Herpes zoster and long-term risk of subjective cognitive decline

Tian-Shin Yeh[1,2,3,4,5,6*], Gary C. Curhan[4,7,8], Barbara P. Yawn[9], Walter C. Willett[3] and Sharon G. Curhan[4,7]

Abstract

Background Herpes zoster (HZ), commonly known as "shingles," may contribute to cognitive decline through mechanisms such as neuroinflammation or direct neuronal injury. However, evidence on the longitudinal association between HZ and cognitive decline is conflicting and whether the risk differs by APOE ε4-carrier status has not been studied; prospective cohort studies on the association between HZ vaccination and cognitive decline are also lacking.

Methods We included 149,327 participants from three large cohorts—the Nurses' Health Study (NHS), NHSII, and Health Professionals Follow-Up Study (HPFS)—to prospectively examine the association between HZ and subsequent subjective cognitive decline (SCD). Poisson regression was used to estimate the multivariable-adjusted relative risk (MVRR) of a 3-unit increment in SCD score according to years since HZ compared with participants with no history of HZ.

Results Compared with individuals with no history of HZ, the MVRR (95% CI) of a 3-unit increment in SCD score was significantly and independently higher among individuals with a history of HZ, but the duration of time since HZ when the elevated risk of SCD was statistically significant differed among the cohorts. In NHS, HZ was associated with higher long-term risk of SCD; compared with individuals with no history of HZ, the MVRR (95% CI) of a 3-unit increment in SCD score was 1.14 (1.01, 1.32) for ≥ 13 years since HZ. In NHS II, HZ was associated with higher risk of SCD in both the short-term [MVRR 1.34 (1.18, 1.53) for 1–4 years] and long-term [MVRR 1.20 (1.08, 1.34) for ≥ 13 years since HZ]. In HPFS, an elevated risk of SCD was suggested across all time points. Among the subset of participants with information on APOE ε4, there was a suggestion that the association differed by APOE ε4 carrier status, but the results were not consistent between women and men. Among the subset of women with information on HZ vaccination, there was a suggestion that the long-term risk of SCD may be greater among women who were not vaccinated against HZ.

Conclusions Data from three large independent cohorts of women and men showed that HZ was associated with higher long-term risk of SCD, and the risk may differ by APOE ε4-carrier status.

Keywords Herpes zoster, Shingles, Subjective cognitive decline, Vaccination, Immunocompromise, APOE ε4, Prospective cohort study

*Correspondence:
Tian-Shin Yeh
tianshin.yeh@gmail.com

Full list of author information is available at the end of the article

Introduction

In the era of rapid population aging, age-related cognitive decline poses a significant global burden and warrants further investigation to better understand its risk factors and potential interventions [1, 2]. There is growing evidence that herpesviruses may influence the risk of cognitive decline and dementia [3]. Herpes zoster (HZ), commonly known as "shingles," is caused by reactivation of the neurotrophic varicella-zoster virus (VZV). VZV is a double-stranded DNA virus that causes varicella (chickenpox) and then establishes lifelong latency in ganglionic neurons in >95% of Americans [4]. VZV reactivation from ganglia and spread to one or more corresponding dermatomes results in HZ, and affects one in three individuals during their lifetime [5]. HZ may potentially contribute to dementia risk through neuroinflammation, cerebral vasculopathy, or direct neuronal damage [6], but current evidence regarding the relationship between HZ and subsequent risk of cognitive decline is conflicting. Some studies found that HZ was associated with a higher risk of Alzheimer's disease (AD) [7–9], but some found no association [10, 11], whereas others indicated that HZ was associated with an unexpected lower risk of dementia [12, 13], and suggested that VZV vaccination may not reduce dementia risk [13]. Although protective associations between HZ vaccination and dementia have been reported [14], existing literature primarily consists of retrospective studies or case-control studies [10, 15], and high-quality prospective cohort studies are needed to deepen the understanding of this topic. Carriage of another herpes virus, herpes simplex virus (HSV1/2), was associated with greater decline in episodic memory function, and a significant interaction between APOE ε4-carrier status and HSV1/2 for episodic memory decline was demonstrated (p for interaction<0.001) [16]. In addition, among individuals who were APOE ε4 carriers, reactivation of herpes simplex virus type 1 (HSV-1) was associated with higher risk of Alzheimer's disease (AD), but no association was found between HSV-1 and AD among those who were APOE ε4 non-carriers [17]. However, to our knowledge, whether the association of HZ and SCD differs by APOE ε4-carrier status remains unexplored.

Subjective cognitive decline (SCD) is a measure of early changes in cognition that captures an individual's self-perceived experience of cognitive decline even before evidence of cognitive impairment may be apparent on standardized neuropsychological tests [18, 19]. Among individuals with SCD, approximately 7% will progress to dementia and 21% to mild cognitive impairment (MCI) [20]. The risk of dementia is 2.17 times for patients with SCD compared to those without [21]. Given the high risk of progression from SCD to MCI and dementia, understanding the association between HZ and subsequent SCD may be crucial for the early detection and prevention of cognitive decline in individuals at risk, and may provide important insight into the relation of VZV and dementia.

Therefore, we prospectively examined the long-term association between HZ and the risk of SCD using data from three large well-characterized cohorts of women and men—the Nurses' Health Study (NHS), NHSII, and Health Professionals Follow-Up Study. We also examined whether the association of HZ and SCD varied by *APOE* e4 carrier status, HZ vaccination status, or immunocompromised status.

