Association of herpesviruses and stroke: Systematic review and meta-analysis

Harriet J. Forbes1,*, Elizabeth Williamson1, Laura Benjamin2,3, Judith Breuer4, Martin M. Brown5, Sinéad M. Langan1, Caroline Minassian1, Liam Smeeth1, Sara L. Thomas1, Charlotte Warren-Gash1

1 Faculty of Epidemiology & Population Health, LSHTM, London, United Kingdom, 2 Institute of Infection and Global Health, University of Liverpool, Liverpool, United Kingdom, 3 Stroke Research Centre, Department of Brain Repair and Rehabilitation, UCL Institute of Neurology, UCL, London, United Kingdom, 4 UCL Division of Infection & Immunity, UCL, London, United Kingdom

* harriet.forbes@lshtm.ac.uk

Abstract

Background
Herpesviruses induce a range of inflammatory effects potentially contributing to an increased risk of stroke.

Objectives
To investigate whether patients with infection, or reactivation of, human herpesviruses are at increased stroke risk, compared to those without human herpesviruses.

Data sources
Six medical databases and grey literature sources from inception to January 2017.

Study eligibility criteria
Studies where the exposure was any human herpesvirus and the outcome was stroke. We included randomised controlled trials, cohort, case-control, case-crossover and self-controlled case series designs.

Methods
Meta-analyses when sufficiently homogeneous studies were available. Quality of evidence across studies was assessed.

Results
We identified 5012 publications; 41 met the eligibility criteria. Across cohort and self-controlled case series studies, there was moderate quality evidence that varicella infection in children was associated with a short-term increased stroke risk. Zoster was associated with a 1.5-fold increased stroke risk four weeks following onset (summary estimate: 1.55, 95%CI 1.46–1.65), which resolved after one year. Subgroup analyses suggested post-zoster stroke risk was greater among ophthalmic zoster patients, younger individuals and those not...
prescribed antivirals. Recent infection/reactivation of cytomegalovirus and herpes simplex viruses, but not past infection, was associated with increased stroke risk; however the evidence across studies was mainly derived from small, very low quality case-control studies.

Conclusions

Our review shows an increased stroke risk following zoster and suggests that recent infection or reactivation of other herpesviruses increases stroke risk, although better evidence is needed. Herpesviruses are common and potentially preventable; these findings may have implications for reducing stroke burden.

Introduction

Globally, stroke is the second most frequent cause of death.[1] There is a growing literature indicating that infections, particularly acute respiratory and urinary infections, may play a role in triggering vascular events.[2] Herpesviruses are a family of common viruses persisting latently after primary infection and reactivating periodically. The viruses induce a range of inflammatory effects,[2] potentially contributing to thrombogenesis, atherosclerosis, vasculopathy and platelet activation and thus an increased risk of stroke.

Six previous reviews support an association between herpes zoster (caused by the reactivation of varicella zoster virus (VZV)) and stroke.[3–8] One reported a risk ratio of 1.36 (95%CI 1.10–1.67) for the association between zoster and stroke pooled across six cohort studies,[4] whilst the other reviews found around 2-fold increased risk shortly after zoster, which decreased over the following year.[3, 5–7] Cytomegalovirus (CMV) is also hypothesised to modulate stroke risk, especially among immunocompromised populations[9] and a recent systematic review concluded that cytomegalovirus infection is associated with an increased risk of cardiovascular disease.[10]

Although these reviews have made a significant contribution, there are certain limitations, such as; exclusion of self-controlled case series (SCCS),[4] exclusion of studies among children,[3–8] limited subgroup analyses (only one study assessed whether antiviral therapy modified stroke risk)[7] and restricted scope by looking exclusively at clinically apparent zoster and stroke risk. Studies assessing any of the eight herpesviruses known to infect humans and utilising laboratory tests and serological analysis, as well as clinical diagnoses, could also help elucidate the role of latent, sub-clinical or clinical infection and stroke risk.

The primary objective of the systematic review was therefore to investigate whether patients with infection, or reactivation of, human herpesviruses are at increased risk of stroke.

Methods

The protocol was published[11] according to the Preferred Reporting Items for Systematic Reviews and Meta Analyses Protocols guidelines (PROSPERO registration number: CRD42017054502).

Study designs and characteristics

Eligible study designs included cohort, case-control, case-cohort, case-crossover and SCCS designs. Randomised controlled trials investigating prevention or treatment of herpesvirus infection or reactivation (using vaccines or antiviral agents) were also eligible. We excluded
cross-sectional studies, ecological studies, case-series, case-reports and reviews. Studies were required to report an effect estimate or the data that allow its calculation. We placed no restrictions on time period, publication status, language, geographical setting or healthcare setting.

Participants
Eligible studies included human participants. No restrictions were placed on participants’ age or immunosuppression status.

Exposure
The exposures of interest were infection with, or reactivation of, the eight human herpesviruses: specifically, herpes simplex virus types 1 and 2 (HSV-1 and HSV-2), VZV, Epstein-Barr virus (EBV), CMV, herpesvirus 6, 7, and 8. The exposure definition could be self-reported or a confirmed diagnosis, either through clinical or laboratory criteria. Vaccination against herpesviruses (e.g. Zostavax vaccine) and treatment for herpesviruses (e.g. antivirals) were also considered as effect modifiers, to investigate whether preventing or treating human herpesviruses attenuated stroke risk.

Comparators
Eligible studies were required to include a comparison group of people (or person time for SCCSs or case-crossover) without the herpesvirus exposure of interest.

Outcomes
Studies were included if stroke (first ever or subsequent) was an outcome, clinically diagnosed or self-reported. Those studies meeting the inclusion criteria were additionally assessed for secondary outcomes: TIA[12] and subtypes of stroke (ischaemic versus haemorrhagic).

Information sources
We searched for eligible articles in six databases, originally from dates of inception to January 2017, and then again in July 2018 limited to the years 2017 and 2018. The databases included Cochrane Central Register of Controlled Trials, Embase, Global Health, Medline, Scopus and Web of Science. We additionally searched the clinical trials registers (ClinicalTrials.gov) and grey literature sources, including the New York Academy of Medicine Grey Literature Report (www.greylit.org) and the Electronic Theses Online Service through the British Library (http://ethos.bl.uk).

Search strategy
We searched medical subject heading terms and free text (in the title and abstract) for the concepts ‘human herpesviruses’ and ‘stroke’ (combined with the Boolean logic operator AND). Search terms were developed for the database Medline, reviewed by all collaborators and subsequently transcribed into search terms for the remaining databases (supplementary information S1 Appendix for search terms). Reference lists of eligible articles and relevant reviews were scanned for additional papers.

Study selection
Eligibility assessment was performed independently in a blinded standardized manner by two reviewers (CWG and HF); all retrieved titles and abstracts were screened.
Data collection process
Data were extracted using a pre-defined standardised template. Extraction criteria were based on the PICOS\cite{13} (Population, Intervention, Comparator, Outcomes and Study design) framework. As this is an aetiological study, “exposure” replaced “intervention” and “study characteristics” broadened to “study design” (S3 Appendix for all items extracted). We also recorded: the most fully adjusted effect estimates (odds ratios, hazard ratios, incidence rate ratios, risk ratios) for the association between the exposure and stroke; confounders adjusted for; and results of additional analyses relevant to our non-primary objectives. If there were no events in one arm of the study, a continuity correction was applied (adding 0.5 to each cell \cite{13}).

Risk of bias in individual studies
Two authors independently assessed risk of bias in three studies and HF completed the remaining studies. In keeping with the Cochrane Collaborations approach,\cite{14–16} a pre-specified set of domains were considered, including bias due to: 1) confounding; 2) selection of participants; 3) differential and non-differential misclassification of exposure and outcome; 4) missing data; and 5) reverse causation. For each domain, a-priori criteria were set-out to assign ‘high’, ‘low’, ‘moderate’, or ‘unclear’ risk. A summary risk of bias table was produced; when a domain had more than one item the highest risk of bias judgment was used (unless the only item at high-risk was non-differential misclassification, which would bias results toward the null).

Synthesis of results
We synthesised the results into a narrative, grouping studies by herpesvirus exposure and study design; subgroup analyses were also described. We classified exposures as past infection or recent infection/reactivation. IgM and IgA antibodies, and DNA, are present in the blood for a limited period following herpesviruses exposure, therefore their presence suggests recent infection or reactivation (though IgM has poor sensitivity for detecting acute infections and poor specificity in immunosuppressed).\cite{17} Conversely, IgG antibodies, although also raised during an acute infection or reactivation, remain during latent infection, therefore were classified as a past infection.\cite{17} We also presented results from studies of high versus low IgG titre, as high IgG titre may reflect recent reactivation.

When at least two studies assessed the same herpesvirus as a stroke risk factor, meta-analysis was considered. For pooling, we required studies to have identical study designs, the same measurement for the herpesvirus (e.g. IgG seropositivity) and identify the outcome within a similar time-frame. We pooled effect sizes (referred to as “summary estimates”) irrespective of the type of effect estimate, due to stroke being rare. Random effects meta-analysis was used throughout, to ensure a consistent approach to all analyses was employed; the $I^2$ statistic indicated moderate heterogeneity ($I^2>25\%$) for many subgroups. We investigated sources of heterogeneity (where there were at least three studies in the meta-analysis) by removing studies at high-risk of bias.

Quality of the evidence
The Grading of Recommendations, Assessment, Development and Evaluation (GRADE)\cite{18} approach was used to summarise the quality of cumulative evidence for each herpesvirus on stroke. Evidence was categorised as ‘high’, ‘moderate’, ‘low’ or ‘very low’ quality, with observational studies starting as ‘low’; five reasons to rate down and three reasons to rate up the quality
of evidence, were then considered.\textsuperscript{[19]} Full criteria for grading is in S4 Appendix. We assessed publication bias when there were at least 10 studies by creating a funnel plot: effect estimates for the exposure on stroke risk were plotted against standard errors of the log odds, and symmetry was assessed visually and using Begg’s test for small-study effects.\textsuperscript{[20]}

**Ethics**

As this is a systematic review, ethical approval is not required.

**Results**

In our initial search 5012 titles and abstracts were screened and 41 observational studies were selected for review (Fig 1). Our updated search retrieved 607 studies, of which seven were selected for review, making a total of 48 studies for the final review.

Study methods and results are summarised in Tables 1 and 2 respectively, risk of bias for individual studies in Table 3 (S5 Appendix for detailed justification) and GRADE assessment in Table 4. Results and meta-analyses are displayed in Figs 2–4.

17 studies assessed the association between zoster and stroke (1 case-control study,\textsuperscript{[21]} 13 cohort studies\textsuperscript{[22–34]} and 3 SCCS\textsuperscript{[35–37]} (Table 1). Ten were based in the US or Europe and six in Asia and one in the Middle East; all studies used routinely collected medical records. Two studies involved an immunosuppressed population. 8/17 studies were considered at low-risk of bias in all domains.

