Also, if the studies measured the levels of HSV antibodies and incidence of these antibodies in patients with dementia compared with a healthy control (HC) group.

Exclusion criteria: (1) animal studies, (2) brain specimen-based studies of dead patients, (3) case reports, (4) case series, (5) editorials, and (6) reviews.

We divided the authors into two groups. Each group conducted the screening and data collection individually. Screening passed by two processes: (1) Title and abstract screening and (2) full-text screening. Two authors from each group performed title and abstract screening of each study using the Covidence platform; the study was included if it seemed eligible for inclusion according to our inclusion criteria, then the two authors performed full-text screening of each study included from the title and abstract screening phase. The first author resolved the disputes and compared the results from the two groups. The study was finally included in our analysis at this phase if it met our inclusion criteria.

Data extraction

Two Excel sheets were created from the data we extracted from the included studies; in the first one, one author extracted baseline characteristics: age, sex, study arms, study design, and the number of patients in each group, and the other contained outcomes: anti-HSV IgG titer, seropositive/prevalence of IgG n (%), anti-HSV IgM titer n (%), HSV DNA n (%), the incidence of dementia, prevalence of dementia after antiherpetic medication, HSV-1-specific IgG3 n (%), and HSV-1 avidity.

Quality assessment

Newcastle–Ottawa Scale (NOS) tool was used to assess the quality of the included observational studies. Each study was ranked as good, fair, or poor quality.

Data analysis

Review Manager Software version 5.4 was used to perform the meta-analysis; the continuous outcomes were measured as mean difference (MD) and standard deviation (SD), and the dichotomous outcomes as risk ratios (RR) with a 95% confidence interval (CI). In case of heterogeneity ($\chi^2 P$-value <0.1), a random

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effect model was adopted, otherwise, a fixed-effect model was employed, in general; the results were considered significant if the *P*-value was less than 0.05.

Results

Summary of studies

After a search of the literature, 553 studies resulted, and then 413 were eligible for the title and abstract screening after duplicate removal. Of the 413, 329 were irrelevant and 84 studies were eligible for full-text screening. Finally, 19 studies[15,24,25,29–42] were included in the meta-analysis after the full-text screening, as shown in the PRISMA in Figure 1.

The overall quality was good in 12 studies and fair in seven studies, as shown in Table 1.

The total number of patients included in the study is 342 535 patients, 96 049 patients in the HSV group and 242 981 in the no HSV control group. In addition to 2011 patients in the AD group and MCI group, and 1494 patients in the control group, other baseline data are shown in Table 2.

Outcomes

We have summarized all the results of the outcomes in Table 3.

Anti-HSV IgG titer (AD), (MCI), and (AD and MCI), respectively

The pooled analysis showed a statistically significant association between the AD group and increased levels of IgG titer compared with the control group (MD = 0.99, 95% CI = 0.36–1.63, *P*-value = 0.002). We observed a significant heterogeneity among studies (*P* < 0.00001, I^2 = 84%). It was solved by leave-one-out test by removing Kobayashi, 2014 (*P* = 0.23, I^2 = 26%), and the analysis showed a statistically significant association between the AD group and increased levels of IgG titer

Figure 1. PRISMA (Preferred Reporting Items of Systematic Reviews and Meta-Analyses) flow diagram.

compared with the control group (MD = 1.16, 95% CI = 0.78–1.54, *P*-value <0.00001), Figure 2. The pooled analysis showed a statistically significant association between the MCI group and increased levels of IgG titer compared with the control group (MD = 0.80, 95% CI = 0.26–1.35, *P*-value = 0.004). We observed a significant heterogeneity among studies (*P* = 0.001, I^2 = 77%). It was solved by leave-one-out test by removing Kobayashi, 2014 (*P* = 0.54, I^2 = 0%), and the analysis showed a statistically significant association between the AD group and increased levels of IgG titer compared with the control group (MD = 1.05, 95% CI = 0.71–1.39, *P*-value <0.00001), Figure 3. The pooled analysis showed no statistically significant difference between the AD group and the MCI group (MD = – 0.10, 95% CI = – 0.27 to 0.07, *P*-value = 0.23). We observed no significant heterogeneity among studies (*P* = 0.12, I^2 = 43%), Figure 4.

Seropositive/prevalence of IgG n (%) (AD), (MCI), and (AD and MCI), respectively

The pooled analysis showed a statistically significant association between the AD group and increased IgG prevalence compared with the control group (RR = 1.04, 95% CI = 1.01–1.07, *P*-value = 0.01). We observed no significant heterogeneity among studies (*P* = 0.23, I^2 = 24%), Figure 5. The pooled analysis showed no statistically significant difference between the MCI group and the control group (RR = 1.05, 95% CI = 0.94–1.16, *P*-value = 0.40). We observed a significant heterogeneity among studies (*P* = 0.006, I^2 = 76%). It was solved by leave-one-out test by removing Kobayashi, 2014 (*P* = 0.14, I^2 = 50%), and the analysis showed no statistically significant difference between the MCI group and the control group (RR = 1.01, 95% CI = 0.94–1.08, *P*-value = 0.78), Figure 6. The pooled analysis showed no statistically significant difference between the AD group and the MCI group (RR = 0.98, 95% CI = 0.93–1.03, *P*-value = 0.37). We observed no significant heterogeneity among studies (*P* = 0.33, I^2 = 13%), Figure 7.

Anti-HSV IgM titer n (%) and HSV DNA n (%) (AD)

The pooled analysis showed no statistically significant difference between the AD group and the control group in anti-HSV IgM titer *n* (%) outcome (RR = 1.35, 95% CI = 0.91–2.01, *P*-value = 0.14), with no heterogeneity between the two studies (*P* = 1.00, I^2 = 0%) and HSV DNA *n* (%) (AD) outcome (RR = 0.42, 95% CI = 0.05–3.75, *P*-value = 0.44), respectively. We observed a significant heterogeneity between the two studies (*P* = 0.03, I^2 = 79%), Figures. 8 and 9, respectively.

Incidence of dementia

The generic inverse variance showed a statistically significant association between the HSV group and increased incidence of dementia compared with no HSV control group (RR = 2.23, 95% CI = 1.18–2.29, *P*-value <0.00001). We observed a significant heterogeneity between two studies (*P* < 0.00001, I^2 = 100%), Figure 10.

Prevalence of dementia after antiherpetic medication

The pooled analysis showed no statistically significant difference between patients who received antiherpetic medication and patients who did not receive antiherpetic medication (RR = 0.45,
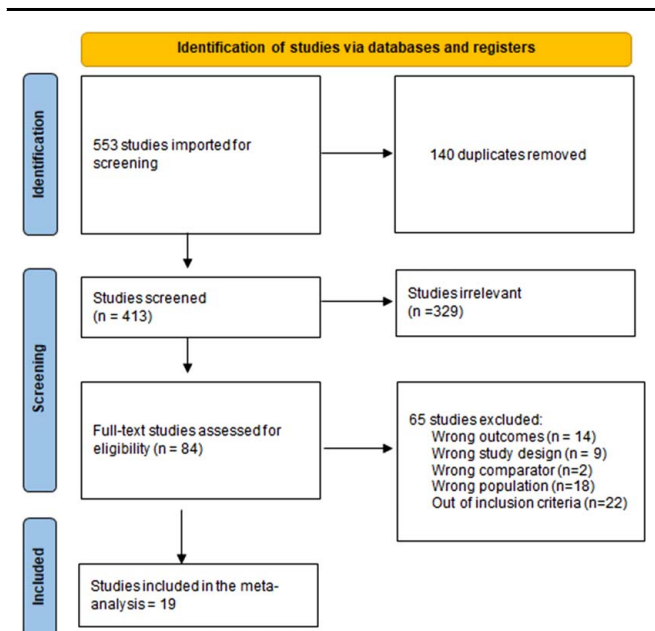
Table 1

Quality assessment

	Selection				Exposure					
Case definition	Representativeness	Selection of controls	Definition of controls	Comparability	Ascertainment	Same method	Non-response rate	Total score	AHRQ standards
NOS scale risk of bias assessment									
1	1	0	1	2	1	1	1	8	Good
1	0	0	1	2	1	1	1	7	Good
1	0	0	1	2	1	1	1	7	Good
1	0	1	1	2	1	1	1	8	Good
1	1	1	1	1	1	1	1	8	Good
0	1	1	0	1	1	1	0	5	Fair
1	0	1	1	1	1	1	1	7	Good
1	0	1	1	1	1	1	1	7	Good
1	0	1	0	1	1	1	1	6	Fair
1	0	0	1	1	1	1	0	5	Fair
1	0	0	0	2	1	1	0	5	Fair
1	0	1	1	2	1	1	0	7	Good
1	1	1	1	2	1	1	0	8	Good
1	1	1	1	2	1	1	1	9	Good
1	1	0	1	2	1	1	0	7	Good
1	0	0	1	1	1	1	1	6	Fair
1	0	1	1	1	1	1	0	6	Good
1	0	0	1	2	1	1	0	6	Fair
1	0	0	1	2	1	1	0	6	Fair

AHRQ, Agency for Health Research and Quality.