Methods

Study population

The Nurses' Health Study (NHS) started in 1976 when 121,700 female registered nurses aged 30–55 years were recruited and completed a baseline questionnaire. The NHSII began in 1989 with 116,429 female registered nurses aged 25–42 years. The Health Professionals Follow-Up Study (HPFS) began in 1986 when 51,529 male US health professionals aged 40–75 years were enrolled. Follow-up questionnaires have been sent to the participants every two years to obtain detailed information on medical history, newly diagnosed diseases, and potential risk factors; the >30-year follow-up exceeds 90% of eligible person-time. For the current study, the baseline was defined as the year when information on the time of HZ occurrence was first available. Participants whose HZ date was unavailable were excluded from the analyses.

Herpes zoster (HZ) ascertainment

Information on HZ, including the date of occurrence, was collected in the years 2000, 2004, 2008, and 2012 for the NHS; in 2001, 2005, 2013, and 2017 for the NHSII; and in 2004, 2006, and 2008 for the HPFS. To ascertain the validity of the self-reported HZ information, we conducted a validation study comparing reports of HZ by questionnaire with medical records. We requested permission to obtain medical records related to the HZ event from a randomly selected subset of NHS and NHSII participants who reported a history of HZ on the 2021 biennial questionnaire. In the subset of participants for whom medical records were obtained, a diagnosis of herpes zoster was confirmed in 230/231 (99.6%), indicating high reliability of self-reported HZ. For the primary analysis, we categorized the exposure according to years since the participant's HZ event; participants without HZ history served as the reference group.

Assessment of subjective cognitive decline (SCD)

SCD was assessed in 2012 and 2014 for the NHS, 2008 and 2012 for the HPFS, and 2017 for NHSII. For the HPFS, the SCD scores were based on the following 6 yes/

no questions: [1] "Do you have more trouble than usual remembering a short list of items, such as a shopping list?"; [2] "Do you have more trouble than usual remembering recent events?"; [3] "Do you have trouble remembering things from one second to the next?"; [4] "Do you have any difficulty in understanding things or following spoken instructions?"; [5] "Do you have trouble finding your way around familiar streets?" and [6] "Do you have more trouble than usual following a group conversation or a plot in a TV program due to your memory?" For the NHS and NHSII, the SCD scores had one additional question: "Have you recently experienced any change in your ability to remember things?" [22] One point was given for each yes, all questions had equal value. For participants who had two SCD assessments, we averaged the two scores to reduce random error; for participants who only had one SCD assessment, the single score was used for analysis.

A previous study demonstrated strong associations between SCD and both concurrent objective cognitive function [22] and subsequent cognitive decline [22], which supports the validity of SCD. SCD was also strongly associated with *APOE* ε4 genotype in both the NHS and HPFS, which further strengthens its validity [23]. In addition, SCD may be a stronger predictor of longitudinal cognitive decline in those with higher educational attainment [24]. A number of risk factors for dementia, including hypertension, hyperlipidemia, type 2 diabetes, cardiovascular disease, and heavy smoking, were shown to be related to higher risk of SCD [22].

Covariates

In all three cohorts, data on covariates of interest were collected prospectively on the baseline and follow-up questionnaires. In our multivariable-adjusted models, we adjusted for the following covariates: age, race (white, black, other), family history of dementia, smoking (pack-years), alcohol consumption (g per day), body mass index (BMI) (kilograms/meters^2), physical activity (metabolic equivalents, MET-hours/week), diabetes, hypertension, elevated cholesterol, stroke, coronary heart disease (CHD) (non-fatal/fatal myocardial infarction, fatal CHD, or coronary revascularization procedure), dietary quality (based on the Alternative Healthy Eating Index [AHEI]-2010 Score), depression (defined as anti-depressant use or self-reported depression), and self-reported medical conditions that potentially compromise immunity because of disease or treatment (e.g., cancer other than nonmelanoma skin cancer, rheumatoid arthritis (RA), Crohn's disease (CD), ulcerative colitis (UC), systemic lupus erythematosus (SLE), asthma, diabetes, chronic obstructive pulmonary disease (COPD), and oral steroid use). For women, information on menopausal status and menopausal hormone therapy use, census tract income (<\$50,000, \$50,000–74,999, or >=\$75,000/y), and husband's education (high school or lower education, college, graduate school) were available. HZ vaccination status was available for NHSII. For men, we further adjusted for profession (dentist, pharmacist, optometrist, osteopath, podiatrist, veterinarian).

Statistical analysis

Time since HZ was categorized as never, 1–4 years since HZ, 5–8 years since HZ, 9–12 years since HZ, and ≥13 years since HZ. We calculated the age-standardized characteristics of participants according to years since the HZ event. Consistent with methods previously used in these cohorts, Poisson regression was used to investigate the association between HZ and SCD because of the nature and distribution of the SCD scores [25]. The SCD score is a discrete count that follows a distribution with a non-negative integer range (0–6 for HPFS and 0–7 for NHS and NHSII) [22]. Due to the right-skewed SCD scores, Poisson regression is a useful statistical method specifically designed for analyzing count data with this property that provides a straightforward interpretation of the relative risk per unit increase in y (SCD). Because three or more positive SCD questions suggest poor cognitive function [22, 26], relative risks (RRs) and 95% confidence intervals (CIs) for a 3-unit increment in SCD were calculated [27]. Due to the non-linear relation between age and SCD, both a linear term and a quadratic term for age were included in all models [28]. For data on covariates for which we did not have information due to the information was missing or reported as 'unknown', a missing/unknown category was included in the multivariate model using an indicator variable for each covariate. The percentage of missing/unknown values for the individual covariates was very low (0 to <5%), except for husband's education in the female cohorts and family history of dementia in NHS.

We conducted stratified analyses among those with and without health conditions or treatments that could potentially compromise immunity. In addition, we conducted analyses stratified according to APOE ε4 allele carrier status (yes/no) among participants whose APOE ε4 was measured or imputed in previous genome-wide association studies [29]. For the NHSII, we further adjusted for HZ vaccination status and we also performed analyses stratified by HZ vaccination status. SAS software, version 9.4 (SAS Institute Inc., Cary, NC) was used for all analyses.

