BRIEF REPORT

Herpes Zoster and Risk of Incident Parkinson's Disease in US Veterans: A Matched Cohort Study

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ABSTRACT: Background: Although some systemic infections are associated with Parkinson's disease (PD), the relationship between herpes zoster (HZ) and PD is unclear.

Objective: The objective is to investigate whether HZ is associated with incident PD risk in a matched cohort study using data from the US Department of Veterans Affairs.

Methods: We compared the risk of PD between individuals with incident HZ matched to up to five individuals without a history of HZ using Cox proportional hazards regression. In sensitivity analyses, we excluded early outcomes.

Results: Among 198,099 individuals with HZ and 976,660 matched individuals without HZ (median age 67.0 years (interquartile range [IQR 61.4–75.7]); 94% male; median follow-up 4.2 years [IQR 1.9–6.6]), HZ was not associated with an increased risk of incident PD overall (adjusted HR 0.95, 95% CI 0.90–1.01) or in any sensitivity analyses.

Conclusion: We found no evidence that HZ was associated with increased risk of incident PD in this cohort. © 2024 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Key Words: herpes zoster; Parkinson's disease; matched cohort study; electronic health records

The global burden of Parkinson's disease (PD) is rising rapidly with population growth and aging.[1] Neurodegeneration in PD, which is characterized by α-synuclein aggregates (Lewy bodies) leading to the loss of midbrain dopaminergic neurons, may occur decades before clinical PD diagnosis.[2] Its complex etiology remains poorly understood. Around 22% of PD risk is accounted for by genetic variation[3]; although associations with several environmental factors have been described, risks of reverse causation, residual confounding, and other biases raise concerns about whether these associations are causal.[4]

Infections have been postulated as triggers of PD for decades.[5] The strongest epidemiological evidence for a relationship comes from large studies showing a long-term increase in the risk of incident PD with influenza,[6] influenza/pneumonia,[7] viral hepatitis,[7] or any hospitalized infection occurring at least 5 years earlier.[8] Studies of herpes zoster (HZ), caused by reactivation of the neurotropic varicella zoster virus that is nearly ubiquitous in adult populations, show conflicting results. Whereas two matched cohort studies using the Taiwanese National Health Insurance Research Database (NHIRD) found increases in PD risk after HZ (HR 1.80 [95% CI: 1.43–2.28][9] and HR 1.17 [95% CI: 1.10–1.25][10]), a nested case–control study using US Medicare claims data showed an inverse association OR 0.88 (95% CI: 0.85–0.91).[11]

We therefore aimed to investigate the association between HZ and incident PD risk in the largest integrated healthcare system in the US, the Department of

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Veterans Affairs (VA), using a matched cohort study design.

Patients and Methods

Data Source

The VA provides comprehensive healthcare to ~9 million patients per year at over 1200 sites of care nationwide, including hospitals, medical centers, and community outpatient clinics. All care within the VA is recorded in an electronic health record (EHR) with daily uploads into the VA Corporate Data Warehouse. Available data include demographics, outpatient and inpatient encounters, diagnoses, laboratory measures, pharmacy fill/refills, smoking and alcohol consumption, and death records.

Study Design and Population

A matched cohort design was used to compare a cohort of patients with incident HZ with a similar cohort of patients without HZ. Patients entered at the latest of: study start (January 1, 2008), 40th birthday, or 1 year after first VA visit. Patients were excluded if they had a history of HZ, PD, or conditions strongly associated with PD (eg, Lewy body dementia, secondary parkinsonism). Eligible patients with incident HZ were matched to up to five eligible patients who had not been diagnosed with HZ on age (within 365 days), sex, race/ethnicity, site of care, and calendar time. Further information on study design and follow-up is provided in Data S1.

