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Effects of herpes zoster infection, antivirals and vaccination on risk of developing dementia: A systematic review and meta-analysis

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ABSTRACT

Herpes zoster (HZ) is a neurotropic virus. We aimed to evaluate the association of HZ infection, protective effects of antiviral treatment or vaccination on dementia. A systematic search of PubMed, MEDLINE, EMBASE, Scopus, Web of Science, CINAHL, and Cochrane CENTRAL was performed from January 1, 1996, to October 31, 2024. Observational studies evaluating HZ infection, antivirals, or vaccination and dementia risk were selected. Risk of bias was examined with the Newcastle-Ottawa scale. A random-effects meta-analysis was performed, with the rate ratio (RR) and corresponding 95% confidence intervals (CIs) being pooled for dementia. Presence of heterogeneity was assessed with I^2, and differences by study-level characteristics were estimated using subgroup meta-analysis and meta-regression. Eighteen studies (N = 9.4 million) were included. Infection was associated with elevated risk of dementia (RR 1.14; 95% CI: 1.04, 1.25, I^2 = 98%); this remained significant in the sensitivity analysis when the two case-control studies were removed (RR 1.17; 95% CI: 1.06, 1.30, I^2 = 98%). Subgroup analysis based on sex, age, study population, bias scores, type of dementia or HZO did not show statistically significant differences in risk. Treatment with antivirals showed a small effect (RR 0.84; 95% CI: 0.71, 0.99, I^2 = 73%), but prophylaxis with HZ vaccination was associated with a significantly lower risk (RR 0.68; 95% CI: 0.56, 0.83, I^2 = 99%). We report a slightly raised dementia risk after HZ infection and reduced risks after antiviral treatment and prevention with vaccination. However, results should be interpreted with caution due to significant heterogeneity in pooled analyses.

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Introduction

Dementia is an increasingly prevalent condition, with Alzheimer's disease (AD) affecting around 55 million people in the world, with 5.8 million people in the US alone.[1] By 2050, the number of people with dementia in the world is expected to grow to 139 million, rising mostly in low- and middle-income countries.[2] Dementia is considered a syndrome, characterized by slow onset of disease, with gradual loss of memory, typically reduced ability to retain new information, eventually leading to impairment in activities of daily living.[1,3] There are a number of different types of dementia such as Alzheimer's disease, vascular dementia, Lewy body dementia and frontotemporal dementia. Although dementia can begin at any age as an adult, it predominantly occurs later in life, with an estimated prevalence of 14% in persons aged 71 years or older, growing to 37.4% in those aged 90 years or older.[4]

The pathophysiology of dementia is complex, but research has shown it involves accumulation of misfolded native proteins in the brain.[5] For now, there is no cure for dementia and, as such, prevention becomes paramount. Non-modifiable risk factors for the development of dementia include age, female sex and genetics. The 2020 report of the Lancet Commission on Dementia Prevention, Intervention, and Care and new research has identified numerous risk factors for dementia.[6] Many of these risk factors are modifiable, such as sleep disturbance, anxiety, cancer, carotid atherosclerosis, peripheral artery disease,

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atrial fibrillation, stroke, metabolic syndrome, renal disease, serum uric acid, pesticide exposure, inflammatory markers, and viral infections.[7]

Infections may cause dementia due to the pathogen crossing into the central nervous system (CNS) through the inflamed and weakened blood-brain barrier.[8] The process activates the immune system in the CNS, such as microglia and astrocytes, macrophages and lymphocytes.[9–11] The resulting neuroinflammation causes critical damage while endeavoring to clear the invading microorganism. Epidemiological studies show an association between viral infections and neurodegenerative diseases. These include links between Epstein-Barr virus and multiple sclerosis,[12] influenza and Parkinson's Disease,[13] and COVID19 and neuroinflammation and/or neurodegeneration.[14] More recently, evidence has emerged supporting an association between herpes simplex virus type 1 (HSV1) and AD.[15–17]

Varicella zoster virus (VZV) lies dormant in the spinal and cranial sensory ganglia; later in life, it can be reactivated, resulting in herpes zoster, which is also called shingles.[18,19] Many people are affected each year by herpes zoster infection. In the United States alone, over one million new cases of herpes zoster are reported yearly, and one in three individuals will experience this infection in their lifetime.[19] The mean age at the onset of herpes zoster among adults is 59.4 years, with 68% of cases occurring in those 50 years and older.[20] Like other viruses that have a predilection for the central nervous system, varicella zoster virus has been linked to cognitive impairment.[17,21]

Antiviral treatment with either acyclovir, famciclovir, or valacyclovir is recommended for all patients with suspected herpes zoster and moderate-to-severe pain, with or without the presence of a rash, or those with symptoms affecting the face.[19] Antivirals reduce the duration, severity, and risk of complications, particularly post-herpetic neuralgia, for patients with zoster infection.[19] For herpes zoster prevention, the Advisory Committee on Immunization Practices recommends "the use of the recombinant zoster vaccine (Shringrix®) in all patients 50 years of age or older, regardless of their past history of herpes zoster reactivation"; the live attenuated vaccine (Zostavax®) may also be used in patients 60 years and older.[22]

Given the myriad of studies evaluating the association between herpes zoster infection and dementia and the use of antiviral agents for the treatment of herpes zoster and/or vaccines for prevention, which could both impact the development of dementia, we conducted a systematic review and meta-analysis. Our objective was to evaluate the current literature on herpes zoster or VZV infection and the risk of developing dementia. Additionally, we examined the association of interventions such as vaccination and antiviral treatment on potentially decreasing the risk of dementia.

Methods

This systematic review and meta-analysis were reported using the updated Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement for reporting of systematic reviews.[23]

Search strategy

A systematic search was conducted using Pubmed, MEDLINE, EMBAASE, Scopus, Web of Science, CINAHL, and Cochrane CENTRAL for articles from January 1, 1996, to October 31, 2024. Key terms and subject headings included Alzheimer's, dementia, vascular dementia, Lewy body, varicella zoster virus infection, chickenpox, herpes zoster, shingles, zoster, mild cognitive impairment, cognitive function, cognitive impairment, cognitive decline, cognitive deficit, varicella zoster vaccine, and antiherpetic medication. There was no language restriction. A manual search was also carried out by conducting a bibliography review of the included studies (S1, Supplementary Material).

Inclusion and exclusion

Studies were included if they were observational or experimental studies cohort, case-control, cross-sectional studies, case-crossover, or randomized controlled trials that evaluated the effect of HZ or VZV infection, vaccine or antiviral exposure on the development of Alzheimer's, Lewy body, or vascular dementia, among adults (≥18 years). Studies were also included if they examined the risk of developing dementia with seropositive studies of herpes zoster or varicella zoster virus. Studies were excluded if they

were reviews, guidelines, meta-analyses, pre-clinical studies, case reports/series, examined other types of viral infections (e.g., herpes simplex, influenza, COVID-19), non-zoster vaccines, or different antivirals (not treated with acyclovir, famciclovir, or valacyclovir), or evaluated cognitive impairment rather than dementia. One independent researcher (EL) and a librarian conducted the initial search. The initial screening of the title and abstracts, and full-text review was conducted by two reviewers (EL/FM), with the third reviewer resolving any discrepancies (JC).

Data extraction

The data extraction process was independently carried out by two researchers (EL and FM), using a standardized form; disagreements were resolved by consulting and discussing with a third researcher (JC). Extracted data included study design, author name, year of publication, country where study was conducted, inclusion/exclusion criteria, study population, sample size (including the number of subjects with the exposure), sex, mean/median age of participants, type of dementia, outcomes assessed, confounders, and mean/median time to follow-up.

Quality assessment

The quality of included studies was assessed independently by two authors (FM/EL). Since all the retrieved studies were observational, we used the Newcastle-Ottawa Scale (NOS) to determine bias scores.[24] Points were awarded for selection, comparability, adjustment for confounders, and outcome. Self-controlled case-series studies were scored with the cohort studies, however we interpreted 'cohort representativeness' in terms of how representative the selected cases were of individuals with dementia in the community. Case-control studies were scored in terms of selection, comparability, and exposure. The maximum score for any type of study was nine, and a score of greater than seven was considered as a low risk of bias. Discrepancies were resolved through discussion with another author (JC).

Statistical analysis

We calculated the pooled risk ratio (RR) and the corresponding 95% CI for all-cause dementia in the population who experienced herpes zoster infection compared to control population, with or without antiviral treatment and the protective effect of herpes zoster vaccine. When both adjusted and crude effect sizes were present, the adjusted effect size was used. All the studies reported their results as a hazard ratio (HR), except four studies that reported an odds ratio (OR) and three that reported a relative risk. We converted all OR to RR, but since the incidence of dementia is less than 10% in these countries, we considered these effect sizes of HR and RR as equivalent.[25–28] We used a random-effects model with Der Simonian Liard method and inverse probability weighting, along with corresponding 95% confidence intervals.[29]

Where possible, we performed subgroup analyses by patient's age, presented in 10-year categories starting from age 40 years, as well as less than or greater than 80 years of age (for the HZ infection analysis) or less than or greater than 75 years of age (for the vaccine studies); we chose this cutoff as most studies reported risk stratified by these age groups. Subgroup analyses were also conducted for sex, country of the study population (Asia, Europe and North America), and risk of bias score. We also stratified on type of dementia, and infection with herpes zoster ophthalmitis (HZO).