Table 2

Baseline characteristics

Study design	Arms of the study	Number of patients in each group		Age (years)		Sex (*n*)	
		Case	Control	Case	Control	Case	Control
Retrospective cohort	HSV patients, healthy control group	87 687	217 895	50–80	50–80	Males = 81893	Males = 206 032
Case–control study	Alzhiemer's disease (AD), healthy controls (HC)	365	365	55–65	55–65	N/A	N/A
Case–control study	AD, MCI, healthy controls	81	67	70–80	70–80	AD (M:F) = (28:42), MCI (30:31)	M:F = (28:39)
Case–control study	AD, MCI, HC	AD = 56, MCI = 48	37	75–85	75–85	AD (M:F) = (24:32), MCI (74.1:5.7)	M:F = (14:23)
Retrospective cohort	HSV patients, healthy control group	8362	25 086	50–65	50–65	Males = 3638	Males = 14 172
Case–control study	AD, MCI, HC	AD = 67, MCI = 58	61	70–80	70–80	AD (M:F) = (29:38), MCI (26:32)	M:F = (27:34)
Case–control study	AD, MCI, HC	AD = 79, MCI = 57	81	70–80	70–80	AD (M:F) = (32:47), MCI (22:35)	(34:47)
Case–control study	AD, HC	128	135	70–80s	70–80	Males = 65	Males = 66
Case–control study	AD, HC	338	324	60–70	60–70	Males = 83	Males = 77
Case–control study	AD, MCI, HC	AD = 83, MCI = 68	74	65–80	65–80	AD (M:F) = (33:50), MCI (31:37)	M:F = (32:42)
Case–control study	AD, MCI, HC	AD = 85, MCI = 34	34	70–85	66, 67	Males: AD = 28.4%, MCI = 44.1%	Males = 57.1%
Case–control study	AD, HC	83	51	70–80	70–80	(M:F) = 33:50	M:F = 20:31
Case–control study	AD, HC	27	13	52–91	62 –87	(15 males, 12 females)	(7 males, 6 females)
Case–control study	AD, HC	46	44	54–96	58–95	10 males	25 males
Case–control study	AD, HC	19	21	64–92	64–92	2 males	7 males
Case–control study	AD, HC	33	28	64–92	59–85	10 males	13 males
Retrospective cohort study	AD, MCI, HC	AD = 43, MCI = 36	25	M = 74.97, SD = 5.49	N/A	(M:F) = 15:21	N/A
Case–control study	AD, HC	34	40	64–94	64–89	(M:F) = 8:26	(M:F) = 20:20
Case–control study	AD, HC	53	39	45–96	58–95	(M:F) = 12:41	(M:F) = 23:16

F, females; HSV, herpes simplex virus; M, males; M, mean; MCI, mild cognitive impairment; SD, standard deviation.

Table 3

Summary of outcomes

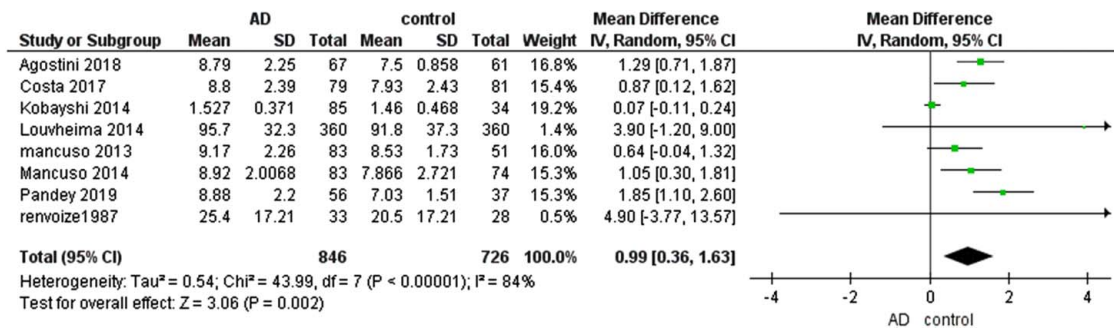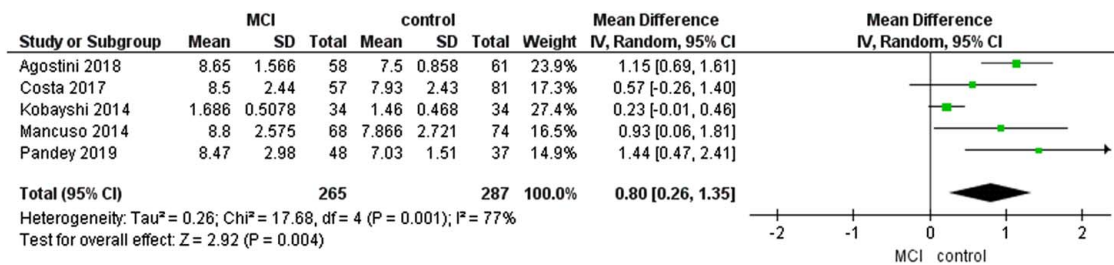| Outcome	Risk ratio	Mean difference	Confidence interval (CI)	P
Anti-HSV IgG titer (AD)		1.16	0.78 – 54	< 0.00001
Anti-HSV IgG titer (MCI)		1.05	0.71 – 1.39	< 0.00001
Anti-HSV IgG titer (AD and MCI)		− 0.10	− 0.27 to 0.07	*0.23*
Seropositive/prevalence of IgG *n* (%) (AD)	1.01		0.94 – 1.08	0.78
Seropositive/prevalence of IgG *n* (%) (MCI)	1.05		0.94–1.16	0.40
Seropositive/prevalence of IgG *n* (%) (AD and MCI)	0.98		0.93–1.03	0.37
Anti-HSV IgM titer *n* (%)	1.35		0.91–2.01	0.14
HSV DNA *n* (%) (AD)	0.42		0.05–3.75	44
Incidence of dementia	2.23		1.18–2.29	< 0.00001
Prevalence of dementia after antiherpetic medication	0.45		0.10–2.07	*= 0.30*
HSV-1-specific IgG3 *n* (%) (AD)	1.16		0.99–1.35	0.07
HSV-1-specific IgG3 *n* (%) (MCI)	1.36		1.18–1.56	< 0.0001
HSV-1-specific IgG3 *n* (%) (AD and MCI)	0.85		0.76–0.95	0.006
HSV-1 avidity (AD)		2.26	− 0.36 to 4.88	0.09
HSV-1 avidity (MCI)		6.07	− 3.65 to 15.70	0.22
HSV-1 avidity (AD and MCI)		− 4.07	− 13.48 to 5.34	0.07
AD IgG titer less than 65 years subgroup		1.89	1.15–2.64	< 0.00001
AD IgG titer equal to or more than 65 years subgroup		1	0.66–1.34	< 0.00001
MCI IGg titer less than 65 years subgroup		1.44	0.47–2.41	0.004
MCI IGg titer equal to or more than 65 years subgroup		1	0.64–1.36	< 0.00001
AD and MCI IgG titer less than 65 years subgroup		0.41	− 0.61 to 1.43	0.43
AD and MCI IgG titer equal to or more than 65-year subgroup		− 0.03	− 0.40 to 0.33	0.86
AD IgG prevalence less than 65 years subgroup	1.04		1.00–1.08	0.02
AD IgG prevalence equal to or more than 65-year subgroup	1.01		0.97–1.04	0.66

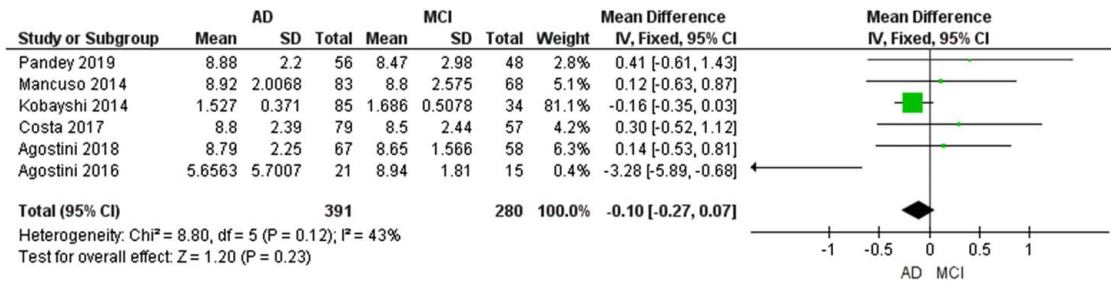**Figure 2.** Anti-HSV IgG titer (AD).

