

Supplement table 1. ICD-10 codes used to define exposure, outcome, and co-variables *

HSV	
B00.5	Herpesviral ocular disease
H03.1	Involvement of eyelid in other infectious diseases classified elsewhere
H13.1	Conjunctivitis in infectious and parasitic diseases classified elsewhere
H19.1	Herpesviral keratitis and keratoconjunctivitis
H22.0	Iridocyclitis in infectious and parasitic diseases classified elsewhere
B00.3	Herpesviral meningitis
B00.7	Disseminated herpesviral disease
B00.8	Other forms of herpesviral infection
B00	Herpesviral [herpes simplex] infections
B00.0	Eczema herpeticum
B00.1	Herpesviral vesicular dermatitis
B00.9	Herpesviral infection, unspecified
A60*	Anogenital herpesviral [herpes simplex] infection
B002	Herpesviral gingivostomatitis and pharyngotonsillitis
VZV	
B02.3	Zoster ocular disease
H03.1	Involvement of eyelid in other infectious diseases classified elsewhere
H13.1	Conjunctivitis in infectious and parasitic diseases classified elsewhere
H19.0	Scleritis and episcleritis in diseases classified elsewhere
H19.2	Keratitis and keratoconjunctivitis in other infectious and parasitic diseases classified elsewhere
H22.0	Iridocyclitis in infectious and parasitic diseases classified elsewhere
B02.1	Zoster meningitis
B02.2	Zoster with other nervous system involvement
B02.7	Disseminated zoster
B02.8	Zoster with other complications
B02	Zoster [herpes zoster]
B02.9	Zoster without complications
Dementia	
F00	Dementia in Alzheimer's disease
F01	Vascular dementia
F02	Dementia in other diseases classified elsewhere
F03	Unspecified dementia
G30	Alzheimer's disease

G31.00	Frontotemporal dementia
Others	
I10	Essential (primary) hypertension
I11	Hypertensive heart disease
I12	Hypertensive renal disease
I13	Hypertensive heart and renal diseases
I15	Secondary hypertension
E10	Type 1 diabetes mellitus
E11	Type 2 diabetes mellitus
E12	Malnutrition-related diabetes mellitus
E13	Other specified diabetes mellitus
E14	Unspecified diabetes mellitus
E78.4	Other hyperlipidaemia
E78.5	Hyperlipidaemia, unspecified
E78.0	Pure hypercholesterolaemia
I70	Atherosclerosis
I63	Cerebral infarction
I64	Stroke, not specified as haemorrhage or infarction
I65	Occlusion and stenosis of precerebral arteries, not resulting in cerebral infarction
I66	Occlusion and stenosis of cerebral arteries, not resulting in cerebral infarction
I20	Angina pectoris
I21	Acute myocardial infarction
I22	Subsequent myocardial infarction
I23	Certain current complication following acute myocardial infarction
I24	Other acute ischaemic heart disease
I25	Chronic ischaemic heart disease
F32	Depressive episode
F33	Recurrent depressive disorder
F34	Persistent mood [affective] disorders
N18	Chronic kidney disease

HSV, herpes simplex virus; VZV, varicella zoster virus.

*Since the purpose of our study was not to investigate acute changes in viral infection, ICD-10 codes for B00.4 (herpesviral meningoencephalitis) and B02.0 (zoster meningoencephalitis), and F05 (delirium, not induced by alcohol and other psychoactive substances) were excluded to define the exposure variable (viral infection) and outcome variable (dementia). Direct viral invasion of the brain can cause cognitive dysfunction, including delirium, and it is a reversible change that can be recovered when the viral infection is treated.

