ORIGINAL ARTICLE

Risk of stroke and transient ischaemic attack after herpes zoster

S. U. Kwon[1], S.-C. Yun[2], M.-C. Kim[3], B. J. Kim[1], S. H. Lee[1], S.-O. Lee[3], S.-H. Choi[3], Y. S. Kim[3], J. H. Woo[3] and S.-H. Kim[3]

1) *Department of Neurology,* 2) *Department of Clinical Epidemiology and Biostatistics and* 3) *Department of Infectious Diseases, Asan Medical Centre, University of Ulsan College of Medicine, Seoul, Republic of Korea*

Abstract

We assessed the association of herpes zoster (HZ) with stroke/transient ischaemic attack (TIA) in the general population according to age with controlling risk factors for stroke, using a nationwide representative cohort. The study was based on a prospective dynamic cohort consisting of 1 million Koreans representing all age groups, genders and geographical areas in the Korea Health Insurance Database. New events of stroke/TIA and HZ were identified using the diagnostic codes in the International Classification of Diseases, tenth revision. The risk for stroke/TIA after HZ was compared with HZ-free stroke/TIA individuals according to age group. A total of 766 179 adults were followed up for 11 years from 2003. The incidence of the first-diagnosed HZ cases was 9.40 per 1000 person-years, and that of the first-diagnosed stroke/TIA cases was 9.77 per 1000 person-years. The risk for stroke/TIA was higher in patients who had previous HZ episodes than in those who had never experienced HZ (incidence rate ratio 1.90; 95% CI 1.85–1.95). In addition, this risk persisted for several years after HZ. The risk of stroke/TIA after HZ gradually decreased with age; adjusted hazard ratio (HR) 2.04 in 18- to 30-year-olds, HR 1.74 in 30- to 40-year-olds, HR 1.43 in 40- to 50-year-olds, HR 1.23 in 50- to 60-year-olds, HR 1.24 in 60- to 70-year-olds, and HR 1.29 in those >70 years old, after controlling risk factors for stroke/TIA. Our findings provide evidence that HZ carries an increased risk of stroke or TIA and that the effect of HZ on stroke decreases with increasing age.

Keywords: Cohort, herpes zoster, shingles, stroke, transient ischaemic attack
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Corresponding author: S.-H. Kim, Department of Infectious Diseases, Asan Medical Centre, University of Ulsan College of Medicine, 388-1 Pungnap-dong, Songpa-gu, Seoul, 138-736, Republic of Korea
E-mail: kimsunghanmd@hotmail.com
S.U. Kwon and S.-C. Yun contributed equally to this study.

Introduction

Stroke is the leading cause of disability and mortality in South Korea and other Asian countries [1], and the second most common cause of death following myocardial infarction in Korea, after all forms of cancer [2]. The mechanisms and causes of stroke vary. Atherosclerosis and embolism due to a diseased heart are the most important causes of stroke. However, a proportion of strokes are caused by uncommon mechanisms such as arterial dissection, vasculitis and coagulopathies, especially in the young [3]. In fact, infections such as syphilis and tuberculosis can also lead to stroke, and it is important to differentiate infection-related stroke from stroke due to other causes because some infectious causes can be treated with antibiotics or prevented by vaccination.

Herpes zoster (HZ), also known as shingles, occurs in about 20% or more of the population, mainly in the elderly [4,5]. Varicella zoster virus (VZV) vasculopathy has been proposed to be associated with stroke [6]. Previous epidemiological studies also reported an association between HZ and stroke [7–11], but there were some biases and limitations to the design of these studies. We therefore conducted a nationwide population-based cohort study using the National Health Insurance Service (NHIS) database of South Korea to investigate

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the association between HZ and stroke/transient ischaemic attack (TIA). This study is unique in that we assessed the real burden of stroke/TIA associated with HZ in the general population by using the time-dependent (dynamic) type of cohort study, which was not adopted in previous studies.