Figure 3. Anti-HSV IgG titer (MCI).

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Study or Subgroup	AD Mean	SD	Total	MCI Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Pandey 2019	8.88	2.2	56	8.47	2.98	48	2.8%	0.41 [-0.61, 1.43]
Mancuso 2014	8.92	2.0068	83	8.8	2.575	68	5.1%	0.12 [-0.63, 0.87]
Kobayshi 2014	1.527	0.371	85	1.686	0.5078	34	81.1%	-0.16 [-0.35, 0.03]
Costa 2017	8.8	2.39	79	8.5	2.44	57	4.2%	0.30 [-0.52, 1.12]
Agostini 2018	8.79	2.25	67	8.65	1.566	58	6.3%	0.14 [-0.53, 0.81]
Agostini 2016	5.6563	5.7007	21	8.94	1.81	15	0.4%	-3.28 [-5.89, -0.68]
Total (95% CI)			**391**			**280**	**100.0%**	**-0.10 [-0.27, 0.07]**

Heterogeneity: Chi² = 8.80, df = 5 (P = 0.12); I² = 43%
Test for overall effect: Z = 1.20 (P = 0.23)

Figure 4. Anti-HSV IgG titer (AD and MCI).

Study or Subgroup	AD Events	Total	Control Events	Total	Weight	Risk Difference M-H, Fixed, 95% CI
Agostini 2018	64	67	57	61	5.6%	1.02 [0.94, 1.11]
Bu 2015	109	128	106	135	9.7%	1.08 [0.97, 1.22]
Itzhaki 1997	49	46	41	44		Not estimable
Kobayshi 2014	66	85	21	34	2.8%	1.26 [0.94, 1.68]
Louvheima 2014	338	360	324	360	30.6%	1.04 [1.00, 1.09]
mancuso 2013	81	83	50	51	5.9%	1.00 [0.95, 1.05]
Mancuso 2014	81	83	73	74	7.3%	0.99 [0.95, 1.03]
Mancuso 2020	63	70	59	67	5.7%	1.02 [0.91, 1.15]
Ounanian 1990	16	19	19	21	1.7%	0.93 [0.73, 1.18]
Pandey 2020	323	365	312	365	29.5%	1.04 [0.98, 1.10]
Wozniak 2005	14	27	9	13	1.1%	0.75 [0.45, 1.25]
Total (95% CI)		**1333**		**1225**	**100.0%**	**1.04 [1.01, 1.07]**
Total events	1204		1071			

Heterogeneity: Chi² = 11.78, df = 9 (P = 0.23); I² = 24%
Test for overall effect: Z = 2.51 (P = 0.01)

Figure 5. Seropositive/prevalence of IgG *n* (%) (AD).

Study or Subgroup	MCI Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Agostini 2018	55	58	57	61	29.5%	1.01 [0.93, 1.11]
Kobayshi 2014	29	34	21	34	9.4%	1.38 [1.02, 1.86]
Mancuso 2014	65	68	73	74	33.7%	0.97 [0.91, 1.03]
Mancuso 2020	58	61	59	67	27.4%	1.08 [0.97, 1.20]
Total (95% CI)		**221**		**236**	**100.0%**	**1.05 [0.94, 1.16]**
Total events	207		210			

Heterogeneity: Tau² = 0.01; Chi² = 12.39, df = 3 (P = 0.006); I² = 76%
Test for overall effect: Z = 0.83 (P = 0.40)
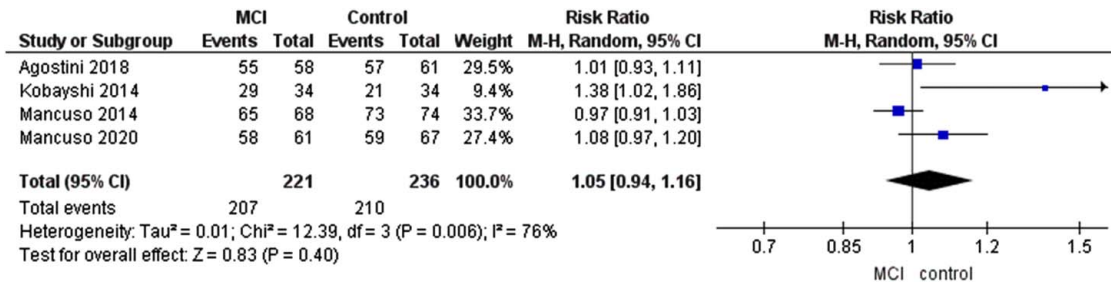
Figure 6. Seropositive/prevalence of IgG *n* (%) (MCI).

Study or Subgroup	AD Events	Total	MCI Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Agostini 2018	64	67	55	58	25.2%	1.01 [0.93, 1.09]
Kobayshi 2014	66	85	29	34	17.7%	0.91 [0.76, 1.09]
Mancuso 2014	81	83	65	68	30.6%	1.02 [0.96, 1.09]
Mancuso 2020	63	70	58	61	26.5%	0.95 [0.86, 1.04]
Total (95% CI)		**305**		**221**	**100.0%**	**0.98 [0.93, 1.03]**
Total events	274		207			

Heterogeneity: Chi² = 3.45, df = 3 (P = 0.33); I² = 13%
Test for overall effect: Z = 0.89 (P = 0.37)

Figure 7. Seropositive/prevalence of IgG *n* (%) (AD and MCI).
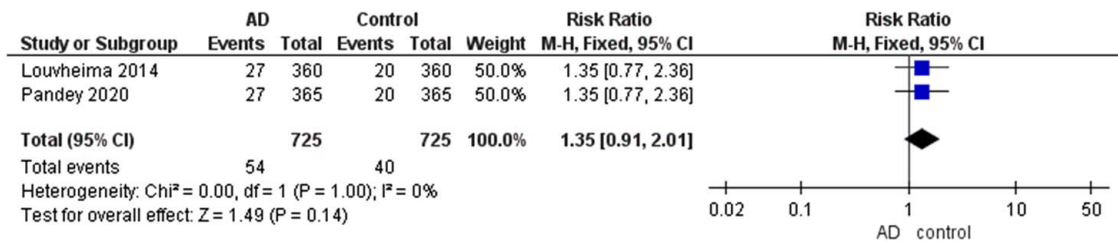
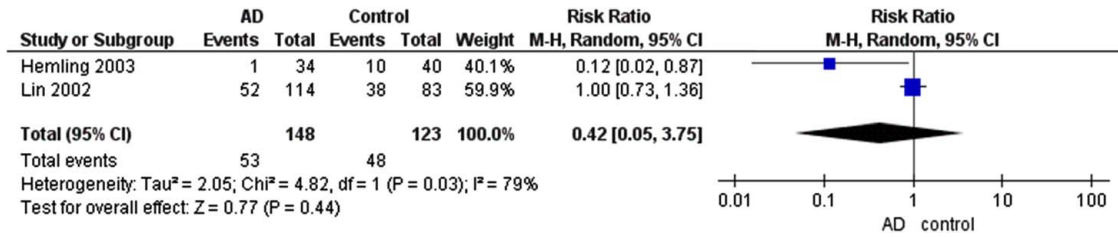**Figure 8.** Anti-HSV IgM titer *n* (%) (AD).
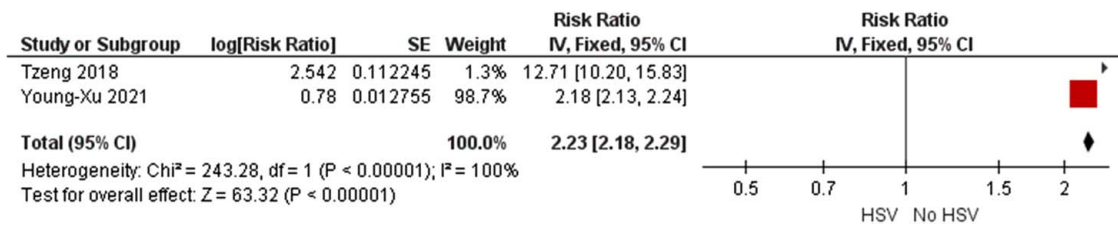
Figure 9. HSV DNA *n* (%) (AD).