To evaluate the stability of our results, we conducted a sensitivity analysis comparing results from the random-effects and fixed-effects models. We also explored the impact on the results when excluding studies that did not use ICD9/10 codes to define HZ infection but rather included patients who were seropositive for varicella zoster virus in cerebrospinal fluid. In addition, we did a sensitivity analysis by removing case-control studies.

The I-squared (I^2) index was used to determine heterogeneity of the included studies, with a -higher percent reflecting increasing heterogeneity. We assumed substantial heterogeneity when the I^2 statistic was >50%. In the presence of heterogeneity, pooled HRs were computed using a random-effects model. To investigate the presence of publication bias and small study bias for the all-cause dementia

outcome, we used funnel plots and Egger's test. Bias was considered absent when both Egger's and Begg's P-values were greater than 0.05 and the funnel plot was generally symmetrical; otherwise, we assessed bias related to potentially unpublished studies by the trim-and-fill method.[30] When applicable, meta-regression was used to assess the heterogeneity in the effects while accounting for study and population characteristics.

All analyses were performed using R Statistical Software (v4.3.1; R Core Team 2021). The meta-analysis and forest plots were completed using the meta (version 6.5.0) and metafor (version 4.6.0) R packages. All P values were two-tailed and less than 0.05 were considered significant.

Standard protocol approvals, registrations, and patient consents

This study was exempt from ethics approved given that it uses data from publicly available sources from published articles, where individual participant information is not accessible. The protocol was not registered with PROSPERO, however a pre-specified protocol was developed before the literature review was conducted.

Results

Study characteristics

Figure 1 identifies the search results and selection process. Of the 1339 articles identified through the database search, 742 remained after removal of duplicates. Abstract and title screening process identified 668 articles that were reviews of literature, articles on pathophysiology, symptoms of herpes zoster, treatment and prevention, leaving 74 articles that were eligible for a detailed review. Of these 74 articles, many were considered an irrelevant topic, studied herpes simplex virus (HSV1), examined a genetic association, evaluated an ineligible outcome (e.g., cognitive impairment), or was a case series, leaving 18 studies for inclusion in the meta-analysis.

As shown in Table 1, of the 18 included studies (N = 9,431,738),[31–48] four were case-control design[33,41,43,45] and the rest were cohort studies.

Of note, three studies reported separate results on multiple cohorts within the same paper.[36,46,48] For example, Schnier et al.[36] used data from four countries (Wales, Germany, Denmark and Scotland), while both Scherrer[46] and Wiemken[48] used the Veterans Health Administration (VA) and IBM® MarketScan® Commercial Claims Medicare cohorts. As such, the current meta-analysis used data from 23 cohorts.

Of the 13 studies that evaluated the impact of herpes zoster infection on dementia, all except 2 studies used ICD9/10 codes,[31–40,45] while 2 studies used patients who were seropositive for VZV from the UK BioBank[41] or were PCR positive[42] in cerebrospinal fluid to determine its impact on the development of dementia. Four of the 13 studies (5 cohorts) also examined the impact of antiviral treatment for herpes zoster infection on dementia.[31,32,34,36] All studies that evaluated herpes zoster infection or antivirals looked at the primary endpoint of all-cause dementia, including AD (N = 5),[31,35,37,38,40] vascular dementia (N = 4),[31,37,38,40] other types of dementia (N = 2),[31,40] and Lewy body (N = 1)[37] as their secondary endpoints. The risk of dementia following HZ ophthalmicus was evaluated in three studies.[33,35,39]

Six studies (8 cohorts) evaluated the impact of shingles vaccination on dementia,[43–48] with one of these studies also reporting on the impact of HZ infection on dementia.[45] All studies that evaluated the impact of HZ vaccine looked at the primary endpoint of all-cause dementia, while three studies (4 cohorts) evaluated AD as their secondary endpoint.[44,46,47]

Risk of bias

We found a low risk of bias amongst 18 included studies (Supplementary Material, S2). The scores (and number of studies) were as follows: 9 out of 9 (N = 5), 8 out of 9 (N = 6), 7 out of 9 (N = 4), and 6 out of 9 (N = 3). Since a score of greater than seven was considered as a low risk of bias, seven studies included in the review did not meet this threshold but were included in the meta-analysis; we conducted a sensitivity analysis excluding these studies.

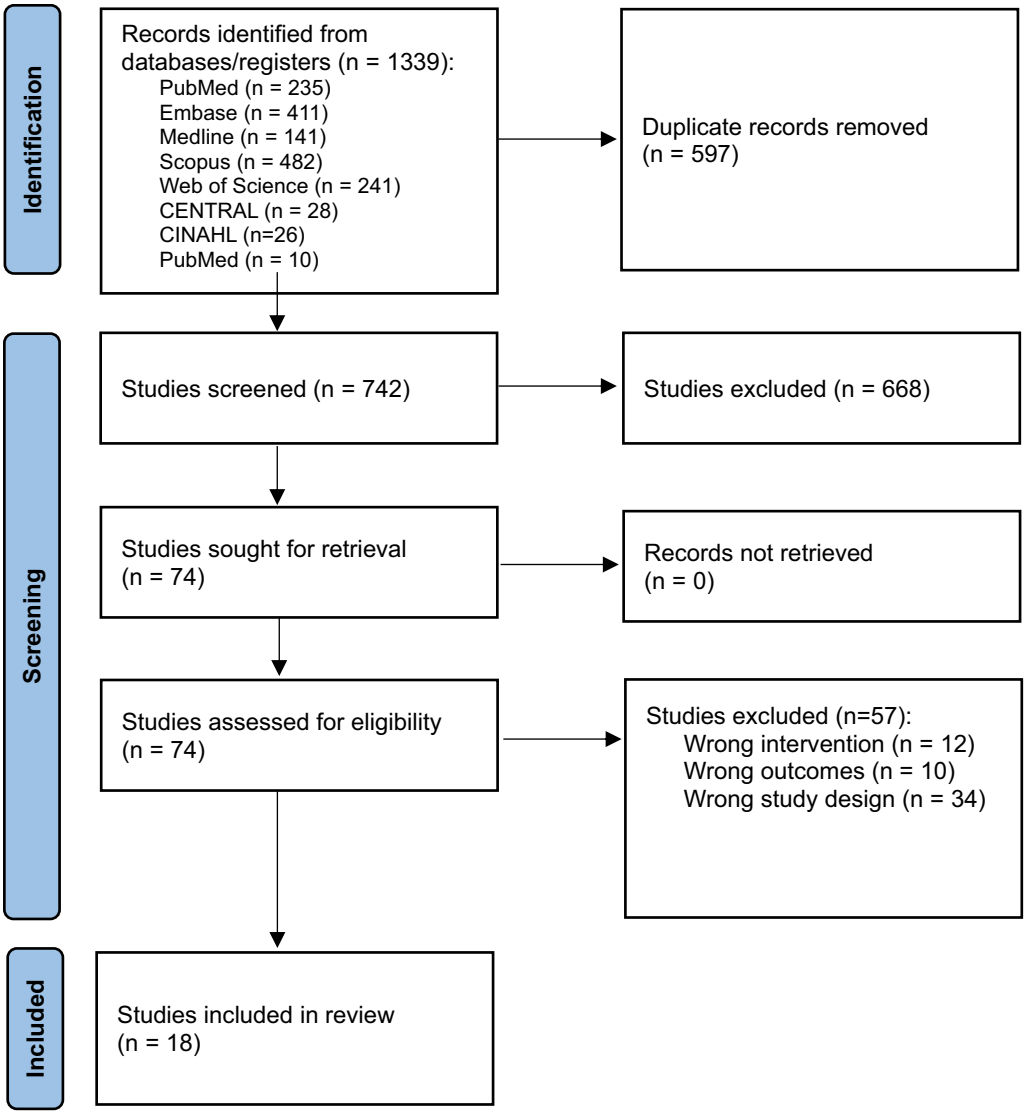

Figure 1. Flow diagram of study selection.

Herpes zoster infection and risk of dementia

Our meta-analysis indicated a slightly elevated risk of all-cause dementia subsequent to a HZ infection (RR 1.14; 95% CI: 1.04, 1.25, I^2 = 98%), and a large amount of heterogeneity, as illustrated in Figure 2. The larger effect size by Tsai et al.[39] is likely related to their study population solely being those affected by HZ ophthalmicus rather than any type of HZ infection.