Methods

Database source and study population

All individuals in South Korea are obligated to enrol in the NHIS, and most of the medical data in the health system are centralized in a large database. Claims are accompanied by data on diagnostic codes, procedures and personal information. In 2002, Korea NHIS built up the national representative cohort database cohort, which comprised 1 025 340 nationally representative random subjects, amounting to 2% of the entire population (46 605 433). Proportionate stratified random sampling was used based on a total of 1476 strata (two categories for sex, 18 categories for age group, and 41 categories for income). This cohort was followed up over 12 years until 2013, and each year between 2003 and 2013 random samples of new infants were added to compensate for loss of individuals through death or emigration. The data consist of complete medical records including sociodemographic variables, diagnostic codes, deaths, medical service use and health examinations. Recently, the NHIS publicly released this National Health Insurance Service-National Sample Cohort 2002–2013 (NHIS-NSC 2002–2013), and this provided a valuable opportunity to evaluate the relationship between HZ and stroke. The detailed information of the NHIS-NSC profile was described in the previous studies [12,13].

We therefore conducted a prospective dynamic cohort study (Fig. 1) to evaluate the impact of HZ on the incidence of stroke. Initially, 1 025 340 individuals were enrolled in this cohort. Of this population, all individuals under 18 years (247 707 persons) were excluded. To identify first-ever episodes of HZ or stroke, we excluded individuals with evidence of HZ and stroke during the first year of the observation period, which we designated the wash-out period (Fig. 1). We therefore excluded 11 454 patients who were diagnosed with HZ or stroke/TIA, and those individuals who died in 2002. A total of 766 179 persons were finally observed over 11 years (Fig. 2).

Identification of zoster, stroke and confounding factors

Among the 766 179 adults who were assumed to be individuals without past history of HZ or stroke/TIA, we identified those with first-ever diagnosis of HZ and first-ever diagnosis of stroke/TIA using the relevant diagnostic codes of the International Classification of Diseases, tenth revision (ICD-10). For subgroup analysis, the cases of HZ were classified into HZ ophthalmicus (ICD-10 code B023), HZ in other divisions of the trigeminal nerve (ICD-10 code B022), HZ of unspecified site (ICD-10 code B027, B028 or B029) and HZ meningitis or