Exposure, Outcome, and Covariates

The primary exposure was incident HZ defined as the presence of at least one inpatient or outpatient diagnosis of HZ or acute HZ complications using *International Classification of Diseases—Ninth Edition/Tenth Edition* (ICD-9/10) codes. We excluded codes indicating chronic complications such as postherpetic neuralgia as the onset date for HZ episodes defined using only those codes would be unclear. The main outcome was incident PD defined as the presence of at least one inpatient or two outpatient diagnoses using ICD-9/10 codes (ICD-9: 332.0 and ICD-10: G20). Covariates included age, sex, race/ethnicity, body mass index, clinical comorbidities (alcohol use disorder, asthma, autoimmune disease, cardiovascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, diabetes, herpes simplex, hypertension, immunosuppression, liver disease, mood disorders, renal disease, traumatic brain injury), oral corticosteroid use, alcohol consumption, smoking status, and summary measures of comorbidity burden and physiologic frailty. Covariate definitions are provided in the Data S1. All codelists are published online at https://datacompass.lshtm.ac.uk/id/eprint/2848/.

Statistical Analysis

We described cohort characteristics by HZ status as well as characteristics of those with and without missing covariate data. We then computed crude rates of incident PD by HZ status. We employed Cox proportional hazards regression models to estimate associations between HZ and PD. All models used age as the underlying timescale and stratified on matched group thereby accounting for all matching factors. Fully adjusted models additionally included covariates specified earlier. In the secondary analysis, we stratified the HZ group by receipt of antiviral therapy (AVT) (acyclovir, valacyclovir, famcyclovir, foscarnet, amantadine) within 7 days of HZ diagnosis. We additionally explored effect modification by age group and frailty.

Sensitivity Analyses

First, we excluded outcomes that occurred within 6, 12, 24 months and 5 years of follow-up to mitigate the potential of reverse causality. Second, we used an expanded definition of PD for the outcome, which additionally included conditions strongly associated with PD (eg, Lewy body dementia, secondary parkinsonism). The analysis was conducted using Stata version 17. (StataCorp. 2021).

Results

Demographic and clinical characteristics are summarized in Table 1. Among 198,099 patients with incident HZ and 976,660 patients without HZ, distributions of age, sex, and race/ethnicity were similar, although the HZ group had a higher prevalence of some comorbidities, including cardiovascular diseases (CVD), hypertension, immunosuppression, mood disorders, and auto-immune disease. Patients with any missing data had a similar median age and years of follow-up to those with no missing data, although their prevalence of comorbidities was lower (eTable 1).

During follow-up, 1779 patients with HZ and 8214 patients without HZ experienced incident PD. Crude rates per 1000 person-years were 1.91 (95% CI: 1.83–2.00) in the HZ group and 1.90 (95% CI: 1.86–1.94) among those without HZ. HZ was not associated with incident PD in the main analysis (adjusted HR 0.95 [95% CI: 0.90–1.01]). In the secondary analysis, there was no evidence for a difference in the association with PD by receipt of AVT, HR 0.95, 95% CI: 0.89–1.03 for no AVT and HR 0.95, 95% CI: 0.87–1.03 for AVT. Findings were similar across sensitivity analyses (Table 2). We found no evidence of effect modification by age group or physiologic frailty (eTable 2).