Figure 3 and Supplementary Material, S3 shows results of the sensitivity analyses. For Mekli[41] and Omland,[42] the larger effect size may be related to their inclusion of non-clinical herpes zoster cases; after removing these two studies, the elevated dementia risk was only marginally statistically significant, with the RR 1.12 (95% CI: 1.02, 1.22, I^2 = 98%) Another sensitivity analysis restricting to cohort studies only (i.e., removing case-control studies)[33,41] showed an 17% (RR 1.17; 95% CI: 1.06,1.30, I^2 = 98%) increase in dementia risk following HZ infection with significant heterogeneity. To check the stability of the pooled results, a sensitivity analysis comparing the results of the fixed-effects and random-effects models was conducted. It did not show a difference in the final pooled risk ratios and confidence intervals between the two models, although we did note a smaller effect size with the fixed effects model (RR 1.05; 95% CI: 1.04, 1.06, I^2 = 98%).

Analysis stratified by sex demonstrated that previous HZ infection was not associated with increased dementia risk in either men (RR 0.90; 95% CI: 0.81, 1.00, I^2 = 87%) or women (RR 1.04; 95% CI: 0.87, 1.25,

Table 1. Characteristics of included studies evaluating herpes zoster infection and dementia.

	Bae	Chen	Choi	Lopatko Lindman	Schmidt	Mekli
Year	2021	2018	2021	2021	2022	2022
Design	Retrospective Cohort	Retrospective Cohort	Case Control	Retrospective Cohort	Retrospective Cohort	Case Control
Data Source, Country	Korean National Health Insurance Service, Korea	Taiwan National Health Insurance Research Database (NHIRD), Taiwan	Korean National Health Insurance Service, Korea	National Board of Health and Welfare, Sweden	Danish Civil Registration System (CRS), Denmark	UK BioBank, United Kingdom
Study period	2002-2013	1997-2013	2002-2013	2005-2017	1997-2017	2006-2020
Number of Cases (HZ and/or HZO)	34,505	39,205	11,445 (No of dementia)	265,172	247,305	85 (No of dementia)
Number of Controls	195,089	39,205	45,780	255,239	1,235,890	9346
Follow-Up Period	12 years	6 years	12 years	5 years	1-21 years	10 years
Gender, % female	55%	54%	68%	58%	61%	55%
Mean / Median age at entry (SD or IQR), years	61.7 (9.4)	63.5 (10)	Not reported	75 (11)	64 (IQR 54-74) (Median)	65.4 (8)
% Receiving AV Therapy	0-100%	5.4%	Not reported	0-100%	50%	Not reported
Case Inclusion Criteria (HZ and/or HZO)	Adults 50 years of age or older diagnosed with incident HZ and prescribed antiviral drugs within 1 month of HZ diagnosis	Adults 50 years of age or older diagnosed with incident HZ	Adults 60 years of age or older diagnosed dementia and previous hx of HZ	Adults 50 years of age or older previous hx of HSV or VZV and prescribed antiviral drugs	Adults 40 years of age or older diagnosed with incident HZ or who received first-time prescription for antivirals	Adults 40-69 years of age who had serology for VZV
Case Exclusion Criteria	Patients who experienced dementia or HZ before index date	Patients who experienced dementia before index date	Patients who had been diagnosed with HZ before the index date	Patients who had been diagnosed with HSV or VZV before the index date	Patients who had a previous diagnosis of HZ, PHN or antiviral receipt, diagnosis of dementia or antidementia medications before index date	Patients not in the original prospective UKBio Bank study
HZ or HZO Definition	Incident HZ diagnosis using ICD10 codes B02 to B02.3, B02.7 to B02.9 (index date as recorded in database)	Incident HZ diagnosis using ICD9 codes 053.0x to 053.9x (index date as recorded in database)	Incident HZ diagnosis using ICD10 code, B02 and treated ≥ 1 time antivirals (index date as recorded in database)	Incident HZ/VZV diagnosis using ICD10 codes for VZV (B01.x) or HZ (B02.x) (index date as recorded in database)	Incident HZ diagnosis using ICD9 codes 053.0x to 053.9x (index date as recorded in database) and filled a single prescription of acyclovir 800mg, valacyclovir or famciclovir 500mg for 35 tablets	Patients who were seropositive or seronegative for VZV
Dementia Definition	Diagnosis as per ICD10 codes for AD (G30 or F00), VD (F01), other ((F02,F03, G23.1, G31.0, G31.1, G31.82, G31.83, G31.88, and F10.7) in addition to received prescription of antidementia drug for at least 30 days	Diagnosis as per ICD9 codes 290.0x to 290.4x, 294.1x, 331.0x to 331.82	Diagnosis as per ICD10 codes for AD (G30) or dementia with AD (F00)	Diagnosis as per ICD10 codes for dementia (F00.x, F01.x, F03.x) or prescription of antidementia drugs	Diagnosis in hospital or outpatient clinic of dementia or received prescription of antidementia drug	Diagnosis in hospital of dementia per ICD10 codes (F00*, G30*, F01*), F02*, G31.0, A81.0, F10.6, F03, F05.1, G31.1, G31.8) and GP codes

(*Continued*)

Table 1. (Continued).

	Bae	Chen	Choi	Lopatko Lindman	Schmidt	Mekli
Control selection	Patients who had no record of HZ or dementia in the year prior to index date, propensity-score matched	Patients who had no record of HZ, matched (1:1) by age (+/-1 year), sex, residence, and index date	Patients with no HZ or dementia before 2002, matched (1:4) on age, group, sex, income, residence, medical hx (HTN, DM, dyslipidemia)	Patients with no HZ or antivirals, matched (1:1) on sex, and year of birth from the population	Patients who had no record of HZ, matched (1:5) by sex and year of birth	Patients in the BioBank that did not have serology for CNS viruses
Confounders (Adjusted for)	Age, sex, SES HTN, DM, dyslipidemia, chronic lung disease, IHD, stroke, CHF, atrial fibrillation, valvular heart disease, CKD, carotid stenosis, PVD, chronic liver disease, RA, IBD, cancer, SOT, HIV, depression	Age, sex, depressive disorder, HSV infection, ischemic stroke, traumatic brain injury, autoimmune disease, alcohol use disorder, antiviral use	Age, sex, IHD, stroke, depression	Age, sex, comorbidity, prescription of drugs, and educational level. Comorbidity included alcohol intoxication, COPD, CHF, MI, Parkinson disease, stroke, depression, HTN, DM	Age, sex, autoimmune disease, CKD, COPD, asthma, cancer, diabetes, use of glucocorticoids, HIV, lipid-lowering therapy, and traumatic head injury, stroke	Not Reported
Primary outcome:	All-cause dementia associated with HZ	All-cause dementia associated with HZ, stratified by age strata, sex	All-cause dementia associated with HZ, stratified by age strata, sex	All-cause dementia associated with HZ	All-cause dementia associated with HZ, stratified by age, sex, cranial nerve involvement, CNS involvement, stroke diagnosis (in year 1 and 1-21yrs)	All-cause dementia associated with HZ
Outcome: herpes zoster ophthalmicus (HZO)			All-cause dementia associated with HZO		All-cause dementia associated with HZO	
Outcome: other types of dementia	Reported for AD, VD, other types of dementia				Reported for AD	
Outcome: antivirals	Impact of antiviral on dementia	Impact of antiviral on dementia		Impact of antiviral on dementia		

(*Continued*)

Table 1. (Continued).

