Journal of the American Heart Association

ORIGINAL RESEARCH

Herpes Zoster and Long-Term Risk of Cardiovascular Disease

Sharon G. Curhan, MD, ScM; Kosuke Kawai, ScD; Barbara Yawn, MD, MSc; Kathryn M. Rexrode, MD, MPH; Eric B. Rimm, ScD; Gary C. Curhan, MD, ScD

BACKGROUND: We investigated the longitudinal association of herpes zoster (HZ), commonly known as "shingles," and long-term risk of stroke or coronary heart disease (CHD) among participants in 3 large US cohorts, the NHS (Nurses' Health Study), NHS II (Nurses' Health Study II), and HPFS (Health Professionals Follow-Up Study).

METHODS AND RESULTS: Participants were 79 658 women in the NHS (2000–2016), 93 932 women in the NHS II (2001–2017), and 31 440 men in the HPFS (2004–2016), without prior stroke or CHD. Information on HZ, stroke, and CHD was collected on biennial questionnaires and confirmed by medical record review. Cox proportional hazards regression models were used to estimate multivariable-adjusted hazard ratios for stroke and for CHD according to years since HZ compared with never HZ. During >2 million person-years of follow-up, 3603 incident stroke and 8620 incident CHD cases were documented. History of HZ was significantly and independently associated with higher long-term risk of stroke and CHD. In pooled analyses, compared with individuals with no history of HZ, the multivariable-adjusted hazard ratios (95% CIs) for stroke were 1.05 (0.88–1.25) among those with 1 to 4 years since HZ, 1.38 (1.10–1.74) for among those with 5 to 8 years since HZ, 1.28 (1.03–1.59) among those with for 9 to 12 years since HZ, and 1.19 (0.90–1.56) among those with ≥13 years since HZ. For CHD, the corresponding multivariable-adjusted hazard ratios (95% CIs) were 1.13 (1.01–1.27) for 1 to 4 years, 1.16 (1.02–1.32) for 5 to 8 years, 1.25 (1.07–1.46) for 9 to 12 years, and 1.00 (0.83–1.21) for ≥13 years.

CONCLUSIONS: HZ is associated with higher long-term risk of a major cardiovascular event. These findings suggest there are long-term implications of HZ and underscore the importance of prevention.

Key Words: coronary disease ■ follow-up studies ■ herpes zoster ■ myocardial infarction ■ public health ■ stroke

Almost all individuals aged ≥50 years in the United States have been infected with the varicella zoster virus (VZV) and therefore are at risk for the development of herpes zoster (HZ), or "shingles." HZ occurs in both immunocompetent and immunocompromised individuals, and the incidence increases with age, reduced cell-mediated immunity, or immunosuppressive therapy.[1–4] Approximately 1 in 3 individuals will develop HZ during their lifetime, and the projected burden is expected to increase because of the demographic shift to a more aged population, increasing numbers of immunocompromised individuals, and increasing use of corticosteroids and immunosuppressive medications.[5–9]

Several serious chronic complications of HZ can occur, most commonly postherpetic neuralgia[5] and HZ ophthalmicus,[10] but long-term longitudinal information on HZ and risk of other adverse health outcomes is scant. VZV vasculopathy can complicate HZ and is caused by productive viral infection of the vasculature.[11] A growing body of evidence suggests VZV-related vasculopathy plays a role in the pathogenesis of cardiovascular disorders, including stroke and coronary heart disease (CHD).[11–17] VZV has been detected in large and small blood vessels; and local inflammation, pathologic vascular remodeling, and chronic arterial changes can increase risk of subsequent vessel occlusion, ischemia,

Correspondence to: Sharon G. Curhan, MD, ScM, Channing Division of Network Medicine, Brigham and Women's Hospital, 181 Longwood Ave, Boston, MA 02115. Email: scurhan@bwh.harvard.edu

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.122.027451

For Sources of Funding and Disclosures, see page 10.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- This study demonstrates that herpes zoster is associated with an almost 30% higher long-term risk of a major cardiovascular event.
- The elevated risk of a major cardiovascular event may persist for ≥12 years following herpes zoster.
- The elevated risk may be greater among those with potentially immunocompromising conditions or immunosuppressive treatments.

What Are the Clinical Implications?

- These findings suggest there are long-term cardiovascular implications of herpes zoster.
- The availability of a safe and effective vaccine provides an opportunity to reduce the burden of herpes zoster and reduce the risk of subsequent cardiovascular complications.

Nonstandard Abbreviations and Acronyms

HPFS	Health Professionals Follow-Up Study
HZ	herpes zoster
MVHR	multivariable-adjusted hazard ratio
NHS	Nurses' Health Study
NHS II	Nurses' Health Study II

and a cardiovascular event.[18,19] HZ-related systemic inflammation, autoimmune responses, or hemodynamic changes could also lead to a cardiovascular event.[12,20,21] Epidemiologic studies of HZ and risk of stroke and myocardial infarction (MI) demonstrate an increased risk of stroke and MI close to the HZ event[13]; however, there is limited information on the long-term association between HZ and cardiovascular events, particularly in the US population. Therefore, we prospectively investigated whether HZ is independently associated with higher long-term risk of subsequent stroke or CHD in >200 000 women and men in 3 large ongoing US cohorts with long-term follow-up, the NHS (Nurses' Health Study), the NHS II (Nurses' Health Study II), and the HPFS (Health Professionals Follow-Up Study). We also evaluated whether the associations differed among adults with potentially immunocompromising conditions.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Population

The NHS was established in 1976 when 121 700 female registered nurses, aged 30 to 55 years, were enrolled by completing a baseline questionnaire. In 1989, the NHS II was established and enrolled 116 429 female registered nurses, aged 25 to 42 years. The HPFS began in 1986 and enrolled 51 529 male health professionals, aged 40 to 75 years. Participants completed questionnaires at baseline and every 2 years on a wide range of demographic, health, diet, and lifestyle factors, including detailed information on health history and medication use. The follow-up rates in all 3 cohorts exceed 90% of eligible person-time.[22,23] For the present analyses, baseline was defined in each cohort based on the year when information on date of HZ event was first available through most recent follow-up cycle (NHS: 2000–2016; NHS II: 2001–2017; and HPFS: 2004–2016). We excluded participants for whom the year of their HZ event was not provided and those with a history of stroke or CHD before study baseline. In total, 79 658 women in the NHS, 93 932 women in the NHS II, and 31 440 men in the HPFS were included in the analyses (total n=205 030). The Institutional Review Boards of Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health approved the study protocol. The return of the questionnaires was considered to imply informed consent.

Ascertainment of HZ ("Shingles")

Information on history of "shingles" (HZ) and the date it occurred was collected on the 2000, 2004, 2008, and 2012 NHS questionnaires, the 2001, 2005, 2013, and 2017 NHS II questionnaires, and the 2004, 2006, and 2008 HPFS questionnaires. Participants were asked about clinician-diagnosed "shingles" and the year of diagnosis. To confirm the validity of self-report in our participants, we mailed a supplemental questionnaire to 99 NHS women that asked for permission to obtain medical records relating to the diagnosis of shingles, which were reviewed by a physician investigator (G.C.C.). The diagnosis of HZ was confirmed in 97%, demonstrating that self-reported diagnosis of shingles (HZ) in this cohort of nurses is highly reliable. Notably, the participants in all 3 of our cohorts are health care professionals, and the reliability of health-related information collected from our participants has been demonstrated for a large number of health outcomes.[22] The primary exposure for this study was categorized according to time (in years) since the participant's HZ event. Those with no history of HZ were the referent group.

Ascertainment of Stroke

Stroke was classified as total stroke, encompassing ischemic stroke and hemorrhagic stroke, confirmed

by physician review of medical records according to criteria specified in the National Survey of Stroke,[24] requiring evidence of a sudden or rapid onset of neurologic deficit that persisted for >24 hours or until death. Participants who reported a nonfatal stroke on a biennial questionnaire were asked for permission to review their medical records. Deaths were reported by next of kin or postal authorities or determined by systematic searches of the National Death Index, and permission for medical records was sought. Our group previously reported that 98% of the deaths in each cohort are ascertained.[25,26] Cases of nonfatal stroke that were confirmed by letter/interview but lacked sufficient medical documentation were considered probable stroke. We considered both stroke confirmed by medical record review and probable stroke as cases in our analyses.