Figure 10. Incidence of dementia.
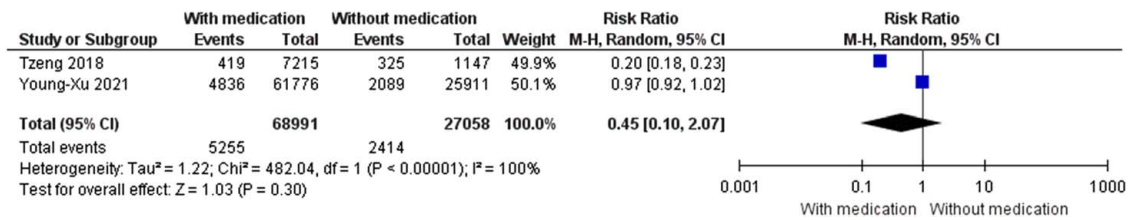
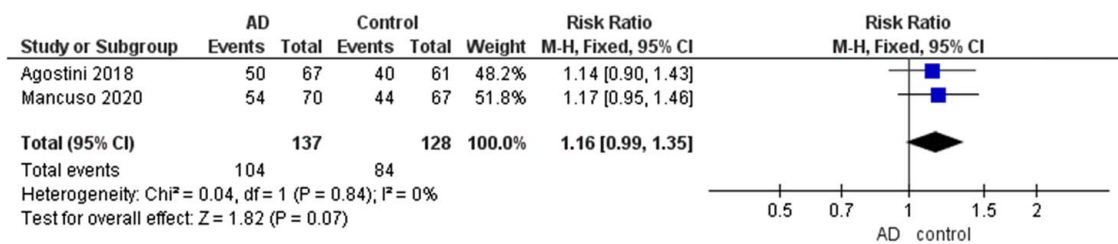**Figure 11.** Prevalence of dementia after antiherpetic medication.
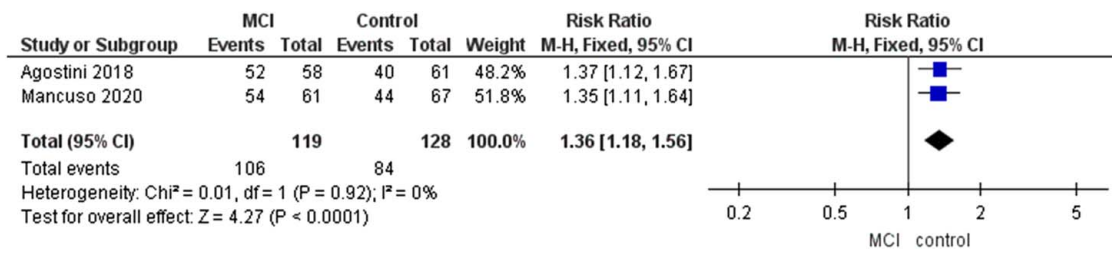
Figure 12. HSV-1-specific IgG3 *n* (%) (AD).

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Figure 13. HSV-1-specific IgG3 *n* (%) (MCI).

95% CI = 0.10–2.07, *P*-value = 0.30). We observed a significant heterogeneity between two studies (*P* < 0.00001, I^2 = 100%), Figure 11.

HSV-1-specific IgG3 n (%) (AD), (MCI), and (AD and MCI), respectively

The pooled analysis showed no statistically significant difference between the AD group and the control group (RR = 1.16, 95% CI = 0.99–1.35, *P*-value = 0.07). We observed no significant heterogeneity between the two studies (*P* = 0.84, I^2 = 0%), Figure 12. The pooled analysis showed a statistically significant association between the MCI group and the increased prevalence of IgG3 compared with the control group (RR = 1.36, 95% CI = 1.18–1.56, *P*-value <0.0001). We observed no significant heterogeneity among two studies (*P* = 0.92, I^2 = 0%), Figure 13. The pooled analysis showed a statistically significant association between the MCI group and decreased prevalence of IgG3 compared with the AD group (RR = 0.85, 95% CI = 0.76–0.95, *P*-value = 0.006). We observed no significant heterogeneity between the two studies (*P* = 0.69, I^2 = 0%), Figure 14.

HSV-1 avidity (AD), (MCI), and (AD and MCI), respectively

The pooled analysis showed no statistically significant difference between the AD group and the control group (MD = 2.26, 95% CI = – 0.36 to 4.88, *P*-value = 0.09). We observed no significant heterogeneity between the two studies (*P* = 0.93, I^2 = 0%), Figure 15. The pooled analysis showed no statistically significant difference between the MCI group and the increased level of HSV-1 avidity compared with the control group (MD = 6.07, 95% CI = – 3.65 to 15.70, *P*-value = 0.22). We observed a significant heterogeneity between the two studies (*P* = 0.006, I^2 = 87%), Figure 16. The pooled analysis showed no statistically significant difference between the AD group and the MCI group (MD = – 4.07, 95% CI = – 13.48 to 5.34, *P*-value = 0.07). We

observed a significant heterogeneity between the two studies (*P* = 0.0007, I^2 = 91%), Figure 17.

AD IgG titer

Less than 65 years subgroup

The pooled analysis showed a statistically significant association between the AD group and increased IgG titer compared with the control group in the subgroup of less than 65 years (MD = 1.89, 95% CI = 1.15–2.64, *P*-value <0.00001). We observed no significant heterogeneity between the two studies (*P* = 0.44, I^2 = 0%), Figure 18.

Equal to or more than 65 years subgroup

The pooled analysis showed a statistically significant association between the AD group and increased IgG titer compared with the control group in the subgroup of equal to or more than 65 years (MD = 0.76, 95% CI = 0.17–1.36, *P*-value = 0.01). We observed a significant heterogeneity among studies (*P* < 0.0001, I^2 = 81%). It was solved by leave-one-out test by removing Kobayashi, 2014 (*P* = 0.57, I^2 = 0%), and the analysis showed a statistically significant association between the AD group and increased IgG titer compared with the control group (MD = 1.00, 95% CI = 0.66–1.34, *P*-value <0.00001), Figure 18.

MCI IgG titer

Less than 65 years subgroup

The pooled analysis showed a statistically significant association between the MCI group and increased IgG titer compared with the control group in the subgroup of less than 65 years (MD = 1.44, 95% CI = 0.47–2.41, *P*-value = 0.004), Figure 19.
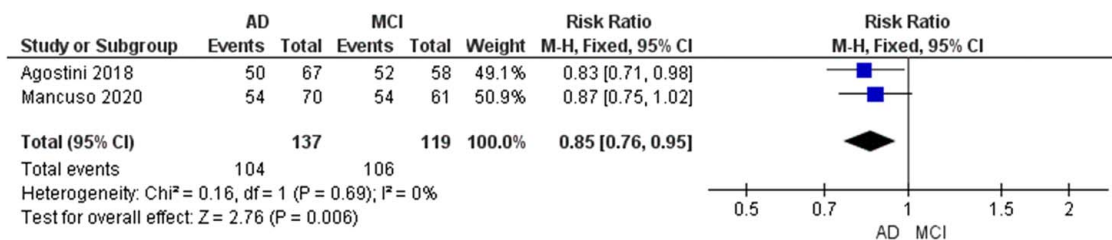

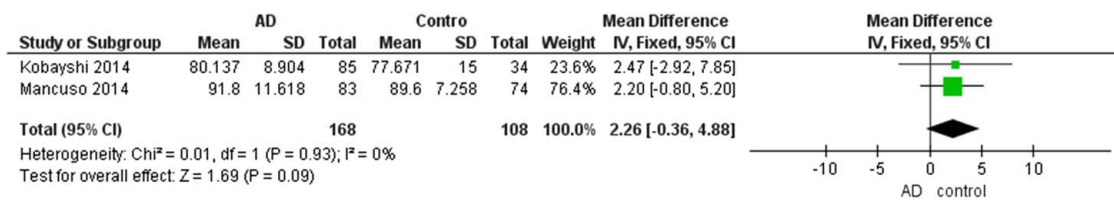**Figure 14.** HSV-1-specific IgG3 *n* (%) (AD and MCI).

Figure 15. HSV-1 avidity (AD).

