Original Contribution

Loss of a Child and the Risk of Amyotrophic Lateral Sclerosis

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Between 1987 and 2005, the authors conducted a case-control study nested within the entire Swedish population to investigate whether loss of a child due to death is associated with the risk of amyotrophic lateral sclerosis (ALS). The study comprised 2,694 incident ALS cases and five controls per case individually matched by year of birth, gender, and parity. Odds ratios and their corresponding 95% confidence intervals for ALS were estimated by using conditional logistic regression models. Compared with that for parents who never lost a child, the overall odds ratio of ALS for bereaved parents was 0.7 (95% confidence interval (CI): 0.6, 0.8) and decreased to 0.4 (95% CI: 0.2, 0.8) 11–15 years after the loss. The risk reduction was also modified by parental age at the time of loss, with the lowest odds ratio of 0.4 (95% CI: 0.2, 0.9) for parents older than age 75 years. Loss of a child due to malignancy appeared to confer a lower risk of ALS (odds ratio = 0.5, 95% CI: 0.3, 0.8) than loss due to other causes. These data indicate that the risk of developing ALS decreases following the severe stress of parental bereavement. Further studies are needed to explore potential underlying mechanisms.

Amyotrophic lateral sclerosis; etiology; stress

Abbreviations: ALS, amyotrophic lateral sclerosis; ICD, International Classification of Diseases.

Amyotrophic lateral sclerosis (ALS) is a progressive and lethal motor neuron degenerative disease of largely unknown cause (1). Established risk factors for ALS include aging (2), male gender (3), and mutations in the superoxide dismutase gene (SOD1) in familial ALS cases (4). Recently, inflammatory mechanisms involved in ALS onset and rate of progression have been a subject of debate. This theory assumes an immune component in the pathogenesis of ALS through activation of microglia in the neighborhood of motor neurons (5). Yet, the effect of stressful life events—a powerful immune system modulator (6)—on the occurrence of ALS has not been studied to our knowledge.

The loss of a child is one of, if not the most, severely stressful events one can encounter and has been associated with increased risk of several conditions in bereaved parents, such as cardiovascular disease, diabetes, and multiple sclerosis (7–9). In contrast to these findings, immune modulation due to stress, causing down-regulation of pro-inflammatory cytokine production, might be neuroprotective (6). Moreover, corticotropin-releasing hormone, one of the major stress hormones, also has neuroprotective effects by enhancing expression of neurotrophic factors and inhibiting toxic processes in the central nervous system (10). In addition, lifestyle changes after the occurrence of stressful life...
events may also affect the risk of ALS, being either protective or injurious, through overabundant or insufficient energy intake (11, 12), increased smoking (13) or alcohol consumption (14), or medication use (15).

Because of the rarity of the disease and the exposure (i.e., loss of a child), as well as difficulties in establishing a temporal relation between the two factors, studying the impact of severe stress on the pathogenesis of ALS is a challenge. By using several nationwide registers with hospital discharge diagnoses, causes of death, and familial information, we were able to explore the association between loss of a child by death and the risk of ALS.

**MATERIALS AND METHODS**

**Health care system**

The public medical service in Sweden is divided into 27 financially and administratively independent areas. Charges for medical services are kept low enough to permit all citizens to have equal access to public health care. Because there is no private inpatient treatment in Sweden, hospital-provided medical services are population based and referable to the county in which the patient lives. Since 1964–1965, the Swedish National Board of Health and Welfare has compiled data on individual hospital discharges coded according to the *International Classification of Diseases* (ICD), Seventh Revision (ICD-7) until 1967, Eighth Revision (ICD-8) from 1968 through 1986, Ninth Revision (ICD-9) from 1987 through 1996, and Tenth Revision (ICD-10) since 1997 (16). Since 1987, the In-patient Register has covered all administratively independent areas, and thereby the entire Swedish population. For this reason, follow-up of our study cohort started on January 1, 1987.

