European Archives of Psychiatry and Clinical Neuroscience (2021) 271:987–997
https://doi.org/10.1007/s00406-020-01157-4

ORIGINAL PAPER

Association of herpes zoster with dementia and effect of antiviral therapy on dementia: a population-based cohort study

Seongman Bae[1] · Sung-Cheol Yun[2] · Min-Chul Kim[3] · Woon Yoon[4] · Joon Seo Lim[5] · Sang-Oh Lee[1] · Sang-Ho Choi[1] · Yang Soo Kim[1] · Jun Hee Woo[1] · Seong Yoon Kim[4] · Sung-Han Kim[1,5]

Received: 9 May 2020 / Accepted: 24 June 2020 / Published online: 1 July 2020

Abstract

We investigated the association between herpes zoster (HZ) and dementia, and the effects of antiviral therapy on the risk of dementia. We used the National Health Insurance Service-National Sample Cohort in South Korea to identify individuals that were followed from January 1, 2002, to December 31, 2013. Occurrences of HZ and dementia were identified using the relevant diagnostic codes. Dementia was defined as the presence of diagnostic codes and history of anti-dementia drug prescription. Propensity score matching (1:1) was carried out among HZ patients according to antiviral therapy. A total of 229,594 individuals aged ≥50 years were analyzed. The incidences of the first-diagnosed HZ and dementia were 16.69 and 4.67 per 1000 person-years (PY), respectively. HZ patients had a higher risk of dementia (incidence rate ratio [IRR], 1.94 [95% CI 1.83–2.06]; adjusted hazard ratio [HR], 1.12 [95% CI 1.05–1.19]). Of the 34,505 patients with HZ, 28,873 (84%) had received antiviral treatment. The crude incidence rates of subsequent dementia in the treated and untreated groups were 7.79 and 12.27 per 1000 PY, respectively, resulting in an IRR of 0.64 (95% CI 0.56–0.72) and covariate-adjusted HR of 0.79 (95% CI 0.69–0.90). After propensity score matching, the treated group showed a significantly lower risk of dementia (HR 0.76; 95% CI 0.65–0.90). In this large population-based cohort study, HZ was associated with a higher risk of dementia. The use of antiviral agents in HZ patients was associated with lower risks of dementia.

Keywords Dementia · Herpes zoster · Herpesviridae · Antiviral therapy

Introduction

Dementia is a major public health concern worldwide [1]. According to the World Alzheimer's Disease Report 2015, it is estimated that 46.8 million people worldwide are currently living with dementia, and that the number will double every 20 years [2]. The prevalence of dementia and the associated socioeconomic burden are rapidly growing in accordance with the population aging in many developed countries [3, 4]. The etiology of dementia is complex and heterogeneous, with advanced age being the most important risk factor [5]. Notably, several studies proposed that infectious agents such as the herpes simplex virus may also play a role in the development of dementia [6, 7].

Varicella zoster virus (VZV), a human alpha-herpes virus, is a member of the *Herpesviridae* family. VZV causes varicella (chickenpox) as primary infection and thereafter establishes latency in ganglionic neurons along the entire neuraxis. When the VZV-specific cell-mediated immunity declines by aging or immunosuppression, VZV may

Seongman Bae and Sung-Cheol Yun equally contributed to the work.

✉ Sung-Han Kim
kimsunghanmd@hotmail.com

[1] Department of Infectious Diseases, Asan Medical Center, University of Ulsan College of Medicine, 88, Olympic-ro-43-gil, Songpa-gu, Seoul 05505, Republic of Korea

[2] Department of Clinical Epidemiology and Biostatistics, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

[3] Division of Infectious Diseases, Department of Internal Medicine, Chung-Ang University Hospital, Seoul, Republic of Korea

[4] Department of Psychiatry, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

[5] Clinical Research Center, Asan Institute for Life Sciences, Asan Medical Center, Seoul, Republic of Korea

reactivate in the sensory ganglia and cause herpes zoster (HZ) [8]. We hypothesized that the two common age-associated diseases—dementia and HZ—may be etiologically and pathophysiologically interrelated. Importantly, recent epidemiologic data showed that the development of HZ may be associated with dementia. However, these studies fell short of providing concrete evidence for the results due to several limitations; one study evaluated only for zoster ophthalmicus [9], and the other study did not extensively controlled covariates [10]. In addition, both studies identified the dementia case only by the diagnostic code without prescription data of anti-dementia drugs, and confounding factors for dementia were not controlled enough in these studies [9, 10]. Therefore, we investigated whether HZ is associated with subsequent development of dementia using a nationwide population-based cohort database, and further evaluated whether antiviral therapy in patients with HZ reduces the risk of dementia using a propensity score-matched cohort.

Methods

Database source

We conducted a population-based cohort study using the National Health Insurance Service–National Sample Cohort in South Korea. This cohort randomly sampled approximately one million individuals, which represented 2% of the total eligible Korean population in January 1, 2002, and followed them until December 31, 2013 unless the participants were disqualified due to death or emigration [11, 12]. All databases in the sample cohort were anonymized to protect individual privacy. The protocol of this study was approved by the Institutional Review Board of Asan Medical Center (S2019-0528), which waived the requirement for written or verbal consent from patients based on the observational nature of the study and the fact that the patient identifiers were fully encrypted prior to analysis.

Study design

This study included subjects aged 50 years or older in the start year of the cohort (2002). We established a washout period by excluding cases that were diagnosed with HZ or dementia in the first year. After a 1-year washout period between January 1, 2002, and December 31, 2002, all subjects with first diagnosed HZ or dementia were identified over 11 years. The incidence of dementia was compared between HZ and non-HZ groups. Among the patients with HZ, we further assessed the difference in the incidence of dementia between those who received antiviral therapy (treated) and those who did not (untreated). Multivariate analysis and propensity score-matched analysis were conducted to minimize the potential bias introduced by the different probabilities of receiving treatment in the two groups. In addition, the all-cause mortality after HZ was assessed as a secondary outcome and compared between the treated and untreated groups.

Definitions

We identified patients diagnosed with HZ and dementia using the relevant diagnostic codes of the *International Classification of Diseases, Tenth Revision* (ICD-10). HZ included the ICD-10 codes for zoster encephalitis (B02.0), zoster meningitis (B02.1), zoster in other divisions of the trigeminal nerve (B02.2), zoster ophthalmicus (B02.3), and other types of zoster (B02.7, B02.8, or B02.9). Dementia included the ICD-10 codes for Alzheimer's disease (F00 or G30), vascular dementia (F01), and other dementia (F02, F03, G23.1, G31.0, G31.1, G31.82, G31.83, G31.88, and F10.7). We restricted the dementia cases as those who had been prescribed with any of the four classes of anti-dementia drugs (i.e., rivastigmine, galantamine, memantine, donepezil hydrochloride) for at least 30 days, as described previously [13]. The cases that received antiviral therapy were defined as the presence of claims data for any of the three antiviral agents (i.e., acyclovir, famciclovir, valaciclovir) within 1 month at the time of HZ diagnosis.