Equal to or more than 65 years subgroup

The pooled analysis showed a statistically significant association between the MCI group and increased IgG titer compared with the control group in the subgroup of equal to or more than 65 years (MD = 0.69, 95% CI = 0.13–1.25, P-value = 0.02). We observed a significant heterogeneity among studies (P = 0.003, I^2 = 78%). It was solved by leave-one-out test by removing Kobayashi, 2014 (P = 0.48, I^2 = 0%), and the analysis showed a statistically significant association between the MCI group and increased IgG titer compared with the control group (MD = 1.00, 95% CI = 0.64–1.36, P-value <0.00001), Figure 19.

AD and MCI IgG titer

Less than 65 years subgroup

The pooled analysis showed no statistically significant difference between the AD group and the MCI group in the subgroup of less than 65 years (MD = 0.41, 95% CI = − 0.61 to 1.43, P-value = 0.43), Figure 20.

Equal to or more than 65 years subgroup

The pooled analysis showed no statistically significant difference between the AD group and the MCI group in the subgroup of equal to or more 65 years (MD = − 0.03, 95% CI = − 0.40 to 0.33, P-value = 0.86). We observed no significant heterogeneity among studies (P = 0.17, I^2 = 38%), Figure 20.

AD IgG prevalence

Less than 65 years subgroup

The pooled analysis showed a statistically significant association between the AD group and increased IgG prevalence compared with the control group in the subgroup of less than 65 years (RR = 1.04, 95% CI = 1.01–1.08, P-value = 0.02). We observed no significant heterogeneity among studies (P = 0.83, I^2 = 0%), Figure 21.

Equal to or more than 65 years subgroup

The pooled analysis showed no statistically significant difference between the AD group and the control group in the subgroup of equal to or more than 65 years (RR = 1.01% CI = 0.97–1.04, P-value = 0.66). We observed no significant heterogeneity among studies (P = 0.26, I^2 = 21%), Figure 21.

Discussion

Our analysis of 19 studies with 342 535 patients revealed a statistically significant association between the AD and MCI groups and elevated anti-HSV IgG titer compared to the control group. There is no statistically significant difference in anti-HSV IgG titer between the AD group and the MCI group. Some studies agree with our findings. For example, Agostini *et al.*, Lövheim *et al.*, and Mancuso *et al.*[29,35,42]. While others contradict these findings as presented in Renvoize *et al.*[43]. On the other hand, when compared to the control group, a significant association between increased IgG prevalence and the AD group, but not the MCI group, is seen. But no significant difference between the AD group and the MCI group is detected regarding the prevalence of IgG. This finding was similarly presented in some studies including Wozniak *et al.*, Agostini *et al.*, Mancuso *et al.*, and Bu *et al.*[29,30,40,42]. Moreover, a subgroup analysis for age is performed. It shows a statistically significant association between the AD and MCI groups and increased IgG titer compared with the control group in all subgroups, those of less than, equal to, or more than 65 years of age. There is no statistically significant difference between the AD group and the MCI group in the subgroups of less than, equal to, or more than 65 years old. Instead, the analysis showed a statistically significant association between the AD group and increased IgG prevalence compared with the control group in the subgroup of fewer than 65 years but not in those equal to or more than 65 years of age.

Furthermore, in contrast to the control group, the pooled analysis uncovers a statistically significant association between the MCI group, but not the AD group, and a higher prevalence of IgG3 according to the results of two studies by Agostini *et al.* published in 2018 and Mancuso *et al.* published in 2020[29,42].
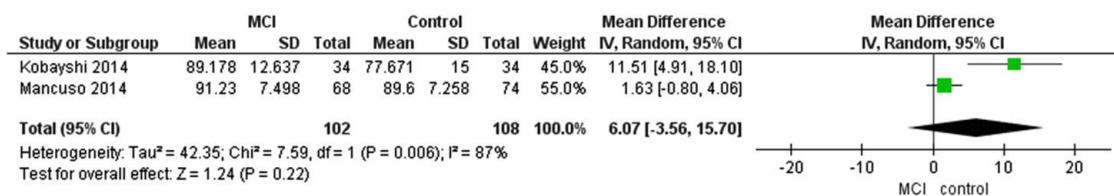

Figure 16. HSV-1 avidity (MCI).

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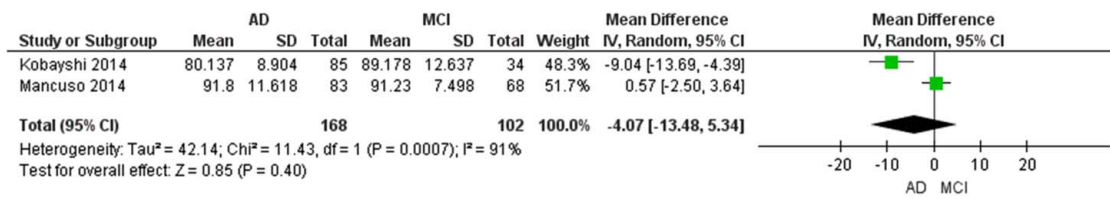
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Figure 17. HSV-1 avidity (AD and MCI).

Also, a statistically significant association between the MCI group and a lower frequency of IgG3 than the AD group was reported. A non-statistically significant association between the MCI group and AD, and higher HSV-1 avidity is noted. Nevertheless, no statistically significant difference is detected between the two groups regarding HSV-1 avidity.

Our analysis also shows no statistically significant differences in HSV DNA or anti-HSV IgM titer between the AD and control groups. We noticed that Hemling et al.[32] support our findings regarding HSV DNA while Lin et al.[34] contradict them. The latter has noted the substantial overlap between HSV-1 but not HSV-2 and being present in AD brains. It has been proposed that the significant difference between the proportion of elder brains harboring HSV-1 and HSV-2 may be due to the latter's lower prevalence among infected individuals or the two viruses' different susceptibilities to the frontotemporal areas. Additionally, anti-HSV IgM titer was presented in two studies: Lövheim et al. and Agostini et al. published in 2016[35,41]. However, in Lövheim et al.[35], the study's large number of clearly defined cases of AD may have made it possible to confirm an association between the presence of anti-HSV IgG antibodies, while the study's small number of individuals who tested positive for anti-HSV IgM may have made it difficult to identify any potential associations. Also, Letenneur et al.[44] reported that individuals had anti-HSV-1 IgM antibodies before the start of AD, showing that HSV reactivation is a risk factor for the development of AD.

Lastly, we find that on comparing the HSV group to the control group with no HSV infection, a statistically significant association between the HSV group and an increased risk of dementia is revealed. However, patients who used antiherpetic medication did not exhibit a significant decline in dementia prevalence compared to those who did not receive antiherpetic medication. This assumption is based entirely on the results of two studies Tzeng et al. and Young-Xu et al.[24,25]. Where Tzeng et al. supported our findings, Young-Xu et al. contradicted them.

Moreover, the adjusted hazard ratio (HR) for the group of HSV-infected patients receiving antiherpetic medications was 0.092. Thus, they demonstrated a lower risk of developing any dementia, including AD, VaD, or other dementia, when compared to the group not receiving antiherpetic medications indicating that antiherpetic therapies could minimize the risk of dementia in patients with HSV infections by nearly 90.8%. Although one study claimed that antiviral drugs in neurodegenerative illnesses could be a new paradigm for treating AD[45], the role of antiherpetic medications for AD prevention has not previously been investigated. However, according to Shen et al.[46], who investigated the seroprevalence of HSV-1 and HSV-2, no significant association between sex and HSV-1 seropositivity was detected, but females had higher rates of HSV-2 seropositivity. Contrarily, Mancuso et al.[42] established a correlation between the damage seen in the brains of AD and MCI patients and serum HSV-1-specific IgG3 antibodies. Additionally, Schnier et al.'s study[47] summarized the findings of four sizable national cohorts. They looked into how the herpes subtype altered the relationship between antiherpetic drugs and incident dementia. They performed a subset analysis that excluded Coinfections and
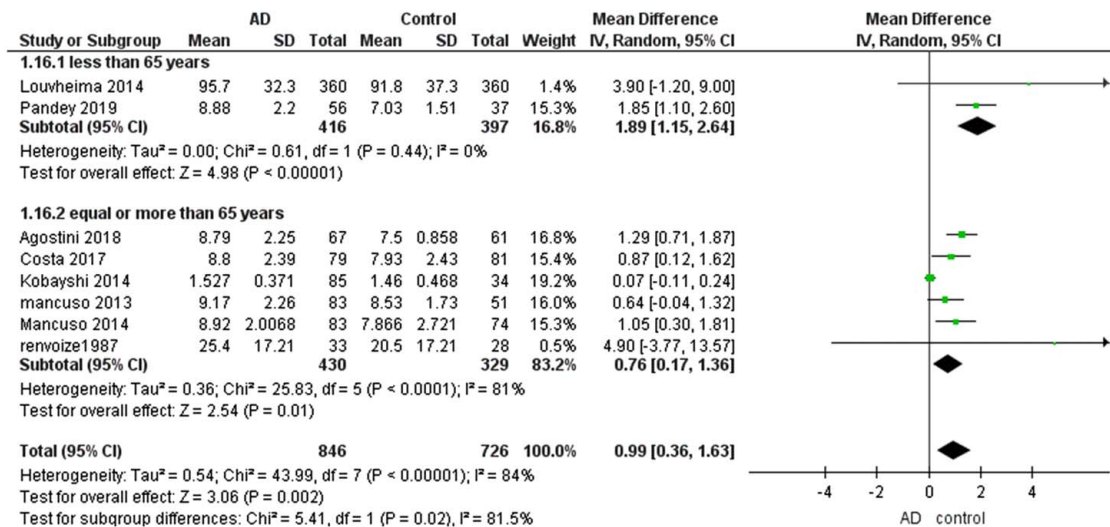