**Study design**

We conducted a case-control study nested within the Swedish Multi-Generation Register held by Statistics Sweden (17). The population in the Multi-Generation Register includes persons born in 1932 or later (index persons) together with their parents. In total, the register includes more than 13 million unique individuals. The register contains information such as the national registration number, birth date, and birth place of these individuals. Trying to exclude a potential genetic predisposition to ALS, that is, incident cases whose onset occurred before age 30 years, we included only individuals aged 30 years or older in 1987. We also restricted the study to subjects born in Sweden, and, since our main exposure of interest was parental bereavement, we excluded those who had no offspring registered in the Multi-Generation Register. Finally, we identified 3,751,183 individuals who satisfied all the above-mentioned criteria and had never emigrated out of Sweden before 1987. Of these individuals, we identified 223 subjects with prevalent ALS diagnosed before January 1, 1987, and recorded in the In-patient Register (ICD-8 code 348.00). There were 436 individuals who had no valid corresponding record in any other registers, including four Swedish National Censuses conducted by Statistics Sweden in 1960, 1970, 1980, and 1990. These individuals were excluded from the cohort, leaving 3,750,524 in the analytic cohort (figure 1).

The study cohort was followed through record linkages to the In-patient Register, the Causes of Death Register, and
the Emigration Register using the individually unique national registration numbers assigned to all residents of Sweden. Follow-up stopped at the date of first diagnosis of ALS, death, emigration out of Sweden, or December 31, 2005, whichever occurred first. During the study period, 2,695 incident cases of ALS were identified from the In-patient Register (ICD-9 code 335C, ICD-10 code G122). After a further check of parity status before case date, one case whose offspring were registered only after diagnosis of ALS was excluded, leaving 2,694 cases in the main analysis. Using the method of incidence density sampling (18), we randomly selected 13,470 controls (five controls for each case). They were alive, had not emigrated or been diagnosed as ALS patients when their corresponding case was diagnosed, and were the same gender and had the same year of birth as ALS patients when their corresponding case was diagnosed, and were the same gender and had the same year of birth as well as parity status as their corresponding case at that time.

Measurement of exposure

Livebirths among cases and controls were first identified through the Multi-Generation Register and were later linked to the Causes of Death Register, where death date (1961–2005) and cause of death (1961–2003) were recorded. Age at first childbirth and educational level as indicators of socioeconomic status were determined from the Multi-Generation Register and the Education Register. The Education Register provides information on the highest attained educational level for all residents of Sweden who were alive in 1985 or later.

We also examined the potential modifying effects on the risk of ALS of cause of bereavement (unnatural (ICD-7, -8, and -9 codes 000–799; ICD-10 codes A00–R99) vs. natural (ICD-7, -8, and -9 codes 800–999; ICD-10 codes V01–Y98)), duration of the stressor (time since bereavement), gender and age of parent at the time of bereavement, and family size (number of children before case date, including deceased ones). The analysis of cause of the children’s death was restricted to cases diagnosed between 1987 and 2003 given the incompleteness of death certificates after that time. All these characteristics were focused on the first bereavement identified from the Causes of Death Register for parents who had lost more than one child.

Statistical analysis

Association between bereavement due to loss of a child and the risk of ALS was measured by odds ratios and their 95 percent confidence intervals derived from conditional logistic regression models (SAS PHREG procedure, version 9.1, SAS Institute, Inc., Cary, North Carolina). Since controls were selected by matching to cases by birth year, gender, and parity status, these variables were inherently adjusted. Effect modification was analyzed through combinations of different potential effect modifiers. A test for linear trends was conducted by using the median values of the categories to create a single continuous variable. In all models, parents who had never lost a child served as the reference group. In this paper, all reported p values are two sided.