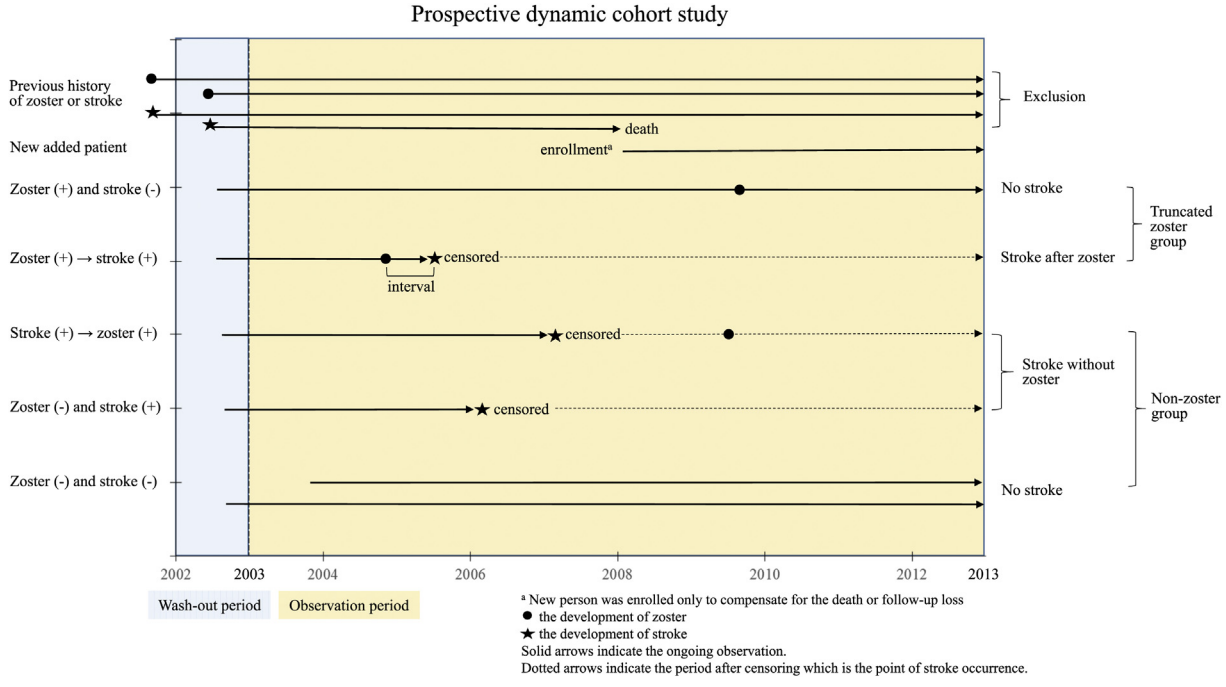

FIG. 1. Flow chart of the study.

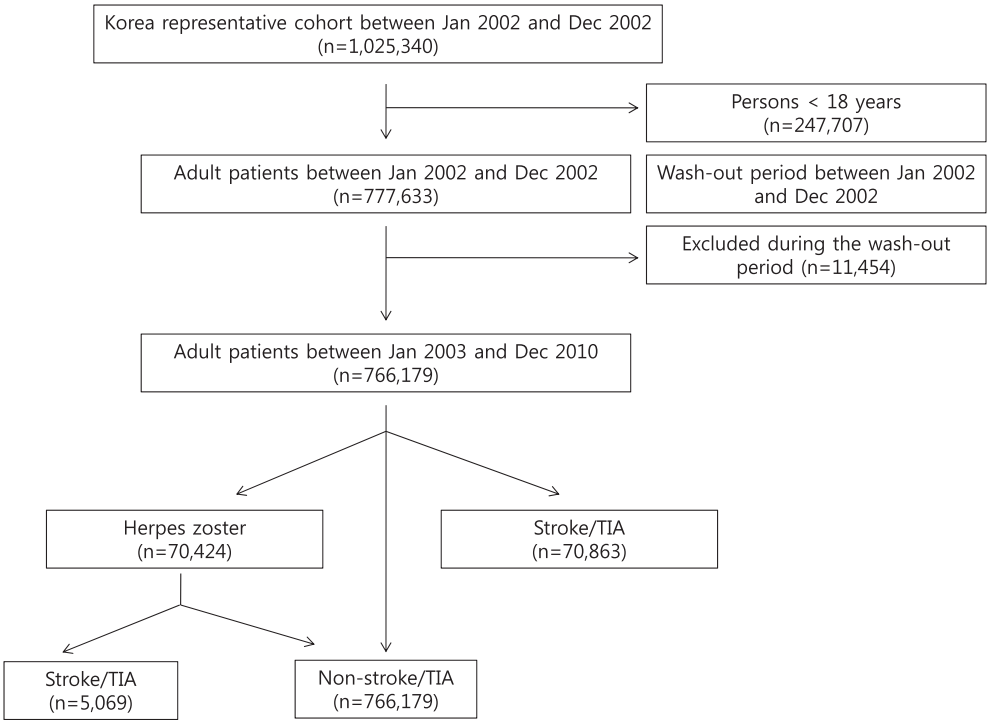

FIG. 2. Structure of the prospective dynamic cohort.

meningoencephalitis (ICD-10 code B020 or B021). Similarly, the cases of stroke were differentiated into ischaemic stroke (ICD-10 code I63), haemorrhagic stroke (ICD-10 code I60, I61, I62), unclassified stroke (ICD-10 code I64) and TIA (ICD-10 code G45).

The well-known risk factors for stroke such as gender, diabetes, hypertension, hyperlipidaemia, atrial fibrillation or flutter, ischaemic heart disease, valvular heart disease, heart failure, chronic renal disease, carotid stenosis and peripheral vascular disease were also searched using the ICD-10 codes. These risk factors were checked at the start of the cohort study.