**First search**

Records identified through database searching (n=9546)
- Medline: 1098
- Embase: 3802
- Global Health: 191
- Cochrane Library: 106
- SCOPUS: 3,303
- Web of Science: 1,046

Ineligible studies removed (n=34)
- Duplicate publication (n=7)
- Ineligible study design (n=10)
- Wrong exposure (n=3)
- Wrong outcome (n=10)
- Insufficient information to calculate an effect estimate (n=4)

Citations for titles and abstract screening (n=5012)

Duplicate records removed (n=4534)

Citations for full-text review (n=75)

Citations selected for review (n=41)

Additional citations selected for review (n=8)

Ineligible studies removed (n=11)
- Duplicate publication (n=3)
- Ineligible study design (n=5)
- Wrong outcome (n=3)

Citations for titles and abstract screening (n=607)

Duplicate records removed (n=419)

Selected for full text review (n=18)

Total citations selected for review (n=48)

**Additional search**

Records identified through database searching from 2017-2018 (n=1026)

Additional citations selected for review (n=8)

**Fig 1. Flow diagram of study selection.**

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| Author, yr | Design | Study period | Setting | Study population at recruitment | Exposure definition and ascertainment | Comparator definition and ascertainment | Outcome type | Outcome definition and ascertainment |
|------------|--------|--------------|---------|--------------------------------|---------------------------------------|---------------------------------------|--------------|----------------------------------|
| **VZV reactivation—Herpes zoster** |
| Breuer, 2014 [22] | Cohort | 2002–2010 UK, primary care records from THIN | Adults (≥18 yr) with HZ and age (≥ 2 yr), sex and GP practice matched (2:1) patients with no HZ. | Non-recurrent HZ: Read codes | Patients without an HZ Read code | Primary: stroke or TIA Secondary: ischaemic, haemorrhagic or unspecified stroke | First ever incident stroke or TIA: Read codes |
| Calabrese, 2017 [23] | Cohort | 2006–2013 United States, Medicare claims data | Adults ≥65 yr with HZ, ≥12mo follow-up at entry, inflammatory disease (ankylosing spondylitis/IBD/ psoriasis/pсорiatric arthritis/RA), no prior stroke or antiviral therapy | Inpatient/outpatient HZ: ICD-9 diagnosis code AND no same day code for zoster vaccine | Time after HZ divided into 3 periods: 0–90 days; 91–365 days; 366–730 days (reference group). | Primary: Any stroke Secondary: ischaemic stroke | Hospitalised stroke: ICD-9 diagnosis code in any position on hospital claim. |
| Hosamirudsari, 2018 [21] | Case-control | 2015–2017 Iran, individuals attending a single hospital | Adults (aged 30–90 years) admitted for stroke, and controls were stroke-free individuals | Self-reported HZ infection in the last 6 months, collected by a team of healthcare specialists. | No self-report of HZ infection | Stroke | Stroke diagnosed by neurologist and confirmed by brain imaging |
| Kang, 2009[24] | Cohort | 1997–2001 Taiwan, National Health Research Institute claims database | Patients (≥18 yr) with HZ and no history of stroke, matched to 3 patients (age, sex) with no history of HZ or stroke before 2001. | Treatment for HZ in ambulatory care: ICD-9 codes. | Patients without a history of HZ | Primary: stroke (any) Secondary: ischaemic, haemorrhagic | ICD-9 codes |
| Kim, 2017[32] | Cohort | 2002–2013 Korea, sample of national health insurance database | Patients (age unknown) with HZ propensity score matched to those without HZ. | HZ diagnosis: ICD-10 codes | Patients without HZ | Stroke | Newly diagnosed stroke: ICD-10 codes |
| Kwon, 2016[25] | Cohort | 2003–2013 Korea, 1 million sample of national health insurance database | All patients (≥18 yr) in database: those with HZ or stroke during 1st yr of observation period excluded. | First HZ in the observation period: ascertained from ICD-10 codes. | Patients without a history of HZ. | Stroke/TIA | First ever stroke or TIA: ICD-10 codes |
| Langan, 2014 [37] | SCCS | 1987–2012 UK, CPRD; routinely collected database of primary and secondary care records. | Adults (≥18 yr) with 1st ever HZ and stroke. Exclusions: incident TIA, subarachnoid haemorrhage, encephalitis in 12 mo after stroke. | 1st ever HZ: Read and ICD-10 codes. Exposed period: day after HZ to 12 mo (wk 1–4, 5–12, 13–26, and 27–52). | All observation time around exposed period, with the exception of the day of HZ and 4-wk pre-HZ | Primary: Arterial stroke Secondary: cerebral infarction, haemorrhagic or unspecified stroke | First ever stroke: Read codes in CPRD and ICD-10 codes in linked hospital data. |
| Liao, 2017[33] | Cohort | 2000–2011 Taiwan, National Health Research Institute claims database | Adults (≥18 yr) with rheumatoid arthritis. Those with HZ matched (on age, sex, disease duration) to those without HZ. Excluded those with HZ or stroke prior to entry | HZ diagnosis after study entry: ICD-9 codes. | Patients without HZ | Stroke | ICD-9 codes |

(Continued)
| Author, yr       | Design   | Study period | Setting                                                                 | Study population at recruitment                                                                 | Exposure definition and ascertainment                                                                 | Comparator definition and ascertainment | Outcome type                                                                 | Outcome definition and ascertainment |
|-----------------|----------|--------------|-------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|----------------------------------------|--------------------------------------------------------------------------------|--------------------------------------|
| Lin, 2010       | Cohort   | 2003–2005    | Taiwan, National Health Research Institute claims database             | Immunocompetent adults (≥18 yr) with HZO, matched (age, gender) to 3 without HZO. Excluded those with stroke prior to entry. | Patients seeking ambulatory care for HZO (patients with HZO in the previous yr excluded; ICD-9 code (053.2)) | Patients without HZO. First ambulatory care visit in 2004 was assigned their index date. | Stroke                                                                                    | Not specified: most likely from ICD-9 codes                                  |
| Minassian, 2015 | SCCS     | 2006–2011    | United States, Medicare claims data                                     | Patients (≥65 yr) with HZ and stroke / TIA. Excluded if had HZ or vascular events pre-entry or subarachnoid haemorrhage or encephalitis in 12 mo post-stroke. | HZ episode; ICD-9 code with antiviral 7 days before or after HZ. Exposed period: 12-mo after HZ (wk 1, wk 2–4, 5–12, 13–26, and 27–52). | All other observation time made up the baseline (unexposed) period, except the day of and the 4 wk before HZ diagnosis. | Primary: ischaemic stroke. Secondary: haemorrhagic stroke | Stroke: ICD-9 codes in outpatient and inpatient (primary diagnostic field) records |
| Patterson, 2018 | Cohort   | 2007–2014    | United States, Medicare and MarketScan data                             | Adults (≥18 yr) at HZ diagnosis, propensity matched to HZ-free controls.                          | HZ diagnosis                                                                                   | Patients without HZ.                                                              | Stroke and TIA                                                                 | Not specified: most likely from ICD-9 codes                                  |
| Schink, 2016    | SCCS     | 2004–2011    | Germany, health claims data from 4 insurance providers, hospitalisations and outpatients data | Patients (any age) with HZ and stroke, ≥12 mo follow-up, no history of stroke or HZ in 12 mo pre-cohort entry. | 1st or recurrent HZ: ICD-10 code or antiviral with HZ outpatient-diagnosis. Exposed period: up to 12 mo from HZ (0–2 wk, 3–4 wk, 2–3 mo, 4–6 mo, 7–12 mo) | All follow-up time outside exposed period.                                            | Primary: First stroke. Secondary: ischaemic, haemorrhagic, stroke unspecified or TIA | Hospitalised stroke: ICD-10 codes for: primary discharge in hospitalisation data. Admission date taken as onset date |
| Sreenivasan,    | Cohort   | 1995–2008    | Denmark, routinely collected civil registration data and health registers | All Danish adults (≥18 yr) alive during study period. Persons with outcome before start of follow-up were excluded. | HZ treated with antivirals; acyclovir prescription (800 mg in packages of 35 tablets)          | Cohort members with no prior history of acyclovir, valacyclovir or famciclovir prescriptions. | Stroke                                                                                     | ICD 8 and 10 codes, from National Patient Registry; a database of all hospitalisations, outpatient visits and emergency department visits. |
| Sundström, 2015 | Cohort   | 2008–2010    | Sweden, routinely collected healthcare data from one county             | All incident cases of HZ occurring during the study period and the general population in the country. No age restrictions. | HZ from ICD-10 codes, with no diagnosis of HZ in the previous yr.                            | General population in the country (no further information given).                 | Stroke                                                                                    | ICD-10 diagnosis within 1 yr of HZ diagnosis.                                  |
| Tseng, 2011     | Cohort   | 2007–2010    | United States, Kaiser Permanente Southern California health care        | HZ cases (≥50 yr) without history of stroke 1 yr pre-HZ, matched (age, date of HZ, setting of medical care) to patients without HZ. | HZ cases who had received treatment for HZ during the study period.                           | Patients without HZ.                                                              | Stroke                                                                                     | Incident stroke, identified from hospitalisation records with a primary diagnosis as stroke. |
| Yawn, 2016      | Cohort   | 1986–2011    | United States, medical records from Olmsted County.                    | All adults (≥50 yr) with HZ, matched (sex, age (+/- 1 yr)) to patients without HZ. Patients with history of stroke excluded. | 1st/recent HZ; ICD-9 code and HZ clinical symptoms in medical records                     | Patients with no HZ.                                                              | Stroke                                                                                     | Diagnostic codes from hospital admissions or death records, <30 days before cohort entry, or until cohort exit. |

(Continued)
Table 1. (Continued)

| Author, yr | Design | Study period | Setting | Study population at recruitment | Exposure definition and ascertainment | Comparator definition and ascertainment | Outcome type | Outcome definition and ascertainment |
|------------|--------|--------------|---------|---------------------------------|--------------------------------------|----------------------------------------|--------------|--------------------------------------|
| Coles, 2003[38] | Case-cohort | 1995–1998 | Australia, Busselton Health Survey, and linked hospital and death data | Adults (40–89 yr) developing stroke and random sample of non-stroke adults, without CVD at baseline, with serum samples from 1981. | IgG antibodies: avidity assay (AxSym) High level sample = ≥250. | Participants without IgG antibodies to CMV | Stroke | First stroke; from ICD-10 codes and defined as either admission to hospital with any diagnosis of stroke or death from stroke. |
| Fagerberg, 1999 [39] | Cohort | 1987–1995 | Sweden, men from intervention study with hypertension and ≥1 other CVD risk factor. | Men (50 to 72 yr). Of 508 recruited into intervention study, 164 (32%) randomly selected to participate in sub-studies. | High IgG antibodies: MEIA on serological samples taken at entry and/or 3.5 yr later. High titre undefined | Participants with low titres against CMV. | Non-fatal stroke | Independently coded by 2 physicians using hospital records, autopsy records, and death certificates. |
| González-Quijada, 2015 [40] | Case-control | 2011–2013 | Spain, random sample of elderly patients from a single hospital | Cases (stroke patients) and controls (non-stroke patients) aged ≥65 yr (unmatched). | High IgG antibodies: ELISA. Defined as top quartile of serological values. Date samples taken unknown. | CMV seropositive participants without high-titre IgG antibodies. | Ischaemic stroke or TIA | Prevalent or incident ischaemic stroke and/or TIA: determined by imaging data or neurology/ internal medicine specialists. |
| Huang, 2012[41] | Case-control | 1997–2000 | China, Stroke Hypertension Investigation in Genetics case-control study | Stroke patients matched to controls without stroke (sex, age ±3 yr, geographic location, blood pressure category. Age unknown). | IgG, IgM antibodies: ELISA DNA: PCR on plasma samples taken after stroke diagnosis (date unknown). | Participants without any CMV infection | Primary: Any stroke Secondary: ischaemic and haemorrhagic. | Stroke patients discharged from hospital with stroke in past 5 yr. Diagnosed by computer tomography or magnetic resonance imaging |
| Kenina, 2010[42] | Case-control | Unclear | Latvia, single hospital. Data collected through clinical evaluation and questionnaires. | Stroke patients and controls aged ≥42 yr. | IgG antibodies: plasma and sera using ELISA | Participants without any CMV infection | Primary: ischaemic Secondary: Atherothrombotic, Cardioembolic or Undetermined | Stroke patients hospitalised in the Clinic of Neurology |
| Oliveras, 2003[43] | Cohort | 1979–2000 | Spain, single hospital. Data collected retrospectively. | Patients who received renal transplants between 1979–2000. | CMV infection from medical records: no further information provided | Participants without any CMV infection | Primary: Any stroke Secondary: ischaemic and haemorrhagic. | Diagnosis based on clinical symptoms and brain CT scan or MRI. |
| Shen, 2011[44] | Case-control | 2009 | China, inpatients and outpatients from neurology department of single hospital | Cases (aged ≤75 years) with cerebral infarction and controls with a noraml carotid ultrascans scan and cerebral CT/MRI scan. | IgM antibodies: ELISA techniques from serum samples. | Participants without any CMV infection | Ischaemic stroke | Diagnosis based on the 1995 National Cerebrovascular Disease Meeting standard for cerebral infarction, combined with a CT/MRI scan. |
| Smieja, 2003[45] | Cohort | 1993–1995 (recruitment) | Canada, multicentre RCT among patients with history of CVD | Patients ≥55 yr with blood samples (N = 3168/9541). Excluded those with MI/ stroke 4 wk before study. | IgG antibodies: quantitative CMV IgG assay. Samples taken at baseline. | Participants with no evidence of CMV infection | Stroke (secondary outcome) | Stroke was defined as a neurologic deficit lasting more than 24 hours |