TABLE 1 *Baseline characteristics by herpes zoster (HZ) status*

Characteristic	Individuals without HZ, N (%) N = 976,660 (83.1)	Individuals with HZ, N (%) N = 198,099 (16.9)
Years of follow-up		
Mean (SD)	4.44 (2.9)	4.70 (2.96)
Median (25th, 75th ptile)	4.1 (1.9,6.6)	4.5 (2.2, 6.9)
Baseline year		
2008/2009	182,593 (18.7)	36,664 (18.5)
2010/2011	184,104 (18.9)	37,184 (18.8)
2012/2013	225,731 (23.1)	46,299 (23.4)
2014/2015	187,214 (19.2)	38,346 (19.4)
2016/2017	131,854 (13.5)	26,505 (13.4)
2018	65,164 (6.7)	13,101 (6.6)
Age at baseline (years)		
Mean (SD)	68.14 (11.0)	68.17 (11.0)
Median (25th, 75th ptile)	67.33 (61.4, 75.7)	67.36 (61.5, 75.8)
Grouped age		
40–< 50	55,001 (5.6)	11,067 (5.6)
50–< 60	146,565 (15.0)	29,202 (14.7)
60–< 70	386,603 (39.6)	78,892 (39.8)
70–< 80	231,014 (23.7)	46,913 (23.6)
80+	157,477 (16.1)	32,025 (16.2)
Gender		
Men	918,407 (94.0)	185,902 (93.8)
BMI		
Mean (SD)	29.60 (5.9)	29.46 (5.9)
Median (25th, 75th ptile)	28.87 (25.7, 32.7)	28.72 (25.5, 32.6)
BMI category		
Underweight	8195 (0.8)	2136 (1.1)
Normal Weight	161,599 (16.6)	39,337 (19.9)
Overweight	311,580 (31.9)	72,003 (36.4)
Obese 1	210,901 (21.6)	47,968 (24.2)
Obese 2	85,733 (8.8)	19,116 (9.7)
Obese 3	43,721 (4.5)	10,045 (5.1)
Missing	154,931 (15.9)	7494 (3.8)
Smoking status		
Never	292,347 (29.9)	61,011 (30.8)
Former	360,685 (36.9)	77,243 (39.0)
Current	285,915 (29.3)	57,500 (29.0)
Missing	37,713 (3.9)	2345 (1.2)

(Continues)

TABLE 1 *Continued*

Characteristic	Individuals without HZ, N (%) N = 976,660 (83.1)	Individuals with HZ, N (%) N = 198,099 (16.9)
AUDIT-C category		
0	436,358 (44.7)	105,884 (53.5)
1–3	290,078 (29.7)	63,452 (32.0)
4–7	95,270 (9.8)	18,972 (9.6)
8+	19,742 (2.0)	3882 (2.0)
Missing	135,212 (13.8)	5909 (3.0)
Race/ethnicity		
White	736,570 (75.4)	149,183 (75.3)
Black	119,376 (12.2)	24,091 (12.2)
Hispanic	49,693 (5.1)	10,177 (5.1)
Asian	5173 (0.5)	1143 (0.6)
American Indian/Alaska Native	5374 (0.6)	1148 (0.6)
Native Hawaiian/Pacific Islander	6290 (0.6)	1252 (0.6)
Mixed	5727 (0.6)	1275 (0.6)
Unknown	48,457 (5.0)	9830 (5.0)
Baseline comorbidity		
Alcohol use disorder	50,628 (5.2)	12,364 (6.2)
Asthma	25,615 (2.6)	7277 (3.7)
Autoimmune disease	38,462 (3.9)	13,292 (6.7)
Cardiovascular disease	138,528 (14.2)	38,991 (19.7)
Cerebrovascular disease	72,229 (7.4)	19,750 (10.0)
COPD	101,278 (10.4)	29,311 (14.8)
Diabetes	277,893 (28.5)	66,202 (33.4)
HSV	2939 (0.3)	1912 (1.0)
Hypertension	530,500 (54.3)	122,734 (62.0)
Immunosuppression	22,176 (2.3)	11,516 (5.8)
Liver disease	39,965 (4.1)	10,624 (5.4)
Mood disorder	223,234 (22.9)	58,467 (29.5)
Renal disease	76,884 (7.9)	22,473 (11.3)
Traumatic brain injury	2977 (0.3)	923 (0.5)
VACS Index score		
Mean (SD)	71.1 (12.2)	72.0 (13.2)
Median (25th, 75th ptile)	69.5 (62.0, 78.9)	70.2 (62.1, 80.2)
VACS Index score quartiles		
1	172,844 (17.7)	41,517 (21.0)
2	174,142 (17.8)	40,161 (20.3)

(Continues)