To allay the concern of case underascertainment due to using only hospitalized cases, we performed a sensitivity analysis by including death-certificate-only cases, that is, cases with ALS as the underlying cause of death but not recorded in the In-patient Register. Since data regarding causes of death during 2004 and 2005 were not available, this analysis was restricted to cases identified between 1987 and 2003. Another concern related to relying on hospitalization data only is the potential difference in initial disease severity between hospitalized and nonhospitalized cases. We performed an additional sensitivity analysis within the stratum with a follow-up time of longer than 10 years.

RESULTS

The distributions of gender, age at diagnosis, age at first childbirth, educational level, and number of children for cases and controls are presented in table 1. The mean age at diagnosis of ALS was 69 years, and the median age was 71 years (range, 33–95 years). Fifty-three percent of the patients were men. The mean age at ALS diagnosis was 68 (median, 69) years for men and 70 (median, 72) years for women. There was no significant difference between ALS cases and controls with regard to age at birth of the first child or educational level. As shown in table 2, we compared the risk of ALS for parents who had lost a child with that for parents who had never lost a child. Altogether, 105 (3.9 percent) of the 2,694 cases and 748 (5.6 percent) of the 13,470 controls had lost at least one child. Seven (0.3 percent) of 105 bereaved ALS cases and 35 (0.3 percent) of 748 controls had lost more than one child. Compared with that for parents who had never lost a child, the overall odds ratio of developing ALS adjusted for matching variables, age at first childbirth, and educational level was 0.7 (95 percent confidence interval: 0.6, 0.8) for parents who had lost a child.

Bereaved mothers and bereaved fathers had a similar relative risk of ALS. The mean and median ages of parents at the time of bereavement were 56 years and 57 years, respectively. The impact of bereavement on the risk of ALS was further investigated in four parental age groups: 48 years or younger (fertility age), 49–65 years (after fertility age but before retirement), 66–75 years (recently retired), and 76 years or older (far into retirement). The relative risks of ALS decreased consecutively with increasing parental age (p < 0.0001); the lowest relative risk was observed for parents who lost a child long after retirement. The relative risk of ALS was somewhat lower among bereaved uniparous parents (odds ratio = 0.6, 95 percent confidence interval: 0.3, 1.1) compared with parents who had more than one child (odds ratio = 0.7, 95 percent confidence interval: 0.6, 0.9), although the difference was not statistically significant.

Parents whose child died because of natural causes had a relative risk of ALS similar to that for parents whose child died because of unnatural causes (table 2). Among parents who lost a child because of unnatural causes, those who lost a child as a result of suicide seemed to have a slightly lower relative risk; among natural causes, deaths due to...
malignancy seemed to confer a lower parental relative risk of ALS. However, none of these differences was statistically significant given the small number of exposed cases. The average time since bereavement was 16 years. Time since bereavement showed a U-shaped modification of the association between bereavement and ALS; the relative risk reached its minimum value 11–15 years after bereavement, yielding an odds ratio of 0.4 (95 percent confidence interval: 0.2, 0.8), and it increased again afterwards.

To identify whether the modifying effects of time since bereavement and parental age at bereavement were confounded by each other, we analyzed potential combinations among them (table 3). To achieve a detailed stratification with reasonable statistical power, we reclassified time since bereavement as 10 years or less, 11–15 years, and 16 years or more and age of parent at bereavement as 60 years or younger and older than 60 years. The modifying effect of time since bereavement and parental age at bereavement was in accordance with the results observed in the overall analyses (table 3). Thus, duration of stress and parental age at bereavement seemed to both have independent roles in the relation between bereavement due to the loss of a child and risk of ALS.

In addition to the 2,368 cases identified from the Inpatient Register between 1987 and 2003, a total of 726 cases were identified by death certificates only. Additional analysis by including all cases, identified from either the Inpatient Register or the Causes of Death Register, found the relative risk of ALS associated with loss of a child to be similar to that in the main analysis (odds ratio = 0.8, 95 percent confidence interval: 0.6, 0.9). A separate analysis limited to the stratum with a follow-up duration of longer than 10 years also showed a similar result (odds ratio = 0.8, 95 percent confidence interval: 0.6, 1.0).