(Continued)
| Author, yr | Design | Study period | Setting | Study population at recruitment | Exposure definition and ascertainment | Comparator definition and ascertainment | Outcome type | Outcome definition and ascertainment |
|------------|--------|--------------|---------|---------------------------------|---------------------------------------|----------------------------------------|--------------|--------------------------------------|
| Tarnacka, 2002 [46] | Case-control | 1998–1999 | Poland, patients with stroke consecutively admitted to neurology department. | Cases were patients with stroke. Two control groups: “old” and “young,” no clinical signs of infection/other systemic diseases/ischaemic stroke. All had increased values of serum IC concentrations | Elevated levels of IC containing anti-CMV antibodies; ELISA. Blood samples taken <24 hrs and 7 to 30 days after stroke onset. | Elevated levels of IC not containing anti-CMV antibodies | Ischaemic stroke | Stroke within 24 hrs after onset. CT imaging, sonography, echocardiography, and laboratory tests confirmed the diagnosis, established from history and examination |
| Yi, 2008 [47] | Case-control | Unclear | China, no further information | Cases (≥50 yrs) died of stroke, matched (age, sex) to controls with no cerebrovascular disease, CMV-associated disease, immune suppression, or IgG for CMV. DNA: immediate early (IE) and late (L) antigen in the intracranial arteries by PCR | Participants without CMV DNA | Ischaemic stroke | Patients died of ischaemic stroke. |
| Zheng, 2016 [48] | Case-control | 2004–2014 | China, cohort study within a rural population with hypertension | Random sample of stroke cases (≥35 yr), matched (age [1 yr], sex, duration follow-up, hypertension stage) to controls without stroke. Patients with stroke and CAD at baseline excluded. DNA: PCR on blood samples taken at recruitment to original cohort study (prior to stroke). | Participants without CMV DNA | Stroke | First ever stroke during follow-up: evidence from imaging data extracted from patients medical records, and independently reviewed by the end-point assessment committee. |
| Ziemann, 2016 [49] | Cohort | 2008 | Germany, trial in patients undergoing cardiac surgery, from single hospital | Patients (≥18 yr) due for cardiac surgery: those with planned off-pump surgery excluded. 195/1178 (16.6%) patients excluded due to inadequate blood samples. IgG antibodies: CMIA DNA: PCR, arterial blood samples taken just before induction of anaesthesia. | CMV seronegative participants | Stroke | Derived from the prospectively sampled cardiac surgery database. Defined as Stroke with Rankin grade ≥1. |

**CMV reactivation**

| Yen, 2016 [9] | Cohort | 1998–2012 | Taiwan, National Health Insurance Research Database. | Adults (≥15 yr) newly diagnosed with HIV, with no history of stroke or CMV infection. CMV end-organ disease: ICD-9 code (0.78.5 Cytomegaloviral disease) and prescription for an anti-CMV drug | Participants without CMV end-organ disease | Primary: Any stroke Secondary: ischaemic and haemorrhagic. | Hospitalisation or stroke from ICD-9 codes |

**HHV6 infection**

| Fullerton, 2017 [58] | Case-control | 2009–2014 | United States, | Children (aged 28 d to 18 yrs) with stroke and stroke-free trauma controls, frequency matched on age. | HHV6 DNA: MassTag PCR | Participants without HHV6 DNA | Ischaemic stroke | Acute diagnosis of ischemic stroke |

(Continued)
| Author, yr | Design | Study period | Setting | Study population at recruitment | Exposure definition and ascertainment | Comparator definition and ascertainment | Outcome type | Outcome definition and ascertainment |
|------------|--------|--------------|---------|---------------------------------|----------------------------------------|----------------------------------------|-------------|------------------------------------|
| **VZV infection, serologically defined** |
| Asiki, 2015[59] | Case-control | Unclear | Uganda, data from population based cohort study in rural setting | Adults stroke patients matched on sex and age to ≥4 controls without stroke. All participants had stored serum samples. | IgG, IgM antibodies; quantitative indirect chemiluminescent immunoassays at/ prior to stroke | IgG and IgM optical densities compared in cases versus controls | Stroke | Prevalent cases from clinical symptoms and deaths due to stroke by verbal autopsy. |
| **VZV infection, clinically defined (varicella)** |
| Askalan, 2001 [60] | Cohort | 1992–1999 | Canada, two hospitals. | Consecutive young children aged 6 mo to 10 yr with acute (or unders 3–6 mo follow-up for) stroke during the study period. | Varicella 12 mo prior to stroke; parental interview | Patients without varicella | Recurrent cerebral ischaemic events | TIAs and cerebral infarctions before or after the index AIS; parental interviews, radiographic films, health-record review |
| Sèbire, 1999[61] | Case-control | 1985–1996 | France, referrals to single hospital for stroke treatment | Children with stroke matched to 4 healthy children (gender, age ±4 mo), site of residence | Varicella in the 9 mo prior to stroke; from an obligatory French health record | Participants without varicella | Ischaemic stroke | First idiopathic arterial ischaemic stroke: angiograms and long-term clinical and angiographic follow-up |
| Thomas, 2014 [62] | SCCS | 1990–2011 | UK, primary and secondary care records from 4 routinely collected databases | Patients (any age) with first ever stroke/ TIA and chickenpox during study period. | Varicella: from Read codes. Exposed period: day after varicella and up to 1 yr after | “Unexposed” time: all follow-up time when individual not “exposed”. | Ischaemic stroke | First stroke within study period; ascertained from Read codes. |
| **Vaccination against herpesviruses** |
| Baxter, 2012 [64] | Cohort | 2006–2007 | United States, Kaiser Permanente Northern California (KPNC), health care system | People (≥60 yr) vaccinated against HZ in routine medical care, with ≥180 days continuous KPNC membership after vaccination. | HZ vaccination: in Kaiser Immunization Tracking system. Exposed period: 1–42 days after vaccination. | Unexposed period: 91–180 days post vaccination. | Stroke | Evidence of stroke (hospitalisations and emergency department visits) in 1–42 days following vaccination |
| Kovac, 2018[63] | RCT | Multi-country, randomised placebo-controlled trial | People (≥50 yr) randomised to placebo or HZ subunit vaccine. Excluded those with history of zoster, VZV vaccination, an immunosuppressive condition. | HZ subunit vaccination | Placebo vaccination. | Stroke | Clinical evidence of stroke (neurological deficit and change in consciousness) and either CT/MRI scan or no other sign of a disorder causing deficits |
| Tseng, 2012[65] | SCCS | 2007–2008 | United States, 8 managed-care systems taking part in Vaccine Safety Datalink Project | Patients ≥50 yr receiving HZ vaccine who experienced stroke. 12 mo continuous membership was required, prior to first event. | HZ vaccination: medical records. Risk windows: 1–14 days, 15–28 days, 29–42 days, 1–42 days from vaccination. | Same length of time after a 30-day “wash-out” period following the risk window. | Stroke | ICD-9 diagnosis codes from inpatients and emergency department records, with no code in the previous 12 mo |
| Author, yr         | Design | Study period | Setting                                                                 | Study population at recruitment                                                                 | Exposure definition and ascertainment                                                                 | Comparator definition and ascertainment                                                                 | Outcome type                                      | Outcome definition and ascertainment                                                                 |
|-------------------|--------|--------------|-------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|--------------------------------------------------|----------------------------------------------------------------------------------------------------------|
| Donahue, 2009     | Cohort | 1991–2004    | United States, 8 managed-care systems taking part in Vaccine Safety DataLink Project | Immunocompetent children (11mo to 17yr), >12 mo continuous enrolment, ≥1 encounter with site. Excluded those with infantile cerebral palsy stroke, or hemiplegia/hemiparesis at ≤11 mo of age | Varicella vaccination: recorded in Vaccine Safety DataLink database. Exposed period: 12-mo period following vaccination. | 1) children without varicella vaccination; 2) exposed children: all other person time not classified as exposed. | Ischaemic stroke                                   | Primary or secondary coded diagnoses in inpatient settings using ICD-9 codes                            |
| MacDonald, 2018    | Cohort | 2006–2013    | Canada, administrative health databases                                   | Children receiving the varicella vaccination between 11 months and 23 months of age, and non-vaccinated children. | Varicella vaccination: recorded in medical records. Exposed period: 12-mo period following vaccination. | Children without varicella vaccination                                                      | Ischaemic stroke                                   | ICD-10 codes recorded in hospital discharge database                                                  |
|                   |        |              |                                                                          |                                                                                                    |                                                                                                         |                                                                                                   |                                                   |
| **Multiple herpesviruses infections**                                                                                                                                                                                                                                                                                                  |
| Al-Ghamdi, 2012    | Case-control | Unclear | Saudi Arabia, a single hospital setting                                   | Patients with atherosclerotic vascular disease, matched (age, sex) to 15 healthy controls. Age not specified. | HSV-1 and EBV IgG antibodies: ELISA kits. CMV IgG antibodies: bioelisa kit.                              | Participants with a negative test result for exposures                                           | Stroke                                           | Not reported                                                                                           |
| Elkind, 2010       | Cohort | 1993–2001    | US, community-based study to investigate epidemiology of stroke.       | Adults >39 yr, with no history of stroke, residing in household with a telephone, with blood samples available. | CMV, HSV-1 and HSV-2: Enzyme-linked immunoassay used to measure IgG antibody titres against exposures. | Participants with a negative test result for exposures                                           | Stroke                                           | Defined using data from annual telephone follow-ups: symptoms and events consistent with stroke and classified by 2 neurologists. |
| Elkind, 2016       | Case-control | 2010–2014 | 9 countries, Vascular Effects of Infection in Paediatric Stroke study | All children (29 days to 18 yr) presenting to an included centre and enrolled ≤3 wk of stroke, with an analysable blood sample. | IgG, IgM antibodies to HSV-1/2, CMV, EBV, VZV: blood samples ≤3 wk from stroke using ELISAs. Clinical infection, previous 6 mo from parent/guardian interview. | Participants without evidence of infection.                                                       | Stroke                                           | Arterial ischaemic stroke: from clinical and imaging data by a trained specialist.                     |
| Kis, 2007          | Case-control | 2003     | Hungary, patients hospitalised in 2003                                | Cases (<65 yr) admitted <72 hr after stroke. Controls (<76 yr) admitted for pain, without ischaemic stroke. Patients with history of MI, atrial fibrillation, valvular or myocardial heart disease excluded. | CMV DNA: PCR IgG, IgA, IgM antibodies to HSV-1, CMV, EBV and HHV-6: ELISA, blood samples taken ≤1 wk from stroke. | Participants without evidence of infection.                                                      | Ischaemic stroke                                   | First noncardiogenic ischaemic stroke: from clinical examinations and imaging techniques.                |