In addition, the following clinical characteristics that may act as potential confounders for HZ and dementia were identified using the appropriate ICD-10 codes: age, sex, economic class, hypertension, diabetes, dyslipidemia, chronic lung disease, ischemic heart disease, stroke, heart failure, atrial fibrillation, valvular heart disease, chronic renal disease, carotid stenosis, peripheral vascular disease, chronic liver disease, rheumatic disease, inflammatory bowel disease, malignancy including hematologic malignancy and solid tumor, solid organ transplantation, human immunodeficiency virus infection, and depression.

Statistical analysis

Categorical data were compared by chi-squared tests and continuous variables were analyzed by unpaired Student's *t* tests. The risk of dementia in the group with zoster compared to that of the non-HZ group was assessed using a Cox regression model with time-dependent covariates. The incidences of dementia and HZ were analyzed and presented as incidence rates per 1000 person-years (PY). The confidence intervals (CI) of the incidence rates were estimated under the assumption that the number of cases followed a Poisson distribution. To compare the HZ group and the non-HZ group, the incidence rate ratio (IRR) and 95% CI were calculated.

Propensity score-matched analysis was carried out to assess the risk of dementia following HZ in groups with or without antiviral treatment. Propensity scores were estimated using multiple logistic regression analysis without regard to the outcome variables. A full nonparsimonious model was developed that included all variables shown in Table 1. The propensity score-matched pairs were created by matching the treated and untreated subjects using calipers of width equal to 0.1 of the standard deviation of the logit of the propensity score. We utilized the standardized difference of means (SDM) to estimate the differences in baseline characteristics. For categorical variables, the multivariate Mahalanobis distance method was used to generalize the SDM metric. Less than 10% SDM has been suggested to denote that the imbalance may be negligible [14, 15]. The risks for dementia and mortality were compared in the propensity score-matched cohort using a Cox proportional hazard model with robust standard errors. Cumulative incidences of dementia were constructed as Kaplan–Meier estimates according to antiviral treatment. We conducted a prespecified subgroup analysis according to age. Furthermore, a number of sensitivity analyses were performed to test the robustness of our findings. First, we repeatedly measured outcome of dementia as defined by diagnostic codes regardless of receiving anti-dementia

Table 1 Baseline characteristics of patients with dementia and herpes zoster

Variables	Total ($n=229,594$)	Dementia ($n=10,482$)	p	HZ ($n=35,017$)	p	HZ without prior dementia[a] ($n=34,505$)	p
Age, mean (SD), years	61.7 (9.4)	68.9 (7.7)	<0.001	60.4 (8.1)	<0.001	60.3 (8.1)	<0.001
50–59	99,751 (43.4)	992 (9.5)		15,987 (45.7)		15,925 (46.2)	
60–69	77,860 (33.9)	3961 (37.8)		13,164 (37.6)		12,958 (37.6)	
≥70	51,983 (22.6)	5529 (52.7)		5866 (16.8)		5622 (16.3)	
Male sex	104,025 (45.3)	3322 (31.7)	<0.001	13,526 (38.6)	<0.001	13,370 (38.7)	<0.001
Economic class							
I	47,139 (20.5)	2427 (23.2)	<0.001	5793 (16.5)	<0.001	5681 (16.5)	<0.001
II	23,660 (10.3)	1285 (12.3)		4966 (14.2)		4908 (14.2)	
III	37,233 (16.2)	1464 (14.0)		5688 (16.2)		5629 (16.3)	
IV	46,728 (20.4)	2040 (19.5)		7436 (21.2)		7317 (21.2)	
V	65,834 (28.7)	3266 (31.2)		11,134 (31.8)		10,970 (31.8)	
Hypertension	55,639 (24.2)	3699 (35.3)	<0.001	9426 (26.9)	<0.001	9233 (26.8)	<0.001
Diabetes	28,502 (12.4)	1891 (18.0)	<0.001	4925 (14.1)	<0.001	4815 (14.0)	<0.001
Dyslipidemia	20,519 (8.9)	1243 (11.9)	<0.001	3995 (11.4)	<0.001	3912 (11.3)	<0.001
Chronic lung disease	36,683 (16)	2247 (21.4)	<0.001	6660 (19.0)	<0.001	6534 (18.9)	<0.001
Ischemic heart disease	13,192 (5.7)	922 (8.8)	<0.001	2333 (6.7)	<0.001	2281 (6.6)	<0.001
Stroke	7104 (3.1)	663 (6.3)	<0.001	1015 (2.9)	0.02	984 (2.9)	0.005
Heart failure	6835 (3)	550 (5.2)	<0.001	1107 (3.2)	0.03	1074 (3.1)	0.11
Atrial fibrillation	1685 (0.7)	129 (1.2)	<0.001	265 (0.8)	0.59	257 (0.7)	0.80
Valvular heart disease	990 (0.4)	69 (0.7)	<0.001	167 (0.5)	0.16	164 (0.5)	0.18
Chronic renal disease	2148 (0.9)	108 (1.0)	0.30	392 (1.1)	<0.001	390 (1.1)	<0.001
Carotid stenosis	62 (0.0)	7 (0.1)	0.01	5 (0.0)	0.12	5 (0.0)	0.12
Peripheral vascular disease	5746 (2.5)	468 (4.5)	<0.001	1049 (3.0)	<0.001	1024 (3.0)	<0.001
Chronic liver disease	1832 (0.8)	70 (0.7)	0.13	262 (0.7)	0.26	255 (0.7)	0.18
Rheumatic disease	10,628 (4.6)	721 (6.9)	<0.001	2057 (5.9)	<0.001	2022 (5.9)	<0.001
Inflammatory bowel disease	929 (0.4)	60 (0.6)	0.005	185 (0.5)	<0.001	181 (0.5)	<0.001
Malignancy	7212 (3.1)	350 (3.3)	0.23	1084 (3.1)	0.60	1062 (3.1)	0.46
Solid organ transplantation	43 (0.0)	0 (0.0)	0.15	11 (0.0)	0.06	11 (0.0)	0.05
HIV infection	19 (0.0)	1 (0.0)	0.88	7 (0.0)	0.009	7 (0.0)	0.007
Depression	1846 (0.8)	143 (1.4)	<0.001	364 (1.0)	<0.001	349 (1.0)	<0.001

Data are no. (%) of persons, unless indicated otherwise

HZ herpes zoster, *SD* standard deviation, *HIV* human immunodeficiency virus

[a]Herpes zoster not experiencing preceded dementia (HZ without prior dementia)

agents. In addition, we re-analyzed study cohort including only those who were observed more than 12 months.