**DISCUSSION**

In this study, we found a reduced risk of developing ALS following the loss of a child. The relative risks decreased up to one decade after loss and were modified by features of the bereavement. Losses due to malignancy, older parental age at the time of bereavement, and loss of an only child all seemed to enhance the inverse association.

Strengthened by the study's large size, population-based design, complete long-term follow-up, and unbiased ascertainment of ALS, the nested case-control design within a strictly defined cohort preserves the validity of a cohort study, thereby eliminating bias due to selection forces and differential misclassification of exposure among cases and controls. The additional cases identified by death certificates only confirmed the main findings, and the separate analysis with longer follow-up duration supported the robustness of the results.

**TABLE 1. Characteristics of cases and controls in a nested case-control study of amyotrophic lateral sclerosis in Sweden, 1987–2005**

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 2,694)</td>
<td>(n = 13,470)</td>
<td>(n = 16,164)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1,431</td>
<td>7,155</td>
<td>8,586</td>
</tr>
<tr>
<td>Female</td>
<td>1,263</td>
<td>6,315</td>
<td>7,578</td>
</tr>
<tr>
<td><strong>Age (years) at diagnosis/ date of referral</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤60</td>
<td>546</td>
<td>2,730</td>
<td>3,276</td>
</tr>
<tr>
<td>61–70</td>
<td>798</td>
<td>3,990</td>
<td>4,788</td>
</tr>
<tr>
<td>71–80</td>
<td>997</td>
<td>4,985</td>
<td>5,982</td>
</tr>
<tr>
<td>≥81</td>
<td>353</td>
<td>1,765</td>
<td>2,118</td>
</tr>
<tr>
<td><strong>Total no. of children</strong></td>
<td>663</td>
<td>3,315</td>
<td>3,978</td>
</tr>
<tr>
<td>1</td>
<td>1,092</td>
<td>5,460</td>
<td>6,552</td>
</tr>
<tr>
<td>2</td>
<td>611</td>
<td>3,055</td>
<td>3,666</td>
</tr>
<tr>
<td>3</td>
<td>1,124</td>
<td>1,640</td>
<td>2,164</td>
</tr>
<tr>
<td>≥4</td>
<td>353</td>
<td>1,765</td>
<td>2,118</td>
</tr>
<tr>
<td><strong>Age (years) at birth of the first child</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤20</td>
<td>183</td>
<td>976</td>
<td>1,159</td>
</tr>
<tr>
<td>21–30</td>
<td>1,806</td>
<td>9,046</td>
<td>10,852</td>
</tr>
<tr>
<td>≥31</td>
<td>705</td>
<td>3,448</td>
<td>4,153</td>
</tr>
<tr>
<td><strong>Educational level (years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤9</td>
<td>1,327</td>
<td>6,802</td>
<td>8,129</td>
</tr>
<tr>
<td>10–12</td>
<td>825</td>
<td>3,935</td>
<td>4,760</td>
</tr>
<tr>
<td>≥13</td>
<td>359</td>
<td>1,804</td>
<td>2,163</td>
</tr>
<tr>
<td>Missing</td>
<td>183</td>
<td>929</td>
<td>1,112</td>
</tr>
</tbody>
</table>

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controls. Our study also has limitations. Given that data from the Causes of Death Register were available from 1961 only, we might have incorrectly assigned some individuals who had actually lost a child before 1961 to the unexposed group. Nevertheless, the analysis restricted to individuals born after 1945 yielded an odds ratio of 0.4 (95 percent confidence interval: 0.1, 1.2). Another potential concern is the completeness of the Multi-Generation Register before 1991; when parish civil registration offices were responsible for local population registration in Sweden, they deleted from the register the deceased individuals together with their linkages to their parents. Since 1991, tax offices have been supplying complete data to the Multi-Generation Register. However, analyses stratified by calendar period (before and after 1991) rendered virtually unchanged relative risks (data not shown).