Ascertainment of CHD

CHD was defined as nonfatal or fatal MI, fatal CHD, or coronary revascularization procedure (coronary artery bypass graft or percutaneous transluminal coronary angioplasty). Participants who reported an incident event on a biennial questionnaire were asked for permission to obtain medical records, which were reviewed by physicians who were blinded to the exposure status and the specifc research question under study. Nonfatal MI was confirmed according to the World Health Organization criteria, which required typical symptoms plus diagnostic electrocardiographic findings or elevated enzyme levels.[27] Fatal CHD was identified by medical records or autopsy reports or if CHD was listed as the cause of death on the death certificate along with prior evidence of CHD. The study designated as probable fatal CHD deaths when no medical records surrounding the death were available, but CHD was the underlying cause on the death certificate or National Death Index search, or a family member provided supporting information on the diagnosis. Deaths were identified by report by the next of kin or the postal system or by searching the National Death Index using the methods described for stroke above.[25,26] We considered both CHD confirmed by medical record review and probable CHD as cases in our analyses, as well as self-reported revascularization procedures.[28,29]

Ascertainment of Covariates

In our multivariable-adjusted analyses, we adjusted for several factors that could potentially be related to HZ and stroke or CHD, including age, race, smoking history, body mass index, waist circumference, physical activity, medical conditions strongly related to cardiovascular risk (eg, diabetes, hypertension, and elevated cholesterol), use of aspirin, thiazide or loop diuretics, statins, and antihypertensive medication, diet quality (Alternative Healthy Eating Index 2010) score, menopausal status (women), postmenopausal hormone therapy use (women), oral contraceptive use (NHS II), family history of heart disease (defined as maternal history of MI before 65 years of age or paternal history of MI before 55 years of age), and self-reported medical conditions that potentially compromise immunity because of disease or treatment (eg, cancer other than nonmelanoma skin cancer, rheumatoid arthritis, Crohn's disease, ulcerative colitis, systemic lupus erythematosus, asthma, diabetes, chronic obstructive pulmonary disease, and oral steroid use). Covariate information, including age, weight, physical activity, smoking status, medication use, and physician diagnosis of chronic diseases, was assessed and updated every 2 to 4 years by biennial questionnaires administered throughout follow-up. Diet information was collected every 4 years using a validated semiquantitative food frequency questionnaire.[30–33] Among the women in the NHS and NHS II, information on menopausal status, postmenopausal hormone therapy, and oral contraceptive use (NHS II only) was also obtained. Self-reported information on height and weight was used to calculate body mass index. If covariate information was missing, we carried the information forward from up to 2 previous questionnaire cycles. The validity of covariate information collected in these cohorts has been demonstrated and is described in previous publications.[22,28,34,35]

Statistical Analysis

The short-term (up to 1 year) relation of HZ and cardiovascular disease (CVD) outcomes has been demonstrated previously.[13] This study focuses on long-term relations. The analyses were conducted using a prospective design, with information on HZ collected before the stroke or CHD event. We had information on the precise date of the CVD event, but the reporting of the date of HZ was less precise. To reduce the possibility that the CVD event preceded the episode of HZ, we censored participants who reported their HZ and had a stroke or CHD event within ±12 months. Thus, our study did not evaluate the short-term relation of HZ and CVD. Person-time was calculated for each participant based on the return date of the questionnaire to the diagnosis of stroke, CHD, death, or the end of follow-up, whichever occurred first. Time (in years) since the HZ event was calculated based on the duration of the time interval from the reported diagnosis of HZ until the beginning of each 2-year time period. HZ and covariate status were updated with each time period. We categorized time since HZ as never, 1 to 4 years since HZ, 5 to 8 years since HZ, 9 to 12 years since HZ, and ≥13 years since HZ. We used Cox proportional hazards models with time-varying covariates

and age as the underlying time scale, with stratification by calendar time (in 2-year intervals), to estimate hazard ratios (MVHRs [95% CIs]) and assess the association between time since HZ and the subsequent risk of stroke or CHD event. In each cohort, separate analyses were conducted for risk of stroke, risk of CHD, and risk of a composite CVD outcome (a composite of stroke or CHD, whichever came first). We also performed pooled analyses for each outcome with the use of fixed-effects meta-analysis with inverse-variance weighting. Heterogeneity was assessed with the I^2 statistic, and low to moderate heterogeneity was observed (I^2<40%). We conducted sensitivity analyses that restricted the CHD outcome to fatal and nonfatal MI and fatal CHD events and censored those who reported coronary revascularization procedures (coronary artery bypass graft or percutaneous transluminal coronary angioplasty) during follow-up. We also conducted stratified analyses among those with and without potentially immunocompromising health conditions, including cancer, rheumatoid arthritis, Crohn's disease, ulcerative colitis, systemic lupus erythematosus, asthma, diabetes, chronic obstructive pulmonary disease, or oral steroid use.

RESULTS

The total study sample included 79 658 women (mean [SD] age, 65.8 [7.1] years at baseline) in the NHS (2000–2021), 93 932 women (mean [SD] age, 46.2 [4.7] years) in the NHS II (2001–2021), and 31 440 men in the HPFS (mean [SD] age, 69.5 [8.6] years) (total n=205 030). The age-standardized characteristics of study participants according to history of HZ at a midpoint during follow-up in each of the cohorts are shown in Table 1 (NHS: 2008; NHS II: 2009; and HPFS: 2008). Participants with a history of HZ were slightly older than those with no history of HZ, and they were slightly more likely to have conditions that could potentially compromise immunity, including cancer, rheumatoid arthritis, Crohn's disease, ulcerative colitis, systemic lupus erythematosus, asthma, chronic obstructive pulmonary disease, and oral steroid use. There were no other appreciable differences.

HZ and Long-Term Risk of Incident Stroke

During a total of 2 471 975 person-years of follow-up, 2461 cases of incident stroke among women in the NHS, 537 incident strokes among women in the NHS II, and 605 incident strokes among men in the HPFS were documented and included in the analysis. History of HZ was significantly and independently associated with higher long-term risk of incident stroke (Table 2). In pooled multivariable analyses accounting for multiple potential confounding factors, compared with individuals with no history of HZ, the MVHRs (95% CIs) for incident stroke were 1.05 (0.88–1.25) among those with 1 to 4 years since HZ, 1.38 (1.10–1.74) among those with 5 to 8 years since HZ, 1.28 (1.03–1.59) among those with 9 to 12 years since HZ, and 1.19 (0.90–1.56) among those with ≥13 years since HZ. The findings for the individual cohorts are also shown in Table 2.

HZ and Long-Term Risk of Incident CHD

During a total of 2 350 066 person-years of follow-up, 4910 cases of incident CHD (nonfatal/fatal MI, fatal CHD, or coronary revascularization procedure) among women in the NHS, 1183 cases among women in the NHS II, and 2527 cases among men in the HPFS were documented and included in the analysis. History of HZ was significantly and independently associated with higher long-term risk of CHD (Table 3). In pooled multivariable analyses accounting for multiple potential confounding factors, compared with individuals with no history of HZ, the MVHRs (95% CIs) for incident CHD were 1.13 (1.01–1.27) among those with 1 to 4 years since HZ, 1.16 (1.02–1.32) among those with 5 to 8 years since HZ, 1.25 (1.07–1.46) among those with 9 to 12 years since HZ, and 1.00 (0.83–1.21) among those with ≥13 years since HZ. The findings for the individual cohorts are also shown in Table 3.

The results from sensitivity analyses that restricted the CHD outcome to fatal and nonfatal MI and fatal CHD and censored those who reported coronary revascularization procedures are shown in Table S1. In the female cohorts, the findings were similar. However, in men, compared with those with no history of HZ, we observed a statistically significant higher risk of CHD among those with a history of HZ using the more restrictive outcome definition; compared with men with no history of HZ, the MVHR (95% CI) for incident MI was 1.36 (1.02–1.81) among those with ≥5 years since HZ.

HZ and Long-Term Risk of Incident CVD

In analyses examining HZ and risk of a composite CVD outcome (stroke or CHD, whichever came first), previous HZ was significantly and independently associated with risk of a major cardiovascular event (Table 4). In the pooled multivariable analyses, compared with individuals with no history of HZ, the MVHRs (95% CIs) for a cardiovascular event were 1.11 (1.01–1.23) among those with 1 to 4 years since HZ, 1.26 (1.13–1.41) among those with 5 to 8 years since HZ, 1.27 (1.11–1.46) among those with 9 to 12 years since HZ, and 1.08 (0.92–1.28) among those with ≥13 years since HZ. Table 4 also shows the findings for the individual cohorts.

