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Herpes zoster as a risk factor for stroke and TIA

A retrospective cohort study in the UK

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ABSTRACT

Objectives: Stroke and TIA are recognized complications of acute herpes zoster (HZ). In this study, we evaluated HZ as a risk factor for cerebrovascular disease (stroke and TIA) and myocardial infarction (MI) in a UK population cohort.

Methods: A retrospective cohort of 106,601 HZ cases and 213,202 controls matched for age, sex, and general practice was identified from the THIN (The Health Improvement Network) general practice database. Cox proportional hazard models were used to examine the risks of stroke, TIA, and MI in cases and controls, adjusted for vascular risk factors, including body mass index >30 kg/m^2, smoking, cholesterol >6.2 mmol/L, hypertension, diabetes, ischemic heart disease, atrial fibrillation, intermittent arterial claudication, carotid stenosis, and valvular heart disease, up to 24 years (median 6.3 years) after HZ occurrence.

Results: Risk factors for vascular disease were significantly increased in cases of HZ compared with controls. Adjusted hazard ratios (AHRs) for TIA and MI but not stroke were increased in all patients with HZ (AHR [95% confidence interval]: 1.15 [1.09–1.21] and 1.10 [1.05–1.16], respectively). However, stroke, TIA, and MI were increased in cases whose HZ occurred when they were younger than 40 years (AHR [95% confidence interval]: 2.42 [1.34–4.36], 1.49 [1.04–2.15], and 1.74 [1.13–2.66], respectively). Subjects younger than 40 years were significantly less likely to be asked about vascular risk factors than were older patients ($p < 0.001$).

Conclusion: HZ is an independent risk factor for vascular disease in the UK population, particularly for stroke, TIA, and MI in subjects affected before the age of 40 years. In older subjects, better ascertainment of vascular risk factors and earlier intervention may explain the reduction in risk of stroke after the occurrence of HZ. ***Neurology*® 2014;82:1–7**

GLOSSARY

AHR = adjusted hazard ratio; **BMI** = body mass index; **GP** = general practitioner; **HR** = hazard ratio; **HZ** = herpes zoster; **HZO** = herpes zoster ophthalmicus; ***ICD*** = *International Classification of Diseases*; **MI** = myocardial infarction; **THIN** = The Health Improvement Network; **VZV** = varicella-zoster virus.

Herpes zoster (HZ) is caused by varicella-zoster virus (VZV), a ubiquitous pathogen that, after primary chickenpox in children, persists asymptomatically (latently) in the sensory ganglia, including the trigeminal ganglion. Reactivation of VZV from latency and translocation, via sensory nerve endings, to the skin where it replicates is associated with the characteristic HZ rash.[1] Both ischemic and hemorrhagic strokes have been described after HZ affecting the ophthalmic branch of the trigeminal nerve.[2] In these patients, virus spreads transaxonally to cerebral arteries via trigeminal and other ganglionic afferents.[2] At autopsy, viral inclusions, DNA, and antigen present in cerebral arteries confirms that VZV vasculopathy in these patients is associated with stroke and TIA.[2] Similar pathology has also been found in strokes and TIA that follow HZ occurring at non-ophthalmic sites and even in the absence of rash, raising the possibility that VZV is more widely implicated in the pathogenesis of cerebrovascular disease.[2,3] This possibility is supported by findings from a Taiwanese population study showing a 30% increase in the incidence of stroke for up to a year after acute HZ, and a 4.5-fold increase after HZ ophthalmicus (HZO).[4,5] We analyzed the risk

Supplemental data at www.neurology.org

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of stroke and TIA after HZ in a large retrospective UK population-based matched cohort study followed for up to 24 years (median 6.3 years). To examine the hypothesis that HZ is a risk factor for vascular disease in general, we also measured the risk of myocardial infarction (MI).

METHODS

Database sources and study population. The THIN (The Health Improvement Network) database is a primary care database that contains anonymous demographic, medical, and prescription information covering more than 3 million active patients in the UK. General practitioner (GP) episodes are coded using READ codes, a standardized hierarchical coding methodology similar to the *ICD* codes, which are used by primary care physicians (GPs) in the UK to classify medical conditions.[6] Patients in the THIN database are representative of the UK population by age, sex, medical conditions, and death rates.[7] Data were extracted from patients routinely attending 464 general practices between 2002 and 2010. General practice is the term used in the UK to denote a group of primary care physicians (GPs).