Study design and outcomes

Our study was designed to analyse, over 11 years, the two time-dependent outcomes, HZ and stroke/TIA, in a cohort population with no history of HZ or stroke/TIA. The patients with first-ever diagnosed HZ were identified first. We defined 'truncated zoster' as HZ without a previous episode of stroke/TIA, by subtracting cases of HZ after a stroke/TIA event from the total cases of HZ during the observation period. Within the 'truncated zoster' population, we identified those patients who were diagnosed with stroke/TIA after HZ (Fig. 1). We also identified the patients who experienced stroke/TIA without any previous HZ event during the observation period. We then compared the incidence of stroke/TIA after HZ with that of HZ-free stroke/TIA.

We hypothesized that HZ infection could affect the occurrence of stroke especially in young persons because they would have fewer risk factors for stroke. If there was a stronger relationship in younger patients than in older patients after adjusting confounding factors, that would be good evidence that HZ increases the risk of stroke. We therefore analysed the relationship between HZ and stroke/TIA according to patient age at intervals of decades.

Statistical analysis

Categorical data were compared by chi-square tests and presented as frequencies. Continuous variables were analysed by unpaired Student's *t* tests and presented as means ± standard deviations or median and interquartile range. The log-rank tests were used to examine the association of baseline characteristics with stroke or TIA and HZ (Table 1). We calculated the incidence rate per 1000 person-years as the number of cases divided by 1000 person-years. That is, the incidence rate = number of cases/the sum of time spent in the study across all participants × 1000. The 95% CI of the incidence rates were also estimated according to 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 and 95% CI were calculated by the delta method [14]. In addition, to assess the association of HZ with stroke or TIA, time-updated Cox models (see Supplementary material, Data S1) [15] were used. The models were adjusted for age, male gender, hypertension,

TABLE 1. Univariate associations of baseline variables with stroke/transient ischaemic attack (TIA), zoster and truncated zoster within 11 years

	Patients	Stroke/TIA	p value	Zoster	p value	Truncated zoster	p value
N	766 179	75 932 (9.9)		77 781 (10.2)		70 424 (9.2)	
Age (Mean/SD, Median/interquartile range)	41.4/15.7, 39.0/22.0						
18–30 years	218 394 (28.5)	2999 (1.4)	<0.001	12 906 (5.9)	< 0.001	12 762 (5.8)	<0.001
30–40 years	187 269 (24.4)	6 866 (3.7)		14 151 (7.6)		13 708 (7.3)	
40–50 years	161 189 (21.0)	14 645 (9.1)		20 299 (12.6)		18 795 (11.7)	
50 60 years	92 143 (12.0)	17 364 (18.8)		15 240 (16.5)		13 274 (14.4)	
60–70 years	67 061 (8.8)	20 892 (31.2)		11 049 (16.5)		8769 (13.1)	
>70 years	40 132 (5.2)	13 166 (32.8)		4136 (10.3)		3116 (7.8)	
Gender							
Male	388 409 (50.7)	41 636 (10.7)	<0.001	31 271 (8.1)	<0.001	28 517 (7.3)	<0.001
Female	377 770 (49.3)	34 296 (9.1)		46 510 (12.3)		41 907 (11.1)	
Hypertension							
Yes	63 661 (8.3)	20 125 (31.6)	<0.001	10 426 (16.4)	<0.001	8170 (12.8)	<0.001
No	702 518 (91.7)	55 807 (7.9)		67 355 (9.6)		62 254 (8.9)	
Hyperlipidaemia							
Yes	26 773 (3.5)	6702 (25.0)	<0.001	4598 (17.2)	<0.001	3775 (14.1)	<0.001
No	739 406 (96.5)	69 230 (9.4)		73 183 (9.9)		66 649 (9.0)	
Ischaemic heart disease							
Yes	15 593 (2.0)	4887 (31.3)	<0.001	2610 (16.7)	<0.001	2028 (13.0)	<0.001
No	750 586 (98.0)	71 045 (9.5)		75 171 (10.0)		68 396 (9.1)	
Diabetes							
Yes	14 153 (1.9)	4102 (29.0)	<0.001	2333 (16.5)	<0.001	1 886 (13.3)	<0.001
No	752 026 (98.1)	71 830 (9.6)		75 448 (10.4)		68 538 (9.1)	
Heart failure							
Yes	7217 (0.9)	2577 (35.7)	<0.001	1153 (16.0)	<0.001	827 (11.5)	<0.001
No	758 962 (99.1)	73 355 (9.7)		76 628 (10.1)		69 597 (9.2)	
Peripheral vascular disease							
Yes	6433 (0.8)	2093 (32.5)	<0.001	1144 (17.8)	<0.001	904 (14.1)	<0.001
No	759 746 (99.2)	73 893 (9.7)		76 637 (10.1)		69 520 (9.2)	
Atrial fibrillation or atrial flutter							
Yes	1794 (0.2)	586 (32.7)	<0.001	284 (15.8)	<0.001	216 (12.0)	<0.001
No	764 385 (99.8)	75 346 (9.9)		77 497 (10.1)		70 208 (9.0)	
Renal disease							
Yes	1670 (0.2)	461 (27.6)	<0.001	267 (16.0)	<0.001	226 (13.5)	<0.001
No	764 509 (99.8)	75 471 (9.9)		77 514 (10.1)		70 198 (9.2)	
Valvular heart disease							
Yes	1222 (0.2)	391 (32.0)	<0.001	190 (15.5)	<0.001	143 (11.7)	<0.001
No	764 957 (99.8)	755 541 (9.9)		77 591 (10.1)		70 281 (9.2)	