Figure 18. Subgroups of less than 65 years and equal to or more than 65 years in the outcome of AD IgG titer.
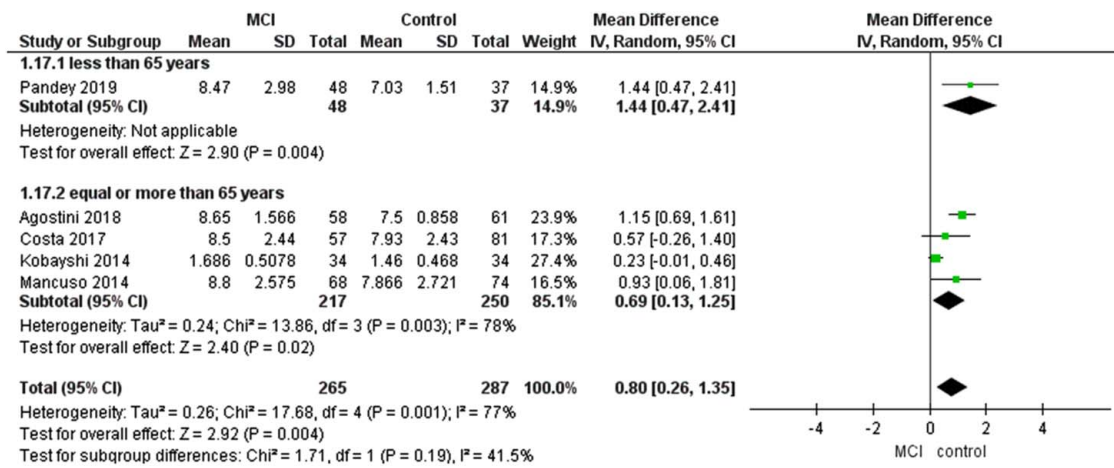
Figure 19. Subgroups of less than 65 years and equal to or more than 65 years in the outcome of MCI IgG titer.

only included people with a diagnosis of Herpes simplex or Herpes zoster. They prescribed acyclovir, its prodrug valacyclovir, famciclovir, and brivudine for medication-specific analyses. According to Schnier et al., those with H. zoster diagnoses who were not subjected to any antiherpetic drugs had a higher rate of dementia compared to the control group, whereas those with H. simplex diagnosis and the control group had no change in dementia incidence. People subjected to antiherpetic medicine similarly showed this trend toward higher HRs in those with H. zoster diagnoses and lower HRs in those with H. simplex diagnoses; however, these differences were not statistically significant.

The examined groups all have similar HSV-1 seroprevalence rates, although AD and MCI patients had higher serum concentrations of HSV-1-specific IgG antibodies than controls. HC, AD patients, and MCI individuals had similar serum concentrations of HSV-1-specific IgG3. However, MCI individuals had a higher detection rate for this subclass of antibodies. Results from MCI patients revealed a negative correlation between HSV-1-specific IgG3 serum concentrations as well as the volumes of the cingulum, right superior temporal gyrus, and transverse temporal

cortex, areas that have been associated with dementia as shown by Frisoni et al. and Rathore et al.[48,49], but not to HSV-1 encephalitis as illustrated by Esiri et al., Damasio et al., Baringer et al., and Agostini et al.[41,50–52]. In line with the presented results, higher IgG3 titers are linked to more severe brain damage in AD but not in MCI. Together, these findings imply that as the disease progresses from MCI to AD, IgG3's capacity to combat HSV-1 decreases.

In addition to proving that the frequency of HSV-1 IgG3 was significantly greater in MCI compared to AD and HC, Agostini et al. published in 2018[29] also made a crucial observation that, whereas total IgG and IgG1 were positively correlated in serum in AD and HC, this correlation was absent in MCI and that total IgG was significantly linked with IgG3, not IgG1. This outcome was unexpected given that IgG1, which is frequently induced by viral infections, is the IgG subclass that is primarily prevalent in human serum[53]. According to these findings, when HC, AD, and MCI people are compared to each other, there is a unique distribution of HSV-1-specific IgG subclasses. Even though IgG1 subclass response to HSV-1 predominates in all groups studied, MCI patients exhibit the IgG3 response far more frequently than
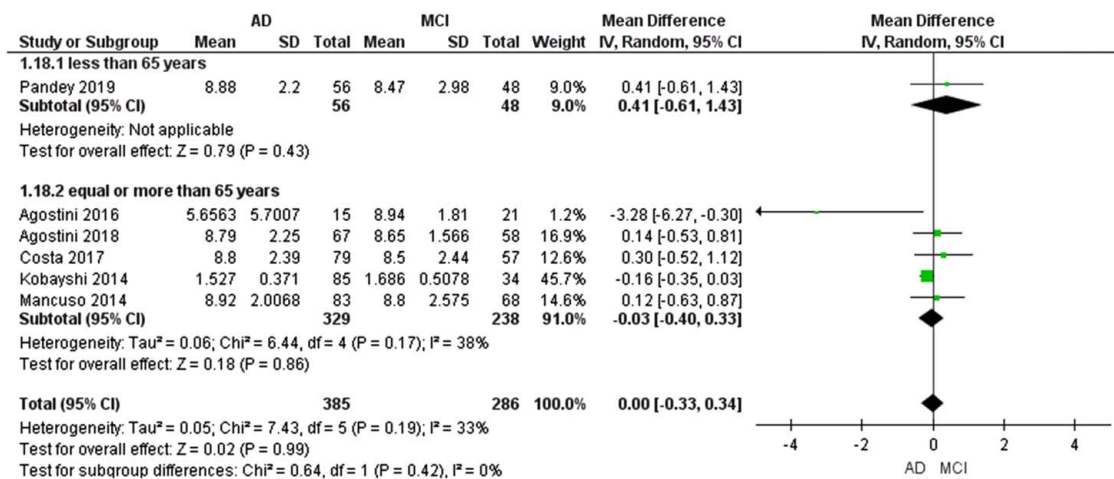

Figure 20. Subgroups of less than 65 years and equal to or more than 65 years in the outcome of AD and MCI IgG titer.

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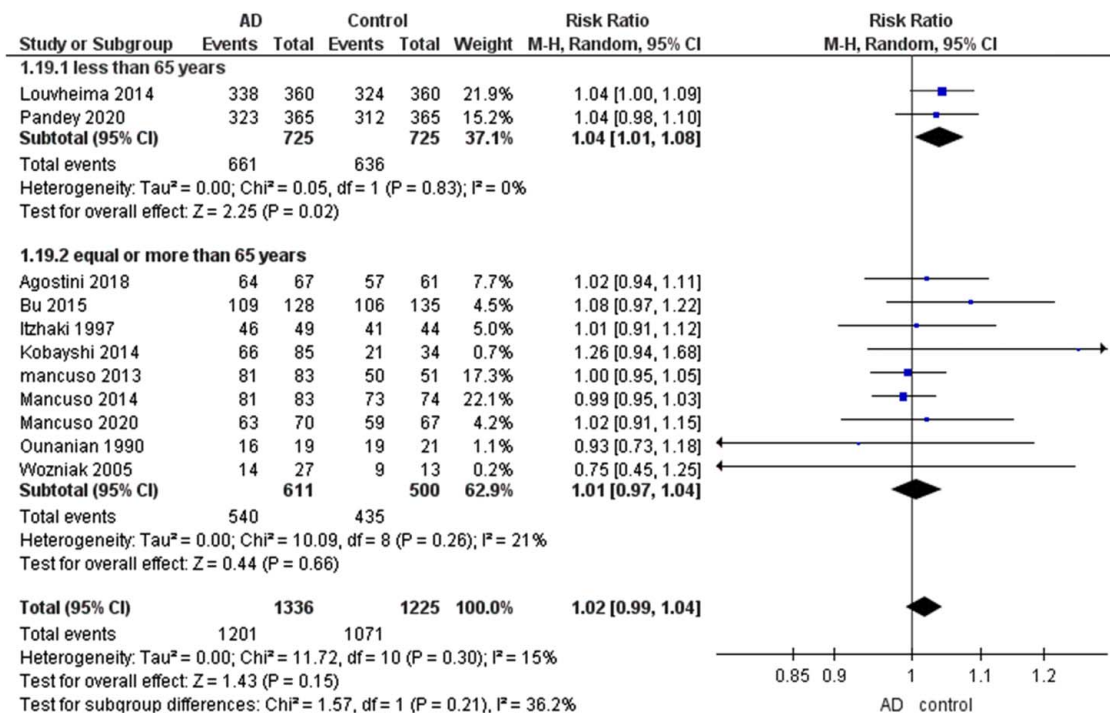**Annals of Medicine & Surgery**

