Psychological Stress as a Trigger for Herpes Zoster: Might the Conventional Wisdom Be Wrong?

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The causes for zoster remain largely unknown. Psychological stress is one commonly considered risk factor. We used self-controlled case series methods to look for increases in zoster following death or catastrophic health event occurring in a previously healthy spouse. We found no increase, although this stressor led to increased mental health visits.

Keywords. zoster; shingles; stress; self-controlled case series; healthcare seeking.

Herpes zoster (HZ) is a localized painful rash illness that is caused by reactivation of latent varicella zoster virus (VZV) and can lead to considerable morbidity and disability [1, 2]. One million persons experience HZ annually in the United States. Whereas there is consensus that T-cell immunity plays a key role in controlling reactivation, proximate causes for HZ remain poorly defined [1–3]. Well-documented risk factors include older age and immunodeficiency, but these factors do not distinguish most of the 30% of persons who experience HZ during their lifetime from those who do not [1–3]. Other risk factors for HZ have been evaluated, but are unsubstantiated or of insufficient prevalence or magnitude to explain most episodes [1–3]. Psychological stress has commonly been considered to be a trigger for HZ [4]; this contention has been supported by several, but not all, studies [5–8]. We used data from a large dataset to investigate this premise.

METHODS

Overview
We evaluated the association of psychological stress with HZ in adults using a self-controlled analysis by comparing episodes of HZ after vs before an acute stressor, defined as an unexpected death or catastrophic health event occurring in a patient’s previously healthy spouse. Because individuals may be less likely to seek medical attention for HZ following such life-altering events, we also assessed HZ as a proportion of all healthcare services after vs before the stressor. We also evaluated prespecified mental health visits after vs before the stressor to serve as a positive control and provide evidence that our definition for stress was valid.

Study Design
We used self-controlled case series methods to assess for increases in HZ risk [9]. These methods compare risks during prespecified risk and control periods within individuals, and eliminate effects of time-invariant confounders (Figure 1). We compared the risk of HZ and mental health visits during a 3-month risk period (days 1–90 following stressor) vs a 3-month control period (days 120–31 before stressor), assessing risk both as incidence (ie, number of episodes) and proportion (ie, divided by all outpatient healthcare services). We also evaluated risk periods of other durations up to 4 months.

Data Source
We used claims data from 2002 to 2011 Truven Health MarketScan Commercial and Medicare Databases, which include beneficiary and co-beneficiary data from employers, health insurance plans, and Medicare. The enrolled population resided in all states and ranged in size from 6 million (2002) to 50 million (2011).

Study Population
The study cohort consisted of MarketScan enrollees aged ≥25 years who experienced stress and a study outcome (HZ, mental health visit) during the observation period.

Study Definitions
Stress
Life-event researchers treat spousal death as the most extreme commonly encountered stress, with catastrophic health event in a spouse also being highly stressful [10–12]. We based our definition of stress on this consensus. We first identified
MarketScan enrollees aged ≥30 years who were not hospitalized or institutionalized during a 365-day washout period (ie, previously healthy) who died or experienced a catastrophic health event during 2003–2010. We captured deaths via death discharge codes from the emergency department or within 14 days of a hospital admission. Catastrophic health events consisted of medical intensive care unit (ICU) stays ≥14 days, and surgical/neurosurgical ICU stays ≥14 days following emergency surgery or injuries (ie, International Classification of Diseases, Ninth Revision [ICD-9] E codes). The stress index date was the first date with the relevant claim during the study period. We defined "spouses" as co-beneficiaries of the opposite sex and within 5 years of age.

**Herpes Zoster**
We defined HZ as outpatient claims with ICD-9 diagnostic codes of 053.xx (excluding 053.12 and 053.13) in the first 2 diagnostic positions. We only included the first HZ episode during the study period.

**Mental Health Visits**
We defined mental health visits as outpatient claims with ICD-9 codes for anxiety (300.0, 300.0x), acute stress (308, 308.x), or adjustment reaction (309.xx) in the first 2 diagnostic positions.