Additional Analyses

We performed stratified analyses that compared the association of HZ and long-term risk of stroke and CHD

Table 1. Age-Standardized Characteristics of Participants in the NHS, NHS II, and HPFS at Midpoint of Follow-Up

Characteristic	Time since HZ, y				
	Never HZ (n=48908)	1–4 (n=2455)	5–8 (n=2068)	9–12 (n=1302)	
NHS (2008)					
Age, y	72.4 (6.7)	73.0 (6.6)	73.9 (6.9)	73.9 (7.0)	
Race, White, %	94.1	95.1	95.1	94.6	
Body mass index, kg/m^2	26.5 (5.3)	26.2 (5.1)	26.5 (5.5)	26.6 (5.3)	
Waist circumference, cm*	86.4 (13.1)	86.4 (12.7)	86.7 (13.6)	86.8 (12.5)	
Physical activity, METS/wk	18.7 (24.0)	18.5 (23.1)	18.1 (21.5)	17.9 (21.8)	
Never smoker, %	46.2	46.5	45.0	45.5	
Past smoker, %	48.2	48.9	50.4	50.3	
Current smoker, %	5.6	4.6	4.6	4.3	
AHEI 2010 score	60.0 (12.2)	60.1 (11.2)	60.2 (12.0)	60.3 (12.1)	
History of cancer, %	21.8	25.1	23.9	27.0	
Rheumatoid arthritis, %	11.2	13.4	14.0	13.4	
Crohn's disease/ulcerative colitis, %	2.6	3.5	3.5	3.6	
Systemic lupus erythematosus, %	1.0	1.4	1.8	1.7	
Asthma, %	13.3	14.4	16.8	14.7	
COPD, %	7.5	7.9	9.3	9.8	
Oral steroid use, %	4.6	6.6	6.4	6.8	
Diabetes, %	12.5	11.3	12.2	12.5	
Hypertension, %	63.4	63.6	64.3	63.2	
Elevated cholesterol, %	72.2	73.3	73.9	75.5	
Aspirin use, ≥2 d/wk, %	61.5	59.9	59.5	58.6	
Antihypertensive use, %	51.5	52.9	53.8	54.7	
Statin use, %	48.3	48.7	49.5	49.6	
Thiazide or loop diuretic use, %	28.4	30.3	31.3	29.8	
Menopausal, yes, %	100	100	100	100	
Past hormone therapy use, %	62.0	65.4	63.9	61.7	
Current hormone therapy use, %	11.4	11.7	12.5	12.4	
Family history of heart disease, %	17.8	18.0	17.8	17.4	
	Never HZ (n=66127)	**1–4 (n=1310)**	**5–8 (n=1486)**	**9–12 (n=1076)**	**≥13 (n=992)**
NHS II (2009)					
Age, y	54.4 (4.6)	55.9 (4.4)	55.5 (4.5)	55.8 (4.6)	55.0 (4.8)
Race, White, %	94.5	95.3	94.6	96.2	95.6
Body mass index, kg/m^2	27.5 (6.4)	28.0 (6.4)	28.0 (6.5)	28.0 (6.7)	27.9 (6.3)
Waist circumference, cm*	87.2 (14.8)	88.2 (14.8)	88.4 (15.0)	88.1 (15.1)	87.9 (14.7)
Physical activity, METS/wk	24.2 (29.6)	23.0 (28.0)	20.9 (27.7)	22.1 (25.7)	21.1 (25.5)
Never smoker, %	65.7	64.7	64.3	65.0	62.7
Past smoker, %	28.4	30.6	29.8	27.8	29.5
Current smoker, %	5.7	4.7	5.6	6.9	7.6
AHEI 2010 score	62.6 (12.8)	62.6 (12.7)	62.3 (12.2)	62.6 (12.5)	61.3 (12.5)
History of cancer, %	9.5	13.4	10.0	11.3	11.1
Rheumatoid arthritis, %	3.6	4.3	6.6	3.7	6.5
Crohn's disease/ulcerative colitis, %	2.0	2.8	3.8	4.0	2.9
Systemic lupus erythematosus, %	0.8	1.4	1.8	1.7	2.4
Asthma, %	17.7	21.7	24.0	23.9	26.3

(*Continued*)

Table 1. Continued

	Never HZ (n=66 127)	1–4 (n=1310)	5–8 (n=1486)	9–12 (n=1076)	≥13 (n=992)
COPD, %	2.9	3.4	4.4	4.6	4.7
Oral steroid use, %	4.5	9.1	8.8	7.9	7.9
Diabetes, %	9.7	9.6	11.7	10.6	11.7
Hypertension, %	32.5	33.5	35.4	35.0	37.0
Elevated cholesterol, %	49.0	52.7	54.4	55.2	52.1
Aspirin use, ≥2 d/wk, %	36.7	36.6	40.2	41.1	39.4
Antihypertensive use, %	24.0	27.0	27.3	27.6	27.0
Current statin use, %	24.7	28.7	29.0	32.9	27.1
Thiazide or loop diuretic use, %	14.5	16.6	17.6	16.9	17.9
Menopausal, yes, %	67.7	70.5	71.5	70.3	70.3
Current hormone therapy use, %	14.0	14.4	16.0	15.9	16.3
Family history of heart disease, %	42.0	42.5	45.0	48.0	44.5
	Never HZ (n=17 574)	**1–4 (n=588)**	**5–8 (n=316)**	**9–12 (n=245)**	**≥13 (n=406)**
HPFS (2008)					
Age, y	71.1 (7.7)	73.2 (7.9)	73.6 (7.8)	73.3 (7.9)	74.0 (8.3)
Race, White, %	90.9	92.9	91.0	90.5	91.6
Body mass index, kg/m^2	26.1 (3.8)	26.1 (3.7)	25.7 (3.5)	25.6 (3.5)	25.8 (3.7)
Waist circumference, cm*	100.3 (10.9)	100.6 (10.9)	99.7 (9.6)	98.9 (10.2)	99.5 (10.4)
Physical activity, METS/wk	42.1 (35.5)	42.0 (35.1)	44.4 (38.1)	36.6 (30.2)	44.6 (34.0)
Never smoker, %	42.1	40.4	41.6	44.1	45.4
Past smoker, %	42.6	46.4	42.0	44.9	41.5
Current smoker, %	2.5	1.8	1.5	2.0	2.7
AHEI 2010 score	62.6 (11.9)	62.6 (11.3)	63.1 (11.7)	63.8 (12.7)	62.2 (11.5)
History of cancer, %	23.8	25.9	23.7	27.5	27.3
Rheumatoid arthritis, %	7.3	8.8	8.0	9.7	7.7
Crohn's disease/ulcerative colitis, %	2.1	2.2	2.9	4.0	3.0
Asthma, %	10.3	11.6	10.9	11.9	8.7
COPD, %	3.6	6.0	3.7	4.5	3.3
Oral steroid use, %	1.6	1.3	2.3	3.0	1.6
Diabetes, %	10.2	11.3	13.5	6.4	9.6
Hypertension, %	53.7	57.5	55.7	52.0	53.9
Elevated cholesterol, %	61.9	64.8	59.0	66.9	66.5
Aspirin use, ≥2 d/wk, %	66.2	63.6	65.0	74.7	65.8
Antihypertensive use, %	46.1	47.5	47.2	47.2	49.4
Current statin use, %	46.4	52.2	47.4	45.8	48.2
Thiazide or loop diuretic use, %	18.0	20.5	15.6	19.5	18.0
Family history of heart disease, %	14.0	14.3	11.2	14.0	16.1

Values are means (SDs) for continuous variables; percentages are given for categorical variables and are standardized to the age distribution of the study population. Values of polytomous variables may not sum to 100% because of rounding. AHEI indicates Alternative Healthy Eating Index; COPD, chronic obstructive pulmonary disease; HPFS, Health Professionals Follow-Up Study; HZ, herpes zoster; METS, metabolic equivalents; NHS, Nurses' Health Study; and NHS II, Nurses' Health Study II.