Omland	Schnier	Schnier	Shim	Shin	Tsai	Warren-Gash
2021	2021a	2021b	2022	2024	2017	2022
Retrospective Cohort	Retrospective Cohort	Retrospective Cohort	Retrospective Cohort	Retrospective Cohort	Retrospective Cohort	Retrospective Cohort
Danish National Health Registry, Denmark	Secure Anonymised Information Linkage Databank (SAIL), Wales	IMS Disease Analyzer, Germany	Korean National Health Insurance Service, Korea	Korean National Health Insurance Service, Korea	Taiwan Longitudinal Health Insurance Database, Taiwan	CPRD general practice database, United Kingdom
1997-2016	1995-2018	1992-2017	2002-2018	2006-2017	2001–2008	2000-2017
517 (VZV DNA in CSF)	37,439	13,643	97,323	113,645	846	177,144
9823	434,689	53,629	183,779	475,884	2,538	706,901
1-12 years	6.7 years	8.8 years	5 years	10.85 years	5 years	6 years
52%	51%	54%	62%	54%	51%	51%
59 (IQR 31-77) (Median)	75 (IQR 71–79) Median	74 (IQR 69–78) Median	63.5 (9)	59.5 (10.1)	61.6 (13)	65.1 (13)
Not reported	9%	19%	Not reported	Not Reported	Not reported	63%
Adults 15 years and older with VZV PCR positive (for DNA) in CSF	Patients with follow-up data from age 60 years onward who had no dementia-related record before their 65th birthday, were alive at their 65th birthday, and had covariate information	Patients with follow-up data from age 60 years onward who had no dementia-related record before their 65th birthday, were alive at their 65th birthday, and had covariate information	Adults 50 years of age or older diagnosed with incident VZV	Adults 45 years of age or older diagnosed with incident HZ or who received prescription for antivirals	Adults 40 years of age or older with incident HZO (index date as recorded in database)	Adults 40 years of age or older diagnosed with incident HZ
None	Patients with dementia related diagnosis before age 65 years	Patients with dementia related diagnosis before age 65 years; people with dementia-related prescription data but no dementia diagnosis; people with antiherpectic medication but no herpes diagnosis	Patients with evidence of VZV, dementia before index date	Patients with evidence of VZV, dementia before index date	Patients diagnosed with HZ during the previous 1-year period. Patients diagnosed with psychosis, SUD, dementia, prior to index date	Individuals with evidence of dementia or HZ before observation period
Patients who had VZV DNA in CSF	Incident HZ diagnosis using ICD10 codes A60[019], B0[02], H191 (index date as recorded in database)	Incident HZ diagnosis using ICD10 codes A60[019], B0[02], H191 (index date as recorded in database)	Incident VZV diagnosis using ICD10 code, B02 (index date as recorded in database)	Incident VZV (eye, CNS, complicated disease) diagnosis using ICD10 codes B02.3, H03.1, H13.1, H19.0, H19.2, H22.0, B02.1, B02.2, B02.7, B02.8, B02, B02.9	Incident HZO diagnosis using ICD9 codes 053.2, 053.20, 053.21, 053.22, or 053.29 (index date as recorded in database)	Incident HZ diagnosis using Read GP codes (index date as recorded in database)

(*Continued*)

Table 1. (Continued).

Omland	Schnier	Schnier	Shim	Shin	Tsai	Warren-Gash
Diagnosis in hospital of dementia per ICD10 codes (F00-F03, F05.1, G30)	Diagnosis in hospital or outpatient clinic or mortality records of dementia. Diagnosis as per ICD10 codes (F0[0-3], F051, G30, G31[018], I673)	Diagnosis in primary care of dementia per ICD10 codes (F0 [0-3], F051, G30, G31[018], I673)	ICD10 codes corresponding to dementia diagnosis. Participants with dementia were subdivided into AD (F00*, G30*), VD (F01*), frontotemporal dementia (G31.00, G31.01, G31.03, G31.04), Lewy body dementia (DLB, G31.82, F02.8*), Parkinson's disease dementia (F02.3*), alcoholic dementia (F10.7), undetermined (F03*), and others (F02*: except F02.3*, G31.82 [F02.8*]). They also had a flag for medical treatment (e.g., donepezil, galantamine, rivastigmine, and memantine) for at least 30 days	ICD-10 codes for dementia (F00, F01, F02, F03, G30, or G31.00), and at least one of the dementia medicine prescriptions [acetylcholinesterase inhibitors (donepezil hydrochloride, rivastigmine, and galantamine) or N-methyl-D-aspartate receptor antagonist (memantine)].	Diagnosis as per ICD9 codes 290.0x to 290.4x, 294.1x, 331.0x to 331.2, or 331.82	Dementia diagnosis as per Read GP codes
Date of birth and sex matching of each patient with VZV DNA with up to 4 patients from general population	Not reported	Not reported	Patients who had no record of VZV, matched (1:3) by sex and age	Selected from remaining patients that had no record of VZV	Selected from remaining patients that had no record of HZ, propensity-score matched (3:1)	Patients who had no record of HZ, matched (1:4) by age, sex, primary care practise and calendar time

(*Continued*)

Table 1. (Continued).

Omland	Schnier	Schnier	Shim	Shin	Tsai	Warren-Gash
Age, sex, immunosuppressive conditions, COPD, IBD, cancer, SLE, RA, AS, psoriasis	Age, sex, SES, comorbidities	Age, sex, SES, comorbidities	Age, sex, comorbidities (HTN, DM, dyslipidemia, stroke, intracranial or unspecified hemorrhage)	Age, sex, comorbidities (HTN, DM, dyslipidemia, stroke, CKD, ischaemic stroke, coronary heart disease and depression	Age, sex, monthly income, geographic location, urbanization level, the year of the index date, hypertension, diabetes, hyperlipidemia, coronary heart disease, and stroke	Age, sex, general practise and calendar time, year of study entry, frailty, health seeking behaviour, harmful alcohol use, BMI, smoking, CKD, asthma, autoimmune disease, COPD, depression, immunosuppression, HTN, IHD liver disease, stroke, traumatic brain injury and HSV.
All-cause dementia associated with HZ (in year 1 and 1-12)	All-cause dementia associated with HZ	All-cause dementia associated with HZ	All-cause dementia associated with HZ	All-cause dementia associated with HZ	All-cause dementia associated with HZO, stratified by age strata, sex	All-cause dementia associated with HZ, stratified by age strata, sex
					All-cause dementia associated with HZO	
			Reported for AD, VD, Lewy body	Reported for AD, VD		Reported for AD, VD, other types of dementia
	Impact of antiviral on dementia	Impact of antiviral on dementia				

Table 1. (Continued).

	Douros	Harris	Lophatananon	Scherrer	Scherrer	Schnier	Wiemken	Wiemken
Year	2023	2023	2021	2021a	2021b	2022	2021a	2021b
Design	Nested case-control	Retrospective Cohort	Nested case-control	Retrospective Cohort	Retrospective Cohort	Retrospective Cohort	Retrospective Cohort	Retrospective Cohort
Data Source, Country	CPRD general practice database, United Kingdom	Clinformatics Data Mart Database, USA	BioBank cohort study, UK	Veterans Health Affairs (VHA), USA	IBM MarketScan® commercial claims and Medicare Supplemental databases, USA	Secure Anonymised Information Linkage Databank (SAIL), Wales	Veterans Health Affairs (VHA), USA	IBM MarketScan® commercial claims and Medicare Supplemental databases, USA
Study period	1996-2018	2009-2019	2006-2020	2008-2019	2009-2018	2013-2020	2011-2019	2012-2018
Number of Cases (HZ vaccination)	212,562 (No of dementia)	1,651,991	2,378 (HZ vaccination)	27,419	24,612	336,341 of which 155,972 were exposed to vaccine	11,434	13,774
Number of Controls	1,623,806	N/A	225,845	108,597	148,178	N/A	63,021	101,819
Follow-Up Period	10 years	8 years	4 years	8-9 years	7-8 years	6 years	7.5 years	3 years
Gender, % female	62%	57%	54%	4%	65%	52%	4%	64%
Mean / Median age at entry (SD or IQR), years	70 (10)	72 (5)	65.4 (6)	75.7 (7)	69.9 (6)	75 (IQR 71–79) Median	76.8 (7)	70.5 (6)
% Receiving AV Therapy	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Case Inclusion Criteria	Adults on 50th birthday or 1 year after date of enrolment in database (whichever occurred later)	Adults 65 years of age or older with ≥ 2 ICD records in the follow-up period	Adults 40 years of age or older diagnosed with dementia diagnosis 3 years or more after cohort entry	Adults 65 years of age or older and free of dementia or cognitive decline for two years prior to baseline	Adults 65 years of age or older and free of dementia or cognitive decline for two years prior to baseline	Adults on 70th birthday of enrolment in database	Adults 65 years of age or older and free of dementia or cognitive decline for two years prior to baseline	Adults 65 years of age or older and free of dementia or cognitive decline for two years prior to baseline

Table 1. (Continued).

	Douros	Harris	Lophatananon	Scherrer	Scherrer	Schnier	Wiemken	Wiemken
Case Exclusion Criteria	Individuals with prior diagnosis of dementia, mild cognitive impairment, or early signs and symptoms suggestive of dementia or prescriptions for treatment of dementia (eg, donepezil, rivastigmine, and galantamine, memantine) before cohort entry; less than 2 years of follow-up; cohort entry in CPRD before 1 January 1996	Individuals with prior diagnosis of dementia, mild cognitive impairment, or early signs and symptoms suggestive of dementia or prescriptions for treatment of dementia (eg, donepezil, rivastigmine, and galantamine, memantine) before cohort entry	Individuals with prior diagnosis of dementia	Individuals with prior diagnosis of dementia, or less than 90 days of follow up time	Individuals with prior diagnosis of dementia or less than 90 days of follow up time	Patients not registered with GP for at least 5 years, covariate information not available in database, any persons with dementia diagnosis before their 70th birthday	Individuals with prior diagnosis of dementia, or less than 90 days of follow up time	Individuals with prior diagnosis of dementia or less than 90 days of follow up time
HZ or HZO Definition	Not reported	Not reported	Incident HZ diagnosis using Read GP codes (index date as recorded in database at least 3 years prior to dementia diagnosis)	Not reported	Not reported	Not reported	Not reported	Not reported

Table 1. (Continued).