TABLE 1 *Continued*

Characteristic	Individuals without HZ, N (%) N = 976,660 (83.1)	Individuals with HZ, N (%) N = 198,099 (16.9)
3	174,492 (17.9)	40,976 (20.7)
4	168,979 (17.3)	45,973 (23.2)
missing	286,203 (29.3)	29,472 (14.9)
Charlson Comorbidity Index		
Mean (SD)	1.3 (1.7)	1.9 (2.1)
Median (25th, 75th ptile)	1 (0, 2)	1 (0, 3)
Charlson Comorbidity Index category		
0	424,814 (43.5)	62,579 (31.6)
1	215,922 (22.1)	44,801 (22.6)
2	150,594 (15.4)	34,408 (17.4)
3	83,019 (8.5)	21,110 (10.7)
4	46,158 (4.7)	13,271 (6.7)
5+	56,153 (5.8)	21,930 (11.1)
Steroid use		
Used oral corticosteroids	80,201 (8.2)	32,882 (16.6)
Secondary exposure		
Unexposed	976,660 (100.0)	0 (0.0)
HZ	0 (0.0)	111,457 (56.3)
HZ + AVT	0 (0.0)	86,642 (43.7)

Abbreviations: AVT, antiviral therapy; BMI, body mass index; COPD, Chronic obstructive pulmonary disease; HSV, herpes simplex virus; SD, standard deviation.

Discussion

We showed no evidence of an increased risk of incident PD after HZ in a large, population-based matched cohort study using data from the US Veterans Health Administration. The null finding was replicated across various sensitivity analyses, including introducing lag times of up to 5 years to reduce the risk of reverse causation and broadening the outcome definition to increase sensitivity.

This null finding may be unsurprising given the decades-long nature of neurodegeneration and long prodromal phase of PD.[12] It seems unlikely that HZ, which typically occurs in later life as cell-mediated immunity declines, would predate the onset of the neurodegenerative process. Although HZ has been linked to acute inflammatory and vascular complications,[13,14] large EHR studies from Europe[15-17] do not support an association with other long-term neurodegenerative conditions such as dementia. National studies from Korea on HZ and incident dementia risk show conflicting results,[18,19] whereas studies using the Taiwan NHIRD have suggested an association between HZ and both dementia[20,21] and PD.[9,10] Differences in those studies' findings may reflect differing methodological approaches. For example, the studies of PD risk from Taiwan identified unexposed matches from among those who did not develop HZ at any time during the study period rather than identifying unexposed matches at the diagnosis date of an exposed individual. This approach tends to select healthier individuals as unexposed matches, who may be less likely to develop a neurodegenerative condition. Further methodological research to understand reasons for the differences between our study and previous matched cohorts would be valuable.

Nevertheless, several studies with long-term follow-up suggest associations between other clinically diagnosed systemic infections (influenza,[6] influenza/pneumonia,[7] hepatitis,[7] or any hospital-treated infection[8]) and incident PD. Although none of these studies investigated HZ specifically, they all used measures that could identify HZ (combined herpes simplex and zoster,[6] chickenpox,[7] hospital-treated skin infections[8]) and found no link with PD risk, consistent with our findings. Mechanisms linking systemic infections to incident PD risk may include systemic inflammation with high levels of cytokine production, in which transfer across the blood–brain-barrier leads to microglial activation, neuronal damage, and cell death.[22] Other studies show that infections such as influenza can induce α-synuclein aggregation in human mesencephalic dopaminergic cells[23] and that norovirus infection may lead to α-synuclein expression in the enteric nervous system.[24]

Strengths of our study include its large size and real-world nature, and the US-wide distribution of clinics enables generalizability to veterans from around the US. Although veterans are majority male and are more likely to have some PD risk factors such as traumatic brain injury than non-veterans, they represent an important and sizeable population for study. Requiring regular engagement with healthcare helped to optimize recording.