(Continued)
| Author, yr | Design | Study period | Setting | Study population at recruitment | Exposure definition and ascertainment | Comparator definition and ascertainment | Outcome type | Outcome definition and ascertainment |
|------------|--------|--------------|---------|---------------------------------|--------------------------------------|---------------------------------------|--------------|-----------------------------------|
| Li, 2005[54] | Case-control | 2001–2002 | China, department of neurology in a single hospital | Cases (age unspecified) of stroke in progression. Excluded those with embolism and reversible ischaemic neurological deficit, cerebral haemorrhage, haemorrhagic infarction, >5 yr history of severe disease. Controls were patients with non-cerebrovascular disease. | CMV, HSV-1 and HSV-2 IgM: dot immunogold labelling staining performed after stroke diagnosis (date unknown). | Patients without herpesvirus IgM in blood | Stroke in progression | Brain damage caused by an obstruction to the blood supply not preventable with conventional treatment (e.g., urokinase for injection) within 72 hours from stroke onset. Confirmed with CT and/or MRI. |
| Ozturk, 2013 [55] | Case-control | Unclear | Turkey, department of neurology in a single hospital | Cases (>40 yrs) were patients presenting with stroke <24 hours of onset matched (age) to controls without ischaemic stroke or TIA. Patients with TIA, subarachnoidal hemorrhage, cerebral venous sinus occlusion with ischemic stroke due to head trauma were excluded. | CMV, EBV IgG: blood samples. CMV tested using ELISA and EBV tested using Viral capsid antigen | Patients without herpesvirus IgG in blood | Ischaemic stroke | Sudden focal or global cerebral impairment and at least one acute lesion. Computed tomography (CT) and magnetic resonance imaging (MRI) were performed in all patients during the first 24 hours. |
| Ridker, 1998 [56] | Case-control | Unclear | US, Physicians Health Study (RCT among male doctors with no history of MI, stroke or cancer). | Cases (age unspecified) were patients developing stroke/MI, matched (age, smoking, follow-up) to controls without MI or stroke. Participants with baseline blood samples included (14916/22071 [68%]). | CMV, HSV1/2 infection: plasma assayed using ELISA for presence or absence of IgG antibodies directed against HSV and CMV. | Seropositivity was compared in cases versus controls | Thromboembolic stroke | Hospital records and autopsy reports were used to confirm each diagnosis according to prespecified criteria |
| Sealy-Jefferson, 2013[57] | Cohort | 1998–2008 | US, cohort of Mexican Americans from the Sacramento Area Latino Study on Aging, community-dwelling | Participants from the cohort (60–101 yr at baseline) without a history of stroke at baseline. | CMV, HSV-1 and VZV IgG antibodies: solid-phase ELISA. Measured at baseline and follow-up visits | Seronegative to herpesviruses of interest. | Incident stroke | Self-reported: determined at follow-up visits and semi-annual telephone calls. Fatal strokes identified from death certificates using the ICD-10 code 164. |
Zoster was associated with a 1.5-fold increased stroke risk four weeks following onset (summary estimate: 1.55, 95%CI 1.46–1.65), with the risk decreasing to baseline after around one year (Fig 2). Removing three studies at high-risk of bias eliminated statistical heterogeneity in cohort studies with "Over 1 year follow-up" ($I^2<0.01\%$, see S1 Table). There were no SCCS at high-risk of bias. There was moderate quality evidence of an increased risk of stroke following zoster, with evidence upgraded due to some strong associations and a clear dose-response gradient over time.

Two studies reported an increased risk of TIA following zoster. The first showed over 50% increased risk (IRR1.56, 95%CI:1.13–2.15) over a maximum of 10 years follow-up[34] and the second around 15% increased risk (HR1.15, 95%CI:1.09–1.21) during a median follow-up of 6.3 years.[22] Only a single SCCS study assessed the effect of zoster vaccination on stroke risk, using Medicare claims data; this study found no evidence that zoster vaccination attenuated stroke risk, however only 3% of study participants were vaccinated which limited the study’s ability to detect an effect.[35]

Results can be found in S1, S2, S3, S4 and S5 Figs. Ophthalmic zoster was associated with a 1.5-fold increased stroke risk four weeks following onset (summary estimate: 1.55, 95%CI 1.46–1.65), with the risk decreasing to baseline after around one year (Fig 2). Removing three studies at high-risk of bias eliminated statistical heterogeneity in cohort studies with "Over 1 year follow-up" ($I^2<0.01\%$, see S1 Table). There were no SCCS at high-risk of bias. There was moderate quality evidence of an increased risk of stroke following zoster, with evidence upgraded due to some strong associations and a clear dose-response gradient over time.

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Table 2. Study results.

| First author, publication yr | Design | Population size (N), follow-up time (yr) | Subjects with outcome [or exposure for case-control studies] (N, %) | Statistical analysis method used | Main reported results | Adjusted for |
|-----------------------------|--------|-----------------------------------------|-------------------------------------------------|---------------------------------|----------------------|------------|
| Breuer, 2014                | Cohort | Exposed = 106,601 Unexposed = 213,202 Follow-up (median): 6.3 yr | Stroke Exposed = 5,252 (2.46%) Unexposed = 2,727 (2.56%) | Cox proportional hazard models Stroke: HR 1.02 (95% CI 0.98–1.07) | Matching variables (age, sex), obesity, smoking, history of cholesterol, hypertension, diabetes, IHD, atrial fibrillation, intermittent arterial claudication, carotid stenosis, heart disease |
| Calabrese, 2017             | Cohort | N = 43,527 Follow-up: up to 7 yr (total 64,528.2 pyr) | N = 680, 1.6% | Generalized linear models 0-90d: IRR 1.36 (1.10–1.68) 91-365d: IRR 1.18 (1.00–1.40) | Baseline: 366-730 days Age, sex, race, diabetes mellitus, hypertension, atrial fibrillation, TIA, glucocorticoids. |
| Hosamirudsari, 2018         | Case-control | Cases = 105 Controls = 105 | Cases: 24/105 (22.9%) Controls: 5/105 (4.8%) | Logistic regression OR, 5.84 (95% CI, 1.98–8.23) | Age, sex, and hypertension. |
| Kang, 2009                  | Cohort | Exposed = 7760 Unexposed = 23,280 Follow-up: up to 1 year | Exposed = 133, 1.7% Unexposed = 306, 1.3% | Cox proportional hazard models Risk of stroke during the 1-yr follow-up period: HR 1.31 (95% CI 1.06–1.60) | Age, sex, income, urbanization, geographical location, hypertension, diabetes, renal disease, CHD, hyperlipidemia, atrial fibrillation, heart failure, heart valve/myocardium disease, and/or carotid/peripheral vascular disease |
| Kim, 2017                   | Cohort | Exposed = 23,213 Unexposed = 23,213 Follow-up: up to 10 yr | Not reported | Not reported HR 1.35 (95% CI 1.18–1.54) | Age, sex, BMI, smoking, drinking, exercise, economic class, hypertension, diabetes, dyslipidemia, angina, TIA, heart failure, atrial fibrillation, heart disease, renal disease, carotid stenosis, peripheral vascular disease, liver disease, rheumatoid disease, inflammatory bowel disease, malignancy, transplantation, HIV, depression. |
| Kwon, 2016                  | Cohort | Exposed = 77,781 Unexposed = 695,755 Follow-up: up to 11 yr (total 7,770,699 years) | Crude incidence rate: 9.8/1000 py | Time-updated Cox models 18–30 yrs: HR 1.52, 95% CI 1.26–1.83 30–40 yrs: HR 1.34, 95% CI 1.19–1.51 40–50 yrs: HR 1.19, 95% CI 1.12–1.29 50–60 yrs: HR 1.12, 95% CI 1.06–1.19 60–70 yrs: HR 1.14, 95% CI 1.08–1.20 >70 yrs: HR 1.14, 95% CI 1.06–1.23 | Age, gender, hypertension, hyperlipidemia, IHD, diabetes, heart failure, peripheral vascular disease, atrial fibrillation or atrial flutter, chronic renal disease, valvular heart disease (time-updated) |
| Langan, 2014                | SCCS | N = 6584 Follow-up (median): 12.5 yr (IQR, 8.7–17.1). | wk 1–4: n = 90 wk 5–12: n = 149 wk 13–26: n = 215 wk 27–52: n = 303 | Conditional Poisson regression wk 1–4: IR 1.63 (1.32–2.02) wk 5–12: IR 1.42 (1.21–1.68) wk 13–26: IR 1.23 (1.07–1.42) wk 27–52: IR 0.99 (0.88–1.12) | Age and time-invariant confounders |
| Liao, 2017                  | Cohort | HZ patients = 2744 Non HZ patients = 5475 | Exposed = 116, 4.2% Unexposed = 186, 3.4% | Cox proportional hazard models 0-90d: HR 2.30 (95% CI 1.13–4.69) 91-365d: HR 1.05 (95% CI 0.58–1.90) 366-730d: HR 1.16 (95% CI 0.70–1.92) >730d: HR 1.18 (95% CI 0.86–1.64) | Age, sex, atrial fibrillation, CKD, COPD, diabetes mellitus, dyslipidemia, and hypertension |
| Lin, 2010                   | Cohort | Exposed = 658 Unexposed = 1974 Follow-up: up to 1 yr | Exposed = 53, 8.1% Unexposed = 33, 1.7% | Cox proportional hazard regressions HR 4.52 (95% CI 2.45–8.33) | Age, gender, hypertension, diabetes, hyperlipidemia, CHD, chronic rheumatic heart disease, other forms of heart disease, and medication habits |