	Douros	Harris	Lophatananon	Scherrer	Scherrer	Schnier	Wiemken	Wiemken
Dementia Definition	Dementia diagnosis as per Read GP codes	Diagnosis as per ICD10 codes for AD (G30) or dementia with AD (F00) plus ≥ 2 AD healthcare records on separate days, or ≥ 1 AD records with ≥ 1 medication record, or ≥ 2 medication records on separate days	Dementia diagnosis as per Read GP codes	ICD10 codes corresponding to dementia diagnosis (F01.x, F02.x, F0.x, G3.x, G31.0x, G31.1) or ICD9 (290.0, 290.1x, 290.2x, 290.3, 290.4x, 294.1x, 294.2x, 331.0, 331.1x, 331.2) with 2 code occurrences on different days in a 12-month period. For AD the codes were 331.0 or G30.x.	ICD10 codes corresponding to dementia diagnosis (F01.x, F02.x, F0.x, G3.x, G31.0x, G31.1) or ICD9 (290.0, 290.1x, 290.2x, 290.3, 290.4x, 294.1x, 294.2x, 331.0, 331.1x, 331.2) with 2 code occurrences on different days in a 12-month period. For AD the codes were 331.0 or G30.x.	Diagnosis in hospital or outpatient clinic or mortality records of dementia. Diagnosis as per ICD10 codes (F0 [0-3], F051, G30, G31[018], I673)	ICD10 codes corresponding to dementia diagnosis (F01.x, F02.x, F0.x, G3. x, G31.0x, G31.1) or ICD9 (290.0, 290.1x, 290.2x, 290.3, 290.4x, 294.1x, 294.2x, 331.0, 331.1x, 331.2) with 2 code occurrences on different days in a 12-month period. For AD the codes were 331.0 or G30.x.	ICD10 codes corresponding to dementia diagnosis (F01.x, F02.x, F0.x, G3.x, G31.0x, G31.1) or ICD9 (290.0, 290.1x, 290.2x, 290.3, 290.4x, 294.1x, 294.2x, 331.0, 331.1x, 331.2) with 2 code occurrences on different days in a 12-month period. For AD the codes were 331.0 or G30.x.
Control selection	Patients who had no record of dementia, matched (1:4) by age, sex, year of cohort entry, duration of follow-up, and CPRD data set	Patients who had no record of dementia, propensity score matched by covariates	Patients who had no record of dementia	Patients who had no record of dementia matched by propensity score and Inverse Probability of Treatment Weighting (IPTW) by HZ, receipt of antivirals	Patients who had no record of dementia matched by propensity score and Inverse Probability of Treatment Weighting (IPTW) by HZ, receipt of antivirals	Not reported	Patients who had no record of dementia matched by propensity score and Inverse Probability of Treatment Weighting (IPTW) by HZ, receipt of antivirals	Patients who had no record of dementia matched by propensity score and Inverse Probability of Treatment Weighting (IPTW) by HZ, receipt of antivirals

Table 1. (Continued).

	Douros	Harris	Lophatananon	Scherrer	Scherrer	Schnier	Wiemken	Wiemken
Confounders (Adjusted for)	Age, sex, ethnicity, BMI, smoking, alcohol disorder, HTN, AF, CHF, CAD, stroke, TIA, PVD, dyslipidemia, DM, CKD, liver disease, depression, epilepsy, Parkinson disease, traumatic brain injury, osteoporosis, hypothyroidism, cancer, and drugs for treatment of VZV infection, antibiotics, oral anticoagulants, antiplatelet agents, lipid-lowering drugs, β-blockers, thiazides, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, proton pump inhibitors, nonsteroidal anti-inflammatory drugs, opioids, immunosuppressants and biologics, antipsychotics, and antidepressants	Age, sex, race, geographic region, number of healthcare encounters, number of annual checkups, BMI, smoking, alcohol disorder, substance use, HTN, AF, CHF, CAD, stroke, TIA, PVD, dyslipidemia, DM, CKD, liver disease, depression, anxiety disorder, epilepsy, Parkinson disease, traumatic brain injury, osteoporosis, hypothyroidism, cancer, COPD, asthma, IHD, and drugs including anticholinergics, antivirals for treatment of VZV infection, lipid-lowering drugs, β-blockers, thiazides, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, proton pump inhibitors, nonsteroidal anti-inflammatory drugs, vaccines	Age, sex, Charleston comorbidity index, shingles	Age, sex, geographic regions, type 2 diabetes, obesity, HTN, stroke, IHD, CHF, atrial fibrillation, asthma, COPD, traumatic brain injury, vitamin B12 deficiency, depression, anxiety disorder, nicotine dependence, alcohol and drug abuse/ dependence, BMI, smoking, anticholinergics, NSAIDS, anti-hypertensives, statins, steroids, antiviral medications, metformin, sulfonylurea, average number of outpatient healthcare encounters/ medical claims, HZ infection, and HZ antiviral	Age, sex, geographic regions, type 2 diabetes, obesity, HTN stroke, IHD, CHF, atrial fibrillation, asthma, COPD, traumatic brain injury, Vitamin B12 deficiency, depression, anxiety disorder, nicotine dependence, alcohol and drug abuse/ dependence, BMI, smoking, anticholinergics, NSAIDS, anti-hypertensives, statins, steroids, antiviral medications, metformin, sulfonylurea, average number of outpatient healthcare encounters/ medical claims, HZ infection, and HZ antiviral	Age, sex, SES, comorbidities	Age, gender, race, SES, marital status, insurance status, geographic region, overall health care utilization, and use of well visits in the 2 years prior to index, cancer, type 2 diabetes, obesity, HTN, stroke, IHD, CHF, atrial fibrillation, asthma, COPD, traumatic brain injury, vitamin B12 deficiency, depression, any anxiety disorder, nicotine dependence, and alcohol and drug abuse, medications that may impact cognitive function (antidepressants, benzodiazepines, anticholinergics, NSAIDS, antihypertensives, statins, steroids, antivirals, metformin, and sulfonylurea)	Sociodemographics, age, gender, geographic region, overall health care utilization, and use of well visits in the 2 years prior to index, cancer, type 2 diabetes, obesity, HTN, stroke, IHD, CHF, atrial fibrillation, asthma, COPD, traumatic brain injury, vitamin B12 deficiency, depression, any anxiety disorder, nicotine dependence, and alcohol and drug abuse, medications that may impact cognitive function (antidepressants, benzodiazepines, anticholinergics, NSAIDS, antihypertensives, statins, steroids, antivirals, metformin, and sulfonylurea)

Table 1. (Continued).

	Douros	Harris	Lophatananon	Scherrer	Scherrer	Schnier	Wiemken	Wiemken
Primary outcome	All-cause dementia associated HZ vaccine (also reported for other vaccines (e.g., pneumococcal, influenza, diphtheria, shingles, tetanus, pertussis)	Alzheimer's dementia associated HZ vaccine, stratified by type of vaccine (Shingrix vs Zostovax)	All-cause dementia associated HZ vaccine, stratified by gender, comorbidity, type of vaccine (Shingrix vs Zostovax)	All-cause dementia associated HZ vaccine, age	All-cause dementia associated HZ vaccine, age	All-cause dementia associated HZ vaccine	All-cause dementia associated HZ vaccine	All-cause dementia associated HZ vaccine
Outcome: other types of dementia		Alzheimer's dementia		Alzheimer's dementia	Alzheimer's dementia	Alzheimer's dementia Vascular dementia		
Other Outcomes			All-cause dementia associated with HZ infection					