Our study nevertheless had some limitations. Although we followed individuals for up to 11 years, the long prodromal phase of PD means that we cannot exclude reverse causation. Our lagged analysis, however, did not suggest any evidence for this. HZ recording in EHRs may be incomplete: although 91% of individuals with HZ typically access healthcare in the US,[25] those with milder symptoms, recurrent zoster, and individuals from some ethnic groups may be less likely to seek medical attention. Any HZ episodes coded only with post-herpetic neuralgia codes would not be captured in our study. This would lead to a

TABLE 2 *Associations between herpes zoster (HZ) and Parkinson's disease*

Type of analysis	N (total)	N (outcome)	HR (95% CI)
Primary analysis			
Adjusted for matching factors only[a]	1,174,759	9993	1.01 (0.96–1.06)
Adjusted for matching factors only[a] among complete cases	798,338	7032	1.00 (0.95–1.06)
Fully adjusted model[b] among complete cases	798,338	7032	0.95 (0.90–1.01)
Secondary analysis			
Fully adjusted model[b] among complete cases			
• Unexposed	798,338	7032	1.00
• No AVT			0.95 (0.89–1.03)
• AVT			0.95 (0.87–1.03)
Sensitivity analysis			
(i) Fully adjusted model,[b] excluding outcomes			
• <6 months	798,338	6289	0.95 (0.90–1.01)
• <12 months	798,338	5618	0.96 (0.90–1.02)
• <24 months	798,338	4390	0.99 (0.92–1.06)
• <5 years	798,338	1768	1.03 (0.92–1.15)
(ii) Expanded outcome (fully adjusted model[b])	798,058	8487	0.94 (0.90–0.99)

Abbreviation: AVT, antiviral therapy.
[a]Adjusted for age, sex, race/ethnicity, site of care, and calendar time.
[b]Adjusted for all variables in (a) in addition to body mass index, clinical comorbidities (alcohol use disorder, asthma, autoimmune disease, cardiovascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, diabetes, herpes simplex, hypertension, immunosuppression [including HIV], liver disease, mood disorder, renal disease, traumatic brain injury), oral corticosteroid use, alcohol consumption, smoking status, Charlson Comorbidity Index, and VACS Index.

small amount of misclassification of HZ status, likely to be non-differential, which would tend to bias results toward the null. PD diagnoses may be misclassified using ICD-9/10 codes. However, a validation study showed that using ICD-9332.0 assigned at least twice in any VA clinic had high sensitivity (89%) and positive predictive values (PPV; 79%) but lower specificity (28%) and negative predictive values (NPV; 46%).[26] Our sensitivity analysis using a broader definition of PD was consistent with the main analysis.

We cannot exclude residual confounding by variables not routinely recorded in EHRs such as genetic susceptibility to PD and exposure to pesticides. Our approach may not have fully accounted for time-varying confounders such as body mass index (BMI) measured within 2 years prior to baseline. Other covariates were incompletely recorded, though results from minimally adjusted models were similar in the full study population and in the subset with complete data available. In addition, lifestyle factors such as smoking and alcohol tend to be well recorded in Veterans' data, with AUDIT-C screening routinely integrated into the VA since 2004.[27] Further studies are needed to generalize findings to non-veteran populations and to women.

In conclusion, we found no evidence that HZ was associated with an increase in incident PD risk in US veterans overall or in any subsets of age-group or frailty, suggesting that HZ is unlikely to play a major role in PD development.

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Data Availability Statement

Due to US Department of Veterans Affairs (VA) regulations and our ethics agreements, the analytic data sets used for this study are not permitted to leave the VA firewall without a data use agreement. This limitation is consistent with other studies based on VA data. However, VA data are made freely available to researchers with an approved VA study protocol. For more information, please visit https://www.virec.research.va.gov or contact the VA Information Resource Center at VIReC@va.gov.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

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(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical analysis: A. Design, B. Execution, C. Review and critique; (3) Manuscript: A. Writing of the first draft, B. Review and critique.

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