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

hyperlipidaemia, ischaemic heart disease, diabetes, heart failure, peripheral vascular disease, atrial fibrillation or atrial flutter, chronic renal disease, valvular heart disease, and HZ as time-dependent covariates. The model was fitted using a SAS PHREG procedure (SAS Institute Inc., Cary, NC, USA). Details were given in the supplementary material (Supplementary material, Data S1). To assess the goodness of fit of the model, Cox–Snell and Deviance residuals plots were used. There is no indication of a lack of fit of the model. Cumulative incidences of stroke or TIA after HZ were constructed as Kaplan–Meier estimates according to the subtype of HZ. All reported p values are two-sided, and $p < 0.05$ was considered statistically significant. Data manipulation and statistical analyses were conducted using SAS® Version 9.2 (SAS Institute Inc.).

Results

Study population

A total of 766 179 persons ≥18 years old were followed up for 11 years from 2003 through to 2013. During this observation period, the number of first-diagnosed HZ cases ('truncated zoster') was 70 424 in 7 488 715 person-years (9.40 per 1000 person-years; 95% CI 9.33–9.47). The associations of baseline variables with stroke/TIA, zoster and truncated zoster within 11 years are shown in Table 1. HZ occurred more frequently in females than in males, and the well-known risk factors for stroke/TIA were higher in the HZ group than the non-zoster group (Table 1). In addition, the incidence of HZ gradually increased with age ($p < 0.001$, Table 2). Truncated HZ, excluding 7357 patients with stroke/TIA followed by HZ, occurred in 70 424 patients (incidence rate 9.40 per 1000 person-years; 95% CI 9.33–9.47).

Incidence of stroke/TIA and its association with HZ, according to the subtype of zoster

The number of first-ever stroke/TIA cases was 75 932 in 7 770 699 person-years (9.77 per 1000 person-years; 95% CI 9.70–9.84) and their incidence increased with age ($p < 0.001$, Table 2). Most importantly, the risk of stroke/TIA was higher in patients with HZ than in those without HZ (incidence rate ratio 1.90; 95% CI 1.85–1.95) and the risk in patients with HZ gradually decreased with age; adjusted HR 2.04 in 18- to 30-year-olds, HR 1.74 in 30- to 40-year-olds, HR 1.43 in 40- to

TABLE 2. Incidences of herpes zoster and stroke/transient ischaemic attack (TIA)