Results

There were a total of 149,327 participants, including 56,142 women in the NHS (mean [SD] age 64.6 [6.7] years at baseline), 66,966 women (47.2 [5.3] years) in the NHSII, and 26,219 men (68.5 [8.0] years) in the HPFS.

The age-standardized characteristics of study participants according to years since HZ are shown in Table 1. Men with a history of HZ were slightly older than those with no history of HZ. In all three cohorts, participants with a history of HZ were more likely to have depression or other conditions that could potentially compromise immunity, including cancer, RA, CD, UC, SLE, asthma, COPD, and oral steroid use. The frequencies of participants with SCD≥3 according to time since HZ in the three cohorts are shown in Supplementary Fig. 1.

A history of HZ was significantly and independently associated with higher long-term risk of SCD in both women and men (Table 2; Fig. 1). The duration of time since the episode of HZ when a significant elevation in risk of SCD was observed differed between the 3 cohorts. In NHS, HZ was associated with higher long-term risk of SCD; compared with individuals with no history of HZ, the MVRR (95% CI) of a 3-unit increment in SCD score was 1.14 (1.01, 1.32) for ≥13 years since HZ. In NHS II, HZ was associated with higher risk of SCD in both the short-term [MVRR 1.34 (1.18, 1.53) for 1–4 years] and long-term [MVRR 1.20 (1.08, 1.34) for ≥13 years since HZ]. In HPFS, an elevated risk of SCD was suggested across all time points. In multivariable-adjusted models that did and did not include stroke and CHD, the results did not materially differ (Supplementary Table 1). For all three cohorts, the point estimates were most attenuated by the adjustment for depression, compared with all other covariates (Supplementary Table 1).

In stratified analyses, we did not observe consistent differences in the association between HZ and long-term risk of SCD among those with and without immunocompromising conditions (p-for-interaction=0.8 in NHS, 0.06 in NHS II, and >0.99 in HPFS) (Table 3). In analyses stratified by *APOE* ε4 allele carrier status, there was a suggestion that the risk of SCD was significantly elevated among women who were non-carriers of the *APOE* ε4 allele, but the p-for-interaction was not significant in either female cohort (p-interaction=0.98 in NHS and 0.08 in NHS II) (Table 4). In contrast, HZ was significantly associated with an elevated risk of SCD among men who were carriers of the *APOE* ε4 allele and the p-for-interaction was significant (p-interaction=0.02). In a stratified analysis by HZ vaccination status in NHSII, there was a suggestion that the long-term risk of SCD may be greater among women who were not vaccinated against HZ (p-interaction=0.09, NHSII) (Supplementary Table 2).

Discussion

In three large independent cohorts, HZ was associated with an approximately 20% higher long-term risk of SCD. Compared to non-carriers, the risk of SCD was significantly higher among APOE ε4 carriers in men but not in women. The association between HZ and risk of SCD did not significantly differ among individuals with and without potentially immunocompromising conditions. Based on data in the NHSII, the risk of SCD following HZ may potentially be greater among those who have not been vaccinated against HZ.

To our knowledge, this is the first large study to examine HZ and the risk of early subjective cognitive decline, which may be the earliest manifestation of age-related cognitive decline and may be especially sensitive among individuals who received higher education [24]. Given the long preclinical phase of dementia [30], identifying a potential association between HZ and early cognitive decline is important as it may provide insight into the complex and possible causal relationship between viral infections and cognitive health, as well as offer opportunities for early risk reduction and improved public health strategies. Several previous studies evaluated HZ and the risk of dementia, but results have been mixed [8–10, 13, 31]. Two studies from a large health insurance database in Taiwan [7, 8] and South Korea [9] found that HZ was associated with a higher risk of Alzheimer's disease (AD), whereas studies from the United Kingdom found no association [10, 11]. Two recent studies reported that HZ was associated with a decreased risk of dementia [12, 13], and suggested that VZV vaccination for the elderly will unlikely reduce the risk of dementia [13]. The inconsistent findings from previous studies may have arisen from the different study population and different data sources utilized, as most studies were based on retrospective reviews of insurance claims or other administrative databases using diagnostic codes, thus capturing only those individuals who sought medical attention for their HZ; misclassification of HZ using this study design has been demonstrated [32–35]. Further, the limited availability of information on health and lifestyle factors related to the risk of cognitive decline or dementia reduced the ability to adjust for these factors. The prospective cohort study design and long-term follow-up of our research enable the establishment of the temporal relationship between HZ and subsequent cognitive decline. In addition, our dataset contained detailed information on potential confounding factors, and accounting for these variables reduced the impact of confounding.

Despite some previous studies that suggested vaccination will unlikely decrease the risk of dementia, other studies have reported the possible association between HZ vaccination and a lower risk of dementia [10, 14, 15, 36]. One retrospective study using data from the Veterans Health Administration and private sector medical claims data (MarketScan) found that HZ vaccination was associated with a 31–35% lower risk of dementia among adults aged≥65 [15]. Another retrospective study in Wales also found a 28% lower risk of dementia among

Table 1 Age-standardized baseline characteristics of women in the Nurses' Health Study I (NHS I), NHS II, and men in the Health Professionals Follow-Up Study (HPFS)