In Korea, the entire population residing within the country is a beneficiary of the Korean National Healthcare System, which provides universal coverage. Healthcare providers are required to bill their medical services for reimbursement from the government, and the insurance claims data incorporate information such as diagnostic codes, procedures or prescription, and personal information. Considering the comprehensive nature of the claims data, we assumed that the database has minimal or no missing values. All reported p values are two-sided, and $p < 0.05$ were considered statistically significant. Data manipulation and statistical analyses were conducted using SAS® version 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

The schematic flow chart of the study is shown in Fig. 1. A total of 229,594 people aged 50 years or older who were not diagnosed with HZ or dementia during the wash-out period were observed for 11 years. During the study period, 10,482 (5%) and 35,017 (15%) were diagnosed with dementia and HZ, respectively. Of these 35,017 patients with HZ, 512 patients with HZ had the precedent diagnosis of dementia, so the remaining 34,505 patients were classified as HZ without prior dementia. The baseline clinical characteristics of the patients who developed dementia and HZ, and HZ without prior dementia during the study period are shown in Table 1.

Incidences and risk of subsequent dementia with or without herpes zoster

The incidences of first-diagnosed HZ, HZ without prior dementia, and first-diagnosed dementia were 16.69, 16.45, and 4.67 per 1000 PY, respectively (Table 2). The incidence of dementia after zoster was 8.53 per 1000 person-years and that of dementia without prior HZ was 4.39 (Table 2). The crude IRR for the risk of dementia in patients with HZ was 1.94, and the adjusted hazard ratio (HR) calculated by multivariate analysis was 1.12 (95% CI 1.05–1.19; Table 3). Among various types of dementia, Alzheimer's disease was significantly associated with HZ by multivariate analysis (Table 3).

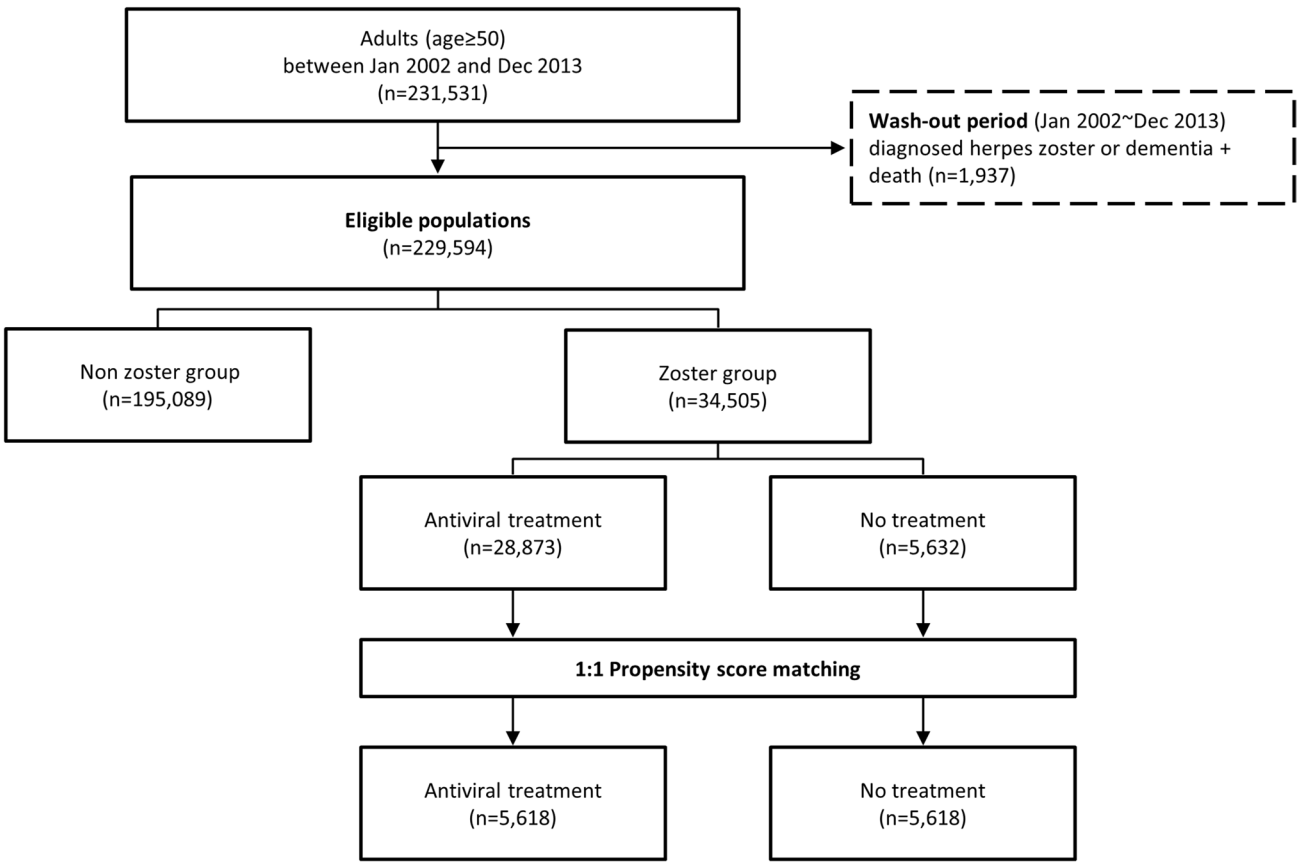

Fig. 1 Flow chart of population selection and propensity score-matched analysis

Table 2 Incidence of herpes zoster and dementia

	N (%)	Incidence[a]	95% CI
Dementia	10,482 (100)	4.67	4.58–4.76
Age group			
50–59	992 (9)	0.93	0.88–0.99
60–69	3961 (38)	5.08	4.92–5.24
≥70	5529 (53)	13.67	13.31–14.03
Zoster	35,017 (100)	16.69	16.52–16.87
Age group			
50–59	15,987 (46)	16.09	15.85–16.34
60–69	13,164 (38)	18.2	17.89–18.51
≥70	5866 (17)	15.39	15.00–15.78
Zoster without prior dementia	34,505 (100)	16.45	16.27–16.62
Age group			
50–59	15,925 (46)	16.03	15.78–16.28
60–69	12,958 (38)	17.92	17.61–18.22
≥70	5622 (16)	14.75	14.36–15.14
Dementia after zoster	1265 (100)	8.53	8.06–9.01
Age group			
50–59	126 (10)	1.84	1.52–2.16
60–69	517 (41)	9.15	8.36–9.94
≥70	622 (49)	26.73	24.63–28.84
Dementia without zoster	9217 (100)	4.39	4.30–4.48
Age group			
50–59	866 (9)	0.87	0.81–0.93
60–69	3444 (37)	4.76	4.60–4.92
≥70	4907 (53)	12.87	12.51–13.23

CI confidence interval

[a]Number indicates incidence rate per 1000 person-years

Impact of antiviral treatment in patients with HZ

In the 34,505 patients with HZ, 28,873 (84%) were treated with antiviral agents. The baseline clinical characteristics of the patients according to antiviral therapy are summarized in Table 4. Compared with patients who were treated with antiviral therapy, untreated patients were more likely to be older, have lower economic status, and higher prevalence of hypertension, diabetes, and various comorbidities including stroke and ischemic heart disease.