(Continued)
| First author, publication yr | Design | Population size (N), follow-up time (yr) | Subjects with outcome or exposure for case-control studies (N, %) | Statistical analysis method used | Main reported results | Adjusted for |
|----------------------------|--------|--------------------------------------|---------------------------------------------------------------|--------------------------------|----------------------|-------------|
| Minassian, 2015 | SCCS | N = 42,954 Follow-up (median): 5 yr (IQR: 4–5 yr) | Baseline: n = 32179 wk 1: n = 499 wk 2–4: n = 967 wk 5–12: n = 1841 wk 13–26: n = 2588 wk 27–52: n = 3981 | Conditional Poisson regression | wk 1: IR 2.37, 95% CI 2.17–2.59 wk 2–4: IR 1.55, 95% CI 1.46–1.66 wk 5–12: IR 1.17, 95% CI 1.11–1.22 wk 13–26: IR 1.03, 95% CI 0.99–1.07 wk 27–52: IR 1.00, 95% CI 0.96–1.03 | Age in 2-yr age bands and time-invariant confounders |
| Patterson, 2018 | Cohort | Exposed = 23,339 Unexposed = 46,378 Follow-up: up to 10 yr | Exposed = 141, 6.0% Unexposed = 262, 5.6% | Multivariate Poisson models | IRR 1.40 (95%CI 0.93–2.11) | Sociodemographic and clinical factors, including smoking status and BMI |
| Schink, 2016 | SCCS | N = 6,035 Follow-up time (mean): 5.6 yr 3 mo following zoster: N = 352 | Log-linear Poisson model | wk 0–2: IRR 2.32 (95%CI 1.00–5.39) wk 3–4: IRR 1.52 (95%CI 1.08–2.14) wk 5–6: IRR 1.24 (95%CI 1.08–1.43) wk 7–12: IRR 1.13 (95%CI 0.99–1.29) | Age, sex, calendar period. |
| Sreenivasan, 2013 | Cohort | General population = 4,707,885 Exposed = 13296 All followed for 1 yr. | General population = unknown | Poisson regression | IRR 1.34 (95% CI 1.12–1.62) | Age and sex. |
| Sundström, 2015 | Cohort | Exposed = 4478 Unexposed = 16,800 Follow-up (mean): 7.1 yr (range 0–28.6 yr) | Not reported | Logistic regression | OR (95% CI): 3 mo: 1.53 (1.01–2.33) 6 mo: 1.28 (0.91–1.80) 1 yr: 1.04 (0.79–1.36) 3 yr: 1.02 (0.86–1.22) | Age, sex, calendar period. |
| Tseng, 2011 | Cohort | Not reported Follow-up: up to 4 years | Not reported | HR 1.11 (95% CI 0.92 to 1.33) | Matching factors (age and sex), race, heart diseases, diabetes, lung, kidney, liver disease, hypertension, dementia |
| Yawn, 2016 | Cohort | Exposed = 4478 Unexposed = 16,800 Follow-up (mean): 7.1 yr (range 0–28.6 yr) | EverExposed = 562, 12.6% Unexposed = 1844, 11.0% | Logistic regression | OR (95% CI): 3 mo: 1.53 (1.01–2.33) 6 mo: 1.28 (0.91–1.80) 1 yr: 1.04 (0.79–1.36) 3 yr: 1.02 (0.86–1.22) | Age, sex, calendar period. |

### CMV infection

| First author, publication yr | Design | Population size (N), follow-up time (yr) | Subjects with outcome or exposure for case-control studies (N, %) | Statistical analysis method used | Main reported results | Adjusted for |
|-----------------------------|--------|--------------------------------------|---------------------------------------------------------------|--------------------------------|----------------------|-------------|
| Coles, 2003 | Case-cohort | Stroke cases = 119 Random sub-cohort = 451 Follow-up time: up to 3 years | CMV IgG: Stroke cases: 84.9%; Random sub-cohort: 85.4% High level CMV IgG: Stroke cases: 40.3%; Random sub-cohort: 38.1% | Cox proportional hazards regression | CMV IgG: RR 0.93 (95% CI 0.46, 1.89) CMV IgG higher titre: RR 0.78 (95% CI 0.49, 1.23) | Age, gender, BMI, cholesterol, triglycerides, diabetes, haemoglobin, treatment for hypertension, systolic blood pressure and smoking. |
| Fagerberg, 1999 | Cohort | N = 152 Follow-up (median): 6.5 yr (range 0–7.5) | Not reported | Poisson regression | Relative Risk of High Titres of Antibodies to CMV for Stroke: RR 1.04 (95% CI 0.13–8.51) | Smoker, presence of previous cardiovascular disease, group allocation in the underlying multiple risk factor intervention study (multifactorial risk factor intervention or usual care) |
| González-Quijada, 2015 | Case-control | Cases = 111 Controls = 523 | Cases: Seropositive CMV = 98, 95.1%; High titre IgG antibodies = 37, 35.0% Controls: Seropositive CMV = 455, 92.9%; High titre IgG antibodies = 109, 22.2% | Logistic regression | High titre IgG antibodies (top quartile) against CMV (OR 2.1, 95% CI 1.3 to 3.5) | Adjusted for sex, age >81 yr, hypertension, dyslipidaemia, smoking habits, diabetes, cardioembolic focus, other vascular diseases, white blood cells, and C-reactive protein. |
Table 2. (Continued)

| First author, publication yr | Design | Population size (N), follow-up time (yr) | Subjects with outcome [or exposure for case-control studies] (N, %) | Statistical analysis method used | Main reported results | Adjusted for |
|-----------------------------|--------|----------------------------------------|---------------------------------------------------------------|--------------------------------|----------------------|-------------|
| Huang, 2012                 | Case-control | Cases = 200 Controls = 200 | CMV DNA Cases (stroke) = 110, 55% Controls = 47, 23.5% | Logistic regression | Odds of stroke associated with CMV DNA Any stroke: OR 3.98 (95% CI 2.50–6.32) | Age, sex, BMI, hypertension and smoking |
| Kenina, 2010                | Case-control | Cases = 102 Controls = 48 | CMV seropositivity Cases = 95/102, 93%; Controls = 45/48, 94% Mean CMV IgG antibody levels (IU/ml) Cases: 6.43 ± 2.6; Controls: 5.83 ± 2.7 | None | OR for CMV seropositivity: OR 0.90 (95% CI 0.22–3.66) [calculated by review authors] | None |
| Oliveras, 2003              | Cohort | N = 403 Time from RT until stroke = 49.3 mo (SD = 25.6 mo) Total: N = 19 (7.97%) at 10 yr follow-up. Denominator inferred to be 238 Exposed: 0/16, 0% Unexposed: 19/387, 4.9% | Chi-squared test | RR 0.60 (95% CI 0.03–10.41) | [calculated by review authors] | None |
| Shen, 2011                  | Case-control | Cases = 81 Controls = 72 | Cases: 40/81 (49.4%) Controls: 13/72 (17.8%) | Chi-squared test | OR 4.51 (95% CI: 2.16–9.40) | None |
| Smieja, 2003                | Cohort | N = 3168 Follow-up (mean) = 4.5 yr | Overall: 107/3164 (3.4%) | Cox proportional hazards | HR 0.93 (95% CI 0.61, 1.42) | Age, sex, smoking status, ramipril randomization, diabetes mellitus, hypertension, and history of hypercholesterolemia |
| Tarnacka, 2002              | Case-control | Cases: n = 56 Old’ controls: n = 53 Young’ controls: n = 57 | IC Containing Anti-CMV Antibodies Cases: 41/55 (74.5%) Old controls: 11/42 (26.2%) Young controls: 23/57 (40.4%) | Not reported | Increased levels of serum CMV-specific IC were connected with increased risk of stroke incidence (odds ratio, 7.60; 95% CI, 3.21 to 17.96)³ | None reported |
| Yi, 2008                    | Case-control | Cases = 35 Controls = 20 | CMV IE genes/proteins Cases: 21/35 (60.0%), Controls: 6/20 (30.0%) CMV L genes/proteins Cases: 7/35 (20.0%), Controls: 4/20 (20.0%) | Chi-squared tests | CMV IE genes/protein: 3.50 (1.08–11.29) CMV L genes/protein: 1.00 (0.25–3.95) [calculated by review authors—matching not accounted for] | No adjustments made—matched on age and sex |
| Zheng, 2016                 | Case-control | Controls = 300 Cases = 300 Follow-up (median): 8.4 yr | Proportion of patients with CMV DNA Cases: 38/300 (12.7%) Controls: 17/300 (5.7%) | Conditional logistic regression | OR 1.46 (95% CI, 1.00–2.14) | Matching factors (age, gender, follow-up, stage of hypertension), pulse rate, BMI, LDL-C, HDL-C, triglycerides, fasting glucose, smoking, drinking, antihypertensives, statins, antiplatelet agents, and anticoagulants |
| Ziemann, 2016               | Cohort | N = 983 Follow-up: unclear | CMV seropositive: n = 8/618 (1%) CMV seronegative: n = 6/365 (2%) | Chi-square test | Risk ratio: 0.79 (95% CI 0.28–2.25) [calculated by review authors] | None reported |

CMV reactivation

| Yen, 2016 | Cohort | Total: N = 22,581Exposed = 439, follow-up time 6.1 yr (SD = 3.8) Unexposed = 22,142, follow-up time 4.8 yr (SD = 3.7) | Exposed: 17/439 (3.2%)Unexposed: 21/22,142 (0.7%) | Cox proportional-hazards model | HR, 3.07; 95% CI, 1.70 to 5.55 | Age, sex, diabetes, CKD, hypertension, CHD, cancer, dyslipidemia, tuberculosis infection, disseminated Mycobacterium avium complex infection, pneumonia, meningitis, Penicillium marneffei infection, toxoplasma encephalitis, candidiasis, HZ and HAART. |

HHV6 infection

| Fullerton, 2017 | Case-control | Cases = 161 Controls = 34 | Cases: 2/161 (1.2%) Controls: 0/34 (0%) | Not reported | OR 1.07 (95% CI 0.05–22.7)¹ [calculated by review authors] | No adjustments made—matched on age |

(Continued)
### Table 2. (Continued)

**VZV infection, serologically defined**

| First author, publication yr | Design | Population size (N), follow-up time (yr) | Subjects with outcome [or exposure for case-control studies] (N, %) | Statistical analysis method used | Main reported results | Adjusted for |
|-----------------------------|--------|-----------------------------------------|---------------------------------------------------------------|-------------------------------|----------------------|-------------|
| Asiki, 2015 Case-control    | Cases = 31, Controls = 132 | All participants had detectable IgG and IgM antibodies against VZV | Mann–Whitney two-sample test | Median VZV IgG (IQR) at index date Cases: 2.06 (1.45–2.42) Controls: 1.91 (1.52–2.26); P value: 0.47 | No adjustments made—matched on age and sex |
| Askalan, 2001 Cohort        | Exposed = 22, Unexposed = 48 Follow-up: up to 12 months | | Not reported | OR 4.1 (95% CI 1.3–12.9) [calculated by review authors] | No adjustments made |
| Sibire, 1999 Case-control   | Cases = 11, Controls = 44 | Cases: 7/11 (64%) Controls: 4/44 (9%) | Fisher’s exact test | OR: 17.5 (95% CI 3.53–86.83) [Calculated by review authors] | No adjustments made—matched on age, sex and site of residence |
| Thomas, 2014 SCCS           | Children = 60, median follow-up 6.6 yr (IQR 4.7–11.7) Adults = 500, median follow-up 14.2 yr (IQR 9.9–18.8) | Children: 49 0–6 mo: 12; 7–12 mo: 6; Unexposed period: 31 Adults = 241 0–6 mo: 20; 7–12 mo: 11; Unexposed period: 210 | Conditional Poisson regression for individual database, meta-analysis for combined databases | Children (fixed effects meta-analysis) 0–6 mo: IR 4.07 (95% CI 1.96–8.45) 7–12 mo: IR 2.37 (95% CI 0.93–6.06) Adults (random effects meta-analysis) 0–6 mo: IR 2.13 (95% CI 1.05–4.36) 7–12 mo: IR 1.23 (95% CI 0.66–2.30) | Age (in 5-yr bands). |