	Years since herpes zoster (HZ)				
NHS I	Never (*n*=48,158)	1–4 years (*n*=1701)	5–8 years (*n*=2509)	9–12 years (*n*=2193)	13+years (*n*=1581)
Age, years	64.5 (6.7)	64.6 (6.6)	65.0 (6.6)	65.4 (6.7)	65.6 (6.9)
Race, white, %	97.3	97.6	98.0	98.4	98.2
Body mass index, kg/m²	26.9 (5.3)	27.0 (5.4)	26.6 (5.0)	27.1 (5.4)	26.9 (5.2)
Physical activity, METs/week	18.7 (22.5)	17.9 (21.8)	18.3 (21.3)	17.7 (20.2)	18.3 (21.4)
Pack-years of smoking					
-Never smoker, %	46.5	48.0	44.2	45.7	44.7
-1-24 pack-years, %	10.7	10.4	12.3	10.0	11.4
-25-44 pack-years, %	22.8	21.1	22.6	23.7	24.3
-45 + pack-years, %	18.4	18.5	19.4	19.4	18.1
AHEI-2010 score	52.1 (9.3)	51.7 (9.4)	52.0 (9.1)	52.4 (9.0)	52.0 (9.3)
Alcohol intake, g/day	5.5 (8.3)	5.3 (7.8)	5.9 (8.6)	5.2 (7.7)	5.5 (8.2)
History of cancer, %	13.5	14.8	15.4	14.2	16.0
Rheumatoid arthritis, %	8.2	9.7	9.5	11.0	9.7
Crohn's disease or Ulcerative colitis, %	1.9	1.6	2.7	2.2	2.2
Systemic lupus erythematosus, %	0.9	1.0	1.3	1.2	1.5
Asthma, %	10.5	11.4	11.1	12.3	10.8
COPD, %	3.8	4.4	4.1	4.4	5.1
Oral steroids use, %	1.9	2.2	2.5	2.6	3.8
Hypertension, %	46.2	48.2	46.9	47.4	45.4
Diabetes, %	7.5	7.4	6.5	7.4	7.7
Elevated cholesterol, %	58.6	60.1	61.3	61.3	61.8
Post-menopausal, %	98.5	98.8	98.4	99.1	98.7
Post-menopausal hormonal therapy use, ever, %	72.2	74.3	74.9	75.1	73.3
Depression, %	14.0	15.9	14.4	16.3	15.2
Family history of dementia, %	19.8	20.1	21.0	20.6	20.4
Husband's education					
-<=high school, %	32.1	33.3	31.8	33.5	32.0
-college graduate, %	22.6	21.5	25.0	24.6	24.3
-graduate school, %	19.7	20.2	20.8	20.5	21.3
Census track income					
-<$50K, %	27.2	28.3	26.8	27.4	25.5
-$50K to <$75K, %	45.1	43.7	44.7	46.8	46.7
-$75K+, %	27.6	27.9	28.5	25.8	27.4
NHS II	Never (*n*=57,585)	1–4 years (*n*=2056)	5–8 years (*n*=2595)	9–12 years (*n*=1363)	13+years (*n*=3367)
Age, years	47.1 (5.4)	47.3 (5.3)	47.7 (4.9)	47.9 (4.7)	47.8 (5.0)
Race, white, %	94.7	95.0	95.1	95.9	95.6
Body mass index, kg/m²	26.7 (6.2)	26.9 (6.3)	26.9 (6.4)	27.3 (6.3)	27.3 (6.5)
Physical activity, METs/week	21.5 (27.2)	20.7 (26.9)	20.0 (25.5)	21.2 (34.2)	19.8 (26.2)
Pack-years of smoking					
-Never smoker, %	66.1	65.9	64.6	64.4	64.3
-1-24 pack-years, %	28.2	27.8	29.6	29.0	28.8
-25-44 pack-years, %	4.5	5.2	4.6	5.2	5.5
-45 + pack-years, %	0.5	0.4	0.6	0.8	0.8
AHEI-2010 score	50.0 (9.9)	50.0 (10.0)	50.1 (10.0)	50.2 (9.8)	49.8 (9.8)
Alcohol intake, g/day	3.7 (6.0)	3.6 (6.0)	3.7 (6.2)	3.5 (6.0)	3.5 (5.6)
History of cancer, %	5.1	5.1	5.3	5.1	5.9
Rheumatoid arthritis, %	2.3	3.5	3.0	2.6	3.9
Crohn's disease or Ulcerative colitis, %	1.2	1.3	1.5	1.5	2.4
Systemic lupus erythematosus, %	0.4	1.0	0.5	1.0	1.1
Asthma, %	12.4	13.7	14.9	14.2	16.9

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Table 1 (continued)