*Waist circumference assessed in 2000 (NHS), 2005 (NHS II), and 1996 (HPFS).

among those with and without potentially immunocompromising conditions. There was a suggestion that the magnitude of the elevated risk for stroke after ≥5 years since HZ was greater among women with potentially immunocompromising conditions; however, the *P* value for interaction was statistically significant only in the NHS II (*P*-interaction=0.05) (Table S2). In men, we did not observe that the risk varied by immune status

Table 2. HZ and Long-Term Risk of Stroke in the NHS, NHS II, and HPFS

Variable	Time since HZ, y				
	Never	1–4	5–8	9–12	≥13
NHS					
Cases/person-years	2181/879 821	95/35 929	99/25 406	61/15 037	25/6169
Age-adjusted HR (95% CI)	1.00 (Reference)	0.98 (0.80–1.21)	1.32 (1.08–1.62)	1.27 (0.98–1.64)	1.33 (0.89–1.99)
Multivariable-adjusted HR (95% CI)*	1.00 (Reference)	0.96 (0.79–1.19)	1.29 (1.05–1.58)	1.25 (0.96–1.62)	1.33 (0.89–1.99)
NHS II					
Cases/person-years	472/1 151 523	17/28 235	22/20 942	16/17 473	10/17 583
Age-adjusted HR (95% CI)	1.00 (Reference)	1.29 (0.79–2.10)	2.23 (1.45–3.42)	1.89 (1.15–3.13)	1.11 (0.59–2.09)
Multivariable-adjusted HR (95% CI)*	1.00 (Reference)	1.19 (0.73–1.94)	2.01 (1.31–3.10)	1.69 (1.03–2.79)	0.97 (0.52–1.82)
HPFS					
Cases/person-years	541/251 884	21/5577	15/5594	9/3974	19/6828
Age-adjusted HR (95% CI)	1.00 (Reference)	1.38 (0.89–2.13)	1.15 (0.69–1.93)	0.93 (0.48–1.79)	1.14 (0.72–1.81)
Multivariable-adjusted HR (95% CI)*	1.00 (Reference)	1.39 (0.90–2.16)	1.14 (0.68–1.91)	0.90 (0.47–1.75)	1.14 (0.72–1.81)
Pooled					
Total No. of cases	3194	133	136	86	54
Multivariable-adjusted HR (95% CI)*	1.00 (Reference)	1.05 (0.88–1.25)	1.38 (1.10–1.74)	1.28 (1.03–1.59)	1.19 (0.90–1.56)

HPFS indicates Health Professionals Follow-Up Study; HR, hazard ratio; HZ, herpes zoster; NHS, Nurses' Health Study; and NHS II, Nurses' Health Study II.
*Multivariable model adjusted for age, race, family history of heart disease (yes/no), smoking history, body mass index, waist circumference (≤70, 71–79, 80–88, and >88 cm), physical activity, diabetes, hypertension, elevated cholesterol, regular use (≥2 days/week) of aspirin, thiazide diuretics, loop diuretics, "statins," or other cholesterol-lowering drugs, calcium-channel blockers, β-blockers, angiotensin-converting enzyme inhibitors, or "other" antihypertensive drugs, Alternative Healthy Eating Index 2010 score, menopausal status (in NHS and NHS II), oral contraceptive use (in NHS II), postmenopausal hormonal therapy use (in NHS and NHS II), history of coronary heart disease, and a report of ≥1 of the following: cancer (other than nonmelanoma skin cancer), rheumatoid arthritis, Crohn's disease/ulcerative colitis (inflammatory bowel disease), systemic lupus erythematosus, asthma, diabetes, chronic obstructive pulmonary disease, or oral steroids/corticosteroid use.

(*P*-interaction=0.68), but the number of cases among men with a history of HZ was small. There was a suggestion that the magnitude of the risk for CHD after ≥5 years since HZ was greater among women with potentially immunocompromising conditions in the NHS II (*P*-interaction=0.03) (Table S3), but there was no evidence that the risk differed by immune status in the other 2 cohorts (*P*-interaction ≥0.2). Similarly, there was a suggestion that the magnitude of the risk for CVD (composite) after ≥5 years since HZ was greater among women with potentially immunocompromising conditions in the NHS II (*P*-interaction=0.02) but not in the other 2 cohorts (*P*-interaction ≥0.28) (Table S4).

In the male cohort, we did not have information on HZ that occurred after 2008; thus, men who had HZ after the return of the 2008 questionnaire were misclassified in the later time periods; this could have biased the results for the 1 to 4 and 5 to 8 years since HZ toward the null. When we conducted sensitivity analyses that ended follow-up in 2010, the findings were similar.

In additional analyses that included intakes of alcohol and specific dietary factors as individual covariates, the results were not materially different (data not shown). To consider the possibility that the true effect size may differ among the cohorts, we also conducted meta-analyses using the random effects approach. The findings were essentially unchanged.

DISCUSSION

In 3 large cohorts of women and men with up to 16 years of follow-up, HZ was associated with higher long-term risk of a major adverse cardiovascular event. The higher risk persisted for 12 years and possibly longer. There was a suggestion that the magnitude of the elevated risk may be greater among those with potentially immunocompromising conditions.

Several mechanisms could underlie the observed association of HZ and long-term risk of a major CVD event. VZV is the only human virus demonstrated to replicate in arteries and lead to vasculopathy,[11] and a growing body of evidence links VZV to vascular disease.[12,13] VZV has been detected in large and small blood vessels and has been implicated in the pathogenesis of several VZV-related cardiovascular disorders.[11,14–17] VZV vasculopathy develops from viral spread along nerve fibers, directly involves both intracranial and extracranial vasculature,[36,37] and has been confirmed by the presence of multinucleated giant cells, herpesvirus particles, VZV DNA, and VZV antigen in arteries.[18] Vascular changes associated with VZV vasculopathy, including disruption of the internal elastic lamina, intimal thickening, and reduced medial smooth muscle cells, can lead to alterations in arterial caliber and contractility,[19] and vessel wall damage, arterial dissection, or aneurysm could trigger an ischemic

Table 3. HZ and Long-Term Risk of CHD in the NHS, NHS II, and HPFS

Variable	Time since HZ, y				
	Never	1–4	5–8	9–12	≥13
NHS					
Cases/person-years	4419/825 984	229/33 176	147/23 345	89/13 832	26/5704
Age-adjusted HR (95% CI)	1.00 (Reference)	1.20 (1.05–1.37)	1.18 (1.00–1.39)	1.30 (1.05–1.61)	0.97 (0.66–1.44)
Multivariable-adjusted HR (95% CI)*	1.00 (Reference)	1.18 (1.04–1.35)	1.16 (1.00–1.37)	1.29 (1.04–1.59)	0.96 (0.65–1.42)
NHS II					
Cases/person-years	1072/1 145 251	34/28 003	31/20 797	27/17 244	19/17 272
Age-adjusted HR (95% CI)	1.00 (Reference)	1.11 (0.79–1.57)	1.35 (0.94–1.93)	1.48 (1.01–2.17)	1.04 (0.66–1.64)
Multivariable-adjusted HR (95% CI)*	1.00 (Reference)	1.04 (0.74–1.46)	1.23 (0.86–1.76)	1.30 (0.89–1.91)	0.90 (0.57–1.41)
HPFS					
Cases/person-years	2301/202 673	57/4320	59/4286	43/3059	67/5120
Age-adjusted HR (95% CI)	1.00 (Reference)	1.02 (0.78–1.32)	1.15 (0.89–1.49)	1.17 (0.86–1.58)	1.07 (0.84–1.37)
Multivariable-adjusted HR (95% CI)*	1.00 (Reference)	1.01 (0.78–1.32)	1.13 (0.87–1.47)	1.15 (0.85–1.56)	1.05 (0.82–1.34)
Pooled					
Total No. of cases	7792	320	237	159	112
Multivariable-adjusted HR (95% CI)*	1.00 (Reference)	1.13 (1.01–1.27)	1.16 (1.02–1.32)	1.25 (1.07–1.46)	1.00 (0.83–1.21)

CHD indicates coronary heart disease; HPFS, Health Professionals Follow-Up Study; HR, hazard ratio; HZ, herpes zoster; NHS, Nurses' Health Study; and NHS II, Nurses' Health Study II.

*Multivariable model adjusted for age, race, family history of heart disease (yes/no), smoking history, body mass index, waist circumference (≤70, 71–79, 80–88, and >88 cm), physical activity, diabetes, hypertension, elevated cholesterol, regular use (≥2 days/week) of aspirin, thiazide diuretics, loop diuretics, "statins," or other cholesterol-lowering drugs, calcium-channel blockers, β-blockers, angiotensin-converting enzyme inhibitors, or "other" antihypertensive drugs, Alternative Healthy Eating Index 2010 score, menopausal status (in NHS and NHS II), oral contraceptive use (in NHS II), postmenopausal hormonal therapy use (in NHS and NHS II), history of coronary heart disease, and a report of ≥1 of the following: cancer (other than nonmelanoma skin cancer), rheumatoid arthritis, Crohn's disease/ulcerative colitis (inflammatory bowel disease), systemic lupus erythematosus, asthma, diabetes, chronic obstructive pulmonary disease, or oral steroids/corticosteroid use.

or hemorrhagic CVD event.[11,20,36,38] Notably, VZV vasculopathy may be chronic and protracted,[39] and thus vascular changes could elevate risk of a CVD event years after an episode of HZ.[11] Furthermore, systemic inflammation, autoimmune reactions, or hemodynamic perturbations related to HZ may also contribute to risk of a CVD event, irrespective of the site of dermatomal involvement.[12,20,21] VZV-related inflammation may also lead to endothelial dysfunction accompanied by disruption of atheromatous plaques and hypercoagulability.[37]

Our study expands on prior studies by demonstrating the association between HZ and long-term risk of stroke and CHD. Elevated risk of a major cardiovascular event within days or weeks after HZ has been reported previously.[20,38,40] A comprehensive review by Wu et al summarized the findings from epidemiologic studies of HZ and risk of stroke and MI.[13] Among the 15 more recent epidemiologic studies from Asia, Europe, and the United States, there was an increased incidence of stroke or MI in individuals with a recent history of HZ; the risk appeared to be highest closest to the HZ event and decreased over time.[13] A meta-analysis found higher odds of a major CVD event within 3 months of HZ onset, but whether the elevated risk persisted for more than a year was unclear.[41] Notably, data on long-term risk were limited and findings were inconsistent across studies. Most studies had limited information on health and lifestyle factors related to risk of stroke or CHD, and most were based on retrospective reviews of insurance claims or other administrative databases using diagnostic codes; thus, they captured only those individuals who sought medical attention for their HZ.[41] Our study included 3 prospective cohorts with long duration of follow-up, controlled for multiple potential confounding cardiovascular risk factors, and captured individuals whose HZ may or may not have come to medical attention, thereby providing new insight into the long-term association of HZ and CVD.

