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Early parental death and late-life dementia risk: findings from the Cache County Study

SIR—Dementia is a major public health problem. Alzheimer’s disease (AD) comprises the majority of dementia cases, and while the causes are still largely unknown, epidemiological studies are investigating a broad array of both genetic and environmental risk factors. Plausible aetiopathological mechanisms include lipid metabolism, inflammation and glucose regulation. Emerging biological evidence suggests that another potential mechanism for increased AD risk is neuronal death through the lifelong cumulative effect of stress reactivity and recovery [1]. Repeated stress causes damage to the CA3 region of the hippocampus via glucocorticoids and excitatory amino acid neurotransmitters released during and immediately after stress. Long-term, chronic stress over many years appears to continue the process and result in neuronal death in the hippocampus [2]. Physiological stress responses may also affect health by modulating the rate of cellular aging via higher oxidative stress, lower telomerase activity and shorter telomere length, all indicators of cell longevity [3] with evidence that neurodegenerative changes may begin decades before clinical manifestation [4, 5].

These potential biological mechanisms, viewed from a life-course perspective, are consistent with observations that poor growth and development and adverse environmental conditions in early childhood are associated with increased disease risk in late life [6]. Socioeconomic adversity in the early years of life, specifically father’s occupation of unskilled manual labourer, has been associated with a 2-fold increase in offspring AD risk [7] and faster rate of late-life cognitive decline in offspring [8]. Early-life parental death is an unexpected and traumatic event which usually poses the greatest adaptive challenges [9] thus introducing a host of potential stressors. These are not only economic but also psychosocial and may have a lifelong impact, especially for individuals with inadequate access to social and emotional resources. Though few studies directly address this question, in a sample of elderly Swedes, a 6-fold increase in dementia risk was demonstrated among participants experiencing a parental death before age 16 [10]. Although early-life adversity is not easily modifiable, establishing a clear link between psychosocial adversity and increased vulnerability to AD and other dementias will aid in the identification of at-risk individuals for more targeted interventions. Effective interventions may reduce the intensity of the body’s physiological stress response and vulnerability to neurodegenerative diseases such as AD and other dementias.

We report here analyses of the relationship between early parental death and dementia risk, in a large population-based epidemiological study. The relative effect of parental death at different stages in the life course was examined. We hypothesised that experiencing early parental death would significantly increase dementia risk, with stronger effects posited for parental deaths occurring earlier in the course of development. Analyses were conducted before and after controlling for gender, age, education and apolipoprotein E (APOE) genotype.

Materials and methods

The Cache County Study on Memory Health and Aging is a population-based epidemiological study of dementia and other cognitive impairments, and the genetic and environmental factors that affect risk for these disorders. The original cohort consisted of 5,092 permanent residents of the county (90% participation rate) aged 65 or older in January 1995. Described in detail elsewhere, four successive data collection waves spaced 3–4 years apart implemented a multi-stage dementia ascertainment protocol to identify prevalent [11] then incident [12] cases of dementia. The diagnostic protocol included a neuropsychological test battery, brief neurological examination, neuropsychiatric inventory and semi-structured clinical history interview with informant. Subjects with a provisional diagnosis of dementia, determined by a geropsychiatrist and the clinical team, also completed MRI brain imaging, lab work, and were re-examined by a study physician. Expert panel consensus conferences generated final diagnoses of dementia, according to DSM-III-R criteria. The published sensitivity of the screening protocol to detect prevalent dementia was 0.99 for the 90/91 cut-off score used in the third wave [13]. Informed consent was obtained for each interview, and all procedures were approved by the Institutional Review Boards of Utah State University, Duke University, and the Johns Hopkins University.
Table 1. Dementia and early-life parental death experience: subject characteristics, bivariate and multivariate logistic regression analyses: odds ratios, 95% confidence intervals (n = 1,793)