**Statistical Analysis**
We used conditional Poisson regression to compare rates and proportion of visits in risk vs control periods. Data were analyzed using SAS 9.2 statistical software. The proc genmod procedure was used to calculate relative incidence (RI), 95% confidence intervals (CIs), and $P$ values. To compare proportions of HZ vs all outpatient healthcare services in the cohort, we used the generalized estimating equation methods for analysis of repeated data as enrollees may have contributed data for multiple visits; these results were reported as relative risk (RR), also with corresponding 95% CIs.

**RESULTS**
Among 39,811 persons experiencing stressful events, 137 developed HZ during the observation period (Table 1). HZ RI in this cohort was not increased during the 90-day risk period (0.76 [95% CI, 0.54–1.06]). Because, plausibly, individuals are less likely to seek care for HZ and other conditions soon after life-altering events, we also evaluated HZ episodes as a proportion of healthcare services during the risk vs control periods, but the RR was not increased (0.99 [95% CI, 0.70–1.39]).

We used a positive control to confirm that the events we selected were in fact associated with clinical evidence of stress. We evaluated the impact of these events on stress-related mental health visits during the risk period and found, as expected, that the risk was increased, whether measured as episodes (RI, 1.75 [95% CI, 1.58–1.93]) or proportions (RR, 1.87 [95% CI, 1.67–2.10]).

We stratified our cohort into ages ≥60 and <60 years, and also explored other risk periods ranging from 1 to 4 months, but still found no evidence for increased HZ risk (Table 1). We evaluated HZ in persons who experienced HZ associated with the unexpected death of their spouse (subset of our case definition for stress); they comprised 20 of the 137 episodes. The RI was <1.0, but with large confidence intervals (data not shown).
### Table 1. Medically Attended Herpes Zoster and Mental Health Visits During Risk Versus Control Periods

<table>
<thead>
<tr>
<th>Age</th>
<th>No. of Patients</th>
<th>Herpes Zoster</th>
<th>Additional Risk Periods</th>
<th>1–90 d Following Stress</th>
<th>1–30 d Following Stress</th>
<th>1–60 d Following Stress</th>
<th>1–120 d Following Stress</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control Period 120–31 d Before Stress</td>
<td>Primary Risk Periods</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>No.</td>
<td>120–31 d Before Stress</td>
<td>1–90 d Following Stress</td>
<td>1–30 d Following Stress</td>
<td>1–60 d Following Stress</td>
<td>1–120 d Following Stress</td>
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<td></td>
</tr>
<tr>
<td>Risk of HZ: HZ episodes</td>
<td>&lt;60</td>
<td>21 405</td>
<td>24</td>
<td>22</td>
<td>0.92 (.51–1.63)</td>
<td>0.10%</td>
<td>0.07%</td>
</tr>
<tr>
<td></td>
<td>≥60</td>
<td>18 406</td>
<td>54</td>
<td>37</td>
<td>0.69 (.45–1.04)</td>
<td>0.08</td>
<td>0.04 (.21–.93)</td>
</tr>
<tr>
<td>All</td>
<td>39 811</td>
<td>78</td>
<td>59</td>
<td>0.76 (.54–1.06)</td>
<td>0.11</td>
<td>0.62 (.36–1.05)</td>
<td>0.08</td>
</tr>
<tr>
<td>Risk of stress-related mental health visits: mental health episodes</td>
<td>&lt;60</td>
<td>21 405</td>
<td>454</td>
<td>750</td>
<td>1.65 (1.47–1.86)</td>
<td>&lt;.001</td>
<td>2.06 (1.82–2.32)</td>
</tr>
<tr>
<td></td>
<td>≥60</td>
<td>18 406</td>
<td>141</td>
<td>289</td>
<td>2.05 (1.68–2.51)</td>
<td>&lt;.001</td>
<td>2.51 (2.04–3.09)</td>
</tr>
<tr>
<td>All</td>
<td>39 811</td>
<td>595</td>
<td>1039</td>
<td>1.75 (1.58–1.93)</td>
<td>&lt;.001</td>
<td>2.51 (2.04–3.09)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HZ, herpes zoster.