The number of first-ever diagnosed dementia cases was 301 in 24,522 PY (12.27 per 1000 PY [95% CI 10.89–13.66]) in untreated patients and 964 in 123,692 PY (7.79 per 1000PY, [95% CI 7.30–8.29]) in treated patients. Importantly, patients who received antiviral therapy had a significantly lower risk of dementia compared with untreated patients (crude IRR, 0.64 [95% CI 0.56–0.72]; Table 5). After multivariate Cox regression analysis, the covariate-adjusted HR was 0.79 (95% CI 0.69–0.90; Table 5).

Propensity score-matched analysis

The treated and untreated patients had a significant imbalance in their baseline demographics, which may have led to bias in treatment assignment. We therefore controlled for potential residual confounding factors using the propensity score-matched analysis. After the propensity score matching, all variables were adjusted and the SMD for each variable was less than 10% (Table 4). In the matched cohort, both groups consisted of 5,618 patients. The incidence of dementia after HZ was 12.26 per 1000 PY in the untreated patients (95% CI 10.87–13.65) and 9.36 per 1000 PY in the treated patients (95% CI 8.20–10.52). The adjusted hazard ratio for the risk of dementia in the treated patients was 0.76 (95% CI 0.65–0.90; Table 5).

Table 3 Risk of dementia after herpes zoster

Age group	IRR (95% CI)	*p*	Adjusted HR[a] (95% CI)	*p*
Type of dementia				
All	1.94 (1.83–2.06)	<0.001	1.12 (1.05–1.19)	<0.001
Alzheimer's disease	1.91 (1.78–2.04)	<0.001	1.11 (1.04–1.19)	0.003
Vascular dementia	2.09 (1.77–2.46)	<0.001	1.17 (0.99–1.38)	0.07
Others	2.00 (1.71–2.35)	<0.001	1.12 (0.95–1.31)	0.18
Age group				
50–59	2.11 (1.75–2.55)	<0.001	1.09 (0.90–1.31)	0.39
60–69	1.92 (1.75–2.11)	<0.001	1.07 (0.97–1.17)	0.17
≥70	2.08 (1.91–2.26)	<0.001	1.16 (1.07–1.27)	<0.001

IRR incidence rate ratio, *CI* confidence interval, *HR* hazard ratio

[a]Adjusted for age, sex, economic class, hypertension, diabetes, dyslipidemia, chronic lung disease, ischemic heart disease, stroke, heart failure, atrial fibrillation, valvular heart disease, chronic renal disease, carotid artery stenosis, peripheral vascular disease, chronic liver disease, rheumatic disease, inflammatory bowel disease, malignancy including hematologic malignancy and solid tumor, solid organ transplant, HIV infection, and depression

Table 4 Baseline demographic characteristics of patients with herpes zoster according to antiviral therapy

	Total population with herpes zoster				Propensity score-matched population			
	untreated ($n=5632$)	treated ($n=28,873$)	p	SDM (%)	untreated ($n=5622$)	treated ($n=5622$)	p	SDM (%)
Age, mean (SD), y	68.4 (8.8)	66.9 (8.1)	<0.001	16.99%	68.4 (8.8)	68.5 (8.9)	0.65	–0.84%
50–59	939 (16.7)	5584 (19.3)		15.02%	936 (16.6)	934 (16.6)		0.67%
60–69	2293 (40.7)	13,084 (45.3)			2289 (40.7)	2273 (40.4)		
≥70	2400 (42.6)	10,205 (35.3)			2397 (42.6)	2415 (43)		
Male sex	2204 (39.1)	11,166 (38.7)	0.52	0.95%	2197 (39.1)	3430 (61)	0.92	0.18%
Economic class			<0.001	6.63%			0.90	1.96%
I	1134 (20.1)	5089 (17.6)			1132 (20.1)	1159 (20.6)		
II	673 (11.9)	3590 (12.4)			671 (11.9)	662 (11.8)		
III	827 (14.7)	4283 (14.8)			826 (14.7)	831 (14.8)		
IV	1108 (19.7)	6027 (20.9)			1106 (19.7)	1069 (19.0)		
V	1890 (33.6)	9884 (34.2)			1887 (33.6)	1901 (33.8)		
Hypertension	3164 (56.2)	14,862 (51.5)	<0.001	9.45%	3155 (56.1)	3127 (55.6)	0.60	1.00%
Diabetes	1890 (33.6)	8127 (28.1)	<0.001	11.73%	1883 (33.5)	1888 (33.6)	0.92	– 0.19%
Dyslipidemia	2104 (37.4)	10,329 (35.8)	0.02	3.29%	2099 (37.3)	2080 (37.0)	0.71	0.70%
Chronic lung disease	2263 (40.2)	10,593 (36.7)	<0.001	7.19%	2258 (40.2)	2197 (39.1)	0.24	2.22%
Ischemic heart disease	1093 (19.4)	4317 (15)	<0.001	11.83%	1088 (19.4)	1044 (18.6)	0.29	2.00%
Stroke	731 (13.0)	2498 (8.7)	<0.001	13.97%	728 (12.9)	707 (12.6)	0.55	1.12%
Heart failure	533 (9.5)	1771 (6.1)	<0.001	12.44%	529 (9.4)	498 (8.9)	0.31	1.91%
Atrial fibrillation	197 (3.5)	581 (2.0)	<0.001	9.09%	193 (3.4)	181 (3.2)	0.53	1.19%
Valvular heart disease	88 (1.6)	251 (0.9)	<0.001	6.33%	86 (1.5)	78 (1.4)	0.53	1.19%
Chronic renal disease	286 (5.1)	688 (2.4)	<0.001	14.26%	279 (5.0)	280 (5.0)	0.97	– 0.08%
Carotid stenosis	22 (0.4)	131 (0.5)	0.51	– 0.97%	22 (0.4)	19 (0.3)	0.64	0.89%
Peripheral vascular disease	999 (17.7)	4781 (16.6)	0.03	3.13%	997 (17.7)	949 (16.9)	0.23	2.26%
Chronic liver disease	149 (2.6)	466 (1.6)	<0.001	7.15%	145 (2.6)	124 (2.2)	0.20	2.44%
Rheumatic disease	561 (10.0)	2392 (8.3)	<0.001	5.82%	558 (9.9)	553 (9.8)	0.87	0.30%
Inflammatory bowel disease	29 (0.5)	125 (0.4)	0.40	1.19%	29 (0.5)	21 (0.4)	0.26	2.14%
Malignancy	706 (12.5)	2307 (8.0)	<0.001	15.02%	698 (12.4)	708 (12.6)	0.78	-0.54%
Solid organ transplant recipient	28 (0.5)	31 (0.1)	<0.001	7.11%	25 (0.4)	19 (0.3)	0.36	1.71%
HIV infection	4 (0.1)	7 (0.0)	0.07	2.14%	3 (0.1)	5 (0.1)	0.48	-1.33%
Depression	118 (2.1)	436 (1.5)	0.001	4.40%	117 (2.1)	111 (2.0)	0.69	0.76%