We observed suggestive evidence of a difference in the association of HZ and risk of a major event among those with potentially immunocompromising conditions or using immunosuppressive medication in the NHS II, but not in the NHS or the HPFS. The magnitude of the elevated risk for stroke or CHD after ≥5 years since HZ was greater among NHS II women with potentially immunocompromising conditions or medication use, but there was no statistically significant evidence that the risk differed in the 2 other cohorts, so this could be a chance finding. Plausibly, reduced T-cell immunity or other host factors could increase the risk of viral reactivation and development of vasculopathy,[42] but further study of whether the association between HZ and long-term CVD risk is modified by factors that may influence immune status is merited.

Table 4. HZ and Long-Term Risk of CVD (Composite) in the NHS, NHS II, and HPFS

Variable	Time since HZ, y				
	Never	1–4	5–8	9–12	≥13
NHS					
Cases/person-years	5960/800 811	287/32 100	219/22 404	134/13 153	47/5379
Age-adjusted HR (95% CI)	1.00 (Reference)	1.12 (0.99–1.26)	1.24 (1.08–1.42)	1.32 (1.11–1.57)	1.17 (0.88–1.57)
Multivariable-adjusted HR (95% CI)*	1.00 (Reference)	1.10 (0.97–1.23)	1.23 (1.07–1.41)	1.31 (1.10–1.56)	1.17 (0.87–1.57)
NHS II					
Cases/person-years	1497/1 131 343	52/27 538	53/20 424	40/16 888	26/16 840
Age-adjusted HR (95% CI)	1.00 (Reference)	1.25 (0.94–1.64)	1.68 (1.27–2.21)	1.57 (1.14–2.15)	1.01 (0.68–1.49)
Multivariable-adjusted HR (95% CI)*	1.00 (Reference)	1.16 (0.88–1.53)	1.53 (1.16–2.01)	1.39 (1.01–1.90)	0.88 (0.59–1.29)
HPFS					
Cases/person-years	2512/198 791	70/4212	67/4154	44/2980	76/4988
Age-adjusted HR (95% CI)	1.00 (Reference)	1.14 (0.90–1.45)	1.21 (0.95–1.54)	1.10 (0.82–1.48)	1.14 (0.90–1.43)
Multivariable-adjusted HR (95% CI)*	1.00 (Reference)	1.13 (0.89–1.44)	1.19 (0.93–1.52)	1.08 (0.80–1.46)	1.11 (0.88–1.40)
Pooled					
Total No. of cases	9969	409	339	218	149
Multivariable-adjusted HR (95% CI)*	1.00 (Reference)	1.11 (1.01–1.23)	1.26 (1.13–1.41)	1.27 (1.11–1.46)	1.08 (0.92–1.28)

CVD is a composite of total stroke and coronary heart disease (CHD), defined as nonfatal or fatal myocardial infarction, fatal CHD, or coronary revascularization procedure. CVD indicates cardiovascular disease; HPFS, Health Professionals Follow-Up Study; HR, hazard ratio; HZ, herpes zoster; NHS, Nurses' Health Study; and NHS II, Nurses' Health Study II.

*Multivariable model adjusted for age, race, family history of heart disease (yes/no), smoking history, body mass index, waist circumference (≤70, 71–79, 80–88, and >88 cm), physical activity, diabetes, hypertension, elevated cholesterol, regular use (≥2 days/week) of aspirin, thiazide diuretics, loop diuretics, "statins," or other cholesterol-lowering drugs, calcium-channel blockers, β-blockers, angiotensin-converting enzyme inhibitors, or "other" antihypertensive drugs, Alternative Healthy Eating Index 2010 score, menopausal status (in NHS and NHS II), oral contraceptive use (in NHS II), postmenopausal hormonal therapy use (in NHS and NHS II), and a report of ≥1 of the following: cancer (other than nonmelanoma skin cancer), rheumatoid arthritis, Crohn's disease/ulcerative colitis (inflammatory bowel disease), systemic lupus erythematosus, asthma, diabetes, chronic obstructive pulmonary disease, or oral steroids/corticosteroid use.

Strengths of this study include the longitudinal design, multiple independent cohorts with large sample sizes, long follow-up with high retention rate, and repeated assessments of exposure and covariate information. Our study also has limitations. Information on HZ was self-reported; however, it was shown to be highly reliable in the NHS. We did not have information on dermatomal involvement, treatment course, or complications, such as HZ opthalmicus; thus, future investigations that evaluate these factors could be informative. We did not have information on the date of HZ at younger ages; therefore, we were not able to examine whether the associations differed among younger individuals. We did not have information on VZV vaccination; however, we do not expect that vaccination status substantially influenced our findings. Notably, the live attenuated VZV vaccine was first recommended for individuals aged ≥60 years by the Centers for Disease Control and Prevention in 2008, a midpoint during follow-up in our study. In 2011, expanded recommendations included individuals aged ≥50 years, but uptake was low; in 2012, uptake was 3.9% of the eligible subjects in one study[43] and 20% in another.[44] The more recent nonlive, recombinant subunit adjuvanted vaccine was not available until after the end of follow-up in our study. As uptake of the VZV vaccine increases, future studies that evaluate whether vaccination status influences the relation of HZ and risk of CVD would be informative. Although we had information on specific stroke subtypes, there was not sufficient power to evaluate the associations of HZ with long-term risk of ischemic versus hemorrhagic stroke. We controlled for several repeated measurements of diet, health, and lifestyle factors, but we cannot rule out the possibility of residual and unmeasured confounding. The generalizability of these findings may be limited because participants were predominantly non-Hispanic White individuals.

CONCLUSIONS

A history of HZ is associated with higher long-term risk of a major cardiovascular event. These findings suggest there are long-term implications of HZ and underscore the importance of public health efforts for prevention.

ARTICLE INFORMATION

Received July 13, 2022; accepted October 18, 2022.

Affiliations

Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, MA (S.G.C., E.B.R., G.C.C.); Harvard Medical School, Boston, MA (S.G.C., K.K., K.M.R., E.B.R., G.C.C.); Institutional

Centers for Clinical and Translational Research, Boston Children's Hospital, Boston, MA (K.K.); Department of Research, Olmsted Medical Center, Rochester, MA (B.Y.); Division of Women's Health, Brigham and Women's Hospital, Boston, MA (K.M.R.); Department of Nutrition (E.B.R.); and Department of Epidemiology (E.B.R., G.C.C.), Harvard T.H. Chan School of Public Health, Boston, MA; and Renal Division, Department of Medicine, Brigham and Women's Hospital, Boston, MA (G.C.C.).

Acknowledgments

We would like to thank Elaine Coughlan-Gifford for her programming help on this project. All authors had access to the data and participated in the preparation of the manuscript.

Sources of Funding

This study was supported by GlaxoSmithKline Biologicals SA Supported Studies Programme Protocol 216148. The NHS (Nurses' Health Study), NHS II (Nurses' Health Study II), and HPFS (Health Professionals Follow-Up Study) cohorts are supported by the following National Institutes of Health grants: R01 HL35464, UM1 CA186107, R01 HL034594, R01 HL088521, U01 CA176726, and U01 CA167552.