Supplement table 2. Working definition of each variable

Viral infection[‡]	Category	ICD-10 diagnostic code
HSV	Eye	B00.5 only or with H03.1, H13.1, H19.1, H22.0
	CNS	B00.3
	Complicated	B00.7, B00.8
	Simple[*]	B00, B00.0, B00.1, B00.9, A60, B00.2
VZV	Eye	B02.3 only or with H03.1, H13.1, H19.0 H19.2, H22.0
	CNS	B02.1, B02.2
	Complicated	B02.7, B02.8
	Simple[*]	B02, B02.9
Dementia subtype[£]		
AD		F00, G30 only or with F03
VD		F01 only or with F03
Other co-variables		
HTN		I10, I11, I12, I13, I14, I15
DM		E10, E11, E12, E13, E14
Dyslipidaemia		E78.4, E78.5, E78.0, I70
Ischaemic stroke		I63, I64, I65, I66
CHD		I20, I21, I22, I23, I24, I25
CKD[§]		N18

DepressionF32, F33, F34

HSV, herpes simplex virus; VZV, varicella zoster virus; CNS, central nervous system; AD, Alzheimer dementia; VD, vascular dementia; HTN, hypertension; DM, diabetes mellitus; CHD, coronary heart disease; CKD, chronic kidney disease.

‡ Each viral infection was defined as ICD-10 diagnostic codes with antiviral medicine prescription within a month of diagnosis.

*Simple skin or genital viral infection was included. Only those diagnostic codes without any other codes combined.

£ Each subtype of dementia was defined by the first prescription of an acetylcholinesterase inhibitor or NMDA receptor antagonist with an ICD-10 code for Alzheimer's disease (F00, G30) and vascular dementia (F01). An additional ICD-10 code for unspecified dementia (F03) is permitted for each category of AD or VD.

§CKD was defined as any of the following three criteria: (1) glomerular filtration rate < 60 mL/min/1.73 m²; (2) ICD-10 code N18; and (3) rare intractable disease codes for CKD (V001, V003) or regular dialysis codes (O7202, O7062, O7093).

Supplement table 3. Impact of viral infection on the risk of dementia via univariate analysis of variables

Variables		Cohort (N = 752,205)	Hazard ratio (95% CI)	p-value
Age (years)	< 65	537,743 (71.5%)	1 (ref)	< 0.0001
	≥ 65	214,462 (28.5%)	19.72 (19.25–20.21)	
Sex	Male	348,125 (46.3%)	1 (ref)	< 0.0001
	Female	404,080 (53.7%)	2.14 (2.10–2.18)	
HSV infection		162,676 (21.6%)	1.20 (1.17–1.22)	< 0.0001
VZV infection		184,331 (24.5%)	1.57 (1.54–1.60)	< 0.0001
HSV or VZV infection	No	475,884 (63.3%)	1 (ref)	< 0.0001
	HSV only	91,990 (12.2%)	1.16 (1.13–1.20)	
	VZV only	113,645 (15.1%)	1.62 (1.58–1.66)	
	Co-infection	70,686 (9.4%)	1.54 (1.49–1.60)	
Depression		58,961 (7.8%)	2.14 (2.09–2.19)	< 0.0001
Dyslipidaemia		137,800 (18.3%)	1.60 (1.57–1.63)	< 0.0001
Ischaemic stroke		30,950 (4.1%)	3.72 (3.62–3.83)	< 0.0001
Coronary heart disease		86,082 (11.4%)	2.19 (2.15–2.24)	< 0.0001
Hypertension		239,976 (31.9%)	3.06 (3.01–3.11)	< 0.0001
Diabetes mellitus		157,642 (21%)	2.26 (2.21–2.30)	< 0.0001
Chronic kidney disease		3,287 (0.4%)	2.12 (1.92–2.35)	< 0.0001
Body mass index	Underweight	15,993 (2.1%)	1 (ref)	< 0.0001
	Normal	220,444 (29.3%)	0.45 (0.43–0.47)	
	Overweight	169,660 (22.6%)	0.37 (0.35–0.38)	
	Obese	226,268 (30.1%)	0.35 (0.33–0.37)	
Household income level	Low	138,623 (18.4%)	1 (ref)	< 0.0001
	Lower middle	136,824 (18.2%)	0.86 (0.83–0.89)	
	Higher middle	181,648 (24.1%)	0.90 (0.87–0.92)	
	High	255,307 (33.9%)	1.03 (1.01–1.06)	

CI, confidence interval; ref, reference; VZV, varicella zoster virus; HSV, herpes simplex virus.

*Univariate Cox proportional hazards regression analysis was used to calculate crude hazard ratios (HRs) and 95% confidence intervals (CIs) for dementia.