Data are no. (%) of persons unless indicated otherwise

SDM standardized difference of mean, *SD* standard deviation, *HIV* human immunodeficiency virus

The cumulative incidence of dementia after HZ was consistently lower in the treated group during the study period (Fig. 2). The effect of antiviral therapy on subsequent dementia was the largest in the 50–59 age group and decreased with age (HR 0.46 [50–59 years], 0.58 [60–69 years], 0.81 [≥70 years]). However, the difference in incidence ratios between the three age groups was not significant ($p=0.47$ for interaction).

Sensitivity analyses

The results were robust in sensitivity analyses in which the definition of dementia was made by diagnostic codes regardless of concomitant anti-dementia drug use. In this analysis, incidences of dementia were significantly higher in HZ group than non-HZ group and were lower in HZ patients with receiving antiviral treatment than untreated

Table 5 Risk of dementia after zoster in patients according to antiviral therapy

	Hazard ratio	95% CI	*p*
Primary analysis			
Unadjusted analysis[a]	0.64	0.56–0.72	<0.001
Multivariate analysis[b]	0.79	0.69–0.90	<0.001
Propensity score-matching analysis	0.76	0.65–0.90	0.001
Subgroup analyses			
Age group			0.47[c]
50–59	0.60	0.19–1.87	
60–69	0.69	0.47–1.01	
≥70	0.79	0.65–0.95	
Sensitivity analyses			
Dementia defined by ICD-code	0.75	0.67–0.83	<0.001
Subjects restricted to those who were observed for more than 12 months	0.80	0.66–0.97	0.02
Subjects restricted to those who were observed for more than 24 months	0.82	0.66–1.01	0.058

[a]Unadjusted analysis was performed in the total cohort population with zoster

[b]The results of the multivariate analysis are presented as adjusted hazard ratios. The following variables were included in the multivariate analysis for adjustment: age, sex, economic class, hypertension, diabetes, dyslipidemia, chronic lung disease, ischemic heart disease, stroke, heart failure, atrial fibrillation, valvular heart disease, chronic renal disease, carotid artery stenosis, peripheral vascular disease, chronic liver disease, rheumatic disease, inflammatory bowel disease, malignancy including hematologic malignancy and solid tumor, solid organ transplant, HIV infection, and depression

[c]*p* for interaction

HZ patients (Tables 5 and 6, respectively). The association of the antiviral therapy with lower incidence of subsequent dementia was consistently observed after limiting the study population restricted to those who was observed for at least 12 months (Table 5).

Association between antiviral treatment and mortality

We further investigated whether there was a difference in mortality between the treated and untreated groups, and observed that the risk of mortality was significantly lower in the treated group (crude hazard ratio, 0.44 [95% CI 0.41–0.47], in Table 7). The lower mortality risk remained significant after covariate-adjustment by multivariate Cox regression analysis (adjusted HR 0.55 [95% CI 0.51–0.60]) and the propensity score-matched analysis (adjusted HR 0.61 [95% CI 0.55–0.68], in Table 7).

Discussion

In this population-based cohort study comprising 229,594 individuals, HZ showed a temporal association with subsequent development of dementia. In addition, propensity score-matched analysis showed that the use of systemic antiviral agents was associated with a significantly lower risk for dementia in patients with HZ. Our findings provide important information on the epidemiologic association between two common age-related diseases as well as the potential protective effect of systemic antiviral agents in patients with first-episode HZ on dementia.

Two recent studies conducted in Taiwanese population showed an epidemiological association between HZ and dementia; compared with the general population without HZ, patients diagnosed with herpes zoster ophthalmicus (HZO) or HZ had 3- and 1.11-fold higher risk for dementia [9, 10]. However, the former study was limited in that dementia was defined only by the diagnostic code and the effectiveness of the antiviral therapy was not evaluated; also, the results lacked sufficient generalizability and applicability because only a minor subtype of zoster (HZO) was studied [9]. The latter study encompassed the entire zoster subtypes and showed that the incidence of dementia in patients who received antiviral treatment was lower than that in untreated patients [10]; however, dementia was defined only by the diagnostic code, and covariates were not sufficiently controlled. In this study, we identified the dementia case by the diagnostic code with the drug reimbursement data to include more refined cases. Several validation studies from various population settings showed that the accuracy of dementia identification is generally improved by ascertaining cases with prescription data of anti-dementia drugs [16–19]. Yet, there was a risk of underestimating the true prevalence of dementia as not all patients with dementia would be on medications. We therefore performed a sensitivity analysis with a modified definition for dementia and reaffirmed the robustness of the results.

We designed the present study to provide more concrete results with the Cox regression model with time-dependent covariates to control for time-related bias [20]. In addition, the propensity score-matched analysis was used to control the imbalances in the probability of receiving antiviral therapy. After such methodological and statistical considerations, we found that HZ was significantly associated with a higher risk of dementia and that antiviral therapy in patients with HZ was associated with a lower risk of dementia. These results were consistent with those of the aforementioned Taiwanese studies [9, 10]. The robustness of our findings was demonstrated in other sensitivity analyses controlling outcome definition or length of