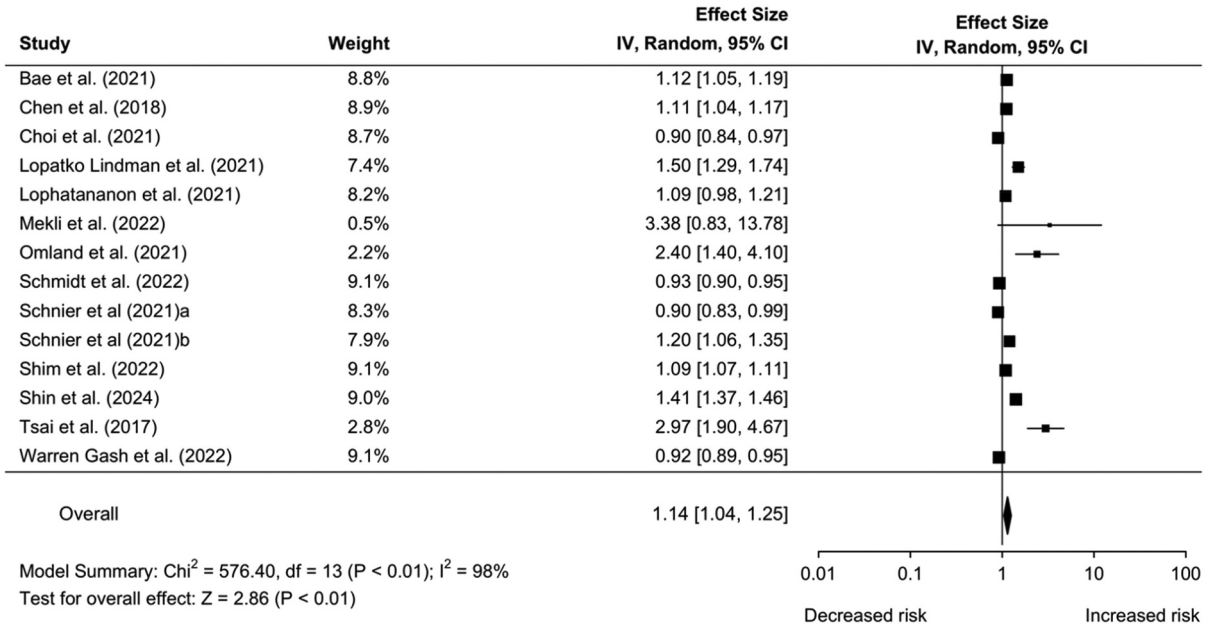

Figure 2. Effect of herpes zoster infection on dementia risk (random-effects model).

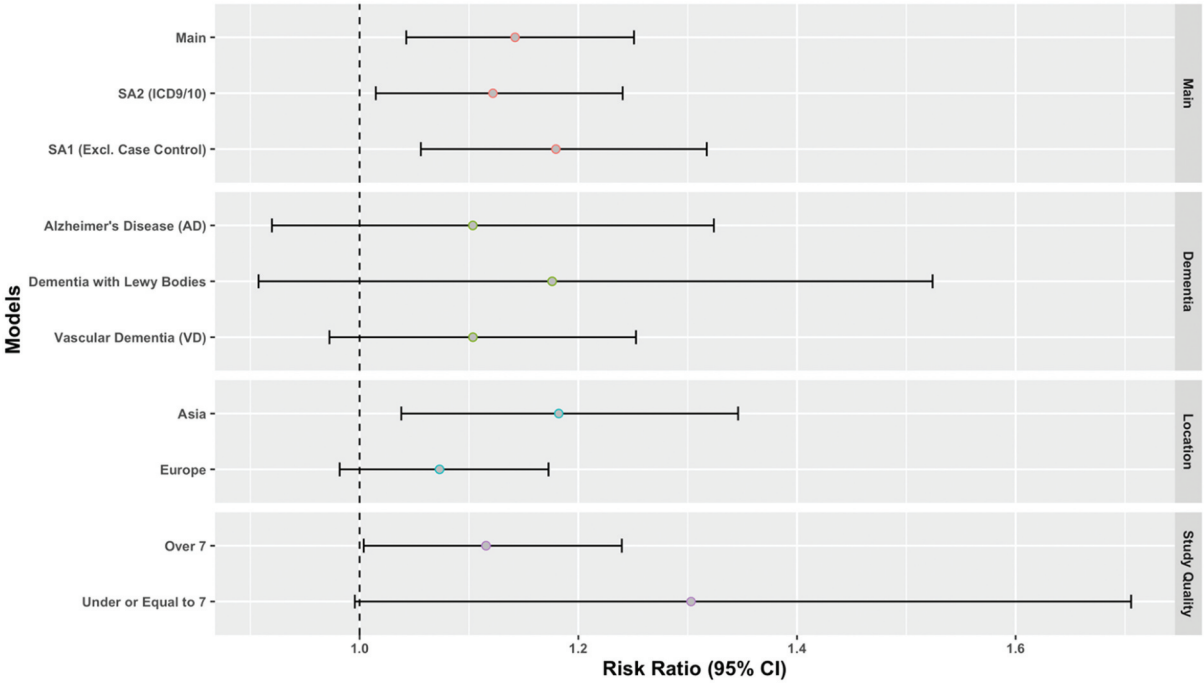

Figure 3. Summary of all primary, sensitivity and subgroup analyses evaluating risk of dementia following herpes zoster infection.

I^2 = 82%) (Supplementary Material, S4). Dementia risk after HZ infection in different age groups showed no significant risk in the younger age groups (RR 1.37; 95% CI: 0.83, 2.26, I^2 = 99%), but the risk increased to RR 7.40 (95% CI: 0.77, 71.0, I^2 = 100%) in those 80 years of age and older compared to less than 80 years, although it was statistically non-significant.

Figure 3 and Supplementary Material, S4 shows further subgroup analyses. An evaluation of the specific type of dementia did not show any association with herpes zoster infection. The pooled RR was 1.10 (95%

CI: 0.92, 1.32, I^2 = 99%) for AD, 1.10 (95% CI: 0.97, 1.25, I^2 = 86%) for vascular dementia, 1.01 (95% CI: 0.82, 1.24, I^2 = 67%) for other dementias, and 1.18 (95% CI: 0.91, 1.52, I^2 = 100%) for Lewy body dementia. The risk of dementia following herpes zoster ophthalmicus was evaluated in three studies. We did not observe a greater risk of dementia with HZO compared to HZ infection only (RR 1.05, 95% CI: 0.88, 1.25, I^2 = 92%).

Stratifying based on study location (i.e., Asia or Europe) revealed a significant association between HZ infection and increased risk of developing dementia in the Asian studies (RR 1.18, 95% CI: 1,04, 1.35, I^2 = 98%) but not the European ones (RR 1.07, 95% CI: 0.98, 1.17, I^2 = 91%). Higher quality studies with a bias score more than 7 did not show an effect on dementia (RR 1.12, 95% CI: 1.00, 1.24, I^2 = 98%), whereas lower score studies showed an effect (RR 1.30, 95% CI: 1.00, 1.71, I^2 = 92%).

Due to the large heterogeneity between studies, a random effects model was used for pooling in the meta-analyses. However, heterogeneity did not diminish when we conducted the subgroup analyses by age, gender, type of dementia, study design, population, and study quality score, suggesting heterogeneity may not be related to these factors.

Antiviral treatment for herpes zoster infection and risk of dementia

Figure 4 shows the results of pooling data from four studies (5 cohorts as Schnier et al. had multiple studies in one paper) that evaluated the impact of antiviral treatment for herpes zoster infection.[31,32,34,36] There was an estimated 16% reduction in the risk of dementia (RR 0.84; 95% CI: 0.71, 0.99, I^2 = 73%). We were unable to do subgroup analyses for these studies as there were only four studies, and they did not stratify by age, sex or type of dementia. Two studies were conducted in Asia and two in Europe, and three studies had a bias score of greater than 7, while one study had a score of 7 or less. Subgroup analyses done on study location or bias score did not change the effect size significantly (data not shown).

Vaccination prevention for herpes zoster infection and risk of dementia

Figure 5 shows the results of pooling data from six studies (8 cohorts as Scherrer et al.[46] and Wiemken et al.[48] had two studies in one paper). We estimated a risk reduction of 32% (RR: 0.68; 95% CI: 0.56, 0.83), in individuals vaccinated against HZ compared with controls, albeit with considerable heterogeneity (I^2 = 99%). Supplementary Material S5 shows the sensitivity analyses. All the studies were of cohort design, using similar methodology and endpoints, but in some cases, there was overlapped between studies and there were differences in terms of covariates that were adjusted for. There was considerable overlap between the Scherrer[46] and Wiemken[48] studies in terms of the study population included. Both investigators used the Veterans Health Affairs (VHA) and IBM MarketScan databases with Wiemken et al. including data that may be contained almost entirely as a subset by Scherrer et al. who used a longer timeframe from 2009 to 2019. The sensitivity analysis conducted by removing the two Wiemken cohorts showed minimal impact on

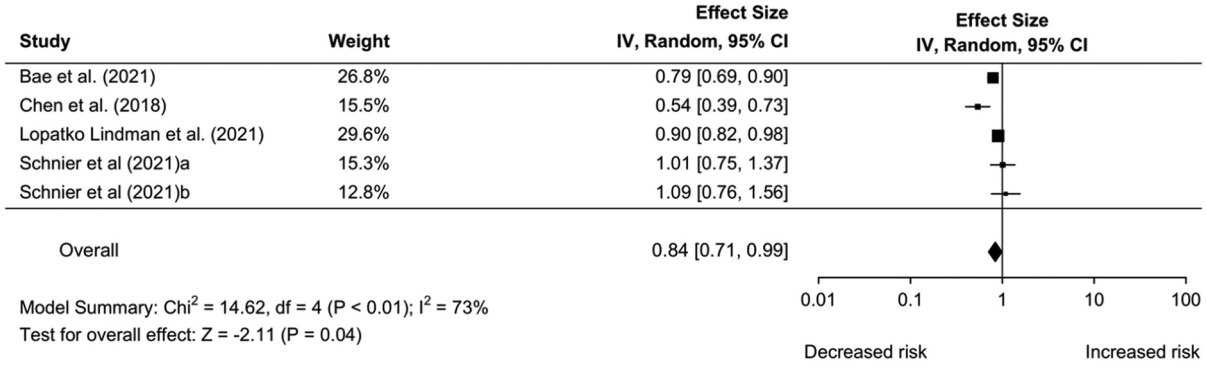

Figure 4. Effect of antiviral treatment for herpes zoster infection on dementia risk. (1) Schnier et al. (2021a) Retrospective, cohort study using data from the Secure Anonymised Information Linkage Databank (SAIL), Wales. (2) Schnier et al. (2021b) Retrospective, cohort study using data from the IMS Disease Analyzer, Germany.