	Years since herpes zoster (HZ)				
COPD, %	1.2	1.7	1.2	1.4	2.0
Oral steroids use, %	1.3	2.4	1.7	2.1	2.9
Hypertension, %	18.2	20.4	20.3	19.6	21.2
Diabetes, %	6.6	7.6	6.5	6.6	7.4
Elevated cholesterol, %	31.9	33.8	33.9	33.8	37.0
Post-menopausal, %	26.4	27.9	27.5	28.5	31.0
Post-menopausal hormonal therapy use, ever, %	0.2	0.2	0.1	0.2	0.2
Depression, %	20.0	21.9	21.2	24.2	24.8
Family history of dementia, %					
Husband's education					
-<=high school, %	15.1	15.8	16.2	16.4	16.5
-college graduate, %	43.5	43.9	42.2	42.6	42.4
-graduate school, %	27.0	26.0	28.0	26.3	25.1
Census track income					
-<$50k, %	11.7	11.7	12.9	12.1	13.7
-$50k to <$75k, %	20.7	20.9	21.1	22.9	23.0
-$75k+, %	43.6	44.3	45.7	44.7	42.9
HPFS	Never ($n=23,722$)	1–4 years ($n=830$)	5–8 years ($n=518$)	9–12 years ($n=437$)	13+years ($n=712$)
Age, years	68.3 (8.0)	70.2 (8.0)	70.3 (7.8)	70.5 (8.0)	70.8 (8.2)
Race, white, %	91.6	93.3	92.5	91.9	92.2
Body mass index, kg/m²	26.2 (3.7)	26.0 (3.3)	26.1 (3.5)	25.6 (3.3)	25.9 (3.7)
Physical activity, METs/week	41.2 (35.0)	40.9 (33.9)	43.5 (37.2)	40.3 (34.9)	43.8 (35.4)
Pack-years of smoking					
- never smoker, %	49.7	48.1	47.9	50.2	46.3
- 1–4 pack-years, %	28.7	30.6	28.9	27.7	30.9
- 5–24 pack-years, %	11.2	10.8	13.7	10.4	10.4
- 25+pack-years, %	5.1	5.5	4.1	5.8	6.1
AHEI-2010 score	55.1 (10.0)	54.9 (10.0)	55.2 (10.2)	56.3 (9.9)	55.4 (10.3)
Alcohol intake, g/day	11.2 (12.9)	10.6 (12.4)	11.5 (12.8)	10.7 (12.2)	11.1 (12.7)
History of cancer, %	19.2	20.2	19.3	19.0	20.5
Rheumatoid arthritis, %	6.7	8.9	7.0	6.9	7.6
Crohn's disease or Ulcerative colitis, %	2.1	2.0	2.7	3.7	1.8
Asthma, %	9.2	11.4	9.5	10.6	8.3
COPD, %	3.0	4.2	5.0	3.1	3.6
Oral steroids use, %	1.2	2.2	1.6	2.2	1.9
Hypertension, %	49.6	52.9	52.3	52.1	49.0
Diabetes, %	9.1	10.5	10.5	10.4	9.7
Elevated cholesterol, %	60.2	62.3	61.8	60.7	65.6
Depression, %	19.9	21.4	23.8	23.3	26.5
Family history of dementia, %	21.0	22.4	17.9	27.4	19.7
Profession					
- Dentist, %	57.9	54.2	56.7	54.3	53.9
- Pharmacist, %	8.3	10.1	8.7	6.4	9.2
- Optometrist, %	6.7	7.6	6.4	8.7	7.6
- Osteopath, %	3.9	4.4	5.4	5.9	2.9
- Podiatrist, %	2.5	2.2	2.5	2.5	3.3
- Veterinarian, %	20.7	21.6	20.5	22.2	23.1

Values are means (SD) for continuous variables; Except for age at baseline, values of means or percentages are standardized to the age distribution of the study population

Not all categories add up to 100% due to rounding or information unknown

COPD: chronic obstructive pulmonary disease

Table 2 Herpes zoster and RR(95% CI) of 3 unit increment in Subjective Cognitive Decline (SCD) in the Nurses' Health Study (NHS), the Nurses' Health Study II (NHS II), and the Health Professionals Follow-Up Study (HPFS)

	Years Since Herpes Zoster				
	Never	1–4 years	5–8 years	9–12 years	≥ 13 years
NHS					
	(*n* = 48,158)	(*n* = 1701)	(*n* = 2509)	(*n* = 2193)	(*n* = 1581)
Age-adjusted RR (95% CI)	1.00 (ref)	1.15 (0.99, 1.32)	0.96 (0.86, 1.08)	1.09 (0.97, 1.23)	1.22 (1.06, 1.40)
MV RR[a] (95% CI)	1.00 (ref)	1.08 (0.94, 1.24)	0.92 (0.82, 1.03)	1.04 (0.92, 1.17)	1.14 (1.01, 1.32)
NHS II					
	(*n* = 57,585)	(*n* = 2056)	(*n* = 2595)	(*n* = 1363)	(*n* = 3367)
Age-adjusted RR(95% CI)	1.00 (ref)	1.42 (1.25, 1.63)	1.10 (0.97, 1.25)	1.12 (0.95, 1.33)	1.38 (1.24, 1.53)
MV RR[a] (95% CI)	1.00 (ref)	1.35 (1.18, 1.54)	1.05 (0.93, 1.19)	1.05 (0.89, 1.24)	1.20 (1.08, 1.33)
MV RR[b] (95% CI)	1.00 (ref)	1.34 (1.18, 1.53)	1.05 (0.93, 1.19)	1.05 (0.89, 1.24)	1.20 (1.08, 1.34)
HPFS					
	(*n* = 23,722)	(*n* = 830)	(*n* = 518)	(*n* = 437)	(*n* = 712)
Age-adjusted RR (95% CI)	1.00 (ref)	1.29 (1.03, 1.62)	1.47 (1.11, 1.95)	1.61 (1.19, 2.18)	1.42 (1.11, 1.82)
MV RR[a] (95% CI)	1.00 (ref)	1.21 (0.97, 1.53)	1.38 (1.04, 1.84)	1.42 (1.04, 1.92)	1.24 (0.97, 1.58)

[a]Multivariable model: NHSI & NHSII adjusted for age, race, family history of dementia, census tract income, husband's education, smoking history, alcohol consumption, body mass index (BMI), physical activity, diabetes mellitus, hypertension, elevated cholesterol, Alternate Healthy Eating Index (AHEI-2010) Score, menopausal status, depression, post-menopausal hormonal therapy use, potentially immunocompromising conditions or treatments (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, chronic obstructive pulmonary disease (COPD), oral steroids/corticosteroid use), stroke, and coronary heart disease (CHD);

HPFS adjusted for age, race, family history of dementia, smoking history, alcohol consumption, body mass index (BMI), physical activity, diabetes mellitus, hypertension, elevated cholesterol, Alternate Healthy Eating Index (AHEI-2010) Score, depression, profession, potentially immunocompromising conditions or treatments (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, chronic obstructive pulmonary disease (COPD), oral steroids/corticosteroid use), stroke, and coronary heart disease (CHD)

[b]Multivariable model further adjusted for herpes zoster vaccination status

NHS: Nurses' Health Study

NHS II: Nurses' Health Study II

HPFS: Health Professionals Follow-Up Study

MV RR: Multivariable-adjusted relative risk

CI: Confidence Interval

vaccinated adults [36]. One nested case-control study in the UK Biobank found a 20% lower dementia risk among adults who received the Zostavax vaccine [10]. Some studies also suggest that antiviral treatment may reduce the risk of dementia among individuals who had HZ [7, 37]. Findings from the current prospective cohort study, NHSII, demonstrated that the magnitude of the risk may be greater among those not vaccinated against HZ, aligning with the aforementioned literature.