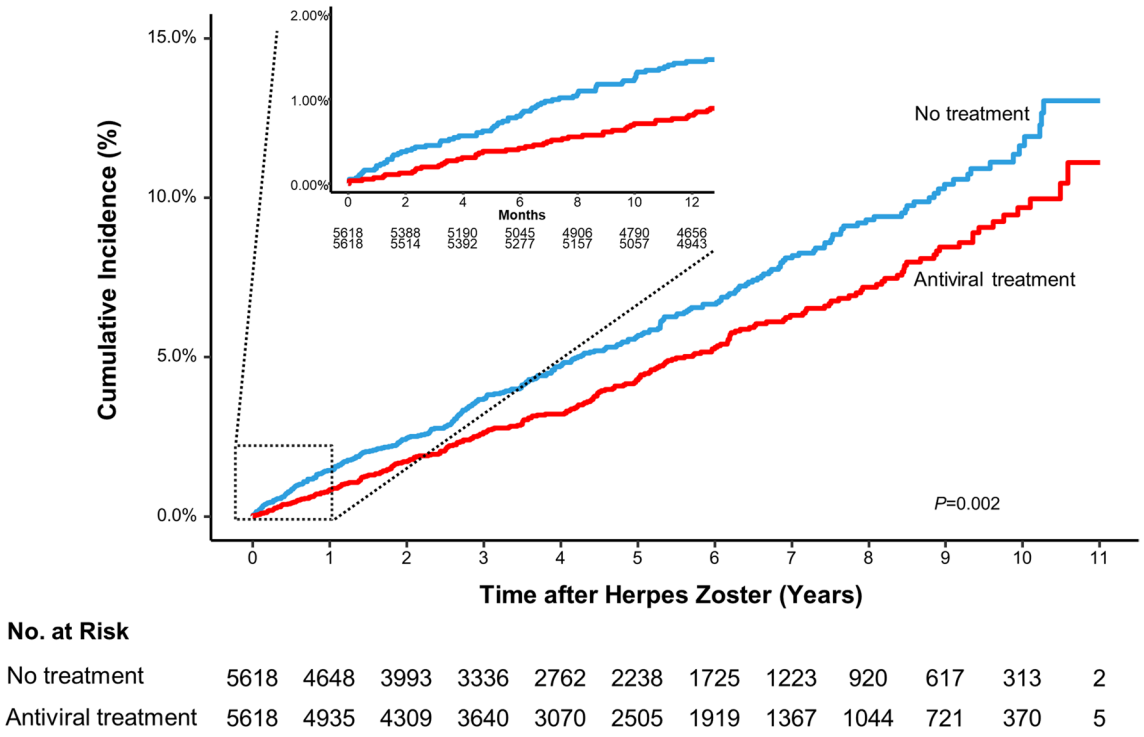

Fig. 2 Cumulative incidence of dementia after zoster stratified by antiviral treatment. The Kaplan–Meier curve represents the cumulative incidence of dementia in the zoster group with or without antiviral therapy ($p=0.002$ by the log-rank test). The first year of the survival curve was zoomed in

Table 6 Adjusted hazard ratios of herpes zoster for dementia defined only by diagnostic code

Age group	Adjusted HR[a] (95% CI)	95% CI	*p*
All	1.08	1.04–1.12	<0.001
50–59	0.96	0.86–1.07	0.45
60–69	1.10	1.04–1.17	0.001
≥70	1.10	1.04–1.16	0.002

[a]Adjusted for age, sex, economic class, hypertension, diabetes, dyslipidemia, chronic lung disease, ischemic heart disease, stroke, heart failure, atrial fibrillation, valvular heart disease, chronic renal disease, carotid artery stenosis, peripheral vascular disease, chronic liver disease, rheumatic disease, inflammatory bowel disease, malignancy including hematologic malignancy and solid tumor, solid organ transplant, HIV infection, and depression

observation period. In our study, the incidence of post-zoster dementia in the treated group was approximately one-fourth lower than that in the untreated group; in the Taiwanese study, the incidence of dementia in patients who received antiviral treatment was about half of that in untreated patients [10]. The relatively weaker effect of antiviral therapy on lowering dementia risk may be due to the rigorous adjustment of possible confounders carried out in our current study.

Table 7 Risk of death after zoster in patients according to antiviral therapy

	Hazard ratio	95% CI	*p*
Primary analysis			
Unadjusted analysis[a]	0.44	0.41–0.47	<0.001
Multivariate analysis[b]	0.55	0.51–0.60	<0.001
Propensity score-matching analysis	0.61	0.55–0.68	<0.001
Sensitivity analyses			
Subjects restricted to those who were observed for more than 12 months	0.74	0.65–0.83	<0.001

[a]Unadjusted analysis was performed in the total cohort population with zoster

[b]The results of the multivariate analysis are presented as adjusted hazard ratios. The following variables were included in the multivariate analysis for adjustment: age, sex, economic class, hypertension, diabetes, dyslipidemia, chronic lung disease, ischemic heart disease, stroke, heart failure, atrial fibrillation, valvular heart disease, chronic renal disease, carotid artery stenosis, peripheral vascular disease, chronic liver disease, rheumatic disease, inflammatory bowel disease, malignancy including hematologic malignancy and solid tumor, solid organ transplant, HIV infection, and depression

Several biological mechanisms have been proposed regarding the virus-related sequelae on dementia. The insulin-degrading enzyme (IDE), which has a major role in

Alzheimer's disease by degrading amyloid-beta (Aβ), also functions as a cellular receptor of VZV [21]. Thus, it may be possible that the binding of VZV to IDE hinders the IDE-mediated degradation of Aβ, thereby leading to increased production of amyloid plaques [22]. Also, VZV may directly contribute to neuronal death and subsequent dementia by inducing local and systemic inflammation [23], as VZV can transaxonally migrate to the central nervous system and induce subclinical inflammation [24]. Recent studies have also shown that viral infection itself may induce the formation of amyloid plaques, as human simplex virus-1 (HSV-1) infection resulted in Aβ accumulation and tau phosphorylation in neuronal cells [25, 26]. Interestingly, Aβ may have a protective effect against HSV-1 infection by interfering with viral replication [27], and one study showed that Aβ peptide oligomers can bind to the surface glycoproteins of HSV-1 and human herpesvirus 6 (HHV-6), thereby leading to viral entrapment and subsequent protection against viral infection [28]. It is possible that such protective effect is followed by accelerated deposition of Aβ and paradoxically contribute to the development of dementia [29]. As VZV and HSV-1 both belong to the family *Herpesviridae*, VZV may also show similar effects on Aβ. Recent studies have introduced an in vitro model of VZV infection and a simian varicella virus infection in non-human primates [30, 31]; therefore, further research utilizing these preclinical models would be invaluable in delineating the role of VZV infection in the development of dementia. VZV may also contribute to the development of dementia by inducing vasculopathy and subsequently increasing the risk of stroke, which in turn acts as a major risk factor for dementia [32, 33]. Thus, the magnitude of the effect of HZ and stroke on dementia should be evaluated.