	No. of patients	Incidence rate per 1000 person-years	95% CI
Herpes zoster	77 781	9.94	9.87–10.01
Zoster ophthalmicus	791	0.10	0.09–0.11
Zoster of other trigeminal area	14 323	1.80	1.80–1.86
Zoster meningitis	256	0.03	0.03–0.04
Other types of zoster	62 411	7.98	7.92–8.04
Age group			
18–30 years	12 906	5.51	5.41–5.60
30–40 years	14 151	7.11	6.99–7.23
40–50 years	20 299	12.20	12.03–12.37
50–60 years	15 240	16.71	16.44–16.97
60–70 years	11 049	17.75	17.42–18.08
>70 years	4136	14.21	13.78–14.65
Truncated herpes zoster	70 424	9.40	9.33–9.47
Zoster ophthalmicus	723	0.10	0.09–0.10
Zoster of other trigeminal area	12 786	1.71	1.68–1.74
Zoster meningitis	221	0.03	0.03–0.03
Other types of zoster	56 695	7.57	7.51–7.63
Age group			
18–30 years	12 762	5.48	5.38–5.57
30–40 years	13 708	7.00	6.88–7.11
40–50 years	18 795	11.77	11.60–11.94
50–60 years	13 274	15.97	15.70–16.24
60–70 years	8769	16.56	16.22–16.91
>70 years	3116	12.86	12.41–13.31
Stroke/TIA	75 932	9.77	9.70–9.84
Ischaemic stroke	40 745	5.24	5.19–5.29
Haemorrhagic stroke	8022	0.34	0.33–0.35
Unclassified stroke	3183	0.41	0.40–0.42
TIA	23 982	3.09	3.05–3.13
Age group			
18–30 years	2999	1.26	1.21–1.30
30–40 years	6866	3.41	3.33–3.49
40–50 years	14 645	8.77	8.62–8.91
50–60 years	17 364	19.58	19.29–19.88
60–70 years	20 892	36.96	36.45–37.46
>70 years	13 166	51.79	50.91–52.68

50-year-olds, HR 1.23 in 50- to 60-year-olds, HR 1.24 in 60- to 70-year-olds, and HR 1.29 in those over 70, after controlling risk factors for stroke/TIA (Tables 3 and 4). We analysed the time to stroke/TIA after HZ, stratifying the subtype of zoster for up to 3 years after zoster. HZ involving the central nerve system such as ophthalmic zoster, other trigeminal zoster, and zoster meningitis were associated with higher risks of stroke/TIA than non-central nerve system HZ (Fig. 3A, B).

TABLE 4. Incidence rate ratio (IRR) and adjusted hazard ratio (AHR) in the general population

Age group	IRR	95% CI	Age group	AHR[a]	95% CI
All	1.90	1.85–1.95	All		
18–30 years	2.04	1.71–2.44	18–30 years	1.52	1.26–1.83
30–40 years	1.74	1.55–1.95	30–40 years	1.34	1.19–1.51
40–50 years	1.43	1.34–1.53	40–50 years	1.19	1.12–1.29
50–60 years	1.23	1.16–1.30	50–60 years	1.12	1.06–1.19
60–70 years	1.24	1.17–1.30	60–70 years	1.14	1.08–1.20
>70 years	1.29	1.20–1.38	>70 years	1.14	1.06–1.23

[a]Adjusted for age, male gender, hypertension, hyperlipidaemia, ischaemic heart disease, diabetes, heart failure, peripheral vascular disease, arterial fibrillation or atrial flutter, renal disease and valvular heart disease.

Discussion

Previous epidemiological studies including a Taiwanese matched cohort study [7] and a UK matched cohort study [8] found an increased risk of stroke after zoster. However, the matching design of these studies raised the possibility of confounding by individual differences in the zoster and control groups [16]. Although a recent Danish nationwide population-based cohort study showed an increased risk of stroke after zoster [8], the study included the use of antiviral treatment as a proxy for zoster, which may have introduced some bias. A recent UK self-controlled case-series study that avoided between-person confounding demonstrated an increased association of stroke after the first 6 months following zoster [10], but this novel self-controlled case-series method did not define the burden of stroke caused by HZ. At the time of writing, Yawn *et al.* demonstrated that HZ was associated with increased risk of stroke within 3 months after HZ in the case–control study derived from a US community cohort [11]. Our study identified the real incidence of stroke/TIA after zoster with adjustment of risk factors for stroke/TIA in a time-dependent fashion in a large cohort representing the national population. Hence, our data defining the association and burden of stroke/TIA following HZ infection in a nationwide population have important implications for public health.