There are several possible mechanisms by which HZ may contribute to cognitive decline, including neuroinflammation, cerebral vasculopathy, direct neuronal damage, and the activation of other herpesviruses like HSV-1. The inflammation induced by VZV, both locally and systemically, has been implicated in neuronal damage and accelerated cognitive decline [38]. Studies have shown increased levels of inflammatory factors in plasma exosomes of individuals with a history of HZ, suggesting a role in triggering proinflammatory responses and thrombotic processes [39].

Cerebrovascular pathologies associated with HZ, such as vasculopathy, pose another potential link to cognitive decline. This complication may lead to local inflammation, abnormal vascular remodeling, and arterial changes, increasing the risk of vascular occlusion, ischemia, and cerebrovascular disease—factors that have been shown to contribute to cognitive decline [40–42]. In the NHS, NHSII, and HPFS cohorts, we previously demonstrated that HZ was associated with up to 38% higher long-term risk of stroke, and the elevated risk persisted for 12 years or longer [43]. Plausibly, HZ is also associated with subclinical cerebrovascular changes that elevate the risk of cognitive decline.

Additionally, evidence suggests that VZV infection may contribute to amyloid-associated pathology, potentially impacting amyloid burden and disease progression in conditions like Alzheimer's disease (AD) [44]. Moreover, HZ may indirectly accelerate cognitive decline in individuals with latent herpes simplex virus type 1 (HSV-1) [45]. HSV-1 infection has been linked to increased risk of dementia, particularly among APOE ε4 carriers [46–48], and in vitro studies suggest that VZV reactivation and neuroinflammation could induce reactivation of HSV-1, leading to AD-related changes [45].

Intriguingly, our study observed some sex differences in the relation between HZ and the risk of SCD,
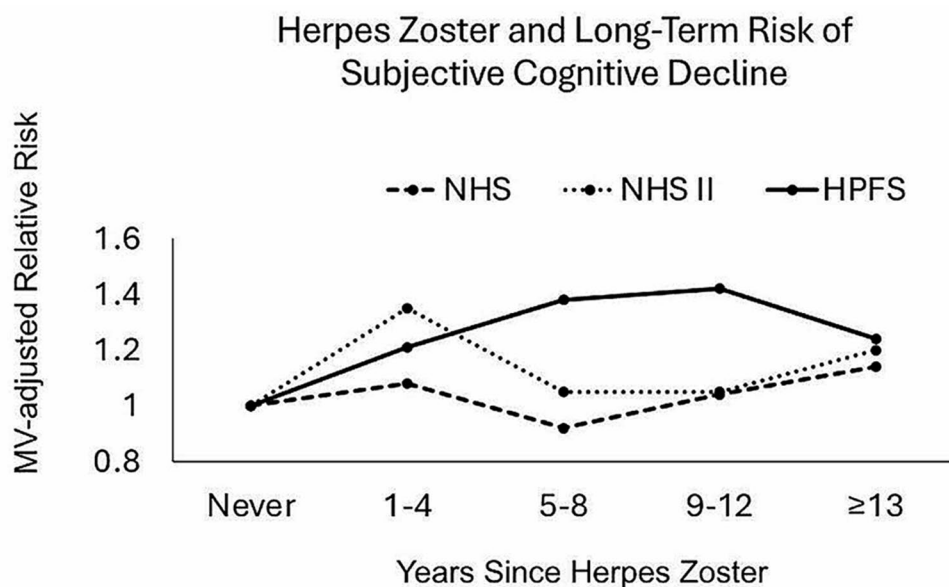
Herpes Zoster and Long-Term Risk of Subjective Cognitive Decline

Fig. 1 Herpes Zoster and Multivariable-Adjusted Relative Risk of 3 Unit Increment in Subjective Cognitive Decline in the Nurses' Health Study (NHS), the Nurses' Health Study II (NHS II), and the Health Professionals Follow-Up Study (HPFS). **NHS, NHS II**: Multivariable models adjusted for adjusted for age, race, family history of dementia, census tract income, husband's education, smoking history, alcohol consumption, body mass index, physical activity, diabetes mellitus, hypertension, elevated cholesterol, diet quality (AHEI-2010 Score), menopausal status, depression, post-menopausal hormonal therapy use, herpes zoster vaccination (NHS II, only), and potentially immunocompromising conditions or treatments [a report of one or more of the following: cancer (other than non-melanoma skin cancer), rheumatoid arthritis, Crohn's disease/ulcerative colitis (inflammatory bowel disease), systemic lupus erythematosus, asthma, chronic obstructive pulmonary disease, oral steroids/corticosteroid use), stroke, and coronary heart disease]. **HPFS**: Multivariable model adjusted for age, race, family history of dementia, smoking history, alcohol consumption, body mass index, physical activity, diabetes mellitus, hypertension, elevated cholesterol, diet quality (AHEI-2010 Score), depression, profession, and potentially immunocompromising conditions or treatments [a report of one or more of the following: cancer (other than non-melanoma skin cancer), rheumatoid arthritis, Crohn's disease/ulcerative colitis (inflammatory bowel disease), systemic lupus erythematosus, asthma, chronic obstructive pulmonary disease, oral steroids/corticosteroid use), stroke, and coronary heart disease

particularly regarding APOE ε4 carrier status. Sex differences in the relation of APOE genotype as well as other risk factors for AD, neurodegeneration, and vascular disease have been described [49–57], but whether these are due to differences in genetics, other factors, or susceptibility to AD pathology remains unclear [58, 59]. Findings regarding sex differences and the prevalence of SCD have been inconsistent [60–62], but sex-specific differences in the prevalence of certain dementia subtypes have been shown [49, 63]. Further investigation of sex differences in the relation between HZ and cognitive decline could be informative.