A retrospective matched cohort study was conducted. Cases were selected as patients who had experienced HZ. Their index date was defined as the date of onset of HZ as recorded in the notes. Patients with recurrent HZ were excluded because this is a rare form of the disease that is often confused with herpes simplex virus infection.[8,9] Patients with HZO, identified using the relevant code, were included as part of the case cohort.

Controls were identified as patients who had no record of HZ. To increase the power of the statistical analysis and reduce bias, 2 controls per case were matched according to their age at index date (± 2 years), sex, and general (primary care) practice. The index date for controls was defined as the index date of the matched case.

Patients and controls younger than 18 years or who had experienced a cardiovascular event (stroke, MI, or TIA) before the index date were excluded. All patients and controls had a minimum follow-up time of 1 year after the index date. The number of patients in the THIN database matching the selection criteria resulted in a power of at least 96% for the statistical analysis.

The THIN codes corresponding to recorded episodes of stroke, TIA, and MI were identified. This set of codes was used to search patient and control records for incident stroke, TIA, and MI after the index date.

Standard protocol approvals, registrations, and patient consents. This study was reviewed and approved through the National Research Ethics Service, Scientific Research Committee reference number 10-013.

Statistical analysis and adjustment for potential sources of bias. Demographic variables, including age and sex, and risk factors for vascular disease, including obesity (body mass index [BMI] >30 kg/m^2), smoking status, history of cholesterol >6.2 mmol/L, hypertension, diabetes, ischemic heart disease, atrial fibrillation, intermittent arterial claudication, carotid stenosis, and valvular heart disease, were compared in cases and controls at the index date using Pearson χ^2 tests. The proportion of cases and controls for which BMI, cholesterol level, and smoking status were recorded was also calculated. Survival analysis was conducted to investigate whether HZ influenced the time to stroke and, independently, to TIA and MI. Kaplan-Meier survival curves were generated and the log-rank test was used to examine differences between the 2 cohorts. Cox proportional hazard regression models were used to calculate the hazard ratio (HR) with 95% confidence interval of each of these outcomes after HZ. The survival models were adjusted for matching variables, risk factors, and potential confounders for stroke and MI,[10,11] including obesity (BMI >30 kg/m^2), smoking status, history of cholesterol >6.2 mmol/L, hypertension, diabetes, ischemic heart disease, atrial fibrillation, intermittent arterial claudication, carotid stenosis, and valvular heart disease. Subgroup analyses were conducted by age at index date (10-year classes) and by sex. All statistical analyses were conducted using SAS software version 9.2 (SAS Institute, Cary, NC).

RESULTS

A total of 113,411 cases of HZ were identified in 3.6 million active patients collected over 23.7 years (median 6.3 years). We excluded 6,696 cases (5.90%) of recurrent zoster because of the possibility that they represented misclassified cases of recurrent herpes simplex.[8,9] In addition, 106,601 HZ cases together with 213,202 controls, 2 for each case, matched for age, sex, and general practice, were further evaluated (figure e-1 on the *Neurology*® Web site at www.neurology.org). The total person-years follow-up for cases of HZ was 781,740.

The characteristics of cases and controls are shown in table 1. The median age of HZ onset was 59.43 years. Risk factors for vascular disease were significantly more common in cases than in controls (table 2).

Study outcomes. Kaplan-Meier curves of the time to stroke for cases and controls, up to a maximum of 23.7 years (8,672 days) after acute HZ, are shown in figure 1. Although the incidence of stroke was higher in cases than controls, Cox proportional HRs adjusted for vascular risk factors showed the difference not to be significant (table 3). The type of stroke (hemorrhage or infarction) was poorly recorded and there were no differences between cases and controls in incidence by stroke pathology (table e-1). Stroke occurring in association with HZO is well described in the literature.[2] HZO normally accounts for approximately 16% of cases of HZ,[12] but was recorded in only 1,600 (1.5%) of cases in the THIN database. Even when cases recorded in free text and HZ of the head and neck were included, the number only increased to 2,324 (2.18%). The incidence of stroke, although higher after HZO, did not differ significantly from that of controls (table 3). However, the risk of stroke was significantly increased for subjects whose HZ occurred when they were younger than 40 years (table 3, figure 2).