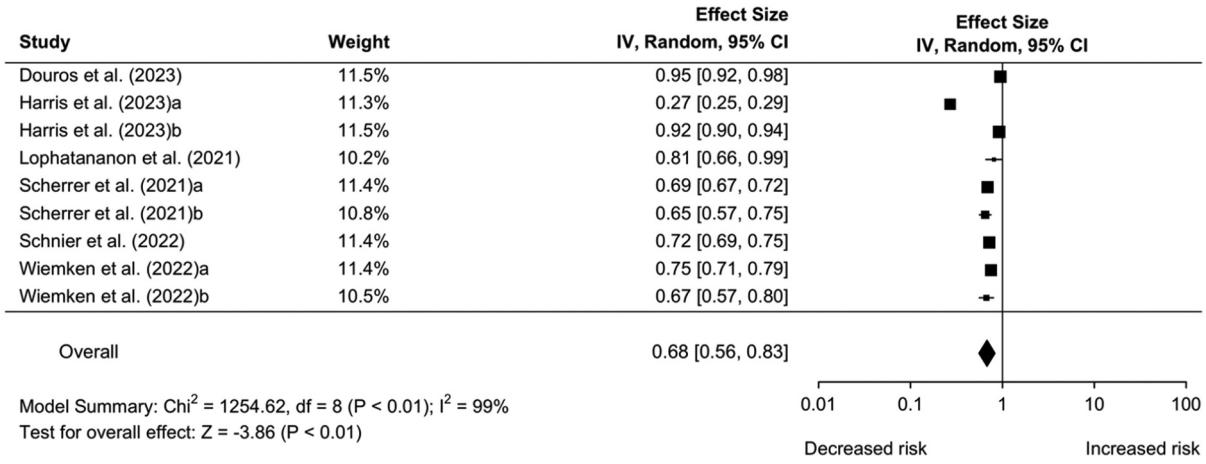

Figure 5. Effect of prevention with vaccination for herpes zoster infection on dementia risk. (1) Harris et al. (2023a) Retrospective, cohort study that presented their data as 1 dose of recombinant herpes zoster vaccine (Shingrix®) and excluding those who received the live attenuated vaccine (Zostovax®). (2) Harris et al. (2023b) Retrospective, cohort study that presented their data as 1 dose of live attenuated vaccine (Zostovax®) and excluding those who received the recombinant herpes zoster vaccine (Shingrix®). (3) Scherrer et al. (2021a) Retrospective, cohort study using data from the Veterans Health Affairs (VHA), USA. (4) Scherrer et al. (2021b) Retrospective, cohort study using data from the IBM MarketScan® commercial claims and Medicare Supplemental databases, USA. (5) Wiemken et al. (2022a) Retrospective, cohort study using data from the Veterans Health Affairs (VHA), USA. (6) Wiemken et al. (2022b) Retrospective, cohort study using data from the IBM MarketScan® commercial claims and Medicare Supplemental databases, USA.

the results (RR: 0.67; 95% CI: 0.53, 0.85, I^2 = 100%). For our second sensitivity analysis, we removed the two studies[45,47] that did not adjust for health seeking behavior and/or number of healthcare encounters, and again saw there was minimal impact on the study results with a risk reduction of 34% (RR: 0.66; 95% CI: 0.52, 0.84, I^2 = 100%). Our third sensitivity analysis related to fixed versus random model also did not change the results significantly (data not shown).

Supplementary Material S6 shows the subgroup analyses for the studies related to the impact of HZ vaccine on dementia. We were unable to conduct a sub-group analysis by vaccine type as only Harris et al. presented results based on live attenuated vaccine versus recombinant zoster vaccine. With respect to age, the vaccine was protective in the older age group of those 75 years and older (RR 0.63; 95% CI: 0.54, 0.73, I^2 = 62%) as well as the younger group of less than 75 years (RR 0.75; 95% CI: 0.60, 0.93, I^2 = 87%) with a lower effect size for the older group. Protection was seen with all-cause dementia as well as AD (RR 0.76; 95% CI: 0.73, 0.80, I^2 = 53%); we were not able to examine vascular dementia or other types of dementia due to lack of information. When restricting to studies in Europe only, the effect was non-significant (RR 0.82; 95% CI: 0.66, 1.03, I^2 = 98%), whereas when restricting to North America only, the effect was statistically significant (RR 0.62; 95% CI: 0.45, 0.85, I^2 = 100%). Bias score did not make a difference, with the risk remaining significantly low in studies with a higher (RR 0.71; 95% CI: 0.68, 0.74, I^2 = 51%) or lower scores (RR 0.66; 95% CI: 0.44, 0.98, I^2 = 100%).

Publication bias

Publication bias testing is seen in Supplementary Material, S7. For the association between herpes zoster infection, as well as antivirals, and dementia significant publication bias was noted by Egger test (P < .0001) but not Begg's test (P = .306). However, the Egger test (P = .639) and Begg test (P = 1.0) revealed no evidence of publication bias for studies evaluating the association of vaccination and dementia; however, the funnel plots exhibited a slight asymmetry, so publication bias was still suspected. The Trim and Fill method identified missing studies for antiviral and vaccine impact studies.

Discussion

The association between HZ infection and dementia risk has been evaluated over the years in many observational studies with mixed results; some finding a positive association while others finding no association. Previous systematic reviews and meta-analysis have been conducted on the topic of dementia risk, but ours is the first comprehensive study to evaluate all three aspects of this research question: the risk with HZ infection, the impact of antivirals used for HZ treatment, and prevention with vaccines. We found that the risk of dementia was increased slightly with HZ infection, by 14%, although the results have high heterogeneity. We did not observe differences between men and women, patients with HZ ophthalmicus infection, subtypes of dementia, or younger age groups and dementia risk.

Gao et al. conducted a similar meta-analysis to ours, looking at HZ infection on dementia risk.[49] They included nine studies (we included 11 studies with one study contributing two cohorts), with a total of 3,326,673 participants, and estimated a statistically significant 11% increased risk of dementia when comparing participants in the previously HZ infected to uninfected groups. Similar to our results, in their sub-group analysis by dementia type, Guo et al. did not observe differences in risk for AD, vascular dementia, or other dementias. In both studies, this may be related to the small number of studies included in the analysis, their sample sizes, large heterogeneity, possible receipt of antiviral therapy for treatment of HZ infection, or use of HZ vaccination for prevention. Both studies also found a significant risk of dementia in Asian studies, but not European. This difference may be related to genetics, treatment differences within the two locations for HZ infection, healthcare structure, health seeking behavior, factors used for adjustment of the hazard ratio, case definitions used for HZ infection and dementia or unmeasured confounding.

Our results are contrasted by two other meta-analysis; both found no increased dementia risk with HZ infection.[49,50] Warren-Gash et al. studied the effect of human herpesviruses (HHV) (i.e., HHV-6, HHV-7, HHV-8, HSV-1, HSV-2, VZV, EBV, and cytomegalovirus), defined by clinical or laboratory criteria, on the development of dementia or mild cognitive impairment.[51] They included 57 studies and concluded that past infection with any type of herpes virus, delineated by IgG seropositivity, was not associated with dementia risk. Specifically for HZ infection, they only included the single cohort study by Tsai et al. looking at HZ reactivation as an ophthalmitis that estimated an adjusted HR of 2.97 (95% CI: 1.89 to 4.66) and incident dementia.[38] Their analysis of four case-control studies on VZV infection, from past infection,[52,53] or recent infection/reactivation from brain or serum samples,[50,54] was not associated with dementia. None of these case control studies were included in our systematic review, either because they were published before 1984 (we started in 1996) or because they used nonspecific viral titer tests to detect VZV antibodies, or they evaluated herpes simplex virus (HSV1). The second meta-analysis by Elhalag et al. also reported no association between HZ infection and dementia or AD risk.[55] In contrast to our study, they only included nine studies in total, of which they had three studies[34,40,42] (compared to our 11 studies) to evaluate the all-cause dementia endpoint and 2 studies[34,40] (compared to our 5 studies) for the AD outcome.