Supplement table 4. Univariate analysis of pairwise hazard ratio of viral infection on dementia

Variables		Hazard ratio 1 (95% CI)	p-value	Hazard ratio 2 (95% CI)	p-value	Hazard ratio 3 (95% CI)	p-value	Hazard ratio 4 (95% CI)	p-value
HSV or VZV infection	No	1 (ref)	.	0.86 (0.83–0.89)	< 0.0001	0.62 (0.60–0.63)	< 0.0001	0.65 (0.63–0.67)	< 0.0001
	HSV only	1.16 (1.13–1.20)	< 0.0001	1 (ref)	.	0.72 (0.69–0.74)	< 0.0001	0.75 (0.72–0.79)	< 0.0001
	VZV only	1.62 (1.58–1.66)	< 0.0001	1.40 (1.35–1.45)	< 0.0001	1 (ref)	.	1.05 (1.01–1.10)	0.02
	Co-infection	1.54 (1.49–1.60)	< 0.0001	1.33 (1.27–1.39)	< 0.0001	0.95 (0.91–0.99)	0.02	1 (ref)	.

CI, confidence interval; VZV, varicella zoster virus; HSV, herpes simplex virus; ref, reference.

*Univariate Cox proportional hazards regression analysis was used to calculate crude hazard ratios (HRs) and 95% confidence intervals (CIs) for dementia.

Supplement table 5. Multivariate analysis of pairwise hazard ratio of viral infection on dementia

Variables		Hazard ratio 1 † (95% CI)	p-value	Hazard ratio 2 † (95% CI)	p-value	Hazard ratio 3 † (95% CI)	p-value	Hazard ratio 4 † (95% CI)	p-value
HSV or VZV infection	No	1 (ref)	.	0.72 (0.70–0.75)	< 0.0001	0.71 (0.69–0.73)	< 0.0001	0.64 (0.61–0.67)	< 0.0001
	HSV only	1.38 (1.33–1.43)	< 0.0001	1 (ref)	.	0.98 (0.94–1.02)	0.33	0.88 (0.84–0.93)	< 0.0001
	VZV only	1.41 (1.37–1.46)	< 0.0001	1.02 (0.98–1.07)	0.3289	1 (ref)	.	0.90 (0.86–0.95)	< 0.0001
	Co-infection	1.57 (1.50–1.63)	< 0.0001	1.13 (1.07–1.20)	< 0.0001	1.11 (1.06–1.16)	< 0.0001	1 (ref)	.

CI, confidence interval; VZV, varicella zoster virus; HSV, herpes simplex virus; ref, reference.

†Adjusted for age, sex, depression, dyslipidaemia, ischaemic stroke, coronary heart disease, hypertension, diabetes mellitus, chronic kidney disease, body mass index, insurance premium level.

Supplement table 6. Multivariate analysis of pairwise hazard ratio of herpes simplex virus infection on dementia

		Hazard ratio 1† (95% CI)	p-value	Hazard ratio 2† (95% CI)	p-value	Hazard ratio 3† (95% CI)	p-value	Hazard ratio 4† (95% CI)	p-value	Hazard ratio 5† (95% CI)	p-value
	None	1 (ref)	.	0.69 (0.64–0.74)	< 0.0001	0.48 (0.16–1.50)	0.21	0.68 (0.60–0.76)	< 0.0001	0.71 (0.69–0.74)	< 0.0001
	eye	1.45 (1.35–1.56)	< 0.0001	1 (ref)	.	0.70 (0.23–2.17)	0.54	0.98 (0.86–1.12)	0.77	1.03 (0.95–1.11)	0.43
HSV infection	CNS	2.07 (0.67–6.42)	0.21	1.43 (0.46–4.44)	0.54	1 (ref)	.	1.40 (0.45–4.37)	0.56	1.47 (0.48–4.57)	0.50
	comp	1.48 (1.32–1.65)	< 0.0001	1.02 (0.89–1.17)	0.76	0.71 (0.23–2.23)	0.56	1 (ref)	.	1.05 (0.94–1.18)	0.39
	simple	1.40 (1.36–1.45)	< 0.0001	0.97 (0.90–1.05)	0.43	0.68 (0.22–2.10)	0.50	0.95 (0.85–1.07)	0.39	1 (ref)	.