Strengths of the current study include the prospective cohort study design, long-term follow-up, large sample size, and comprehensive information on potential confounding factors. In addition, we have data on APOE and immunocompromising status, and HZ vaccination status was available for the NHSII, enabling us to explore potential variations in the association based on these statuses. Potential limitations of our study include self-reporting of HZ and cognitive function. However, our validation study comparing the assessment of HZ by questionnaire with medical records showed that self-reported shingles in these cohorts were highly reliable.

The questions regarding subjective cognitive function used in this study have been validated against objective features of dementia and clinically established cognitive testing questionnaires [18, 26, 64–66]. Also, although we performed a validation study to determine the positive predictive value of HZ cases, which showed that 99.6% of self-reported HZ cases were true cases as confirmed by medical records, there is still the possibility of false negatives. However, if there were misclassification of HZ status, it would likely have been random and would have biased the findings towards the null or had minimal impact on the overall results due to the larger size of the non-case group. In addition, this study was observational, and residual confounding by unmeasured factors is possible. Nonetheless, our dataset has detailed information on potential confounding factors that were measured repeatedly using well-validated instruments, and the adjustment for these variables helped reduce residual confounding. Our study was limited to predominantly white healthcare professionals with generally high socioeconomic status and education, which could limit generalizability. Although this uniformity may also reduce variability and enhance internal validity of health-related

Table 3 Herpes zoster and RR (95% CI) of 3 unit increment in Subjective Cognitive Decline (SCD) in the Nurses' Health Study (NHS), the Nurses' Health Study II (NHS II), and the Health Professionals Follow-Up Study (HPFS), stratified by potentially immunocompromising conditions[*]

Years Since Herpes Zoster					
Immunocompromising Conditions (Yes/No)	**Never**	**1–4 years**	**5–8 years**	**9–12 years**	**≥ 13 years**
NHS					
Yes	(n = 10,473)	(n = 415)	(n = 630)	(n = 570)	(n = 413)
MV RR[a] (95% CI)	1.00 (ref)	1.05 (0.81, 1.38)	0.84 (0.67, 1.06)	1.13 (0.90, 1.40)	1.18 (0.92, 1.53)
No	(n = 37,685)	(n = 1286)	(n = 1879)	(n = 1623)	(n = 1168)
MV RR[a] (95% CI)	1.00 (ref)	1.10 (0.93, 1.29)	0.95 (0.83, 1.09)	1.01 (0.87, 1.16)	1.13 (0.96, 1.33)
	p-interaction = 0.8				
NHS II					
Yes	(n = 9392)	(n = 386)	(n = 512)	(n = 259)	(n = 791)
MV RR[a] (95% CI)	1.00 (ref)	1.40 (1.05, 1.85)	1.03 (0.79, 1.33)	0.80 (0.56, 1.17)	1.22 (0.99, 1.50)
No	(n = 48,193)	(n = 1670)	(n = 2083)	(n = 1104)	(n = 2576)
MV RR[a] (95% CI)	1.00 (ref)	1.34 (1.15, 1.55)	1.06 (0.92, 1.22)	1.12 (0.93, 1.35)	1.19 (1.06, 1.36)
	p-interaction = 0.06				
HPFS					
Yes	(n = 4469)	(n = 195)	(n = 115)	(n = 103)	(n = 149)
MV RR[b] (95% CI)	1.00 (ref)	1.33 (0.87, 2.03)	1.13 (0.66, 1.95)	1.19 (0.66, 2.13)	1.05 (0.64, 1.73)
No	(n = 19,253)	(n = 635)	(n = 403)	(n = 334)	(n = 563)
MV RR[b] (95% CI)	1.00 (ref)	1.17 (0.89, 1.54)	1.52 (1.08, 2.11)	1.50 (1.05, 2.14)	1.27 (0.96, 1.69)
	p-interaction = 0.99				

[a]Multivariable model adjusted for: age, race, family history of dementia, census tract income, husband's education, smoking history, alcohol consumption, body mass index (BMI), physical activity, diabetes mellitus, hypertension, elevated cholesterol, Alternate Healthy Eating Index (AHEI-2010) Score, menopausal status, depression, post-menopausal hormonal therapy use, potentially immunocompromising conditions or treatments (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, chronic obstructive pulmonary disease (COPD), oral steroids/corticosteroid use), stroke, and coronary heart disease (CHD).