The prevalence of TIA and MI in this population is shown in table 1. After adjustment for confounding vascular disease risk factors, the time to TIA and MI was reduced in cases followed for a median of 6.3 years (2,301 days) (range 1.0–23.7 years) (figure 1). Cox proportional HRs, adjusted for vascular risk factors, showed a 15% increased risk of TIA and to a lesser extent MI, associated with HZ (table 3). TIA itself was a risk factor for stroke, increasing the incidence 7-fold compared with age-matched controls (14.32% vs 2.07%).

As with stroke, TIA and MI were significantly increased (2.4- and 1.5-fold, respectively) in those

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Table 1 Comparison of patients with HZ and matched controls

Characteristic	Patients with HZ (n = 106,601)	Matched controls (n = 213,202)	Total (N = 319,803)
Mean age at index date, y (SD)	57.9 (17.7)	57.7 (17.7)	
Sex, female	63,183 (59.3)	124,620 (59.2)	
HZO	1,710 (1.6)		
HZ in the head (including HZO)	2,324 (2.1)		
Other form of HZ/not specified	104,277 (97.8)		
Stroke	5,252 (2.46)	2,727 (2.56)	7,979 (2.49)
Myocardial infarction	4,835 (2.27)	2,762 (2.59)	7,597 (2.38)
TIA	3,904 (1.83)	2,275 (2.13)	6,179 (1.93)
Stroke in patients with HZO (n = 1,710)	130 (3.80)	68 (3.98)	198 (3.86)

Abbreviations: HZ = herpes zoster; HZO = HZ ophthalmicus.
Data are numbers (percentage) unless otherwise marked.

whose HZ occurred at ages 18 to 40 years, even when adjusted for vascular risk factors (figure 2). Most risk factors for vascular disease were also more common in subjects whose HZ occurred at age 18 to 40 years, as compared with matched controls (table e-2). Analysis of BMI, cholesterol level, and smoking status showed these to be recorded significantly more frequently in cases of HZ than in controls (table e-3) but less frequently in subjects aged 18 to 40 years than in older subjects (table e-4).

DISCUSSION This retrospective cohort study is the largest to examine HZ as a risk factor for stroke, TIA, and MI. The study identifies HZ as an independent risk factor for TIA and MI occurring up to 24 years after the acute episode in UK adults older than 18 years and for stroke in those aged 18 to 40 years. The data also confirm that, irrespective of age, conditions that predispose to vascular disease, including lifestyle factors such as smoking and obesity, which have not previously been examined, are significantly more common in subjects with HZ (table 2), although some of this could be attributable to better recording of risk factors in patients who present with HZ (table e-3).

Table 2 Comparison of vascular disease risk factors in cases and controls

	Cases		Controls		
Risk factor	No.	%	No.	%	*p* Value of the χ^2 test
Obesity	19,161	18.0	35,597	16.7	<0.0001
Smoking	37,637	35.3	71,763	33.7	<0.0001
Cholesterol >6.2 mmol/L	14,962	14.0	26,921	12.6	<0.0001
Hypertension	26,396	23.8	46,928	22.0	<0.0001
Diabetes	5,893	5.5	10,372	4.9	<0.0001
Ischemic heart disease	6,536	6.1	10,274	4.8	<0.0001
Atrial fibrillation	2,775	2.6	4,683	2.2	<0.0001
Intermittent arterial claudication	1,042	1.0	1,754	0.8	<0.0001
Carotid stenosis	74	0.1	99	0.1	0.0084
Valvular heart disease	1,190	1.1	1,977	0.9	<0.0001