Our meta-analysis estimated the risk of dementia is reduced when antivirals are administered for HZ treatment compared to the untreated. These results were observed in the meta-analysis conducted by Gao et al. who estimated a 16% reduction in dementia risk when antivirals were taken by individuals for HZ treatment.[55] However, in both studies, the results were statistically non-significant and may be related to the low number of studies in this category.

We observed that patients receiving HZ vaccine had a reduced dementia risk (by 32%) compared to those not receiving HZ vaccination (either zostovax or shingrix). This finding was robust to the various subgroup analyses that we conducted. Interestingly, although we were unable to conduct a sub-group analysis by vaccine type, we note that the data presented by Harris et al. shows a much larger and protective effect with the recombinant zoster vaccine compared to the live attenuated vaccine. This is further supported by a recent study that we were not able to include in our meta-analysis that compared the dementia risk of live attenuated zoster vaccine versus the recombinant vaccine.[56] Taquet et al. used electronic health records of about 208,000 people in the US, half of whom received the live attenuated zoster vaccine, chosen from the cohort before November 2017, and the other half who received the recombinant zoster vaccine choose from a cohort of individuals after November 2017. Individuals in the group that predominantly received the recombinant vaccine were at a lower risk of developing dementia over their follow-up time of 6 years (restricted mean time lost (RMTL) ratio, 0.83; 95% CI: 0.80, 0.87; $P < .0001$) than were those in the group

that predominantly received the live vaccine, translating into 17% more time lived diagnosis-free, or 164 additional diagnosis-free days among those affected with dementia. The recombinant vaccine protected women and men, but the effect was greater in women. Similar results were obtained for the different dementia subtypes.

Wu et al. published a systematic review and meta-analysis of studies that compared the risk of dementia in vaccinated individuals versus unvaccinated populations.[57] They included 17 studies and evaluated the risk associated with following vaccinations: rabies, tetanus-diphtheria-acellular pertussis (TdaP), influenza, hepatitis A, hepatitis B, typhoid, or herpes zoster. They concluded that adult vaccinations are associated with a 35% reduction in dementia risk. Specific to herpes zoster vaccination, they estimated a risk reduction of 31% (HR 0.69; 95% CI 0.67–0.72); similar in magnitude to our analysis. In the study conducted by Taquet et al., they showed both zoster vaccines were associated with lower dementia risk compared to influenza and tetanus-diphtheria-pertussis vaccines (RMTL ratios, 0.73–0.86; all $P < .0001$).

For the present meta-analysis, the variation seen in the pooled data and resulting heterogeneity may be related to the study designs (cohort studies versus case control), follow-up period (ranging from 1 to 21 years), inclusion and exclusion criteria (some specifying exclusion of herpes zoster and/or dementia diagnosis prior to index date while others excluding just a diagnosis of herpes zoster prior to index date), type of matching for controls (some studies used propensity score matching, whereas others matched on only age, sex plus/minus geographic region), definitions for herpes zoster (use of ICD 9/10 codes versus identifying patients through varicella zoster virus seropositivity or DNA in the cerebrospinal fluid), and definitions for dementia (identified through ICD 9/10 codes or plus receipt of antidementia medications). The high heterogeneity may also be related to baseline comorbidities of the study population, and we found that adjustment for confounders varied greatly among the 17 studies, with some studies adjusting for a plethora of covariates (e.g., age, sex, general practice, calendar time, year of study entry, frailty, health seeking behavior, alcoholism, smoking, obesity, chronic kidney disease, liver disease, asthma, COPD, depression, autoimmune disease, immunosuppression, hypertension, ischemic heart disease, stroke, traumatic brain injury and HSV), while others only adjusted for age, sex and a limited number of comorbidities.

For the association between herpes zoster infection, as well as antivirals, and dementia, significant publication bias was noted by Egger's test, but this was not seen in the vaccination studies. The presence of publication bias can compromise the validity of pooled effect estimates by disproportionately reflecting studies with statistically significant or positive results. In the context of our findings, the potential over-representation of studies reporting an association between antivirals and dementia may exaggerate the observed effect size, inflating confidence in a relationship that may be weaker or even null if unpublished data were included. Similarly, while bias tests were nonsignificant for vaccination studies, the observed funnel plot asymmetry and Trim and Fill adjustment imply that the true effect may be attenuated once missing or unpublished studies are accounted for. This underscores the importance of cautious interpretation, as publication bias can lead to an overestimation of benefit or harm, and may affect the strength of recommendations for clinical or public health interventions based on the current evidence base.

Healthy initiator bias may arise through confounding by indication,[58] and individuals with underlying conditions known to promote the use of antiviral or vaccines (many of which are risk factors for dementia) were expected to be more likely to receive treatment or vaccination against zoster. Many studies adjusted for HZ vaccine and dementia risk factors, comorbidities and frailty, but it made minimal difference to the results. It is also possible that the protective effect seen with antivirals or vaccination may be related to the different lifestyles and health seeking behavior of populations receiving treatment or vaccination compared to untreated/unvaccinated populations. For example, it is often argued that health-seeking populations are more likely to reside in urban areas, have higher educational and income levels, engage in greater physical activity and possess increased knowledge of disease prevention. While many of the studies included in this meta-analysis adjusted for several of these potential confounders, unmeasured or residual confounding may still be present. Specifically, certain lifestyle-related variables such as physical activity or health literacy are difficult to measure consistently and may not have been adequately controlled for, potentially biasing the observed associations.

Another important consideration is the potential impact of concomitant drug therapies on dementia risk, which may confound the observed associations in our meta-analysis. Certain medications commonly used in older populations have been implicated in either increasing or decreasing the risk of dementia. For

instance, beta-blocker therapy has been associated with a reduced risk of vascular dementia, potentially through mechanisms involving blood pressure regulation and cerebrovascular protection.[59] Similarly, calcium channel blockers may influence amyloid beta peptide production and oxidative stress pathways, possibly affecting the progression to dementia.[60] Although many included studies adjusted for medication use, heterogeneity in how drug exposures were defined and captured across studies may lead to residual confounding. This should be considered when interpreting the pooled effect estimates.

As a neurotropic virus, varicella zoster remains dormant in the central nervous system.[18] During latency, the virus resides in the cranial nerve, dorsal root, and autonomic ganglionic neurons and there is not much transcription or viral activity. It has been postulated that reactivation promotes neuroinflammation[11,61] that could result in neuronal death or stimulate creation of misfolded oligomers, thereby promoting the accumulation of amyloid plaques and hyperphosphorylated tau protein.[62] Another possible cause is the binding of varicella zoster virus to insulin-degrading enzyme (IDE), which degrades Aβ, leading to more amyloid plaque production.[63] It is also possible that VZV may directly infect astrocytes, which promote production of intracellular amyloid and aggregation of amyloid fibrils in the extracellular matrix.[9] Studies have shown that cranial nerve involvement with HZ causes cerebral vasculopathy and stroke[64] resulting in neural damage, which could promote changes in brain proteins. Finally, the severe encephalitis related to herpes zoster infection could induce dementia, similar to what is observed for HIV and syphilis. It is unclear as to how treatment with antivirals or prevention of infection with vaccination reduces dementia. The main theory is that these interventions limit the CNS-related damage caused by the virus and/or reduces the inflammatory processes that take place with an infection.[65,66]

Conclusion

Dementia risk may be slightly increased after acute herpes zoster infection; the risk is decreased with antivirals. Vaccination against HZ appears to significantly reduce the risk of dementia. Increased efforts should be made to recommend vaccinations to older adults, especially those at higher dementia risk.

Acknowledgements

FM conceived the study, was involved in interpretation, and wrote the first draft of the manuscript. EL conducted the literature review, and contributed to manuscript writing. FM and EL reviewed all titles, abstracts and full texts to select studies for inclusion. FM and EL extracted data and assessed risk of bias. JC supervised literature review, reviewed papers/abstracts if disagreements, provided methodological advice on the meta-analysis, interpreted findings, reviewed further drafts and approved the final version. KG and NKV provided methodological advice, conducted the meta-analysis and meta regression, reviewed further drafts and approved the final version. KR provided methodological advice on the meta-analysis, interpreted findings, reviewed further drafts and approved the final version. All authors have read and approved the final manuscript.

Author contributions

CRediT: **Fawziah Marra:** Conceptualization, Data curation, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing; **Kyle Gomes:** Formal analysis, Visualization, Writing – review & editing; **Emily Liu:** Data curation, Writing – review & editing; **Nirma Khatri Vadlamudi:** Formal analysis, Methodology, Validation, Visualization, Writing – review & editing; **Kathryn Richardson:** Methodology, Validation, Visualization, Writing – review & editing; **Jacquelyn J. Cragg:** Methodology, Visualization, Writing – review & editing.

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