[b]Multivariable model adjusted for: age, race, family history of dementia, smoking history, alcohol consumption, body mass index (BMI), physical activity, diabetes mellitus, hypertension, elevated cholesterol, Alternate Healthy Eating Index (AHEI-2010) Score, depression, profession, potentially immunocompromising conditions or treatments (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, chronic obstructive pulmonary disease (COPD), oral steroids/corticosteroid use), stroke, and coronary heart disease (CHD)

NHS: Nurses' Health Study

NHS II: Nurses' Health Study II

HPFS: Health Professionals Follow-Up Study

MV RR: Multivariable-adjusted relative risk

CI: Confidence Interval

Table 4 Herpes zoster and RR (95% CI) of 3 unit increment in Subjective Cognitive Decline (SCD) in the Nurses' Health Study (NHS), the Nurses' Health Study II (NHS II), and the Health Professionals Follow-Up Study (HPFS), stratified by APOE Ɛ4 carrier status

	Years Since Herpes Zoster		
APOE Ɛ4 carrier status (Yes/No)	**Never**	**1–4 years**	**≥ 5 years**
NHS			
Yes	(n = 2255)	(n = 75)	(n = 328)
MV RR (95% CI)	1.00 (ref)	1.53 (0.85, 2.76)	0.96 (0.71, 1.29)
No	(n = 7110)	(n = 298)	(n = 1113)
MV RR (95% CI)	1.00 (ref)	0.80 (0.57, 1.13)	1.25 (1.06, 1.49)
	p-interaction = 0.98		
NHSII			
Yes	(n = 2193)	(n = 71)	(n = 364)
MV RR (95% CI)	1.00 (ref)	1.09 (0.55, 2.15)	0.87 (0.62, 1.22)
No	(n = 6650)	(n = 244)	(n = 950)
MV RR (95% CI)	1.00 (ref)	1.19 (0.80, 1.76)	1.32 (1.07, 1.62)
	p-interaction = 0.08		
HPFS			
Yes	(n = 1780)	(n = 68)	(n = 139)

Table 4 (Continued)

	Years Since Herpes Zoster		
APOE Ɛ4 carrier status (Yes/No)	**Never**	**1–4 years**	**≥ 5 years**
MV RR (95% CI)	1.00 (ref)	2.83 (1.49, 5.35)	1.81 (1.10, 2.98)
No	(*n* = 4984)	(*n* = 213)	(*n* = 421)
MV RR (95% CI)	1.00 (ref)	1.19 (0.76, 1.86)	0.90 (0.65, 1.26)
	p-interaction = 0.02		

[a]Multivariable model adjusted for: age, race, family history of dementia, census tract income, husband's education, smoking history, alcohol consumption, body mass index (BMI), physical activity, diabetes mellitus, hypertension, elevated cholesterol, Alternate Healthy Eating Index (AHEI-2010) Score, menopausal status, depression, post-menopausal hormonal therapy use, potentially immunocompromising conditions or treatments (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, chronic obstructive pulmonary disease (COPD), oral steroids/corticosteroid use), stroke, and coronary heart disease (CHD).

[b]Multivariable model adjusted for: age, race, family history of dementia, smoking history, alcohol consumption, body mass index (BMI), physical activity, diabetes mellitus, hypertension, elevated cholesterol, Alternate Healthy Eating Index (AHEI-2010) Score, depression, profession, potentially immunocompromising conditions or treatments (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, chronic obstructive pulmonary disease (COPD), oral steroids/corticosteroid use), stroke, and coronary heart disease (CHD).

NHS: Nurses' Health Study

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information, further studies among other populations are warranted.

Conclusion

Findings from these three large independent cohorts of women and men suggest herpes zoster was associated with a higher long-term risk of subjective cognitive decline. The risk may be greater for the APOE ε4 allele carriers among men, but not among women. The relation did not differ among those with potentially immunocompromising conditions. The magnitude of the elevated long-term risk of SCD may potentially be reduced by HZ vaccination, but further study is needed.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13195-024-01511-x.

> Supplementary Material 1

Author contributions
TSY and SGC formulated the study question and design, designed and conducted the statistical analyses, interpreted the results, and wrote and revised the manuscript. SGC contributed to the data acquisition. GCC contributed to the study conception, data acquisition, design, and interpretation of the results. BY contributed to the interpretation of the results. WCW supervised the project and played major roles in data acquisition, contributed to the interpretation of the results, and critical revision of the manuscript. All authors approved the final version and made the decision to submit the manuscript for publication.

Data availability
Any data not published within the article will be shared at the request of other qualified investigators for purposes of replicating procedures and results. Our NHS and HPFS websites (nurseshealthstudy.org and sites.sph.harvard.edu/hpfs/) include guidelines for external users and links to all questionnaires.

Declarations

Ethics approval and consent to participate
The Institutional Review Boards of Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health approved the study protocol. Written informed consent were provided by all participants.

Consent for publication
Not applicable.

Competing interests
SGC received an investigator-initiated grant from GlaxoSmithKline Biologicals SA to examine the long-term outcomes potentially associated with herpes zoster. GCC is an employee of OM1, receives support from an investigator-initiated grant from GlaxoSmithKline Biologicals SA to examine the long-term outcomes potentially associated with herpes zoster, and receives royalties from UpToDate for being an author and Section Editor. BY 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. GSK was provided with the opportunity to review a preliminary version of this manuscript for factual accuracy, but the authors are solely responsible for the final content and interpretation. TSY and WCW have no disclosures to report.

Author details
[1]Department of Physical Medicine and Rehabilitation, School of Medicine, College of Medicine, Taipei Medical University, No.250, Wuxing St, Taipei 11031, Taiwan
[2]Department of Physical Medicine and Rehabilitation, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan
[3]Department of Epidemiology and Nutrition, Harvard T. H. Chan School of Public Health, Harvard University, Boston, MA, USA
[4]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA
[5]Department of Physical Medicine and Rehabilitation, National Taiwan University Hospital, Taipei, Taiwan
[6]Department of Physical Medicine and Rehabilitation, College of Medicine, National Taiwan University, Taipei, Taiwan
[7]Harvard Medical School, Boston, MA, USA
[8]Renal Division, Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA
[9]Department of Family and Community Health, University of Minnesota, Minneapolis, MN, USA

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