**VZV infection, clinically defined (varicella)**

| First author, publication yr | Design | Population size (N), follow-up time (yr) | Subjects with outcome [or exposure for case-control studies] (N, %) | Statistical analysis method used | Main reported results | Adjusted for |
|-----------------------------|--------|-----------------------------------------|---------------------------------------------------------------|-------------------------------|----------------------|-------------|
| Askalan, 2001 Cohort        | Exposed = 22, Unexposed = 48 Follow-up: up to 12 months | | | Not reported | OR 4.1 (95% CI 1.3–12.9) [calculated by review authors] | No adjustments made |
| Sibire, 1999 Case-control   | Cases = 11, Controls = 44 | Cases: 7/11 (64%) Controls: 4/44 (9%) | Fisher’s exact test | OR: 17.5 (95% CI 3.53–86.83) [Calculated by review authors] | No adjustments made—matched on age, sex and site of residence |
| Thomas, 2014 SCCS           | Children = 60, median follow-up 6.6 yr (IQR 4.7–11.7) Adults = 500, median follow-up 14.2 yr (IQR 9.9–18.8) | Children: 49 0–6 mo: 12; 7–12 mo: 6; Unexposed period: 31 Adults = 241 0–6 mo: 20; 7–12 mo: 11; Unexposed period: 210 | Conditional Poisson regression for individual database, meta-analysis for combined databases | Children (fixed effects meta-analysis) 0–6 mo: IR 4.07 (95% CI 1.96–8.45) 7–12 mo: IR 2.37 (95% CI 0.93–6.06) Adults (random effects meta-analysis) 0–6 mo: IR 2.13 (95% CI 1.05–4.36) 7–12 mo: IR 1.23 (95% CI 0.66–2.30) | Age (in 5-yr bands). |

**Vaccination against herpesviruses**

| First author, publication yr | Design | Population size (N), follow-up time (yr) | Subjects with outcome [or exposure for case-control studies] (N, %) | Statistical analysis method used | Main reported results | Adjusted for |
|-----------------------------|--------|-----------------------------------------|---------------------------------------------------------------|-------------------------------|----------------------|-------------|
| Baxter, 2012 Cohort         | N = 29,010 Cohort followed for 180d | N = 193, with 38 confirmed after case review by specialists (risk period of the stroke unknown) | Exact conditional method | RR = 0.91; 95% CI: 0.43–1.81 | None (design accounts for within person confounding) |
| Kovac, 2018 RCT             | Vaccinated group: 13,881 Placebo group: 14,035 Follow-up (mean): 3.9 ± 0.7 years | | None | OR: 1.01 (95% CI 0.02–51.0) [Calculated by review authors] | None (randomised design accounts for confounders) |
| Tseng, 2012 SCCS            | Days 1–14: n = 167 Days 15–28: n = 147 Days 29–42: n = 169 Days 1–42: n = 468 Follow-up: 42 days | No. of cases in risk window/control window. Days 1–14: 81/86 Days 15–28: 74/73 Days 29–42: 83/86 Days 1–42: 233/235 | Conditional Poisson regression | Days 1–14: RR 0.94 (95% CI 0.70–1.28) Days 15–28: RR 1.03 (95% CI 0.74–1.42) Days 29–42: RR 0.97 (95% CI 0.71–1.30) Days 1–42: RR 0.99 (95% CI 0.83–1.19) | None (design accounts for within person confounding) |
| Donahue, 2009 Cohort        | N = 3240473 Vaccinated: 1,142,920 Unvaccinated: 2,097,553 Follow-up: up to 13 yr (total py 17.2 million) | Vaccinated: n = 39 (0.003%) (6 occurred in 12 mo risk period following vaccination) Unvaccinated: n = 164 (0.008%) | Cox regression | adjHR (95% CI) after vaccination 0 to <1 mo: 1.1 (0.1–9.2) 1 to <3 mo: 0.7 (0.1–5.7) 3 to <6 mo: 1.3 (0.3–5.6) 6 to <9 mo: 1.3 (0.4–4.9) 9 to <12 mo: 0.4 (0.0–3.2) | Gender, calendar time, geographical site, cardiac disease, rheumatic heart disease and endocarditis, CVD, sickle cell disease, conditions predisposing to vasculopathy, coagulation abnormalities, and diseases leading to a hypercoagulable state. |
| MacDonald, 2018 Cohort      | Vaccinated: 325,729 Unvaccinated: 43,263 Follow-up: 1 yr | Vaccinated group: 25 (0.01%) Unvaccinated group: 6 (0.01%) | Cox proportional hazards model | HR 1.6 (95% CI 0.7–3.7) | Moyamoya disease, Sickle cell disease, Congenital heart disease, Meningitis, Severe sepsis, Intracranial injury, Varicella infection, AIS history before 11 months of age. | (Continued) |
### Table 2. (Continued)

| First author, publication yr | Design | Population size (N), follow-up time (yr) | Subjects with outcome [or exposure for case-control studies] (N, %) | Statistical analysis method used | Main reported results | Adjusted for |
|-----------------------------|--------|------------------------------------------|-----------------------------------------------------------------|-------------------------------|-----------------------|-------------|
| **Multiple herpesviruses infections** | | | | | | |
| Al-Ghamdi, 2012 | Case-control | Cases = 20 Controls = 15 | HSV-1—Cases: n = 20, 100%; controls n = 14, 93.3% | Chi-squared test | HSV-1: OR 2.86 (95% CI 0.09–91.16) | No adjustments made—matched on age and sex |
| Elkind, 2010 | Cohort | N = 1625; Median follow-up 7.6 yr (IQR: 6.4–9.0) | Overall: 67 strokes (56 ischaemic) | Cox proportional hazards models | CMV IgG: HR 2.19 (95% CI 0.84–5.70) | Age, sex, ethnicity, education, systolic blood pressure, cholesterol level, alcohol use, smoking status, waist circumference, physical activity, and CAD |
| Elkind, 2016 | Case-control | Cases = 326 Controls = 115 | Past infection:HSV-1/2: Cases: 53, 16.3%; controls 1402 (86.3%); HSV-2 = 928 (57.1%) | Logistic regression | Past infection:HSV-1/2: OR 0.78 (95% CI 0.45–1.35) | Age. * Age, Race, Residence (urban, rural, suburban), country income (low/middle or high income) |
| Kis, 2007 | Case-control | Cases = 59 Controls = 52 | CMV DNA—Cases: n = 1, 1.7%; Controls: n = 0, 0% | Logistic regression | Highest tertile v. lower two tertiles | Age, gender, smoking, alcohol, lipid, hypertension, sedimentation rate |
| Li, 2005 | Case-control | Cases = 47 Controls = 193 | CMV: Cases: 20/47 (43%); Controls: 20/193 (10%) | Chi-squared test | CMV: OR 6.41 (95% CI 3.05–13.44) | None |
| Ozturk, 2013 | Case-control | Cases = 72 Controls = 60 | CMV: Cases: n = 71/72 (98.6%); Controls: n = 58/60 (96.7%); EBV: Cases: n = 41/72 (56.9%); Controls: n = 28/60 (48.3%) | Logistic regression | CMV: OR 2.45 (95% CI 0.22–27.68) | None |

(Continued)
CMV infection, defined largely using laboratory criteria, was investigated in 22 studies\[9, 30, 38–57\] using data from a variety of settings including electronic healthcare records, survey data and trial data (Table 1).

Among studies assessing CMV infection (past or recent), 19/22 studies had at least one domain at high-risk of bias, including: confounding (ten studies had no age-adjustment) and reverse causation (10 studies recorded CMV following stroke).

14 studies investigated past CMV infection and stroke risk (Fig 3); IgG seropositivity and/or high titre IgG antibodies were investigated. IgG seropositivity was not associated with stroke when combining six case-control studies (summary estimate:1.40, 95% CI:0.67–2.96; $I^2 = 78.8\%$) nor in cohort studies (summary estimate:1.01,95%CI:0.73–1.39, $I^2 < 0.001\%$). While having a high IgG titre compared to a low titre was associated with stroke when combining two case-control studies (summary estimate:2.61,95%CI:1.26–5.43, $I^2 = 33.4\%$) it was not associated with stroke when pooling three cohort studies (summary estimate:0.80,95%CI:0.62–1.05, $I^2 < 0.001\%$).

Recent CMV infection or reactivation was investigated in 11 case-control studies (Fig 3), using a variety of exposure definitions. In a meta-analysis of two studies, IgM seropositivity was associated with increased stroke risk (summary estimate:5.53,95%CI:2.83–10.81, $I^2 < 0.001\%$). When pooling three studies, CMV DNA was also associated with increased stroke risk (summary estimate:2.34,95%CI:0.95–5.74, $I^2 = 81.4\%$). In two of three studies among immunosuppressed patients, clinical CMV reactivation was associated with around 3-fold increased risk of stroke.

There was very low-quality evidence suggesting there is no association between past infection with CMV and stroke and an increased risk of stroke following recent infection/reactivation with CMV.

### Table 2. (Continued)

| First author, publication yr | Design | Population size (N), follow-up time (yr) | Subjects with outcome [or exposure for case-control studies] (N, %) | Statistical analysis method used | Main reported results | Adjusted for |
|-----------------------------|--------|------------------------------------------|----------------------------------------------------------------|-------------------------------|-----------------------|-------------|
| Ridker, 1998                | Case-control | Cases = 643 (only 271 were stroke patients); Controls = 643 | HSV-1/2: Stroke cases: n = 271 (73.6%); Controls: n = 643 (69.4%); CMV: Stroke cases: n = 271 (65.3%); Controls: n = 643 (70.2%) | Conditional logistic regression | HSV-1/2: RR 1.0 (95% CI 0.7–1.5); CMV: RR 0.67 (95% CI 0.4–1.0) | Matching factors (age, smoking, follow-up), treatment assignment, BMI, hypertension, hypercholesterolemia, diabetes, and a family history of premature atherosclerosis. |
| Sealy-Jefferson, 2013       | Cohort | Total N = 1621; CMV: 979 (60.4%); VZV: 299 (18.4%); HSV-1: 1014 (62.6%); Follow-up: up to 10 yr | CMV: Exposed: 97 (9.9%); Unexposed: 67 (10.4%); VZV: Exposed: 36 (12.0%); Unexposed: 128 (9.7%); HSV-1: Exposed: 94 (9.3%); Unexposed: 70 (11.5%) | Discrete-time logistic regression | IgG in the 75th versus 25th percentile | Hypertension, diabetes, hyperlipidaemia, smoking, atrial fibrillation, BMI, coronary heart disease and/or peripheral artery disease, education, age and gender. |
| Yen, 2017                  | Cohort | HIV patients: N = 21,375. Mean follow-up time 4.65 yr (SD 3.36). | CMV infection: 10/311 (3.2%); No CMV infection 242/21064 (1.2%); HZ: 238/20020 (1.2%); No HZ: 14/1355 (1.0%) | Cox regression model | CMV infection: HR 2.71 (95% CI 1.34 to 5.49); HZ: HR 0.80 (95% CI 0.46 to 1.40) | Age, sex, diabetes, chronic kidney disease, hypertension, coronary heart disease, cancer, dyslipidaemia, and systemic lupus erythematosus and HAART. |

Abbreviations: RCT = randomised controlled trial, SCCS = self-controlled case series, RR = risk (or rate) ratio, CI = confidence interval, transient ischaemic attack = TIA, COPD = chronic obstructive pulmonary disorder, CKD = chronic kidney disease, HZ = herpes zoster, HZO = herpes zoster ophthalmicus, ESRD = End-stage renal disease, CT = computerised tomography, MRI = magnetic resonance imaging, yr = year, mo = mo, wk = wk, pyr = person years

1Due to zero events in specific cells, 0.5 was added to all cells to calculate an effect estimate.