Given the large number of cases we accrued in our study, it was not feasible to review the medical records of all cases and verify the correctness of diagnosis. However, the accuracy of the In-patient Register is generally high. In a randomly selected sample of diagnoses of trauma, ischemic heart disease, and malignant tumors in the register, the false-negative rates were 5 percent, 7 percent, and 3 percent and the false-positive rates 1 percent, 2 percent, and 2 percent, respectively, when diagnoses made by an expert panel based on the medical records as the “gold standard” were

### TABLE 2. Odds ratios of amyotrophic lateral sclerosis for bereaved parents according to bereavement characteristics in a nested case-control study of amyotrophic lateral sclerosis in Sweden, 1987–2005

<table>
<thead>
<tr>
<th>Bereavement characteristics</th>
<th>No. of cases</th>
<th>No. of controls</th>
<th>OR*, †</th>
<th>95% CI*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No bereavement‡</td>
<td>2,589</td>
<td>12,722</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td>Bereavement</td>
<td>105</td>
<td>748</td>
<td>0.7</td>
<td>0.6, 0.8</td>
</tr>
<tr>
<td>Time since bereavement (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5</td>
<td>24</td>
<td>180</td>
<td>0.6</td>
<td>0.4, 1.0</td>
</tr>
<tr>
<td>6–10</td>
<td>18</td>
<td>116</td>
<td>0.8</td>
<td>0.5, 1.2</td>
</tr>
<tr>
<td>11–15</td>
<td>8</td>
<td>107</td>
<td>0.4</td>
<td>0.2, 0.8</td>
</tr>
<tr>
<td>16–20</td>
<td>11</td>
<td>80</td>
<td>0.7</td>
<td>0.4, 1.3</td>
</tr>
<tr>
<td>≥21</td>
<td>44</td>
<td>265</td>
<td>0.8</td>
<td>0.6, 1.1</td>
</tr>
<tr>
<td>Gender of parent at bereavement</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>48</td>
<td>356</td>
<td>0.7</td>
<td>0.5, 0.9</td>
</tr>
<tr>
<td>Female</td>
<td>57</td>
<td>392</td>
<td>0.7</td>
<td>0.5, 0.9</td>
</tr>
<tr>
<td>Age (years) of parent at bereavement</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤48</td>
<td>42</td>
<td>235</td>
<td>0.9</td>
<td>0.6, 1.2</td>
</tr>
<tr>
<td>49–65</td>
<td>36</td>
<td>247</td>
<td>0.7</td>
<td>0.5, 1.0</td>
</tr>
<tr>
<td>66–75</td>
<td>17</td>
<td>161</td>
<td>0.5</td>
<td>0.3, 0.8</td>
</tr>
<tr>
<td>≥76</td>
<td>10</td>
<td>105</td>
<td>0.4</td>
<td>0.2, 0.9</td>
</tr>
<tr>
<td>Nature of bereavement§</td>
<td>2,276</td>
<td>11,189</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td>Unnatural</td>
<td>36</td>
<td>243</td>
<td>0.7</td>
<td>0.5, 1.0</td>
</tr>
<tr>
<td>Suicide</td>
<td>10</td>
<td>82</td>
<td>0.6</td>
<td>0.3, 1.2</td>
</tr>
<tr>
<td>Other</td>
<td>26</td>
<td>161</td>
<td>0.8</td>
<td>0.5, 1.2</td>
</tr>
<tr>
<td>Natural</td>
<td>56</td>
<td>408</td>
<td>0.7</td>
<td>0.5, 0.9</td>
</tr>
<tr>
<td>Malignancy</td>
<td>14</td>
<td>136</td>
<td>0.5</td>
<td>0.3, 0.9</td>
</tr>
<tr>
<td>Other</td>
<td>42</td>
<td>272</td>
<td>0.7</td>
<td>0.5, 1.0</td>
</tr>
</tbody>
</table>