Our study has several limitations. First, due to its observational nature and unmeasured confounding in nonrandomized longitudinal study, our study falls short of drawing a definite conclusion on the causal relationship between dementia and HZ. As an example, it is possible that elderly patients who take multiple medications are less likely to be prescribed additional antiviral therapy. In addition, due to their acute symptoms, patients who were diagnosed as HZ might have an early opportunity to be assessed or better recognized as dementia. Alternatively, patients with postherpetic neuralgia might be more prone to be neurologically assessed and have a better chance for early diagnosis of dementia. Furthermore, there may be a deviation in the purchase of antiviral drugs due to economic differences between patients; however, medical expenses—especially for low-income patients—are fully covered by the national insurance program in Korea, so this scenario may be less likely in our study cohort. Second, there is a possibility of misclassification due to the uncertainty of events or outcomes as defined by the health insurance claims data. Nevertheless, the reliability of the diagnostic code for HZ has been validated [34, 35] and we tried to improve the specificity of our working definition of dementia by including the prescription history of patients with dementia. The incidence of dementia in our study cohort was 5.1 per 1000 PY in the 60–69-years age group and 13.7 in the ≥70-years age group, which is consistent with those reported in previous epidemiologic studies in East Asian populations (4.9–7.0 per 1000 PY in the 60–69-years age group and 10.3–15.4 per 1000 PY in the ≥70-years age group) [2, 36]. Such consistency reflects the validity of the working definition of dementia used in this study. In addition, we further conducted the sensitivity analysis in which dementia was defined only by ICD-10 codes, and found similar results. Finally, given the high prevalence of HSV-1 among Asian populations [37], the coincidental suppression of HSV-1 by antiviral treatment for HZ may have conferred some effects in the prevention of dementia. Indeed, the association between antiviral therapy and the dramatic reduction in subsequent dementia incidence in patients with HSV has been previously reported [7]. Further studies are needed to assess the role of antiviral agents against HZ in the prevention of dementia by controlling for the presence of HSV. Despite these limitations, our data demonstrated the epidemiologic association between two common age-associated diseases, HZ and dementia, and added weight to this association by showing the protective effect of antiviral agents on dementia in patients with HZ. Therefore, our data suggest important public health intervention and warrant further studies on the causal relationship by investigating the pathophysiological mechanisms and conducting interventional trials.

In conclusion, our results suggest that HZ increases the risk of dementia and that intervention with antiviral therapy may be useful in reducing the risk of dementia. The biological mechanism of the association between HZ and dementia should be further investigated. Meanwhile, physicians should consider the higher risk of dementia in patients with HZ and the potential beneficial effect of systemic antiviral therapy.

Author contributions All authors critically revised the manuscript for important intellectual content. SHK, SYK, JHW, YSK, SHC, and SOL contributed to the study conception and design. Acquisition, analysis, and interpretation of data was performed by SCY, SB, WY, and MCK. SB and JSL drafted the manuscript. SCY carried out the statistical analysis. SB and SCY equally contributed to the work. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Funding This study was supported by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health and Welfare, Republic of Korea (grant no. HI15C1763).

Conflict of interest All authors have completed the ICMJE uniform disclosure form at https://www.icmje.org/coi_disclosure.pdf and de-

clare: support from the Ministry of Health and Welfare, Republic of Korea; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

Availability of data and material (data transparency) Not applicable.

Code availability (software application or custom code) Not applicable.