Figure 21. Subgroups of less than 65 years and equal to or more than 65 years in the outcome of AD IgG prevalence.

the other groups do. These results are intriguing since different IgG subclasses have different structural and functional characteristics, and in the context of HSV-1 infection, HSV-1 is unable to hinder IgG3 function as part of its innate defense strategy. Surprisingly, AD sera have a diminished capacity to neutralize HSV-1, regardless of IgG3 or C3 titers. Therefore, additional research is required to comprehend the possible biological significance of these findings.

Lastly, the HSV-1 Avidity Index is an interesting finding that we also attempt to explore. It was presented by three studies Agostini et al., Mancuso et al., and Kobayashi et al.[36,41,54], which assessed the prevalence of the HSV-1 avidity index in AD and MCI patients. Avidity, which quantifies an antibody's affinity for a particular antigen, is defined as the strength with which antibodies attach to antigens. This parameter distinguishes between primary and secondary infections; as a result, the avidity of antibodies in primary infections is typically lower than 35%, whereas the avidity of antibodies in subsequent infections can range from 30 to 45%[55]. According to the assumption of Agostini et al.[41], people with aMCI showed extremely high levels of HSV-1 avidity (>85%). Similarly, Kobayashi et al.[54] claimed that MCI patients have higher levels of HSV-1-specific IgG than HC or AD patients do. Thus, it is evident that the aMCI group (the prodromal stage of AD) experiences HSV-1 reactivation more frequently than the HC and AD groups. Both the anti-HSV-1 IgG avidity index and anti-HSV-1 IgG antibody titer were different between the HC and aMCI groups. This comprehensively supports the idea of HSV-1 engagement as people move from a healthy state to the onset of aMCI. Also, given that it can be easily tested using peripheral blood, anti-HSV-1 IgG avidity index – a sign of HSV-1 reactivation – could be a promising biomarker for the early identification of aMCI and AD.

Additionally, the study suggested administering antiviral medications to guard against reactivation and hence avoid AD development. Conversely, Mancuso et al.[36] did not find any variations in the avidity of these antibodies among AD, MCI, or HC groups.

To draw attention to the assorted studies on the development of dementia in HSV patients, we came across numerous studies attempting to determine the root cause of HSV patients developing AD. Although the underlying mechanisms of aberrant tau phosphorylation and NFT in AD are unknown, Wozniak et al.[56] studied whether HSV-1 may cause these effects. They discovered that HSV promotes AD-specific tau phosphorylation at amino acids T212 and S214. Increased phosphorylation was also seen at S396, S404, and S202, as well as an increase in a structurally aberrant type of tau. The total tau level was also raised. Thus, HSV-1 could cause aberrant tau phosphorylation by either raising or lowering the activity of the relevant kinases and phosphatases. Wozniak et al.[57] also demonstrated that the infected cultured neuronal and glial cells with HSV-1 increase intracellular levels of amyloid (A) 1-40 and 1-42 while decreasing levels of amyloid precursor protein (APP). A1-42 deposits were also found in the mouse brain after HSV-1 infection. The method in cultured cells requires increased A production rather than simply increased cellular A retention, as levels of site APP-cleaving enzyme (BACE-1) and nicastrin, a component of gamma-secretase, both increase in HSV-1-infected cells. These new findings indicate that HSV-1 can directly contribute to the formation of senile plaques.

Future implications

Regular follow-up after HSV infection must be done to guard against the development of AD or MCI. This can be achieved in various ways including MRI imaging or calculating the anti-HSV IgG avidity index, a marker of HSV-1 reactivation, which can be

quickly assessed using peripheral blood and employed as a biomarker for the early detection of aMCI and AD. Moreover, the use of antiherpetic medications as a protective method to guard against the development of dementia or MCI after HSV infection should be further investigated.

Strengths and limitations

The overall quality is good in most of the studies included in our analysis. A good number of studies were subjected to analysis as 19 studies were included. Along with a decent sample size, 342 535 patients were included in our analysis. Our study shows some limitations. For, example all the studies included were non-randomized observational, not randomized clinical trials, and hence might be subjected to bias. Prospective multicenter studies are needed to further evaluate the relationship between HSV and AD development. Moreover, significant heterogeneity was detected in some outcomes, including the incidence of dementia and HSV avidity, which is demonstrated as a primary limitation of our analysis. It could not be solved by the leave-one-out test owing to the few studies discussing these outcomes.

Conclusion

Our study revealed a significant association between HSV and an increased risk of dementia. Our findings thus pave the way for the development of new AD treatments. It is necessary to undertake future clinical trials examining antiherpetic medications and assess the HSV avidity index as a biomarker for AD and MCI. In the future, their usage in high-risk AD patients might be promising as a primary or secondary prophylaxis.

Ethical approval

Not applicable.

Consent

Not applicable.

Sources of funding

The authors declare they received no fund for this study.

Author contribution

R.H.E.: study design and writing; K.R.M.: supervision and writing; N.E.T.: analysis and writing; S.R.: writing; N.M., E.M.H., S.M.R., M.M., and J.S.: screening, data extraction, and quality assessment. All authors approved the manuscript.

Conflicts of interest disclosure

The authors declare that they have no conflicts of interest.

Research registration unique identifying number (UIN)

Not applicable.

Guarantor

Karam R. Motawea and Jaffer Shah.

Data availability statement

Data and materials are available within the manuscript.

Provenance and peer review

Not commissioned, externally peer-reviewed.

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References

[1] Organization WH. Dementia: a Public Health Priority. World Health Organization; 2012.
[2] Elahi FM, BL Miller. A clinicopathological approach to the diagnosis of dementia. Nat Rev Neurol 2017;13:457–76.
[3] Prince MJ, Wimo A, Guerchet MM, , et al. World Alzheimer Report 2015 – The global impact of dementia: an analysis of prevalence, incidence, cost and trends, 2015.
[4] Sloane PD, Zimmerman S, Suchindran C, et al. The public health impact of Alzheimer's disease, 2000–2050: potential implication of treatment advances. Annu Rev Public Health 2002;23:213–31.
[5] Crous-Bou M, Minguillón C, Gramunt N, et al. therapy. Alzheimer's disease prevention: from risk factors to early intervention. Alzheimers Res Ther 2017;9:1–9.
[6] Alzheimer's Association Report. 2017 Alzheimer's disease facts and figures. Alzheimers Dement 2017;13:325–73.
[7] Takizawa C, Thompson PL, van Walsem A, et al. Epidemiological and economic burden of Alzheimer's disease: a systematic literature review of data across Europe and the United States of America. J Alzheimers Dis 2015;43:1271–84.
[8] Petersen RC, Smith GE, Waring SC, et al. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 1999;56:303–8.
[9] Petersen RC. Mild cognitive impairment as a diagnostic entity. J Intern Med 2004;256:183–94.
[10] Winblad B, Palmer K, Kivipelto M, et al. Mild cognitive impairment–beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. J Intern Med 2004;256:240–6.
[11] Anderson ND. State of the science on mild cognitive impairment (MCI). CNS Spectr 2019;24:78–87.
[12] Farias ST, Mungas D, Reed BR, et al. Progression of mild cognitive impairment to dementia in clinic- vs community-based cohorts. Arch Neurol 2009;66:1151–7.
[13] DP Perl. Neuropathology of Alzheimer's disease. Mt Sinai J Med 2010; 77:32–42.
[14] Kirova A-M, Bays RB, Lagalwar S. Working memory and executive function decline across normal aging, mild cognitive impairment, and Alzheimer's disease. Biomed Res Int 2015;2015:748212.
[15] Roizman B, RJ Whitley. An inquiry into the molecular basis of HSV latency and reactivation. Annu Rev Microbiol 2013;67:355–74.
[16] Looker KJ, Magaret AS, May MT, et al. Global and regional estimates of prevalent and incident herpes simplex virus type 1 infections in 2012. PLoS One 2015;10:e0140765.
[17] Looker KJ, Welton NJ, Sabin KM, et al. Global and regional estimates of the contribution of herpes simplex virus type 2 infection to HIV incidence: a population attributable fraction analysis using published epidemiological data. Lancet Infect Dis 2020;20:240–9.
[18] Moir RD, Lathe R, Tanzi RE. The antimicrobial protection hypothesis of Alzheimer's disease. Alzheimers Dement 2018;14:1602–14.
[19] Mori I, Nishiyama Y, Yokochi T, et al. Olfactory transmission of neurotropic viruses. J NeuroVirol 2005;11:129–37.
[20] Whitley RJ, Herpes simplex virus infections. In: Remington JS, Klein JO, eds. Infectious Diseases of the Fetus and Newborn Infants. 3rd ed. Philadelphia: W.B. Saunders Company, 1990:282–305.