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>% with dementia</th>
<th>Unadjusted odds ratio(^a)</th>
<th>Father’s death adjusted odds ratio(^b)</th>
<th>Mother’s death adjusted odds ratio(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F death: 0–4 years</td>
<td>25% (6/24)</td>
<td>4.0 (1.6–10.3)</td>
<td>3.0 (1.1–8.4)</td>
<td>–</td>
</tr>
<tr>
<td>F death: 5–18 years</td>
<td>8.7% (11/126)</td>
<td>1.2 (0.6–2.2)</td>
<td>1.1 (0.6–2.2)</td>
<td>–</td>
</tr>
<tr>
<td>F death: 19+ years</td>
<td>Reference group</td>
<td>Reference group</td>
<td>Reference group</td>
<td>Reference group</td>
</tr>
<tr>
<td>M death: 0–4 years</td>
<td>11% (8/76)</td>
<td>1.5 (0.5–4.2)</td>
<td>–</td>
<td>1.2 (0.4–3.7)</td>
</tr>
<tr>
<td>M death: 5–18 years</td>
<td>10% (8/81)</td>
<td>1.3 (0.6–2.7)</td>
<td>–</td>
<td>1.0 (0.4–2.2)</td>
</tr>
<tr>
<td>M death: 19+ years</td>
<td>7.8% (131/1,676)</td>
<td>Reference group</td>
<td>Reference group</td>
<td>Reference group</td>
</tr>
<tr>
<td>Women</td>
<td>7.8% (82/1,047)</td>
<td>0.95 (0.7–1.3)</td>
<td>1.3 (0.9–1.8)</td>
<td>1.2 (0.9–1.8)</td>
</tr>
<tr>
<td>Men</td>
<td>8.2% (61/746)</td>
<td>Reference group</td>
<td>Reference group</td>
<td>Reference group</td>
</tr>
<tr>
<td>e4 allele present</td>
<td>10.9% (61/562)</td>
<td>1.7 (1.2–2.4)</td>
<td>2.2 (1.5–3.2)</td>
<td>2.2 (1.5–3.1)</td>
</tr>
<tr>
<td>e4 allele absent</td>
<td>6.7% (82/1,231)</td>
<td>Reference group</td>
<td>Reference group</td>
<td>Reference group</td>
</tr>
<tr>
<td>Age: (mean, SD)</td>
<td>76.2 (6.5)</td>
<td>1.1 (1.1–1.2)</td>
<td>1.2 (1.1–1.2)</td>
<td>1.2 (1.1–1.2)</td>
</tr>
<tr>
<td>Education: (mean, SD)</td>
<td>13.3 (2.7)</td>
<td>0.95 (0.9–1.0)</td>
<td>1.0 (0.9–1.0)</td>
<td>1.0 (0.9–1.0)</td>
</tr>
</tbody>
</table>

\(^a\) Bivariate relationships tested with each independent variable analysed in a separate model.

\(^b\) Multivariate-adjusted models adjusted for subject age, gender, education and apolipoprotein e4.

The present study utilised data from the study’s third wave only, because parental death data were not collected until this time. Thus, the present work constitutes a prevalence analysis, given that the risk variable was collected in the same wave as the dementia ascertainment. There were 2,318 participants screened in the third wave, and of these, 2,048 completed their cognitive evaluation while 270 had incomplete assessments. Individuals with complete data were younger (P < 0.001), had higher education (P < 0.001), but were equally likely to have father’s death (P = 0.071) or mother’s death (P = 0.544) during childhood, and were equally likely to be women (P = 0.288), or have the APOE e4 allele (P = 0.445), compared to those lost to attrition between screener and clinical assessment. Of the 2,048 subjects retained for the present study, 255 had missing data on one or more independent variable (primarily parents’ death dates), resulting in a final analysis sample of 1,793. The sample includes 143 cases of dementia: 81 AD and no other dementia, 12 AD in combination with other dementia, 21 vascular dementia and 29 mixed other dementias.

Parental death dates were provided at the screening interview by self-report for 98% of those without dementia and 72% of those with dementia whose cognitive screening score and interviewer clinical judgment suggested capacity to provide these data, and by proxy for the remainder. A subject’s age at parental death was coded as 0–4 years (infancy and early childhood), 5–18 years (middle childhood and adolescence) and 19 years or older or parent still living (adulthood). From buccal DNA samples, the APOE genotype was determined using polymerase chain reaction (PCR) amplification and restriction isotyping [14] which was then recoded into a dichotomous variable indicating the presence or absence of at least one e4 allele [15].

A set of logistic regressions was estimated to examine the bivariate relationship between the outcome of dementia with each of the separate parental death variables and covariates. Separate models were also computed to test for effects of early father’s death and early mother’s death, adjusting for age, gender, education and the presence of at least one e4 allele at the APOE locus (Table 1). Additionally, interactions between parental death and gender were tested but removed as all were non-significant. Analyses were performed using SPSS version 15.0.

Results

There were 141 subjects whose father (only) died during childhood, 108 subjects whose mother (only) died during childhood and 9 subjects for whom both parents died during childhood. The prevalence of dementia was higher among those with the e4 allele and those whose father died during childhood (Table 1). Subjects with dementia were older but with comparable education and equally likely to be female and to have mother’s death in childhood, compared to subjects without dementia.

