Incident Herpes Zoster and Risk of Dementia
A Population-Based Danish Cohort Study

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Study Question
Is herpes zoster associated with an increased long-term risk of dementia?

What Is Known and What This Paper Adds
Herpes zoster is a vaccine-preventable infection caused by reactivation of the neurotropic varicella-zoster virus. It may contribute to the development of dementia through neuro-inflammation, cerebral vasculopathy, or direct neural damage, making it a potential modifiable dementia risk factor. This study’s results suggest that zoster is not associated with an increased risk of dementia, except possibly in those with CNS infection; thus, universal zoster vaccination is unlikely to reduce dementia risk.

Methods
This nationwide cohort study used data from linked nationwide Danish registries to examine the association between zoster and dementia during 1997–2017. An exposed cohort of people aged 40 years or older with incident zoster defined as a first-time hospital-based diagnosis or prescription for an antiviral for zoster medication (n = 247,305) was compared with a general population comparison cohort matched 5:1 by sex and birth year (n = 1,235,890). Cohorts were followed until incident dementia (hospital diagnosis or prescription of an antidementia drug), death, emigration, or end of 2017. Cox regression was used to compute hazard ratios for dementia associated with zoster during 0–1 year and 1–21 years of follow-up (adjusted for matching factors and comorbidities). Cumulative incidences of dementia at the end of follow-up were also compared. Secondary analyses focused on zoster involving cranial nerves or the CNS and on Alzheimer disease as a separate outcome. Analyses were also performed according to age, sex, mode of zoster identification (hospital diagnosis/prescription), and presence/absence of stroke.

Results and Study Limitations
The hazard ratio of all-cause dementia in people with zoster vs matched comparators was 0.98 (95% CI: 0.90–1.04) during the first year and 0.93 (95% CI: 0.90–0.95) thereafter. The risk of dementia by the end of follow-up was 9.7% for patients with zoster and 10.3% for matched comparators. There was no increased long-term risk of dementia in subgroup analyses, except for a possible twofold increase in people with CNS infection. Analyses of Alzheimer disease as a secondary outcome showed similar results. Study limitations include potential detection bias for severe zoster (including CNS infections), missed zoster in those with early undiagnosed dementia, confounding by factors that predict antiviral treatment (e.g., health-seeking), and a lack of generalizability to untreated zoster.

Study Funding and Competing Interests
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Table
Relative Risk of Dementia 1–21 Years After Herpes Zoster

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (primary analysis)</td>
<td>0.93 (0.90–0.95)</td>
</tr>
<tr>
<td>Zoster involving cranial nerves</td>
<td>1.07 (0.79–1.45)</td>
</tr>
<tr>
<td>Zoster with CNS involvement</td>
<td>1.94 (0.78–4.80)</td>
</tr>
<tr>
<td>Alzheimer disease as a specific outcome</td>
<td>0.93 (0.90–0.97)</td>
</tr>
</tbody>
</table>

Abbreviation: HR = hazard ratio.
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