2Percentages in paper recalculated due to assumed rounding error

3Unclear which controls were used in the calculation of the effect estimate

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Table 3. Risk of bias summary showing judgements about each risk of bias domain.

| First author, publication yr | Confounding | Selection of participants | Misclassification of variables | Bias due to missing data | Reverse Causation |
|------------------------------|-------------|---------------------------|-------------------------------|-------------------------|--------------------|
| **VZV reactivation—Herpes zoster** |             |                           |                               |                         |                    |
| Breuer, 2014                  | *           | *                         | •                             | *                       | •                  |
| Calabrese, 2017               | *           | *                         | •                             | *                       | •                  |
| Hosamirudarsi, 2018           | *           | ◊                         | ◊                             | *                       | •                  |
| Kang, 2009                    | *           | *                         | •                             | *                       | •                  |
| Kim, 2017                     | ◊           | *                         | •                             | *                       | •                  |
| Kwon, 2016                    | ◊           | *                         | •                             | *                       | •                  |
| Langan, 2014                  | *           | *                         | •                             | *                       | •                  |
| Liao, 2017                    | *           | *                         | •                             | *                       | •                  |
| Lin, 2010                     | *           | *                         | •                             | *                       | •                  |
| Minassian, 2015               | *           | *                         | •                             | *                       | •                  |
| Patterson, 2018               | ◊           | *                         | •                             | *                       | •                  |
| Schink, 2016                  | *           | *                         | •                             | *                       | •                  |
| Sreenivasan, 2013             | *           | *                         | •                             | *                       | •                  |
| Sundström, 2015               | ◊           | ◊                         | ◊                             | *                       | •                  |
| Tseng, 2011                   | ◊           | *                         | •                             | *                       | •                  |
| Yawn, 2016                    | *           | *                         | •                             | *                       | •                  |
| **CMV infection**             |             |                           |                               |                         |                    |
| Coles, 2003                   | *           | *                         | •                             | *                       | •                  |
| Fagerberg, 1999               | ◊           | *                         | •                             | *                       | •                  |
| González-Quijada, 2015        | *           | ◊                         | ◊                             | *                       | •                  |
| Huang, 2012                   | *           | *                         | •                             | *                       | •                  |
| Kenina, 2010                  | ◊           | ◊                         | ◊                             | *                       | •                  |
| Oliveras, 2003                | ◊           | ◊                         | ◊                             | *                       | •                  |
| Shen, 2011                    | ◊           | ◊                         | ◊                             | *                       | •                  |
| Smieja, 2003                  | *           | *                         | •                             | *                       | •                  |
| Tarnacka, 2002                | ◊           | ◊                         | ◊                             | *                       | •                  |
| Yi, 2008                      | ◊           | ◊                         | ◊                             | *                       | •                  |
| Zheng, 2016                   | *           | *                         | •                             | *                       | •                  |
| Ziemann, 2016                 | ◊           | ◊                         | ◊                             | *                       | •                  |
| **CMV reactivation**          |             |                           |                               |                         |                    |
| Yen, 2016                     | *           | *                         | •                             | *                       | •                  |
| **HHV 6 infection**           |             |                           |                               |                         |                    |
| Fullerton, 2017               | ◊           | ◊                         | ◊                             | *                       | •                  |
| **VZV infection, serologically defined** |         |                           |                               |                         |                    |
| Asiki, 2015                   | *           | ◊                         | ◊                             | •                       | •                  |
| **VZV infection, clinically defined (varicella)** |       |                           |                               |                         |                    |
| Askalan, 2001                 | ◊           | ◊                         | ◊                             | •                       | •                  |
| Sèbire, 1999                  | *           | ◊                         | ◊                             | •                       | •                  |
| Thomas, 2014                  | *           | *                         | •                             | *                       | •                  |
| **Vaccination against herpesviruses (e.g. zostavax vaccine)** |         |                           |                               |                         |                    |
| Baxter, 2012                  | *           | *                         | •                             | *                       | •                  |
| Kovac, 2018                   | *           | *                         | •                             | *                       | •                  |
| Tseng, 2012                   | *           | *                         | •                             | *                       | •                  |
| Donahue, 2009                 | *           | *                         | •                             | *                       | •                  |
| MacDonaled, 2018              | ◊           | *                         | •                             | •                       | •                  |

(Continued)
CMV was the only outcome for which sufficient studies were available to assess publication bias; there was no evidence of publication bias (see S6 Fig).

One case-control study assessed the association between HHV-6 and stroke; no association was found.[58] Four case-control studies examined the association between EBV and stroke (Table 1);[50, 51, 53, 55] three were hospital-based among older adults and one a multi-country study among children (under 18 years). All studies were small (N < 500) and at high-risk of bias.

There was no evidence that past infection (IgG seropositivity) was associated with stroke risk, when combining data from three studies (summary estimate: 1.28, 95%CI:0.89–1.84; $I^2<0.001$) (Fig 4). The study among children found no evidence that recent infection/reactivation of EBV (measured from IgM seropositivity) was associated with stroke risk (OR 1.44, 95% CI 0.12–16.75).

There was very low quality evidence of no association between past infection and an increased risk following recent infection/reactivation with EBV and stroke; the quality of evidence was downgraded due to high-risk of bias and imprecise estimates.

Associations between HSV-1 or HSV-2 and stroke risk were explored in seven studies[50–54, 56, 57] (Table 1) using population survey data and an RCT, and data from a hospital setting. A high-risk of bias was identified in all seven studies. No clear patterns were observed, although there was some indication that recent HSV1 infection/reactivation (IgM seropositivity or IgA high titre) was associated with increased stroke risk.

Two case-control studies[51, 59] and one US-community based cohort study[57] assessed the effect of serologically-defined VZV infection on stroke risk (Table 1). Past infection (IgG seropositivity or high titre) was not associated with stroke risk in two studies (Fig 4); quality of evidence was graded very low due to a high-risk of bias. However, a multi-country case-control study among children (under 18 years) found recent infection/reactivation (IgM seropositivity) was associated with increased stroke risk; quality of evidence was graded as low, because although there was a high-risk of bias, the association was very strong.

Varicella and the risk of stroke among children was assessed in three studies from Canada and Europe;[60–62] a high-risk of bias was identified in 2/3 studies. Different study designs

**Table 3.** (Continued)

| First author, publication yr | Confounding | Selection of participants | Misclassification of variables | Bias due to missing data | Reverse Causation |
|-----------------------------|-------------|---------------------------|-------------------------------|-------------------------|-------------------|
| Al-Ghamdi, 2012 (HSV-1, CMV, EBV) | ◇ | ◇ | * | ◇ | ◇ |
| Elkind, 2010 (CMV, HSV1 and HSV2) | ● | ● | * | ◇ | * |
| Elkind, 2016 (HSV1/2, CMV, EBV, VZV) | ● | ● | * | ◇ | ◇ |
| Kis, 2007 (HSV-1, CMV, EBV and HHV-6) | ● | ● | * | ◇ | ◇ |
| Li, 2005 (CMV, HSV1 and HSV2) | ◇ | ◇ | * | ◇ | ◇ |
| Ozturk, 2013 (CMV, EBV) | ● | ◇ | * | ◇ | ◇ |
| Ridker, 1998 (CMV, HSV1/2) | ● | ● | ◇ | ◇ | * |
| Sealy-Jefferson, 2013 (CMV, HSV1 and VZV) | ● | ● | ◇ | ◇ | * |
| Yen, 2017 (HZ and CMV disease) | ● | ● | ◇ | ◇ | ◇ |

Key

◇ High risk
● Moderate risk
• Low risk
○ Unclear risk

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Table 4. Assessment of quality of evidence for outcomes.

| Quality assessment | Quality |
|--------------------|---------|
| **VZV: reactivation (herpes zoster)** | |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** |
| 17 observational studies | not serious | not serious | not serious | serious | strong association | ⊕⊕⊕◯ |
| | | | | | dose response gradient | MODERATE |
| **CMV: past infection** | |
| 14 observational studies | serious | not serious | not serious | serious | none | ⊕◯◯◯ |
| | | | | | VERY LOW |
| **CMV: recent infection/reactivation** | |
| 11 observational studies | serious | not serious | serious | serious | strong association | ⊕◯◯◯ |
| | | | | | VERY LOW |
| **HHV6: infection/reactivation** | |
| 1 observational studies | very serious | not serious | not serious | very serious | none | ⊕◯◯◯ |
| | | | | | VERY LOW |
| **EBV: past infection** | |
| 4 observational studies | serious | not serious | serious | serious | none | ⊕◯◯◯ |
| | | | | | VERY LOW |
| **EBV: recent infection/reactivation** | |
| 1 observational studies | very serious | not serious | not serious | very serious | none | ⊕◯◯◯ |
| | | | | | VERY LOW |
| **HSV-1: past infection** | |
| 4 observational studies | not serious | serious | not serious | serious | none | ⊕◯◯◯ |
| | | | | | VERY LOW |
| **HSV-1: recent infection/reactivation** | |
| 2 observational studies | serious | serious | not serious | serious | strong association | ⊕◯◯◯ |
| | | | | | VERY LOW |
| **HSV-2: past infection** | |
| 1 observational studies | not serious | not serious | not serious | serious | none | ⊕◯◯◯ |
| | | | | | VERY LOW |
| **HSV-2: recent infection/reactivation** | |
| 1 observational studies | very serious | not serious | not serious | serious | none | ⊕◯◯◯ |
| | | | | | VERY LOW |
| **HSV-1/2: past infection** | |
| 2 observational studies | serious | not serious | not serious | serious | none | ⊕◯◯◯ |
| | | | | | VERY LOW |
| **HSV-1/2: recent infection/reactivation** | |
| 1 observational studies | serious | not serious | not serious | serious | none | ⊕◯◯◯ |
| | | | | | VERY LOW |
| **VZV infection, serologically defined: past infection** | |
| 2 observational studies | serious | not serious | not serious | not serious | none | ⊕◯◯◯ |
| | | | | | VERY LOW |
| **VZV infection, serologically defined: recent infection/ reactivation** | |
| 1 observational studies | serious | not serious | not serious | serious | very strong association | ⊕⊕◯◯ |
| | | | | | LOW |
| **VZV infection, clinically defined (varicella—adults)** | |
| 1 observational studies | not serious | not serious | not serious | serious | strong association | ⊕◯◯◯ |
| | | | | | LOW |
| **VZV infection, clinically defined (varicella—children)** | (Continued) |
and time periods during which stroke was recorded were used, therefore estimates were not pooled. However, each study found varicella was associated with a greater risk of stroke within a year from diagnosis. Because of the dose-response gradient over time and very strong associations observed, the evidence was classified as moderate quality.