* Used generalized estimating equation methods for analysis of repeated data to adjust for enrollees contributing data for multiple visits.
Clinicians and patients alike have assumed that HZ can be triggered by psychological stress, but few studies have explored this hypothesis directly [5–8]. We used case-only methods to investigate this premise, and found no evidence that stress triggers HZ. Case-only methods are powerful because they are self-matched, eliminating effects of selection bias and measured or unmeasured time-invariant confounders [9]. We selected specific, well-established stressors to test this hypothesis [10–12]—a catastrophic health event or death occurring to a spouse—and validated the stressors by showing they increased stress-related mental health visits. We assessed risk as incidence and as proportion of total healthcare services to account for the possibility that the stressor might lead patients to postpone or forego all healthcare services, including those for HZ. Our conclusions remained unchanged with different time windows and age strata.

Three earlier studies explored the impact of stress on HZ; all involved survey methods [5–8]. Two case-control studies found a higher portion of HZ patients reporting negative (by self-definition) life events within 2, 3, and 6 months prior to HZ [5, 8]. However, a follow-up cohort study by one of these research teams found no HZ increase following self-identified negative life events when the recall period was as long as 3 years [6, 7]. Aside from the lack of interviewer blinding in these studies, serious limitations have been described for this type of research (termed life-events research), particularly when they involve retrospective methods [5]. Limitations include recall bias, subjective weighting of different life events, and uncertainty regarding how to categorize and aggregate life events. Indeed, the positive findings of retrospective life-events studies are often repudiated when reevaluated using prospective studies [5].

Other studies relate indirectly to impacts of stress on HZ. Measures of VZV-specific immunity are blunted among persons with depression, although implications of these changes on HZ risk are unknown [13]. Virologic evidence of VZV reactivation has been detected in astronauts during space travel [14, 15] and children in ICUs [16], but implications of these findings for development of HZ are unclear, and the relationship of these provocations to psychological stress are conjectural. Finally, evidence that psychological stress can cause reactivation of the closely related herpes simplex viruses and trigger herpes labialis or genitalis has been equivocal [5].

Our study has limitations. It is based on administrative data, so misclassifications (eg, of HZ, catastrophic health event, spouse) are possible, but do not necessarily bias our conclusions. Persons would plausibly neglect to seek care for HZ following our stressor; indeed, HZ episodes declined during our risk period, significantly at times, consistent with this phenomenon. Our findings are a reminder that the confounding role of variable healthcare-seeking on study outcomes should be considered in health services research. We controlled for the phenomenon by evaluating HZ as a proportion of healthcare services, reasoning that many or most services would be similarly deferred. Assessed this way, the RRs approached unity. Although this approach remains crude as deferral of healthcare-seeking would likely vary for different services, we feel comfortable that it would be hard to hide a stress-related increased risk of HZ in our results, particularly because population surveys suggest that in general, ~95% of patients with HZ seek healthcare [17].

We found no evidence that psychological stress triggers HZ. The risk factors for HZ remain unknown, as are the molecular pathophysiological triggers for reactivation of VZV; these are areas of ongoing study. Patients should, however, immediately seek care for suspected HZ so that the illness can be controlled and curtailed with timely antiviral treatment and pain management, regardless of the underlying HZ trigger. Meanwhile, for persons aged 60 years and older, an effective vaccine is available that can help prevent this disabling disease [1].

Notes

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Author contributions. J. W. L. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: R. H. Acquisition of data: J. W. L. Analysis and interpretation of data: all authors. Drafting of the manuscript: R. H. Critical revision of the manuscript for important intellectual content: R. H., J. W. L. Statistical analysis: All authors. Study supervision: R. H.

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References