* OR, odds ratio; CI, confidence interval.
† Derived from conditional logistic regression models and thus automatically adjusted for matching variables including gender, year of birth, and number of children at case diagnosis.
‡ Parents who had never lost a child served as the reference group for all data in this table.
§ Because of unavailable data regarding causes of death for 2004 and 2005, analyses were focused on cases diagnosed between 1987 and 2003, including 2,368 cases and 11,840 controls. Unnatural bereavement: International Classification of Diseases (ICD), Seventh Revision (ICD-7), Eighth Revision (ICD-8), and Ninth Revision (ICD-9) codes 800–999; Tenth Revision (ICD-10) codes V01–Y98. Natural bereavement: ICD-7, -8, and -9 codes 000–799; ICD-10 codes C00–D09. Suicide: ICD-7 codes 9639, 971–979; ICD-8 and -9 codes 950–959; ICD-10 codes X60–X84, Y870. Malignancy: ICD-7, -8, and -9 codes 140–209; ICD-10 codes C00–D09.
used (19). In addition, even if some individuals were incorrectly diagnosed as ALS patients, this misclassification is not likely differential between parents who lost a child because of death and parents who never lost a child because of death.

Because we relied solely on hospitalization data to identify ALS cases, concerns may be raised regarding underascertainment of cases and differential initial severity between hospitalized and nonhospitalized cases. However, the similar results in the sensitivity analysis we obtained by also including death-certificate-only cases implies that potential underascertainment did not have any important influences. Furthermore, the long follow-up duration in our study might have ensured that most cases were identified from the In-patient Register, although we might have missed some recent cases—those whose onset of ALS occurred during the most recent calendar years of follow-up or who had a less aggressive subtype—those who survived longer than 10 years. Again, however, the similar result in another sensitivity analysis, confined to the stratum with a follow-up duration of longer than 10 years, allayed such a concern.

Our findings indicate that the magnitude of the association between bereavement and risk of ALS may depend on whether it is a loss of the only child, loss of a child due to malignancy, and the duration of the stressor. Compared with multiparous parents, uniparous parents who lose a child have previously been reported to be at increased risk of hospitalizations for mental health problems (20) and have higher total mortality (21). We also observed a slightly stronger inverse association between bereavement and the risk of ALS among uniparous compared with multiparous parents. Although some studies have reported a stronger impact of an unnatural death than of a natural loss in terms of mental health (22) or overall mortality (21), loss of a child due to natural reasons, for example, malignancy, may result in an earlier onset of and longer-lasting stress compared with that initiated in the case of an unnatural loss. In providing care for the terminally ill child, the parents are exposed to severe emotional stress far earlier than the actual date of the child’s death and may even be emotionally exhausted for longer periods after the bereavement. Traumatic memories of the child’s unrelieved pain and difficult moment of death have been reported to affect the parents for many years after the loss (23). Indeed, we observed the strongest negative association between bereavement and risk of ALS about one decade after bereavement. Our data are further supported by two prospective studies in Denmark that assessed the risk of multiple sclerosis and total mortality due to natural causes among parents who had lost a child; the strongest effect was observed 8–9 years after bereavement (9, 21).

We hypothesized that the impact of bereavement would be smallest when the parents were of a fertile age and thus still able to have more children, and that it would increase at retirement with the potential loss of the social network, financial benefits, and health. We did find such a trend in relation to older parental age at the time of loss. This modification by parental age could be due to some unknown interaction between stress and increased age or the additional impact of either divorce or spousal bereavement in the middle-aged and retired groups (24, 25). We had no data on civil status for our cases and controls, precluding analyses of parental bereavement among single, married or cohabitating, divorced, or widowed parents.