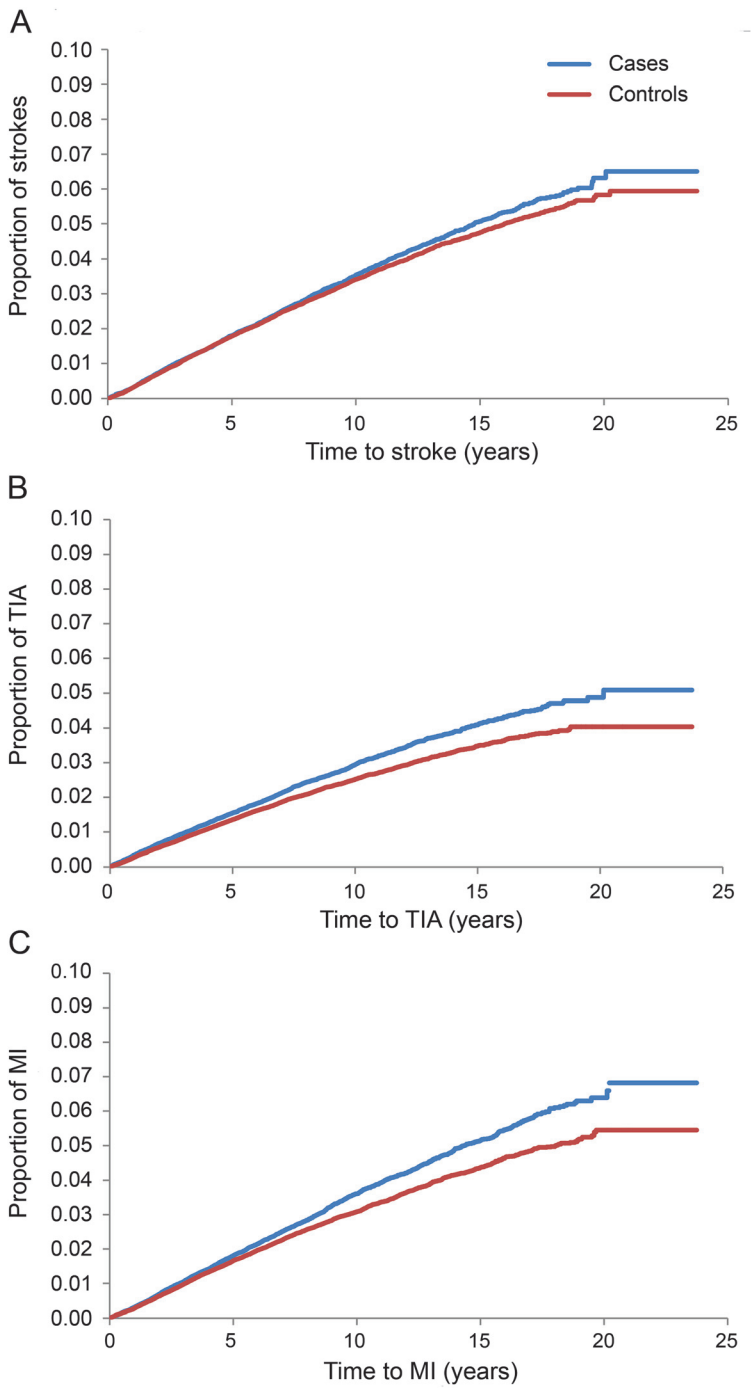
Our study has a number of potential limitations. Although representative of UK general practices, the THIN database depends on accurate coding by GPs.[7] Dermatomal HZ is easily diagnosed and coding has been shown to be accurate in other database studies.[13] To reduce miscoding, we excluded recurrent HZ, which can be confused with herpes simplex.[8,9] The THIN database does not require GPs to specify location of the HZ, which may explain the 10-fold lower than expected percentage of HZO cases in this study compared with previous UK studies (table 1).[12] Low levels of HZO recording have also been observed for another database, the UK General Practice Research Database.[13] The low numbers in this study limited robust evaluation of HZO as a risk factor for stroke or other vascular disease.

Recording by GPs of transient neurologic symptoms mimicking TIA, for example benign positional vertigo, which do not predispose to stroke, may have led to overestimates of the incidence of TIA after HZ occurrence.[14] However, patients with TIA in this study had a 7-fold higher prevalence of stroke compared with patients who did not experience TIA (14.32% vs 2.07%). This suggests that records of TIA in the THIN database, in the main, reflected typical disease, a finding in line with previous observations.[14]

Although the overall prevalence of TIA and MI was in agreement with published data,[14] the prevalence of stroke in this population (2.5%) was higher than for recently reported studies based on other UK population databases[15] (table 1). This could be attributable to the comparatively longer time span over

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Figure 1 Kaplan-Meier curves for the risk of stroke, TIA, and MI over the study follow-up period



The time to stroke (A) after the index date does not differ significantly for cases of herpes zoster and matched controls, but is significantly shorter for TIA (B) and myocardial infarction (MI) (C) in cases compared with controls.

which this analysis was conducted, 24 vs 8 years for other studies,[15] during which time the prevalence of stroke decreased.[15]