Disclosures

Dr S. G. Curhan received an investigator-initiated grant from GlaxoSmithKline Biologicals SA to examine the long-term outcomes potentially associated with herpes zoster. Dr Yawn reports consulting with GlaxoSmithKline related to herpes zoster epidemiology and receipt of an investigator-initiated grant related to herpes zoster and chronic obstructive pulmonary disease. Dr Kawai was employed by Boston Children's Hospital during the study and is now an employee of and a shareholder in Moderna, Inc. Dr G. C. Curhan is an employee of OM1, has equity in Allena Pahrmaceuticals, and receives royalties from UpToDate for being an author and Section Editor. The remaining authors have no disclosures to report.

Supplemental Material

Tables S1–S4

REFERENCES

1. Cohen JI. Clinical practice: herpes zoster. *N Engl J Med.* 2013;369:255–263. doi: 10.1056/NEJMcp1302674
2. Yawn BP, Saddier P, Wollan PC, St Sauver JL, Kurland MJ, Sy LS. A population-based study of the incidence and complication rates of herpes zoster before zoster vaccine introduction. *Mayo Clin Proc.* 2007;82:1341–1349. doi: 10.4065/82.11.1341
3. Yawn BP, Wollan P, St Sauver J. Comparing shingles incidence and complication rates from medical record review and administrative database estimates: how close are they? *Am J Epidemiol.* 2011;174:1054–1061. doi: 10.1093/aje/kwr206
4. Smeeth L, Thomas SL, Hall AJ, Hubbard R, Farrington P, Vallance P. Risk of myocardial infarction and stroke after acute infection or vaccination. *N Engl J Med.* 2004;351:2611–2618. doi: 10.1056/NEJMoa041747
5. Schmader K. Herpes zoster in older adults. *Clin Infect Dis.* 2001;32:1481–1486. doi: 10.1086/320169
6. Edmunds WJ, Brisson M, Rose JD. The epidemiology of herpes zoster and potential cost-effectiveness of vaccination in England and Wales. *Vaccine.* 2001;19:3076–3090. doi: 10.1016/S0264-410X(01)00044-5
7. Drolet M, Oxman MN, Levin MJ, Schmader KE, Johnson RW, Patrick D, Mansi JA, Brisson M. Vaccination against herpes zoster in developed countries: state of the evidence. *Hum Vaccin Immunother.* 2013;9:1177–1184. doi: 10.4161/hv.23491
8. Brisson M, Edmunds WJ, Law B, Gay NJ, Walld R, Brownell M, Roos LL, De Serres G. Epidemiology of varicella zoster virus infection in Canada and the United Kingdom. *Epidemiol Infect.* 2001;127:305–314. doi: 10.1017/S0950268801005921
9. Johnson RW, Wasner G, Saddier P, Baron R. Herpes zoster and postherpetic neuralgia: optimizing management in the elderly patient. *Drugs Aging.* 2008;25:991–1006. doi: 10.2165/0002512-200825120-00002
10. Yawn BP, Wollan PC, St Sauver JL, Butterfield LC. Herpes zoster eye complications: rates and trends. *Mayo Clin Proc.* 2013;88:562–570. doi: 10.1016/j.mayocp.2013.03.014
11. Gilden D, Cohrs RJ, Mahalingam R, Nagel MA. Varicella zoster virus vasculopathies: diverse clinical manifestations, laboratory features, pathogenesis, and treatment. *Lancet Neurol.* 2009;8:731–740. doi: 10.1016/S1474-4422(09)70134-6
12. Breuer J, Pacou M, Gauthier A, Brown MM. Herpes zoster as a risk factor for stroke and TIA: a retrospective cohort study in the UK. *Neurology.* 2014;82:206–212. doi: 10.1212/WNL.0000000000000038
13. Wu PH, Chuang YS, Lin YT. Does herpes zoster increase the risk of stroke and myocardial infarction? A comprehensive review. *J Clin Med.* 2019;8:547.
14. Gilden DH, Kleinschmidt-DeMasters BK, LaGuardia JJ, Mahalingam R, Cohrs RJ. Neurologic complications of the reactivation of varicella-zoster virus. *N Engl J Med.* 2000;342:635–645. doi: 10.1056/NEJM200003023420906
15. Nagel MA, Cohrs RJ, Mahalingam R, Wellish MC, Forghani B, Schiller A, Safdieh JE, Kamenkovich E, Ostrow LW, Levy M, et al. The varicella zoster virus vasculopathies: clinical, CSF, imaging, and virologic features. *Neurology.* 2008;70:853–860. doi: 10.1212/01.wnl.0000304747.38502.e8
16. Eidelberg D, Sotrel A, Horoupian DS, Neumann PE, Pumarola-Sune T, Price RW. Thrombotic cerebral vasculopathy associated with herpes zoster. *Ann Neurol.* 1986;19:7–14. doi: 10.1002/ana.410190103
17. Amlie-Lefond C, Kleinschmidt-DeMasters BK, Mahalingam R, Davis LE, Gilden DH. The vasculopathy of varicella-zoster virus encephalitis. *Ann Neurol.* 1995;37:784–790. doi: 10.1002/ana.410370612
18. Gilden DH, Kleinschmidt-DeMasters BK, Wellish M, Hedley-Whyte ET, Rentier B, Mahalingam R. Varicella zoster virus, a cause of waxing and waning vasculitis: the New England Journal of Medicine case 5-1995 revisited. *Neurology.* 1996;47:1441–1446. doi: 10.1212/WNL.47.6.1441
19. Nagel MA, Traktinskiy I, Azarkh Y, Kleinschmidt-DeMasters B, Hedley-Whyte T, Russman A, VanEgmond EM, Stenmark K, Frid M, Mahalingam R, et al. Varicella zoster virus vasculopathy: analysis of virus-infected arteries. *Neurology.* 2011;77:364–370. doi: 10.1212/WNL.0b013e3182267bfa
20. Minassian C, Thomas SL, Smeeth L, Douglas I, Brauer R, Langan SM. Acute cardiovascular events after herpes zoster: a self-controlled case series analysis in vaccinated and unvaccinated older residents of the United States. *PLoS Med.* 2015;12:e1001919. doi: 10.1371/journal.pmed.1001919
21. Josephson C, Nuss R, Jacobson L, Hacker MR, Murphy J, Weinberg A, Manco-Johnson MJ. The varicella-autoantibody syndrome. *Pediatr Res.* 2001;50:345–352. doi: 10.1203/00006450-200109000-00009
22. Bao Y, Bertoia ML, Lenart EB, Stampfer MJ, Willett WC, Speizer FE, Chavarro JE. Origin, methods, and evolution of the three Nurses' health studies. *Am J Public Health.* 2016;106:1573–1581. doi: 10.2105/AJPH.2016.303338
23. Hu FB, Leitzmann MF, Stampfer MJ, Colditz GA, Willett WC, Rimm EB. Physical activity and television watching in relation to risk for type 2 diabetes mellitus in men. *Arch Intern Med.* 2001;161:1542–1548. doi: 10.1001/archinte.161.12.1542
24. Walker AE, Robins M, Weinfeld FD. The National Survey of stroke. Clinical findings. *Stroke.* 1981;12:I13–I44.
25. Rich-Edwards JW, Corsano KA, Stampfer MJ. Test of the national death index and equifax nationwide death search. *Am J Epidemiol.* 1994;140:1016–1019. doi: 10.1093/oxfordjournals.aje.a117191
26. Stampfer MJ, Willett WC, Speizer FE, Dysert DC, Lipnick R, Rosner B, Hennekens CH. Test of the national death index. *Am J Epidemiol.* 1984;119:837–839. doi: 10.1093/oxfordjournals.aje.a113804
27. Mendis S, Thygesen K, Kuulasmaa K, Giampaoli S, Mahonen M, Ngu Blackett K, Lisheng L; Writing group on behalf of the participating experts of the WHOcfroWHOdomi. World Health Organization definition of myocardial infarction: 2008–09 revision. *Int J Epidemiol.* 2011;40:139–146. doi: 10.1093/ije/dyq165
28. Colditz GA, Martin P, Stampfer MJ, Willett WC, Sampson L, Rosner B, Hennekens CH, Speizer FE. Validation of questionnaire information on risk factors and disease outcomes in a prospective cohort study of women. *Am J Epidemiol.* 1986;123:894–900. doi: 10.1093/oxfordjournals.aje.a114319
29. Shan Z, Li Y, Baden MY, Bhupathiraju SN, Wang DD, Sun Q, Rexrode KM, Rimm EB, Qi L, Willett WC, et al. Association between healthy eating patterns and risk of cardiovascular disease. *JAMA Intern Med.* 2020;180:1090–1100. doi: 10.1001/jamainternmed.2020.2176
30. Willett WC, Sampson L, Stampfer MJ, Rosner B, Bain C, Witschi J, Hennekens CH, Speizer FE. Reproducibility and validity of a semiquantitative food frequency questionnaire. *Am J Epidemiol.* 1985;122:51–65. doi: 10.1093/oxfordjournals.aje.a114086