References

1. Frankish H, Horton R (2017) Prevention and management of dementia: a priority for public health. Lancet 390(10113):2614–2615. https://doi.org/10.1016/s0140-6736(17)31756-7
2. Prince M, Wimo A, Guerchet M et al (2015) World Alzheimer report 2015: the global impact of dementia. Alzheimer's Disease International, London
3. Wortmann M (2012) Dementia: a global health priority—highlights from an ADI and World Health Organization report. Alzheimers Res Ther 4(5):40. https://doi.org/10.1186/alzrt143
4. Park JH, Eum JH, Bold B, Cheong HK (2013) Burden of disease due to dementia in the elderly population of Korea: present and future. BMC Public Health 13:293. https://doi.org/10.1186/1471-2458-13-293
5. Elahi FM, Miller BL (2017) A clinicopathological approach to the diagnosis of dementia. Nat Rev Neurol 13(8):457–476. https://doi.org/10.1038/nrneurol.2017.96
6. Itzhaki RF (2018) Corroboration of a major role for herpes simplex virus type 1 in Alzheimer's disease. Front Aging Neurosci 10:324. https://doi.org/10.3389/fnagi.2018.00324
7. Tzeng NS, Chung CH, Lin FH, Chiang CP, Yeh CB, Huang SY, Lu RB, Chang HA, Kao YC, Yeh HW, Chiang WS, Chou YC, Tsao CH, Wu YF, Chien WC (2018) Anti-herpetic medications and reduced risk of dementia in patients with herpes simplex virus infections-a nationwide population-based cohort study in Taiwan. Neurotherapeutics 15(2):417–429. https://doi.org/10.1007/s13311-018-0611-x
8. Cohen JI (2013) Clinical practice: herpes zoster. N Engl J Med 369(3):255–263. https://doi.org/10.1056/NEJMcp1302674
9. Tsai MC, Cheng WL, Sheu JJ, Huang CC, Shia BC, Kao LT, Lin HC (2017) Increased risk of dementia following herpes zoster ophthalmicus. PLoS ONE 12(11):e0188490. https://doi.org/10.1371/journal.pone.0188490
10. Chen VC, Wu SI, Huang KY, Yang YH, Kuo TY, Liang HY, Huang KL, Gossop M (2018) Herpes zoster and dementia: a nationwide population-based cohort study. J Clin Psychiatry. https://doi.org/10.4088/JCP.16m11312
11. Lee J, Lee JS, Park SH, Shin SA, Kim K (2017) Cohort profile: The National Health Insurance Service-National Sample Cohort (NHIS-NSC). South Korea Int J Epidemiol 46(2):e15. https://doi.org/10.1093/ije/dyv319
12. Cheol Seong S, Kim YY, Khang YH, Heon Park J, Kang HJ, Lee H, Do CH, Song JS, Hyon Bang J, Ha S, Lee EJ, Ae Shin S (2017) Data resource profile: the National Health Information Database of the National Health Insurance Service in South Korea. Int J Epidemiol 46(3):799–800. https://doi.org/10.1093/ije/dyw253
13. Jang HD, Park JS, Kim DW, Han K, Shin BJ, Lee JC, Choi SW, Suh SW, Yang JH, Park SY, Cho WJ, Hong JY (2019) Relationship between dementia and ankylosing spondylitis: a nationwide, population-based, retrospective longitudinal cohort study. PLoS ONE 14(1):e0210335. https://doi.org/10.1371/journal.pone.0210335
14. Normand ST, Landrum MB, Guadagnoli E, Ayanian JZ, Ryan TJ, Cleary PD, McNeil BJ (2001) Validating recommendations for coronary angiography following acute myocardial infarction in the elderly: a matched analysis using propensity scores. J Clin Epidemiol 54(4):387–398
15. Austin PC (2011) An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivar Behav Res 46(3):399–424. https://doi.org/10.1080/00273171.2011.568786
16. St Germaine-Smith C, Metcalfe A, Pringsheim T, Roberts JI, Beck CA, Hemmelgarn BR, McChesney J, Quan H, Jette N (2012) Recommendations for optimal ICD codes to study neurologic conditions: a systematic review. Neurology 79(10):1049–1055. https://doi.org/10.1212/WNL.0b013e3182684707
17. Solomon A, Ngandu T, Soininen H, Hallikainen MM, Kivipelto M, Laatikainen T (2014) Validity of dementia and Alzheimer's disease diagnoses in Finnish national registers. Alzheimers Dement 10(3):303–309. https://doi.org/10.1016/j.jalz.2013.03.004
18. Jaakkimainen RL, Bronskill SE, Tierney MC, Herrmann N, Green D, Young J, Ivers N, Butt D, Widdifield J, Tu K (2016) Identification of physician-diagnosed alzheimer's disease and related dementias in population-based administrative data: a validation study using family physicians' electronic medical records. J Alzheimers Dis 54(1):337–349. https://doi.org/10.3233/jad-160105
19. Andreu-Reinon ME, Gavrila D, Chirlaque MD, Colorado-Yohar SM, Amiano P, Ardanaz E, Navarro-Mateu F, Navarro C, Huerta JM (2019) Ascertainment of dementia cases in the Spanish European Prospective Investigation into Cancer and Nutrition-Murcia Cohort. Neuroepidemiology 52(1–2):63–73. https://doi.org/10.1159/000493209
20. Altman DG, De Stavola BL (1994) Practical problems in fitting a proportional hazards model to data with updated measurements of the covariates. Stat Med 13(4):301–341
21. Li Q, Ali MA, Cohen JI (2006) Insulin degrading enzyme is a cellular receptor mediating varicella-zoster virus infection and cell-to-cell spread. Cell 127(2):305–316. https://doi.org/10.1016/j.cell.2006.08.046
22. Bernstein HG, Keilhoff G, Dobrowolny H, Steiner J (2019) Binding varicella zoster virus: an underestimated facet of insulin-degrading enzyme s implication for Alzheimer s disease pathology? Eur Arch Psychiatry Clin Neurosci. https://doi.org/10.1007/s00406-019-00995-1
23. Wang JP, Kurt-Jones EA, Shin OS, Manchak MD, Levin MJ, Finberg RW (2005) Varicella-zoster virus activates inflammatory cytokines in human monocytes and macrophages via toll-like receptor 2. J Virol 79(20):12658–12666. https://doi.org/10.1128/jvi.79.20.12658-12666.2005
24. Haanpaa M, Dastidar P, Weinberg A, Levin M, Miettinen A, Lapinlampi A, Laippala P, Nurmikko T (1998) CSF and MRI findings in patients with acute herpes zoster. Neurology 51(5):1405–1411. https://doi.org/10.1212/wnl.51.5.1405
25. Wozniak MA, Frost AL, Itzhaki RF (2009) Alzheimer's disease-specific tau phosphorylation is induced by herpes simplex virus type 1. J Alzheimers Dis 16(2):341–350. https://doi.org/10.3233/jad-2009-0963
26. Wozniak MA, Itzhaki RF, Shipley SJ, Dobson CB (2007) Herpes simplex virus infection causes cellular beta-amyloid accumulation and secretase upregulation. Neurosci Lett 429(2–3):95–100. https://doi.org/10.1016/j.neulet.2007.09.077
27. Bourgade K, Garneau H, Giroux G, Le Page AY, Bocti C, Dupuis G, Frost EH, Fulop T Jr (2015) beta-Amyloid peptides display protective activity against the human Alzheimer's disease-associated herpes simplex virus-1. Biogerontology 16(1):85–98. https://doi.org/10.1007/s10522-014-9538-8
28. Eimer WA, Vijaya Kumar DK, Navalpur Shanmugam NK, Rodriguez AS, Mitchell T, Washicosky KJ, Gyorgy B, Breakefield XO,

Tanzi RE, Moir RD (2018) Alzheimer's disease-associated beta-amyloid is rapidly seeded by herpesviridae to protect against brain infection. Neuron 99(1):56–63.e53. https://doi.org/10.1016/j.neuron.2018.06.030

29. Cribbs DH, Azizeh BY, Cotman CW, LaFerla FM (2000) Fibril formation and neurotoxicity by a herpes simplex virus glycoprotein B fragment with homology to the Alzheimer's A beta peptide. Biochemistry 39(20):5988–5994. https://doi.org/10.1021/bi000029f
30. Baird NL, Zhu S, Pearce CM, Viejo-Borbolla A (2019) Current in vitro models to study varicella zoster virus latency and reactivation. Viruses. https://doi.org/10.3390/v11020103
31. Mahalingam R, Gershon A, Gershon M, Cohen JI, Arvin A, Zerboni L, Zhu H, Gray W, Messaoudi I, Traina-Dorge V (2019) Current in vivo models of varicella-zoster virus neurotropism. Viruses. https://doi.org/10.3390/v11060502
32. Kim MC, Yun SC, Lee HB, Lee PH, Lee SW, Choi SH, Kim YS, Woo JH, Kim SH, Kwon SU (2017) Herpes zoster increases the risk of stroke and myocardial infarction. J Am Coll Cardiol 70(2):295–296. https://doi.org/10.1016/j.jacc.2017.05.015
33. Pendlebury ST, Rothwell PM (2019) Incidence and prevalence of dementia associated with transient ischaemic attack and stroke: analysis of the population-based Oxford Vascular Study. Lancet Neurol 18(3):248–258. https://doi.org/10.1016/s1474-4422(18)30442-3
34. Donahue JG, Choo PW, Manson JE, Platt R (1995) The incidence of herpes zoster. Arch Intern Med 155(15):1605–1609
35. Mullooly JP, Riedlinger K, Chun C, Weinmann S, Houston H (2005) Incidence of herpes zoster, 1997–2002. Epidemiol Infect 133(2):245–253. https://doi.org/10.1017/s095026880400281x
36. Bae JB, Kim YJ, Han JW, Kim TH, Park JH, Lee SB, Lee JJ, Jeong HG, Kim JL, Jhoo JH, Yoon JC, Kim KW (2015) Incidence of and risk factors for Alzheimer's disease and mild cognitive impairment in Korean elderly. Dement Geriatr Cogn Disord 39(1–2):105–115. https://doi.org/10.1159/000366555
37. Khadr L, Harfouche M, Omori R, Schwarzer G, Chemaitelly H, Abu-Raddad LJ (2019) The epidemiology of herpes simplex virus type 1 in Asia: systematic review, meta-analyses, and meta-regressions. Clin Infect Dis 68(5):757–772. https://doi.org/10.1093/cid/ciy562