In the UK, the incidence of stroke has decreased by more than 30% in the past 10 years.[15] This has been attributed in part to government initiatives encouraging GPs to screen opportunistically for and treat vascular risk factors in subjects older than 45 years.[15,16] By contrast, in those aged 45 years or younger, in whom these policies have not been implemented, the incidence of stroke has remained unchanged over the same time period.[15] The possibility that better ascertainment and treatment of vascular risk factors in older subjects may underlie these differences is supported by our finding that BMI, smoking status, and cholesterol levels were recorded less frequently in the notes of those younger than 40 years (tables e-3 and e-4). Better control of vascular risk factors in older patients presenting with TIA, which itself increases the risk of stroke, would also explain why, after HZ, the incidence of TIA but not stroke was increased in the THIN patient population as a whole. Together with published data linking stroke in children with a recent history of chickenpox,[17–19] these results support a significant role for VZV, independently of other vascular risk factors, in the pathogenesis of stroke and cerebrovascular disease in the UK population, particularly at younger ages. The results are corroborated by population cohort studies conducted in Taiwan[4] and Denmark,[20] both of which identified HZ as a risk factor for stroke[4] or stroke plus TIA.[20] The Danish study also identified the risk of stroke and TIA to be highest in those whose HZ occurred when they were younger than 40 years.[20] While the risks identified were higher for the Danish and Taiwanese studies, this may reflect differences in the study populations and designs. Neither the Danish nor Taiwanese study controlled for smoking and BMI, which may have biased results, while the former reported risks for stroke and TIA combined. The Danish study was designed to capture cerebrovascular events associated with acute HZ, whereas this and the Taiwanese study excluded subjects without a year's follow-up data. The incidence of stroke was higher in the Taiwanese study (1.41% at a year vs 0.3% in this study), but vascular risk factors were 3 to 5 times more common in the UK. This could either reflect differences between the populations, or, after current government recommendations, more complete ascertainment and treatment of risk factors in the UK.

How then might the findings of long-term increases in cerebrovascular and MI after HZ be explained? In the case of HZO, with which strokes are unequivocally and temporally associated, cranial artery pathology arises from direct VZV infection via afferent branches of the ophthalmic branch of the trigeminal nerve.[2,21,22] In such cases, transmural spread of virus from the adventitia leads to disruption of the internal elastic lamina, intimal hypertrophy, and proinflammatory conditions that increase the risk of stroke.[21] However, these mechanisms cannot easily explain the pathogenesis of stroke or TIA after HZ

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Table 3 Hazard ratios (95% CI) for stroke, TIA, and MI after herpes zoster occurrence

Vascular event[a]	Cases (n = 106,601), n (%)	Controls (n = 213,202), n (%)	Hazard ratio (95% CI)	
			Unadjusted	Adjusted[b]
Stroke	2,727 (2.49)	5,252 (2.46)	1.04 (0.99–1.09)	1.02 (0.98–1.07)
MI	2,762 (2.59)	4,835 (2.38)	1.15 (1.09–1.20)	1.10 (1.05–1.16)[c]
TIA	2,275 (2.13)	3,901 (1.83)	1.17 (1.11–1.23)	1.15 (1.09–1.21)[c]
Stroke in patients with HZO (n = 2,324)	68 (3.98)	130 (3.90)	1.06 (0.79–1.42)	1.03 (0.77–1.39)
Stroke in subjects 18–40 y (n = 19,301)	40 (0.21)	45 (0.12)	1.79 (1.17–2.73)	1.74 (1.13–2.66)[c]
MI in subjects 18–40 y (n = 19,301)	51 (0.26)	67 (0.17)	1.53 (1.06–2.20)	1.49 (1.04–1.15)[c]
TIA in subjects 18–40 y (n = 19,301)	25 (0.13)	20 (0.05)	2.51 (1.39–4.52)	2.42 (1.34–4.36)[c]