31. Salvini S, Hunter DJ, Sampson L, Stampfer MJ, Colditz GA, Rosner B, Willett WC. Food-based validation of a dietary questionnaire: the effects of week-to-week variation in food consumption. *Int J Epidemiol.* 1989;18:858–867. doi: 10.1093/ije/18.4.858
32. Yuan C, Spiegelman D, Rimm EB, Rosner BA, Stampfer MJ, Barnett JB, Chavarro JE, Rood JC, Harnack LJ, Sampson LK, et al. Relative validity of nutrient intakes assessed by questionnaire, 24-hour recalls, and diet records as compared with urinary recovery and plasma concentration biomarkers: findings for women. *Am J Epidemiol.* 2018;187:1051–1063. doi: 10.1093/aje/kwx328
33. Al-Shaar L, Yuan C, Rosner B, Dean SB, Ivey KL, Clowry CM, Sampson LA, Barnett JB, Rood J, Harnack LJ, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire in men assessed by multiple methods. *Am J Epidemiol.* 2021;190:1122–1132. doi: 10.1093/aje/kwaa280
34. Rimm EB, Stampfer MJ, Colditz GA, Chute CG, Litin LB, Willett WC. Validity of self-reported waist and hip circumferences in men and women. *Epidemiology.* 1990;1:466–473. doi: 10.1097/00001648-199011000-00009
35. Wolf AM, Hunter DJ, Colditz GA, Manson JE, Stampfer MJ, Corsano KA, Rosner B, Kriska A, Willett WC. Reproducibility and validity of a self-administered physical activity questionnaire. *Int J Epidemiol.* 1994;23:991–999. doi: 10.1093/ije/23.5.991
36. Nagel MA, Bubak AN. Varicella zoster virus vasculopathy. *J Infect Dis.* 2018;218:S107–S112. doi: 10.1093/infdis/jiy425
37. Nagel MA, Jones D, Wyborny A. Varicella zoster virus vasculopathy: the expanding clinical spectrum and pathogenesis. *J Neuroimmunol.* 2017;308:112–117. doi: 10.1016/j.jneuroim.2017.03.014
38. Schink T, Behr S, Thone K, Bricout H, Garbe E. Risk of stroke after herpes zoster - evidence from a German self-controlled case-series study. *PLoS One.* 2016;11:e0166554. doi: 10.1371/journal.pone.0166554
39. Silver B, Nagel MA, Mahalingam R, Cohrs R, Schmid DS, Gilden D. Varicella zoster virus vasculopathy: a treatable form of rapidly progressive multi-infarct dementia after 2 years' duration. *J Neurol Sci.* 2012;323:245–247. doi: 10.1016/j.jns.2012.07.059
40. Langan SM, Minassian C, Smeeth L, Thomas SL. Risk of stroke following herpes zoster: a self-controlled case-series study. *Clin Infect Dis.* 2014;58:1497–1503. doi: 10.1093/cid/ciu098
41. Erskine N, Tran H, Levin L, Ulbricht C, Fingeroth J, Kiefe C, Goldberg RJ, Singh S. A systematic review and meta-analysis on herpes zoster and the risk of cardiac and cerebrovascular events. *PLoS One.* 2017;12:e0181565. doi: 10.1371/journal.pone.0181565
42. Gershon AA, Gershon MD, Breuer J, Levin MJ, Oaklander AL, Griffiths PD. Advances in the understanding of the pathogenesis and epidemiology of herpes zoster. *J Clin Virol.* 2010;48:S2–S7. doi: 10.1016/S1386-6532(10)70002-0
43. Langan SM, Smeeth L, Margolis DJ, Thomas SL. Herpes zoster vaccine effectiveness against incident herpes zoster and post-herpetic neuralgia in an older US population: a cohort study. *PLoS Med.* 2013;10:e1001420. doi: 10.1371/journal.pmed.1001420
44. Williams WW, Lu PJ, O'Halloran A, Bridges CB, Pilishvili T, Hales CM, Markowitz LE; Centers for Disease Control and Prevention. Noninfluenza vaccination coverage among adults - United States, 2012. *MMWR Morb Mortal Wkly Rep.* 2014;63:95–102.

SUPPLEMENTAL MATERIAL

Table S1. Sensitivity Analysis: Herpes Zoster and Long-term Risk of Myocardial Infarction* and Total CHD† in the Nurses' Health Study, the Nurses' Health Study II, and the Health Professionals Follow-up Study.

CHD Outcome	Years Since Herpes Zoster		
	Never	1-4 years	≥5 years
NHS			
MI*			
Cases/person-years	886/820954	47/32917	66/42604
Multivariable-adjusted‡ HR (95% CI)	1.00 (ref)	1.22 (0.91, 1.64)	1.12 (0.87, 1.45)
Total CHD†			
Cases/person-years	4419/825984	229/ 33176	262/42880
Multivariable-adjusted‡ HR (95% CI)	1.00 (ref)	1.18 (1.04, 1.35)	1.18 (1.04, 1.34)
NHS2			
MI*			
Cases/person-years	238/1144385	8/27973	14/55238
Multivariable-adjusted‡ HR (95% CI)	1.00 (ref)	1.14 (0.56, 2.32)	0.97 (0.56, 1.67)
Total CHD†			
Cases/person-years	1072/1145251	34/28003	77/55314
Multivariable-adjusted‡ HR (95% CI)	1.00 (ref)	1.04 (0.74, 1.46)	1.15 (0.91, 1.45)
HPFS			
MI*			
Cases/person-years	460/200811	14/4275	53/12350
Multivariable-adjusted‡ HR (95% CI)	1.00 (ref)	1.20 (0.70, 2.06)	1.36 (1.02, 1.81)
Total CHD†			
Cases/person-years	2301/202673	57/4320	169/12464
Multivariable-adjusted‡ HR (95% CI)	1.00 (ref)	1.01 (0.78, 1.32)	1.10 (0.94, 1.29)

*MI (myocardial infarction) outcome includes fatal and non-fatal myocardial infarction and fatal coronary heart disease. Individuals with coronary revascularization procedure (coronary artery bypass graft or percutaneous transluminal coronary angioplasty) were censored were censored during follow-up.
†Total CHD includes fatal and non-fatal myocardial infarction, fatal coronary heart disease and coronary revascularization procedure (coronary artery bypass graft or percutaneous transluminal coronary angioplasty).
‡ Multivariable model adjusted for age, race, family history of heart disease (yes/no), smoking history, body mass index (BMI), waist circumference (≤70, 71-79,80-88, >88 cm), physical activity, diabetes mellitus, hypertension, elevated cholesterol, regular use (2+ days/week) of aspirin, thiazide diuretics, loop diuretics, "Statins" or other cholesterol-lowering drugs, calcium-channel blockers, beta blockers, angiotensin-converting-enzyme inhibitors, or "other" anti-hypertensive drugs, AHEI-2010 Score, menopausal status (in NHS and NHS II), oral contraceptive use (NHS II), post-menopausal hormonal therapy use (in NHS and NHS II), history of coronary heart disease (CHD), and a report of one or more of the following: cancer (other than non-melanoma skin cancer), rheumatoid arthritis (RA), Crohn's disease/ulcerative colitis (inflammatory bowel disease), systemic lupus erythematosus (SLE), asthma, diabetes, chronic obstructive pulmonary disease (COPD), oral steroids/corticosteroid use.
NHS: Nurses' Health Study NHS II: Nurses' Health Study II HPFS: Health Professionals Follow-up Study
HR: hazard ratio CI: confidence interval

NHS: Nurses' Health Study
NHS II: Nurses' Health Study II
HPFS: Health Professionals Follow-up Study
HR: Hazard Ratio
CI: Confidence Interval

Table S2. Herpes Zoster and Long-term Risk of Stroke in the Nurses' Health Study, the Nurses' Health Study II, and the Health Professionals Follow-up Study, Stratified by Potentially Immunocompromising Conditions[*].