CI, confidence interval; HSV, herpes simplex virus; ref, reference; CNS, central nervous system; comp, complicated

†Adjusted for age, sex, depression, dyslipidaemia, ischaemic stroke, coronary heart disease, hypertension, diabetes mellitus, chronic kidney disease, body mass index, insurance premium level.

Supplement table 7. Multivariate analysis of pairwise hazard ratio of varicella zoster virus infection on dementia

		Hazard ratio 1† (95% CI)	p-value	Hazard ratio 2† (95% CI)	p-value	Hazard ratio 3† (95% CI)	p-value	Hazard ratio 4† (95% CI)	p-value	Hazard ratio 5† (95% CI)	p-value
	None	1 (ref)	.	0.63 (0.55–0.72)	< 0.0001	0.56 (0.54–0.58)	< 0.0001	0.61 (0.58–0.64)	< 0.0001	0.81 (0.78–0.83)	< 0.0001
	eye	1.59 (1.39–1.82)	< 0.0001	1 (ref)	.	0.89 (0.77–1.02)	0.10	0.97 (0.84–1.12)	0.68	1.28 (1.12–1.47)	0.0004
VZV infection	CNS	1.79 (1.71–1.87)	< 0.0001	1.12 (0.98–1.29)	0.10	1 (ref)	.	1.09 (1.02–1.16)	0.01	1.44 (1.36–1.52)	< 0.0001
	comp	1.64 (1.56–1.73)	< 0.0001	1.03 (0.89–1.19)	0.68	0.92 (0.86–0.98)	0.01	1 (ref)	.	1.32 (1.24–1.40)	< 0.0001
	simple	1.24 (1.20–1.29)	< 0.0001	0.78 (0.68–0.90)	0.0004	0.70 (0.66–0.73)	< 0.0001	0.76 (0.71–0.80)	< 0.0001	1 (ref)	.

CI, confidence interval; VZV, varicella zoster virus; ref, reference; CNS, central nervous system; comp, complicated.

†Adjusted for age, sex, depression, dyslipidaemia, ischaemic stroke, coronary heart disease, hypertension, diabetes mellitus, chronic kidney disease, body mass index, insurance premium level.

Supplement table 8. Sensitivity analysis including viral infection for the diagnosis group without medication

All dementia			
Variables		Hazard ratio (95% CI)	p-value†
Age (years)	< 65	1 (ref)	< 0.0001
	≥ 65	14.68 (14.28–15.08)	
Sex	Male	1 (ref)	< 0.0001
	Female	1.46 (1.43–1.50)	
HSV infection	No	1 (ref)	< 0.0001
	HSV infection	1.20 (1.14–1.27)	
VZV infection	No	1 (ref)	< 0.0001
	VZV infection	1.40 (1.34–1.47)	
Depression		1.41 (1.37–1.45)	< 0.0001
Dyslipidaemia		0.93 (0.91–0.96)	< 0.0001
Ischaemic stroke		1.55 (1.50–1.60)	< 0.0001
Coronary heart disease		1.10 (1.07–1.13)	< 0.0001
Hypertension		1.40 (1.37–1.43)	< 0.0001
Diabetes mellitus		1.33 (1.30–1.36)	< 0.0001
Chronic kidney disease		1.12 (1.00–1.27)	
Body mass index	Underweight	1 (ref)	< 0.0001
	Normal	0.64 (0.61–0.67)	
	Overweight	0.52 (0.49–0.54)	
	Obese	0.45 (0.42–0.47)	
Household income level	Low	1 (ref)	< 0.0001
	Lower middle	0.96 (0.94–0.99)	
	Higher middle	0.88 (0.86–0.91)	
	High	0.89 (0.86–0.91)	

CI, confidence interval; VZV, varicella zoster virus; HSV, herpes simplex virus; ref, reference.