The SCCS study also assessed the association among adults; an increased risk of stroke within 6-months of varicella was found (IR 2.13, 95% CI: 1.05–4.34). Although this association was strong, the confidence interval was wide, thus the evidence was graded low quality.

Five studies evaluated the short-term effect of VZV vaccination on stroke risk, by comparing vaccinated with unvaccinated people (or person time in the same individuals). One was a multi-country RCT[63] and the others used Canadian or US electronic healthcare records (Table 1);[64–67] these studies were at very low-risk of bias. No decreased risk of stroke in those vaccinated against varicella or zoster was noted (Fig 4); evidence across studies was graded very low and low quality for varicella and zoster vaccination, respectively.

One small (N = 111) case-control study among older hospitalised patients found no association between HHV-6 IgG seropositivity and stroke (Table 1), in unadjusted analysis (OR 0.90, 95%CI:0.41–1.98).[53] No studies assessed herpesvirus-7 or 8.

Table 4. (Continued)

|                                                                 | observational studies | serious | not serious | very strong association | dose response gradient | Varicella vaccination |
|----------------------------------------------------------------|-----------------------|---------|-------------|------------------------|------------------------|-----------------------|
| 3                                                               | serious               | not serious | very serious |           | MODERATE                |

Explanations
a. None of meta-analyses suffered from considerable heterogeneity and trend of effects were very clear across studies using different study designs.
b. Wide confidence interval(s)
c. <50% studies have two or more domains at high risk of bias and contribute <50% weight to the meta-analysis
d. Some point estimates across studies in different directions, some overlap of confidence intervals, where meta-analyses were possible I² statistic indicates substantial heterogeneity (although subgroup analyses demonstrated heterogeneity was driven by a single study).
e. Some variance of point estimates across studies (yet the majority are in the in same direction), some overlap of confidence intervals, where meta-analyses were possible I² statistic indicates statistical heterogeneity (yet only very few studies included in meta-analyses).
f. ≥50% studies have two or more domains at high risk of bias, however contribute <50% weight to the meta-analysis
g. Some variance of point estimates across studies, confidence intervals overlap, no statistical evidence of heterogeneity
h. Study/studies suffered from two or more domains at high risk of bias.
i. 1/4 studies suffered from two domains at high risk of bias; this study only contributed 5% weight to the meta-analyses.
j. Study may have suffered from three domains at high risk of bias: confounding, reverse causality, and selection bias
k. Study/studies had one domain at high risk of bias.
l. 2/3 studies suffered from 2 or more domains at high risk of bias, however one study had a very low risk of bias

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Discussion
Our review identified 48 studies assessing the association between infection with or reactivation of herpesviruses and risk of stroke. Consistent with previous reviews, there was moderate quality evidence that zoster was associated with a short-term increased risk of stroke, and that increased risk was greatest shortly after zoster (decreasing to baseline by around one year). Some evidence suggested the risk was greater among ophthalmic zoster patients, younger age
Fig 2. Effect of clinically diagnosed herpes zoster on stroke risk by study design and length of follow-up. †Outcome was ischaemic stroke ‡Outcome was stroke/TIA μ: among patients 50–60 years of age. •Study population was immunosuppressed †Comparators group was person time 366-730 days after HZ.

https://doi.org/10.1371/journal.pone.0206163.g002
Fig 3. Effect of CMV (serological evidence of infection or clinical reactivation) on stroke risk. †Outcome was ischaemic stroke ‡Outcome was stroke/TIA •Study population was immunosuppressed. ††No age adjustment/matching for age.

https://doi.org/10.1371/journal.pone.0206163.g003
Fig 4. Effect of EBV, HSV, VZV infection, clinically diagnosed varicella and VZV vaccination on stroke risk. †Outcome was ischaemic stroke ‡Outcome was stroke/TIA †No age adjustment/matching for age.

https://doi.org/10.1371/journal.pone.0206163.g004
groups and patients not prescribed antivirals. Moderate quality evidence suggests varicella was associated with increased stroke risk in children. Similar to findings for VZV, there may also be an increased stroke risk with recent CMV and HSV infection/reactivation, however the evidence was very low quality. Finally, there might be an increased stroke risk associated with recent CMV infection or reactivation based on studies carried out in immunosuppressed populations.

Two main pathophysiological mechanisms are proposed by which herpesviruses may increase stroke risk. Systemic infection with, or reactivation of, herpesviruses induces acute inflammation,[2] which may lead to endothelial dysfunction accompanied by disruption of atheromatous plaques and hypercoagulability.[68] This biological hypothesis is consistent with our finding that latent herpesvirus infection (that is, presence of viral DNA in host cells without producing infectious viral particles)[69] does not appear to increase stroke risk, as latent infection does not cause acute inflammation in host cells. Herpesviruses may also directly invade cerebral arteries, producing vasculopathy, leading to increased stroke risk;[70] this could explain why younger individuals, normally free from traditional vascular risk factors, were at higher risk of stroke following a recent infection/reactivation of VZV. VZV is the only virus with clear evidence of virus DNA in cerebral arteries; the stronger association between ophthalmic zoster and stroke also supports this hypothesis. CMV is associated with vasculopathy in immunocompromised patients, however the mechanism, and the risk in immunocompetent subjects are unclear.[71]

A larger effect of zoster on stroke risk was identified in people aged below 40 years. This has also been reported in a Korean-based cohort study. However, the absolute risk of stroke is low in younger ages, so a large relative effect may be small in absolute terms. This finding, together with the clinical efficacy of the currently available zoster vaccine becoming limited beyond 5–8 years,[72, 73] means vaccinating younger age groups may not be cost-effective.

This is the first study to systematically review the literature on all eight human herpesviruses as stroke risk factors and the results are broadly in-line with previous review assessing individual herpesviruses and cardiovascular disease (including stroke risk).[3–8, 10] Strengths included: following a pre-specified protocol; undertaking a comprehensive search; using articles published in any language; and carrying out a complete risk of bias assessment for each study and an assessment of the accumulated evidence using GRADE. Most studies ascertained stroke from pre-existing health care records (n = 33/41), potentially leading to similar stroke definitions across studies. A further strength of this review is that it not only included studies of clinically apparent herpesviruses reactivation, but subclinical reactivation. A further strength of this review is that it not only included studies of clinically apparent herpesviruses reactivation, but subclinical reactivation. It is possible that those with clinical manifestations of reactivated infection (e.g. zoster), or those who are immunosuppressed (as in some CMV studies), may have higher viral titres which plausibly could affect the risk of short term triggering of stroke.

However, limitations included having little data from low-income countries, which make up around 75% of stroke deaths worldwide[74] whether different populations have different susceptibilities to stroke following herpesvirus infections is unclear. Some meta-analyses combined very few studies, limiting the strength of our pooled results. Overall, the quality of evidence for CMV, EBV and HSV was low or very low.

The studies of VZV, particularly zoster, were well-powered to assess the association between VZV and stroke and rarely suffered from a high-risk of bias; however, subgroup analyses were underpowered, limiting confidence in the findings. Studies of the other herpesviruses (CMV, EBV and HSV) had more limitations; many had small sample sizes, inadequate adjustment for confounders In addition to this, the majority of non-VZV studies relied on laboratory, rather than clinical, identification of possible recent infection or reactivation. The
strength of the evidence for zoster and stroke risk lies in the studies all using clear clinical diagnoses of reactivated VZV, which was recorded prior to stroke. In contrast to VZV infection or reactivation which presents with clear clinical symptoms, other herpesviruses may reactivate without any clinical symptoms. Studies that measured markers of infection after stroke may suffer from reverse causality (all but one cases-control study—see Table 3) herpesvirus exposures were defined following stroke and stroke may trigger stress, leading to detection of herpesviruses reactivation after 24 hours (and blood samples were rarely taken immediately after stroke). This may explain why CMV IgG high (versus low) titre was associated with increased stroke risk in most case-control studies,[18] but not cohort studies (in which CMV antibodies were recorded prior to stroke). However, most case-control studies used hospital-based controls, so any stress associated with hospitalisation itself may affect cases and controls equally.

In terms of future research, high-powered cohort or SCCS studies assessing the association between recent infection with, and reactivation of, herpesviruses (aside from VZV), ideally collecting serology samples regularly during follow-up are needed. Furthermore, as zoster vaccination uptake increases, better-powered studies could confirm our findings that vaccination is not associated with a short-term increased stroke risk, and establish whether the vaccine reduces the long-term risk of stroke.

In terms of clinical practice, this review indicated that antivirals might attenuate stroke risk among zoster patients. As patients with more severe zoster are more likely to get antivirals, and also potentially more likely to have a stroke, this might have led to underestimation of their effect through confounding by indication. Antiviral drugs shorten zoster healing time and reduce pain severity[75] therefore these drugs may plausibly reduce stroke risk, by reducing inflammation. Antivirals for zoster are under-prescribed in UK primary care[76] and this review strengthens the argument for better adherence to prescribing guidelines.

Our review highlights that we have a good understanding of a short-term increased stroke risk following VZV infection and reactivation. It also suggests infection and reactivation of other herpesviruses may increase stroke risk, yet better evidence is required. Herpesviruses are common, therefore improved understanding of whether they increase the risk of stroke could provide additional strategies for stroke prevention.

Supporting information

S1 Appendix. Search terms.
(PDF)

S2 Appendix. Changes to the original protocol.
(DOCX)

S3 Appendix. Extracted data items.
(DOCX)

S4 Appendix. Grade assessment of quality: Down/ up-grading reasons.
(DOCX)

S5 Appendix. Reference list for selected studies.
(DOCX)

S1 Fig. Effect of clinically diagnosed ophthalmic zoster on stroke risk, by study design and length of follow-up.
(DOCX)
S2 Fig. Effect of zoster on stroke risk by length of follow-up and antiviral use during acute zoster. (DOCX)

S3 Fig. Effect of zoster on stroke risk by length of follow-up and age group. (DOCX)

S4 Fig. Effect of zoster on stroke risk by length of follow-up and gender. (DOCX)

S5 Fig. Effect of zoster on stroke risk by length of follow-up and type of stroke. (DOCX)

S6 Fig. Assessment of publication bias for CMV IgG seropositivity as a risk factor for stroke. (DOCX)

S1 Table. Exploring statistical heterogeneity identified in meta-analyses. (DOCX)

S2 Table. Risk of bias. (PDF)

Author Contributions
Conceptualization: Harriet J. Forbes, Elizabeth Williamson, Laura Benjamin, Judith Breuer, Martin M. Brown, Sinéad M. Langan, Caroline Minassian, Liam Smeeth, Sara L. Thomas, Charlotte Warren-Gash.

Data curation: Harriet J. Forbes.

Formal analysis: Harriet J. Forbes.

Methodology: Harriet J. Forbes, Elizabeth Williamson, Laura Benjamin, Judith Breuer, Martin M. Brown, Sinéad M. Langan, Caroline Minassian, Liam Smeeth, Sara L. Thomas, Charlotte Warren-Gash.

Supervision: Charlotte Warren-Gash.

Writing – original draft: Harriet J. Forbes.

Writing – review & editing: Harriet J. Forbes, Elizabeth Williamson, Laura Benjamin, Judith Breuer, Martin M. Brown, Sinéad M. Langan, Caroline Minassian, Liam Smeeth, Sara L. Thomas, Charlotte Warren-Gash.

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