Stroke	Years Since Herpes Zoster		
Immunocompromising Conditions (Yes/No)	**Never**	**1-4 years**	**≥5 years**
NHS			
Yes			
Cases/Person-years	1076/362841	51/17146	114/24395
MVHR[†] (95% CI)	1.00 (ref)	0.95 (0.72, 1.26)	1.37 (1.12, 1.67)
No			
Cases/Person-years	1105/ 516980	44/ 18783	71 / 22216
MVHR[†] (95% CI)	1.00 (ref)	0.98 (0.73, 1.33)	1.17 (0.91, 1.49)
p-interaction	0.45		
NHS II			
Yes			
Cases/Person-years	192/824368	8/17644	15/32998
MVHR[†] (95% CI)	1.00 (ref)	1.28 (0.66, 2.51)	2.09 (1.44, 3.04)
No			
Cases/Person-years	280/824544	12/17724	25/32861
MVHR[†] (95% CI)	1.00 (ref)	1.11 (0.55, 2.25)	1.03 (0.61, 1.73)
p-interaction	0.05		
HPFS			
Yes			
Cases/Person-years	260/98370	8/2456	21/7724
MVHR[†] (95% CI)	1.00 (ref)	0.99 (0.49, 2.01)	0.97 (0.62, 1.52)
No			
Cases/Person-years	281/153515	13/3121	22/8672
MVHR[†] (95% CI)	1.00 (ref)	1.79 (1.02, 3.16)	1.19 (0.77, 1.85)
p-interaction	0.68		

[*]Potentially immunocompromising conditions and treatments included a report of one or more of the following: cancer (other than non-melanoma skin cancer), rheumatoid arthritis (RA), Crohn's disease/ulcerative colitis (inflammatory bowel disease), systemic lupus erythematosus (SLE), asthma, diabetes, chronic obstructive pulmonary disease (COPD), oral steroids/corticosteroid use.

[†]Multivariable model adjusted for age, race, family history of heart disease (yes/no), smoking history, body mass index (BMI), waist circumference (≤70, 71-79,80-88, >88 cm), physical activity, diabetes mellitus, hypertension, elevated cholesterol, regular use (2+ days/week) of aspirin, thiazide diuretics, loop diuretics, "Statins" or other cholesterol-lowering drugs, calcium-channel blockers, beta blockers, angiotensin-converting-enzyme inhibitors, or "other" anti-hypertensive drugs, AHEI-2010 Score, menopausal status (in NHS and NHS II), oral contraceptive use (NHS II), post-menopausal hormonal therapy use (in NHS and NHS II), and history of coronary heart disease.

NHS: Nurses' Health Study
NHS II: Nurses' Health Study II
HPFS: Health Professionals Follow-up Study
MVHR**:** Multivariable-adjusted Hazard Ratio
CI: Confidence Interval

Table S3. Herpes Zoster and Long-term Risk of CHD in the Nurses' Health Study, the Nurses' Health Study II, and the Health Professionals Follow-up Study, Stratified by Potentially Immunocompromising Conditions.[*]

CHD	Years Since Herpes Zoster		
Immunocompromising Conditions (Yes/No)	**Never**	**1-4 years**	**≥5 years**
NHS			
Yes			
Cases/Person-years	2146/335777	113/15636	147/22073
MVHR[†] (95% CI)	1.00 (ref)	1.08 (0.89, 1.31)	1.13 (0.95, 1.34)
No			
Cases/Person-years	2273/ 490208	116/17540	115/20807
MVHR[†] (95% CI)	1.00 (ref)	1.29 (1.07, 1.55)	1.24 (1.02, 1.50)
p-interaction	0.20		
NHS II			
Yes			
Cases/Person-years	431/328608	15/10545	52/22782
MVHR[†] (95% CI)	1.00 (ref)	0.94 (0.56, 1.58)	1.48 (1.11, 1.98)
No			
Cases/Person-years	641/816644	19/17458	25/32532
MVHR[†] (95% CI)	1.00 (ref)	1.15 (0.73, 1.82)	0.79 (0.53, 1.18)
p-interaction	0.03		
HPFS			
Yes			
Cases/Person-years	988/75766	23/1822	83/5777
MVHR[†] (95% CI)	1.00 (ref)	0.86 (0.56, 1.30)	1.07 (0.85, 1.34)
No			
Cases/Person-years	1313/126907	34/2498	86/6687
MVHR[†] (95% CI)	1.00 (ref)	1.14 (0.81, 1.61)	1.13 (0.90, 1.40)
p-interaction	0.49		

[*]Potentially immunocompromising conditions and treatments included a report of one or more of the following: cancer (other than non-melanoma skin cancer), rheumatoid arthritis (RA), Crohn's disease/ulcerative colitis (inflammatory bowel disease), systemic lupus erythematosus (SLE), asthma, diabetes, chronic obstructive pulmonary disease (COPD), oral steroids/corticosteroid use.

[†]Multivariable model adjusted for age, race, family history of heart disease (yes/no), smoking history, body mass index (BMI), waist circumference (≤70, 71-79,80-88, >88 cm), physical activity, diabetes mellitus, hypertension, elevated cholesterol, regular use (2+ days/week) of aspirin, thiazide diuretics, loop diuretics, "Statins" or other cholesterol-lowering drugs, calcium-channel blockers, beta blockers, angiotensin-converting-enzyme inhibitors, or "other" anti-hypertensive drugs, AHEI-2010 Score, menopausal status (in NHS and NHS II), oral contraceptive use (NHS II), post-menopausal hormonal therapy use (in NHS and NHS II), and history of stroke.

CHD: Coronary heart disease, defined as fatal or non-fatal myocardial infarction, fatal CHD, or coronary revascularization procedure (coronary artery bypass graft or percutaneous transluminal coronary angioplasty)
NHS: Nurses' Health Study
NHS II: Nurses' Health Study II
HPFS: Health Professionals Follow-up Study
MVHR**:** Multivariable-adjusted Hazard Ratio
CI: Confidence Interval

Table S4. Herpes Zoster and Long-term Risk of Cardiovascular Disease (Composite)[*] in the Nurses' Health Study, the Nurses' Health Study II, and the Health Professionals Follow-up Study, Stratified by Potentially Immunocompromising Conditions[†]

CVD[*]	Years Since Herpes Zoster		
Immunocompromising Conditions (Yes/No)	**Never**	**1-4 years**	**≥5 years**
NHS			
Yes			
Cases/Person-years	2866/323356	146/15095	227/20983
MVHR[‡] (95% CI)	1.00 (ref)	1.04 (0.88, 1.23)	1.23 (1.07, 1.41)
No			
Cases/Person-years	3094/477455	141/17005	173/19952
MVHR[‡] (95% CI)	1.00 (ref)	1.16 (0.98, 1.37)	1.27 (1.09, 1.49)
p-interaction	0.41		
NHS II			
Yes			
Cases/Person-years	607/322700	24/10313	78/22164
MVHR[‡] (95% CI)	1.00 (ref)	1.09 (0.72, 1.64)	1.60 (1.26, 2.03)
No			
Cases/Person-years	890/808644	28/17225	41/31988
MVHR[‡] (95% CI)	1.00 (ref)	1.24 (0.85, 1.82)	0.93 (0.68, 1.28)
p-interaction	0.02		
HPFS			
Yes			
Cases/Person-years	1080/73955	28/1766	90/5626
MVHR[‡] (95% CI)	1.00 (ref)	0.94 (0.64, 1.37)	1.07 (0.86, 1.33)
No			
Cases/Person-years	1432/124836	42/2446	97/6496
MVHR[‡] (95% CI)	1.00 (ref)	1.30 (0.95, 1.77)	1.17 (0.95, 1.45)
p-interaction	0.28		

[*]Cardiovascular disease (CVD) is a composite of total stroke and coronary heart disease (CHD), defined as non-fatal or fatal myocardial infarction, fatal CHD, or coronary revascularization procedure
[†]Potentially immunocompromising conditions and treatments included a report of one or more of the following: cancer (other than non-melanoma skin cancer), rheumatoid arthritis (RA), Crohn's disease/ulcerative colitis (inflammatory bowel disease), systemic lupus erythematosus (SLE), asthma, diabetes, chronic obstructive pulmonary disease (COPD), oral steroids/corticosteroid use.
[‡]Multivariable model adjusted for age, race, family history of heart disease (yes/no), smoking history, body mass index (BMI), waist circumference (≤70, 71-79,80-88, >88 cm), physical activity, diabetes mellitus, hypertension, elevated cholesterol, regular use (2+ days/week) of aspirin, thiazide diuretics, loop diuretics, "Statins" or other cholesterol-lowering drugs, calcium-channel blockers, beta blockers, angiotensin-converting-enzyme inhibitors, or "other" anti-hypertensive drugs, AHEI-2010 Score, menopausal status (in NHS and NHS II), oral contraceptive use (NHS II), post-menopausal hormonal therapy use (in NHS and NHS II), and history of stroke.

CHD: Coronary heart disease, defined as fatal/non-fatal myocardial infarction, fatal CHD, or coronary revascularization procedure (coronary artery bypass graft, percutaneous transluminal coronary angioplasty)
NHS: Nurses' Health Study
NHS II: Nurses' Health Study II
HPFS: Health Professionals Follow-up Study
MVHR**:** Multivariable-adjusted Hazard Ratio
CI: Confidence Interval