Supplement table 9. Sensitivity analysis of various non-linear association between age and dementia in another NHIS cohort

		Model 1 ^a		Model 2 ^b		Model 3 ^c	
Variables		Hazard ratio (95% CI)	p-value ^d	Hazard ratio (95% CI)	p-value ^d	Hazard ratio (95% CI)	p-value ^d
HSV or VZV infection	No	1 (ref)		1 (ref)		1 (ref)	
	HSV only	1.17 (1.16-1.18)	< 0.0001	1.16 (1.12-1.19)	< 0.0001	1.16 (1.12-1.19)	< 0.0001
	VZV only	1.07 (1.06-1.07)		1.06 (1.04-1.09)		1.06 (1.04-1.09)	
	Co-infection	1.24 (1.22-1.25)		1.26 (1.21-1.31)		1.26 (1.21-1.31)	
Age, years^e		1.11 (1.11-1.11)	< 0.0001	1.24 (1.23-1.26)	< 0.0001	1.11 (1.11-1.11) ^e	< 0.0001
Sex	Male	1 (ref)	< 0.0001	1 (ref)	< 0.0001	1 (ref)	< 0.0001
	Female	1.43 (1.42-1.43)		1.46 (1.43-1.48)		1.46 (1.43-1.48)	
Depression		1.56 (1.55-1.57)	< 0.0001	1.55 (1.51-1.59)	< 0.0001	1.55 (1.51-1.59)	< 0.0001
Dyslipidaemia		1.03 (1.02-1.03)	< 0.0001	1.02 (1-1.04)	0.093	1.02 (1-1.04)	0.089
Ischaemic stroke		1.48 (1.46-1.49)	< 0.0001	1.46 (1.42-1.5)	< 0.0001	1.46 (1.42-1.5)	< 0.0001
Coronary heart disease		1.11 (1.1-1.11)	< 0.0001	1.11 (1.08-1.13)	< 0.0001	1.11 (1.08-1.13)	< 0.0001
Hypertension		1.06 (1.06-1.07)	< 0.0001	1.05 (1.03-1.07)	< 0.0001	1.05 (1.03-1.07)	< 0.0001
Diabetes mellitus		1.21 (1.21-1.22)	< 0.0001	1.21 (1.19-1.24)	< 0.0001	1.21 (1.19-1.24)	< 0.0001
Chronic kidney disease		1.19 (1.15-1.23)	< 0.0001	1.19 (1.06-1.34)	0.004	1.19 (1.06-1.34)	0.0038
Body mass index	Underweight	1 (ref)	< 0.0001	1 (ref)	< 0.0001	1 (ref)	< 0.0001
	Normal	0.87 (0.86-0.88)		0.87 (0.83-0.91)		0.87 (0.84-0.91)	
	Overweight	0.82 (0.81-0.83)		0.81 (0.78-0.85)		0.81 (0.78-0.85)	
	Obese	0.8 (0.79-0.81)		0.8 (0.76-0.83)		0.8 (0.76-0.83)	
Household income level	Low	1 (ref)	< 0.0001	1 (ref)	0.2053	1 (ref)	0.205
	Lower middle	1.01 (1-1.02)	0.011	1.02 (0.99-1.04)	0.227	1.02 (0.99-1.04)	0.23
	Higher middle	1 (0.99-1.01)	0.631	1.02 (0.99-1.04)	0.201	1.02 (0.99-1.04)	0.2
	High	0.95 (0.94-0.95)	< 0.0001	0.98 (0.96-1)	0.104	0.98 (0.96-1)	0.11

CI, confidence interval; VZV, varicella zoster virus; HSV, herpes simplex virus; ref, reference.

The cohort was collected from NHIS database with identical inclusion/exclusion criteria and definition of all variables. HSV and VZV were considered time-varying

variables.

^a From multivariable cox proportional hazards regression model with age as linear variable.

^b Further adjusted for age-squared term.

^c From multivariable cox proportional hazards regression model with age using a penalised spline function.

^d Adjusted for age, sex, VZV & HSV infection, depression, dyslipidaemia, ischaemic stroke, coronary heart disease, hypertension, diabetes mellitus, chronic kidney disease, body mass index, household income level.

^e This is the adjusted hazard ratio of age (continuous variable) which assumes the linear association with the risk of dementia. For Model 2, the adjusted hazard ratio of age-squared term (HR = 0.99, 95% CI:0.99-0.99, P-value <0.0001) was not shown. For Model 3, The model showed a significant non-linear association of age on the risk of dementia after adjusting the other variables. And non-linear trend of adjusted hazard ratio which varies across the age values was not shown.