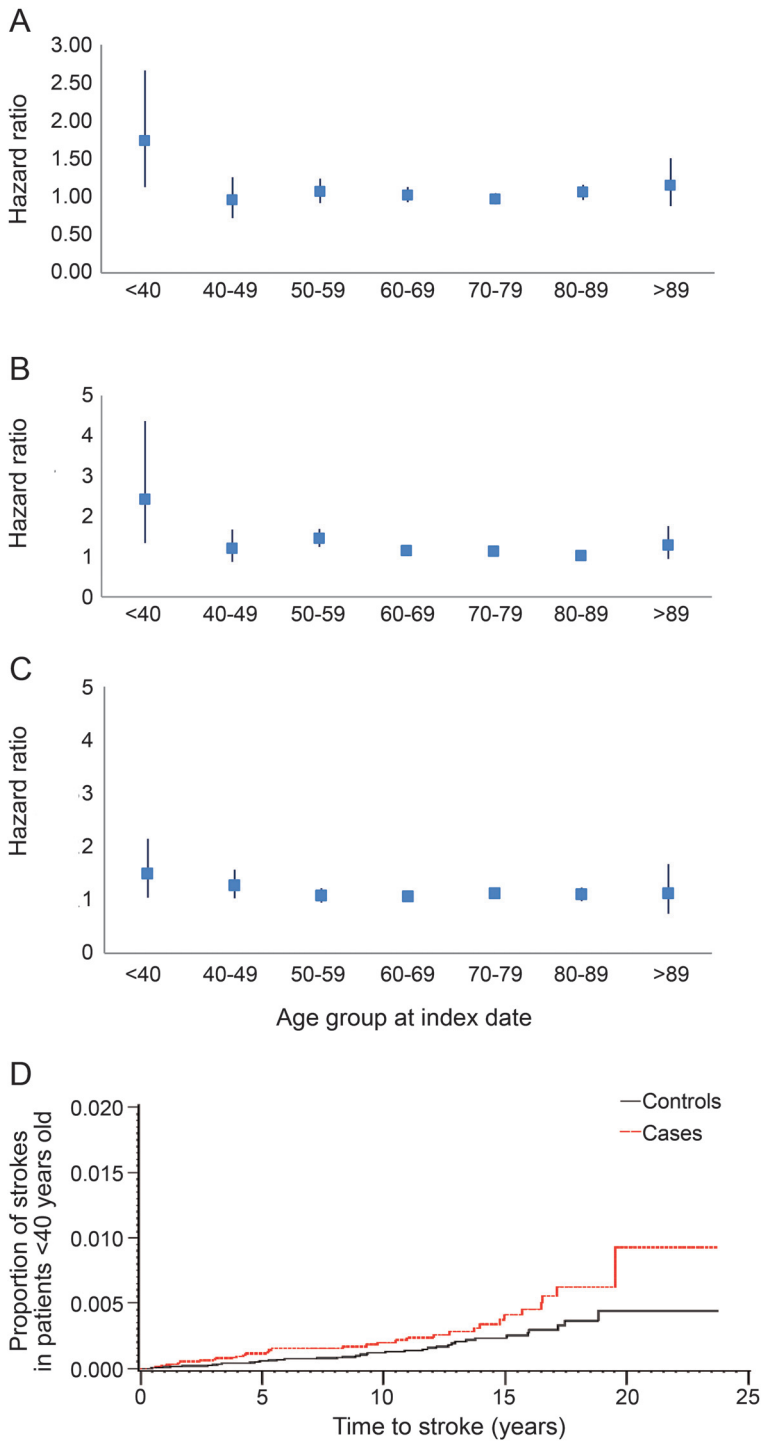
Abbreviations: CI = confidence interval; HZO = herpes zoster ophthalmicus; MI = myocardial infarction.
[a] Period of follow-up 1 to 23.7 years.
[b] Hazard ratios were adjusted for sex, age, obesity (body mass index >30 kg/m^2), smoking status, history of cholesterol >6.2 mmol/L, hypertension, diabetes, ischemic heart disease, atrial fibrillation, intermittent arterial claudication, carotid stenosis, and valvular heart disease.
[c] $p < 0.05$.