TABLE 3. Comparison of the incidence rate of stroke/transient ischaemic attack (TIA) after herpes zoster and of stroke/TIA without herpes zoster

Stroke/TIA after herpes zoster				Stroke/TIA without herpes zoster			
Age group	**No. of patients**	**Incidence[a]**	**95% CI**	**Age group**	**No. of patients**	**Incidence[a]**	**95% CI**
All	5069	17.98	17.48–18.47	All	70 863	9.46	9.39–9.53
18–30 years	128	2.52	2.08–2.95	18–30 years	2871	1.23	1.19–1.28
30–40 years	314	5.82	5.18–6.47	30–40 years	6552	3.34	3.26–3.43
40–50 years	908	12.30	11.50–13.10	40–50 years	13 737	8.60	8.46–8.75
50–60 years	1318	23.73	22.44–25.01	50–60 years	16 046	19.31	19.01–19.61
60–70 years	1616	44.98	42.79–47.17	60–70 years	19 276	36.41	35.90–36.92
>70 years	785	65.76	61.16–70.36	>70 years	12 381	51.11	50.21–52.01

[a]Incidence per 1000 person-year.

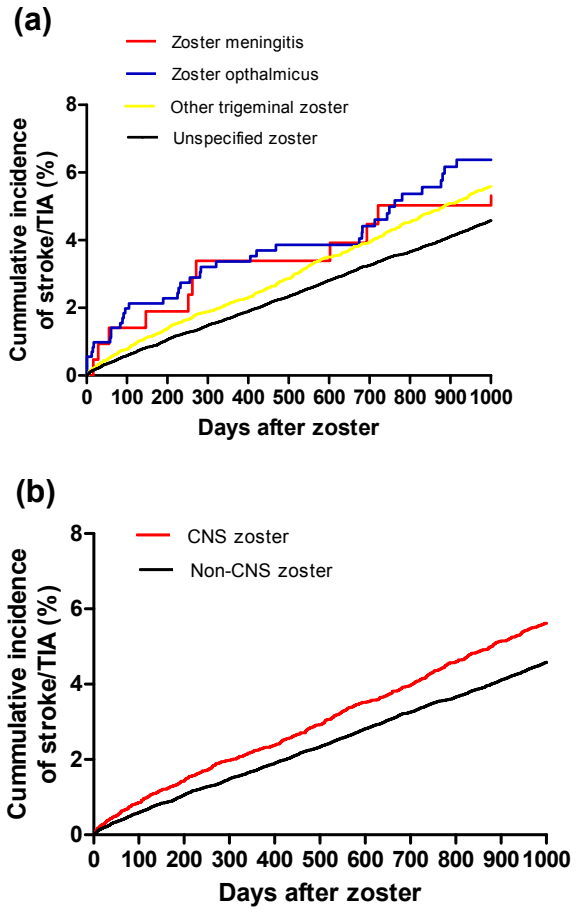

FIG. 3. Cumulative incidence of stroke/TIA after HZ, stratified for subtype of HZ, for 3 years after HZ (A). The *P* value for the comparison with central nerve system (CNS) HZ includes ophthalmic zoster, other trigeminal zoster, and zoster meningitis with non-CNS HZ and is < 0.001 by the log-rank test (B).