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Annals of Medicine & Surgery

[21] Chen VC-H, Wu S-I, Huang K-Y, et al. Herpes zoster and dementia: a nationwide population-based cohort study. J Clin Psychiatry 2018;79:16m11312.

[22] Itzhaki RF. Corroboration of a major role for herpes simplex virus type 1 in Alzheimer's disease. Front Aging Neurosci 2018;10:324.

[23] Tsai M-C, Cheng W-L, Sheu J-J, et al. Increased risk of dementia following herpes zoster ophthalmicus. PLoS One 2017;12:e0188490.

[24] Tzeng N-S, Chung C-H, Lin F-H, et al. Anti-herpetic medications and reduced risk of dementia in patients with herpes simplex virus infections—a nationwide, population-based cohort study in Taiwan. Neurotherapeutics 2018;15:417–29.

[25] Young-Xu Y, Powell EI, Zwain GM, et al. Symptomatic herpes simplex virus infection and risk of dementia in US veterans: a cohort study. Neurotherapeutics 2021;18:2458–67.

[26] Higgins JP, Green SJL, Cochrane Handbook for Systematic Reviews of Interventions. The Cochrane Collaboration, 2011.

[27] Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097.

[28] Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Int J Surg 2021;88:105906.

[29] Agostini S, Mancuso R, Hernis A, et al. HSV-1-specific IgG subclasses distribution and serum neutralizing activity in Alzheimer's disease and in mild cognitive impairment. J Alzheimers Dis 2018;63:131–8.

[30] Bu XL, Yao XQ, Jiao SS, et al. A study on the association between infectious burden and Alzheimer's disease. Eur J Neurol 2015;22:1519–25.

[31] Costa AS, Agostini S, Guerini FR, et al. Modulation of immune responses to herpes simplex virus type 1 by IFNL3 and IRF7 polymorphisms: a study in Alzheimer's disease. J Alzheimers Dis 2017;60:1055–63.

[32] Hemling N, Röyttä M, Rinne J, et al. Herpes viruses in brains in Alzheimer's and Parkinson's diseases. Ann Neurol 2003;54:267–71.

[33] Itzhaki RF, Lin WR, Shang D, et al. Herpes simplex virus type 1 in brain and risk of Alzheimer's disease. Lancet 1997;349:241–4.

[34] Lin WR, Wozniak MA, Cooper RJ, et al. Herpesviruses in brain and Alzheimer's disease. J Pathol 2002;197:395–402.

[35] Lövheim H, Gilthorpe J, Johansson A, et al. Herpes simplex infection and the risk of Alzheimer's disease: a nested case-control study. Alzheimers Dement 2015;11:587–92.

[36] Mancuso R, Baglio F, Agostini S, et al. Relationship between herpes simplex virus-1-specific antibody titers and cortical brain damage in Alzheimer's disease and amnestic mild cognitive impairment. Front Aging Neurosci 2014;6:285.

[37] Mancuso R, Baglio F, Cabinio M, et al. Titers of herpes simplex virus type 1 antibodies positively correlate with grey matter volumes in Alzheimer's disease. J Alzheimers Dis 2014;38:741–5.

[38] Pandey JP, Kothera RT, Liu S, et al. Immunoglobulin genes and immunity to HSV1 in Alzheimer's disease. J Alzheimers Dis 2019;70:917–24.

[39] Pandey JP, Olsson J, Weidung B, et al. An Ig γ marker genotype is a strong risk factor for Alzheimer disease, independent of apolipoprotein E ε4 genotype. J Immunol 2020;205:pp. 1318–1322.

[40] Wozniak MA, Shipley SJ, Combrinck M, et al. Productive herpes simplex virus in brain of elderly normal subjects and Alzheimer's disease patients. J Med Virol 2005;75:300–6.

[41] Agostini S, Mancuso R, Baglio F, et al. High avidity HSV-1 antibodies correlate with absence of amnestic mild cognitive impairment conversion to Alzheimer's disease. Brain Behav Immun 2016;58:254–60.

[42] Mancuso R, Cabinio M, Agostini S, et al. HSV-1-specific IgG(3) titers correlate with brain cortical thinning in individuals with mild cognitive impairment and Alzheimer's disease. Vaccines 2020;8:255.

[43] Renvoize EB, Awad IO, Hambling MH. A sero-epidemiological study of conventional infectious agents in Alzheimer's disease. Age Ageing 1987;16:311–4.

[44] Letenneur L, Pérès K, Fleury H, et al. Seropositivity to herpes simplex virus antibodies and risk of Alzheimer's disease: a population-based cohort study. PLoS One 2008;3:e3637.

[45] Ball MJ. Limbic predilection in Alzheimer dementia: is reactivated herpesvirus involved? Can J Neurol Sci 1982;9:303–6.

[46] Shen J-H, Huang K-YA, Chao-Yu C, et al. Seroprevalence of herpes simplex virus type 1 and 2 in Taiwan and risk factor analysis, 2007. PLoS One 2015;10:e0134178.

[47] Schnier C, Janbek J, Williams L, et al. Antiherpetic medication and incident dementia: observational cohort studies in four countries. Eur J Neurol 2021;28:1840–8.

[48] Frisoni GB, Fox NC, Jack CR Jr, et al. The clinical use of structural MRI in Alzheimer disease. Nat Rev Neurol 2010;6:67–77.

[49] Rathore S, Habes M, Iftikhar MA, et al. A review on neuroimaging-based classification studies and associated feature extraction methods for Alzheimer's disease and its prodromal stages. Neuroimage 2017;155:530–48.

[50] Baringer JR, Pisani P. Herpes simplex virus genomes in human nervous system tissue analyzed by polymerase chain reaction. Ann Neurol 1994;36:823–9.

[51] Damasio AR, Van Hoesen GW. The limbic system and the localisation of herpes simplex encephalitis. J Neurol Neurosurg Psychiatry 1985;48:297–301.

[52] Esiri MM. Herpes simplex encephalitis. An immunohistological study of the distribution of viral antigen within the brain. J Neurol Sci 1982;54:209–26.

[53] McKendall RR, Woo W. Murine IgG subclass responses to herpes simplex virus type 1 and polypeptides. J Gen Virol 1988;69(Pt 4):847–57.

[54] Kobayashi N, Nagata T, Shinagawa S, et al. Increase in the IgG avidity index due to herpes simplex virus type 1 reactivation and its relationship with cognitive function in amnestic mild cognitive impairment and Alzheimer's disease. Biochem Biophys Res Commun 2013;430:907–11.

[55] Ebralidze LK, Vedunova SL, Mal'tseva NN, et al. [Detection of low avidity IgG as a promising approach to diagnosis of primary herpetic infection]. Voprosy Virusologii 2004;49:46–9; Vyiavleniie nizkoavidnykh IgG-antitel--perspektivnyĭ podkhod v diagnostike pervichnoĭ gerpeticheskoĭ infektsii.

[56] Wozniak MA, Frost AL, Itzhaki RF. Alzheimer's disease-specific tau phosphorylation is induced by herpes simplex virus type 1. J Alzheimers Dis 2009;16:341–50.

[57] Wozniak MA, Itzhaki RF, Shipley SJ, et al. Herpes simplex virus infection causes cellular beta-amyloid accumulation and secretase upregulation. Neurosci Lett 2007;429:95–100.