located outside the head and neck or even of MI after HZ. Vascular events occurring within days of HZ could be due to the associated inflammatory response, as has been described for stroke and MI after acute respiratory or urinary tract infections.[23] However, this cannot explain the increased risk persisting for months and years after acute HZ. The discovery in recent years that VZV DNA can be detected in oral fluid and blood both in subjects whose rash is outside the head and neck and even in the absence of rash provides a possible explanation.[24–27] In theory, asymptomatic reactivation of VZV from cranial nerves, detectable as virus in saliva, could also lead to infection of cranial arteries, stroke, and TIA, including in the absence of HZ rash and when the rash occurs in noncranial dermatomes.[26] This hypothesis is supported by findings from simian varicella virus infection of macaques, a model for VZV.[28] In this model, asymptomatic reactivation of simian varicella virus from trigeminal ganglia with the potential to spread to cranial arteries has been detected in macaques with thoracic zoster.[29] In humans, VZV antigen has been demonstrated in arterial adventitial tissue, together with intimal hypertrophy, within skip lesions present in the cerebral arteries of diabetics without a history of HZ.[30] Notwithstanding the lack of history in these cases, diabetics are known to be at increased risk of HZ.[31] Furthermore, asymptomatic shedding of virus in saliva is significantly more common in those with a history of HZ.[26] Taken together, the possibility remains that certain individuals who are predisposed to HZ are also more likely to shed virus asymptomatically, and that both represent a risk for cerebrovascular disease. At the same time, asymptomatic reactivation of VZV from latency in thoracic sympathetic ganglia[32] with transaxonal spread via adrenergic nerves to systemic arteries could explain the ongoing risk of MI long after an episode of HZ. Although accounting for 15% to 20% of all cases,[33] the incidence of HZ is comparatively low for those younger than 40 years.[12] This together with the fact that those whose HZ occurs at ages 18 to 40 years are less likely to have predisposing immunosuppressive conditions[33] suggest a predisposition in this group to VZV reactivation and a lifetime increased risk of vascular disease. VZV DNA has also been detected in blood for months after the resolution of HZ[34] and in asymptomatic children receiving intensive care.[27] If circulating virus is able to infect arterial tissue, particularly when damaged by preexisting risk factors, this too could contribute to prolonged inflammation with increased vascular insult. In this scenario, control of risk factors that predispose to arterial damage might mitigate the risk from HZ, which in turn might explain our findings that strokes are not more common in UK citizens older than 40 years. Taken together, the finding that virus reacts asymptomatically from cranial nerves resulting in prolonged oral shedding,[24,25,34] particularly in subjects with a history of HZ,[26] and circulation in the blood,[27,34] provides a set of testable hypotheses to explain the increased risk of TIA, MI, and in some cases stoke, persisting for years after an episode of HZ particularly in the presence of risk factors for vascular disease. The possibility that VZV directly exacerbates preexisting arterial damage would also explain why effective management of risk factors has reduced the incidence of stroke after HZ occurrence in the older UK subjects.

Overall, these data add to the growing body of evidence linking VZV, a ubiquitous pathogen that establishes persistent infection in more than 95% of individuals, to vascular disease. Immunization with the licensed zoster vaccine has been shown to significantly reduce the incidence of HZ as well as

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Figure 2 Adjusted risk (hazard ratio and 95% confidence interval) of stroke, TIA, and MI by age group at index date



Risk of (A) stroke, (B) TIA, and (C) myocardial infarction (MI) by decade. (D) Time to stroke in cases and controls younger than 40 years. Hazard ratios adjusted for vascular risk factors for stroke, TIA, and MI are significantly higher for cases of herpes zoster occurring before 40 years of age compared with matched controls.

significantly decrease the severity of neuropathic complications.[35] Population studies are now needed to evaluate whether immunization to prevent HZ could also reduce the incidence of vascular events including stroke, TIA, and MI. More research is needed to understand the pathogenesis of increased HZ in patients with risk factors for vascular disease and to determine the impact of treatment on risk. Importantly, the role, if any, of asymptomatic VZV reactivation in the pathogenesis of vascular disease and how this might be affected by zoster immunization needs further clarification. In the meantime, the vaccine could now be offered to adults with risk factors for vascular disease, irrespective of age, to reduce the associated risk of HZ.[4,31] At the same time, screening for vascular risk factors in patients presenting with HZ, especially younger patients in whom intervention may have the most impact, should now be encouraged. Ultimately, high-coverage childhood varicella vaccination to reduce latency with wild-type virus is altogether desirable.

AUTHOR CONTRIBUTIONS

Judith Breuer conceived and designed the study and wrote the manuscript. Maud Pacou and Aline Gauthier undertook analysis of the THIN database and contributed to the study design and writing of the manuscript. Martin M. Brown contributed to the study design and writing of the manuscript.

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DISCLOSURE

J. Breuer has received funding from SPMSD for the VZV Identification Programme, which undertakes genotyping of VZV from vaccine adverse events. J.B. also heads the VZV reference laboratory, which has genotyped VZV for GlaxoSmithKline. M. Pacou, A. Gauthier, and M.M. Brown report no disclosures. Go to Neurology.org for full disclosures.

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