Common genetic and shared environmental confounds in the association between life events and dementia

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Research Questions

- Is there an effect of life events on dementia after adjusting for genetic and shared environmental confounds?
- To what extent do common genetic and shared environmental confounds account for the association between life events and dementia?

Background

- Negative life events correlate with dementia risk.
- Life event measures index stress but also encompass other factors:
  - Social engagement, socioeconomic conditions, and physical health.
  - Life events consist of factors considered to raise dementia risk.
- It is unclear whether genetic and shared environmental effects account for the correlation between negative life events and dementia risk.

Methods

- Participants
  - 865 families of same-sex MZ/DZ twins ≥ 50 years (range: 50.1 – 92.9 years) from the Swedish Adoption/Twin Study of Aging (SATSA) measured between 1 – 3 occasions from 1984 to 1990.
  - 15.06% of the sample received a dementia diagnosis ≥ 1990.
- Measures
  - Life events
    - A 25-item negative and positive life event scale assessing whether life events ever occurred up to 1990.2
    - Factor analysis determined that items encompass 6 domains:
      - General loss; negative life events of children; illness of self; family strife; negative life events of spouse; and positive life events.
  - Dementia diagnosis
    - Clinical and registry sources of diagnosis:
      - Clinical – Cognitive screening administered (cognitive battery, including MMSE and/or TELE screening).
      - A diagnostic consensus board assigned a consensus clinical diagnosis (DSM-III-R and DSM-IV criteria for dementia and NINCDS-ADRDA criteria for AD).
      - Registry – All who did not receive a cognitive screening or lost to follow-up were linked to the Swedish National Patient Register (NPR) and Cause of Death Register (CDR) containing International Classification of Disease (ICD) dementia codes.
- Data Analysis
  - Preliminary analyses (not shown):
    - Exploratory Factor Analysis of 25 life event items
  - Total phenotypic effect of life events on dementia (Table 1)
  - Biometric regression models of MZ/DZ twins for life events and dementia using Mplus 8.2 (Figure 1)
    - Model-fitting results for significant effects of life events on dementia (general loss and negative spousal events) on dementia (Table 2)
    - Model sequence:
      - Baseline (unrestricted)
      - A=C
      - AE
      - CE
    - Estimated rA, rC, rE from best-fitting models (Table 3)

Results

- The phenotypic effect of life events on dementia could only be detected for two life events, general loss and negative spousal events.
- Social selection factors likely play a role in the association between these life events and dementia.
- No significant within-family (E) effect of life events on dementia:
  - LE 1: βE = 0.006, p = 0.955
  - LE 5: βE = -0.027, p = 0.855

Table 1. Phenotypic effect of life events on dementia

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Estimate</th>
<th>SE</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LE1</td>
<td>0.143</td>
<td>0.049</td>
<td>0.003</td>
</tr>
<tr>
<td>LE2</td>
<td>0.029</td>
<td>0.112</td>
<td>0.793</td>
</tr>
<tr>
<td>LE3</td>
<td>-0.049</td>
<td>0.075</td>
<td>0.511</td>
</tr>
<tr>
<td>LE4</td>
<td>-0.016</td>
<td>0.062</td>
<td>0.797</td>
</tr>
<tr>
<td>LE5</td>
<td>0.098</td>
<td>0.049</td>
<td>0.045</td>
</tr>
<tr>
<td>LE6</td>
<td>0.094</td>
<td>0.089</td>
<td>0.286</td>
</tr>
</tbody>
</table>

Conclusions

- Independent ACE effects underlying life events unable to account for significant phenotypic effect of life events on dementia.
- Social selection factors most likely explain the association between life events and dementia.
- Limited evidence of a quasi-causal effect of life events on dementia.
- rCE may explain the association between general loss and dementia.
- rGE may explain the association between negative spousal events and dementia.
- Low power likely limiting factor for inferring etiological mechanisms.

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References