The apparent inverse association between loss of a child and the risk of ALS may be mediated by immune system modulation. Microglial cells, the resident immune effector cells in the central nervous system, may cause neuronal degeneration by up-regulating proinflammatory cytokine and glutamate production together with down-regulating neurotrophic factor production (26, 27). On the other hand, stress hormones (e.g., cortisol and norepinephrine) have been shown to inhibit T-helper lymphocyte 1–derived proinflammatory cytokine production but to potentiate T-helper lymphocyte 2–derived anti-inflammatory cytokine production (6). Both inhibition and stimulation are dose and time.

### Table 3: Odds ratios of amyotrophic lateral sclerosis stratified by time since bereavement and age of parents at the time of bereavement in a nested case-control study of amyotrophic lateral sclerosis in Sweden, 1987–2005

<table>
<thead>
<tr>
<th>Age of parent at the time of bereavement</th>
<th>No. of cases</th>
<th>No. of controls</th>
<th>OR*, †</th>
<th>95% CI*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No bereavement‡</td>
<td>2,589</td>
<td>12,722</td>
<td>Referent</td>
<td></td>
</tr>
<tr>
<td>Age of parent at the time of bereavement</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤60 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bereavement 11–15 years</td>
<td>10</td>
<td>53</td>
<td>0.9</td>
<td>0.5, 1.9</td>
</tr>
<tr>
<td>Bereavement 16 years</td>
<td>51</td>
<td>297</td>
<td>0.8</td>
<td>0.6, 1.1</td>
</tr>
<tr>
<td>Age of parent at the time of bereavement</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;60 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bereavement 10 years</td>
<td>32</td>
<td>243</td>
<td>0.6</td>
<td>0.4, 0.9</td>
</tr>
<tr>
<td>Bereavement 11–15 years</td>
<td>1</td>
<td>50</td>
<td>0.1</td>
<td>0.0, 0.7</td>
</tr>
<tr>
<td>Bereavement 16 years</td>
<td>4</td>
<td>48</td>
<td>0.4</td>
<td>0.1, 1.1</td>
</tr>
</tbody>
</table>

* OR, odds ratio; CI, confidence interval.
† Derived from conditional logistic regression models and thus automatically adjusted for matching variables including gender, year of birth, and number of children at case diagnosis.
‡ Parents who had never lost a child served as the reference group for all data in this table.
dependent. For instance, acute stress could stimulate neuro-
trphin release (28) or delayed-type hypersensitivity reac-
tions (29), while long-lasting, major stressful circumstances
may lead to a consistent rise in stress hormones concentra-
tions and thus long-lasting immune suppression (30). Con-
ditions associated with significant changes in stress response
activity through modulation of the systemic or local, pro-
or antiinflammatory cytokine balance may suppress or poten-
tiate disease activity and progression accordingly (6). Be-
side their immune-regulatory function, stress hormones
such as corticotropin-releasing hormone have been sug-
gested to have a neuroprotective role either by enhancing
the excretion of neurotrophic factors or by protecting neu-
ronal cells against oxidative stress, apoptosis, or the toxic
effects of glutamate (10, 31, 32).

Bereavement might also influence the risk of ALS
through lifestyle changes after stressful life events. It is
not known how such lifestyle changes—possibly excessive
smoking, alcohol misuse, changed nutrition, or medication
use—might affect the neurodegeneration process. We were
not able to monitor such lifestyle changes following be-
reavement with our data. However, to our knowledge, no
single lifestyle factor has yet been established as a risk fac-
tor for ALS.

In summary, in this case-control study nested within the
entire Swedish population, we found that bereavement due
to loss of a child was associated with a decreased risk of
ALS. Further studies are needed to understand the underly-
ing mechanisms—whether immune system modulation or
direct neuroprotective effects of stress hormones alone, or
in combination with other factors, mediate the protective
effect of stress on the development of ALS.

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