It is worth noting that the increased risk of stroke/TIA after HZ continued for years (Fig. 3A, B). This finding of a long-term increase in cerebrovascular events after HZ is consistent with a previous study [8]. Some may argue that since the patients with HZ share the common risk factors for stroke/TIA such as old age, hypertension and diabetes, the occurrence of HZ simply reflects the sum of such vascular risk factors for stroke/TIA. However, these associations were significant after adjustment of these risk factors for stroke/TIA. In addition, if HZ were not involved in the pathophysiological mechanism of stroke/TIA, it would be difficult to explain the dependence of the risk of stroke/TIA after HZ on the type of HZ (Fig. 3A, B). A likely explanation of this dependence is that HZ is an independent risk factor in the pathogenesis of stroke/TIA. In other words, the occurrence of HZ changes the life-time set point of risk for stroke/TIA. In this context, it is an interesting clinical question whether antiviral therapy for zoster or zoster vaccination would alter the risk of stroke/TIA.

We assume that the biological mechanisms of stroke/TIA after zoster vary. First of all, the risk of stroke following HZ was greatest in patients with zoster ophthalmicus, which is found in almost all studies [8,10]. The possible mechanism for this association may be the pathway of the nerve fibres in the trigeminal ganglion, which enter the brain and travel along the cerebral arteries. The reactivation of VZV in the trigeminal ganglion leads not only to zoster ophthalmicus but also to VZV replication along the cerebral arteries. VZV replication adjacent to an artery in turn leads to inflammation in the artery and subsequent thrombosis and stroke [17]. Therefore, viral replication directly damages and weakens the cerebral artery walls, which results in thrombosis, occlusions, infarctions, aneurysms and haemorrhages [16]. In addition, 'shingles' as a skin manifestation may reflect subsequent repeated subclinical reactivation of VZV, sometimes in cranial nerves that have a more direct effect on the cerebral arteries [18]. It is possible that the reactivated VZV spreads transaxonally in a centripetal direction like rabies [19], and reaches the cerebral arteries, and this is followed by transmural spread of the virus. Another possible mechanism is that zoster itself or post-herpetic neuralgia increases sympathetic status and adverse emotional reactions, theoretically increasing cerebrovascular risk [20]. Alternatively, the reactivation of HZ could alter overall immunological status and increase vulnerability to cerebrovascular events. Further studies are needed to elucidate the mechanisms underlying HZ-related stroke.

This study has a few limitations. TIA are now being considered as minor strokes, and this is an area of ongoing controversy [21]. So, the code for TIA diagnosis was prone to be misdiagnosed. However, we assume that the observed effect of HZ on risk of cerebrovascular accident as a whole would be greater than as a stroke diagnosis only because TIA and stroke have similar pathogenesis [22]. In addition, the sensitivity and positive predictive value of ICD codes for stroke was >82% and >81% in most studies, respectively [23]. The previous study also demonstrated that the simple administrative data studies using a code of HZ can overestimate the 10% to 15% of HZ [24]

However, diagnostic codes have been validated and shown to have high sensitivity and positive predictive values (>85%) of identification of new cases of HZ [25,26]. Furthermore, a misclassification caused by ICD diagnostic codes would more likely lead to a bias towards the null. Finally, some may argue that heterogeneity of ethnic group or the inclusion of HIV-infected patients in a young population may affect the relationship of zoster with stroke. However, the Korean ethnic group accounts for approximately 96% of the total population of South Korea (https://en.wikipedia.org/wiki/Demographics_

of_South_Korea#Ethnic_groups), and the non-native population (non-citizens) were excluded in this national representative cohort. In addition, South Korea has maintained a low prevalence of HIV/AIDS, about 2 per 10 000 persons [27]. Although we did not retrieve the ICD-10 for HIV infection or psychiatric illness or the information about ethnicity, only a minority of HIV-infected patients might be included in the 1 025 340 population cohort.

In conclusion, our data definitely demonstrated that HZ is associated with an increased risk of stroke and TIA and the effect of HZ on stroke is diluted with increasing age. Further studies are needed to demonstrate the causal relationship of HZ with stroke and TIA by investigating the pathophysiological mechanism and intervention trial evaluating that some proportion of stroke/TIA cases, especially in the young, could be avoided by aggressive antiviral treatment and vaccination.

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Transparency Declaration

There are no potential conflicts of interest for any authors.

Appendix A. Supporting information

Additional Supporting Information related to this article can be found at http://dx.doi.org/10.1016/j.cmi.2016.03.003.

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