Bivariate relationships between each independent variable and dementia status were evaluated with unadjusted logistic regression models (Table 1). Subjects whose father died before subject age 5 had a 4-fold risk (OR = 4.0; 95% CI: 1.6–10.3) for dementia, compared to those whose father was either still living or had died during subject’s adulthood, with no significant increased risk of dementia among those whose father died during subject’s middle childhood or adolescence. The effect of mother’s death was not significant during early childhood, middle childhood or adolescence. There was no effect for gender or education; however, the presence of the e4 allele and older age were both associated with significantly greater dementia risk in separate models. In the adjusted model for father’s death, the effect of father’s death
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decreased somewhat to a 3-fold risk (OR = 3.0; 95% CI: 1.1–8.4) prior to subject age 5.

Discussion

Early-life death of a father, but not of a mother, was associated with increased risk for dementia in late life in the Cache County, Utah, population. Given that mothers generally have stronger biological and behavioural connections to their infants and young children than fathers, these results were somewhat paradoxical. Chronic psychoemotional stress may result from the non-normative event of either parent’s death during childhood with the resultant loss of both instrumental and emotional support from the deceased parent, as well as, for many, the stigma of no longer living in a nuclear family constellation. Additionally, death of a father typically results in an immediate reduction in economic resources (which may or may not be ameliorated by the mother’s employment or remarriage). This may have resulted in economic adversity in terms of exposure to poverty, lower quality health care, limited access to cognitively stimulating activities during childhood and other lost opportunities. Since widowers tend to remarry more readily than widows, both the economic and psychoemotional adversity from father’s death may be greater than from mother’s death. Childhood economic disadvantage could also lead to lower levels of educational attainment and higher risk lifestyle for offspring, leading to higher dementia risk. Yet, the effect of early father’s death remained significant after adjustment for education and other covariates ($P = 0.035$).

The association between higher dementia risk and early paternal death might have been due to a cohort effect in which earlier birth cohorts may have had a greater likelihood of early paternal death. However, the proportion of subjects whose father died during their childhood was 7.3%, 9.8% and 7.8% for those born between 1900 and 1910, between 1911 and 1920 and between 1921 and 1930, respectively.

These results are limited by the fact that analyses were cross-sectional, and self and proxy reports of parental death dates had an unknown degree of recall bias. Residents of the close-knit, rural communities in Cache County, Utah, may have had a higher level of social support than individuals in other communities; however, this phenomenon would tend to generate a more conservative estimate of the deleterious effects of early paternal death.

In this community-based sample, a 3-fold increased risk for dementia was observed when death of a father occurred during the early developmental years of life, suggesting a decades-long adverse effect on cognitive health. While the present study does not definitively clarify the relative influence of biological, economic and psychological effects, results were robust after consideration of birth cohort effects (age covariate), socioeconomic status (education covariate) and genetic risk (APOE covariate).

Future studies could examine socioeconomic status change after parental death, the subjective assessment of the psychoemotional meaning of the loss of the parent during childhood and the potential effect of remarriage. The specific causes of parental death should be examined because early occurrence of infectious or chronic diseases may play a role in the foetal programming of adult disease risk (including dementia) through genetic and epigenetic mechanisms. Other possible mechanisms such as biological effects of advanced paternal age at conception, associated with premature mortality in offspring [16], need further study. It will be important to evaluate the extent to which this early adversity may result in greater vulnerability to other stressors throughout the lifespan in terms of cumulative risk for dementia in late life, and to investigate in more depth what the underlying sociopsychobiological mechanisms may be. Such knowledge may help us to inform both the content of stress management interventions and the characteristics of those in greatest need of such primary prevention strategies.

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Key points

- There is evidence that neurodegenerative changes of dementia may begin decades before clinical manifestation.
- Long-term chronic psychosocial stress has been associated with hippocampal cell death.
- Early-life parental death is an unexpected and traumatic event posing many adaptive challenges.
- In this community-based sample, a 3-fold increased risk for dementia was observed among those with paternal death prior to age 5, even after adjustment for socioeconomic status, birth cohort and genetic risk.

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Conflicts of interest

Dr Norton directed all aspects of this manuscript including conception and design, data acquisition of clinical data, statistical analysis and interpretation, writing original draft and approving all revisions, including the final submitted manuscript. Dr Ostbye contributed to the design, data analysis and interpretation, provided a careful review for intellectual content and gave approval of the final manuscript.
Dr Smith contributed to the design, data analysis and interpretation, provided a careful review for intellectual content and gave approval of the final manuscript. Dr Munger was principal investigator of the ‘Cache County family-based Cohort Study on Aging’, the companion study that collected initial screening test scores and parental death data, and he provided a careful review of this manuscript for intellectual content and gave approval of the final manuscript. Dr Tschanz contributed to the design, data analysis and interpretation, provided a careful review for intellectual content and gave approval of the final manuscript. Each of the authors, Drs Norton, Østbye, Smith, Munger and Tschanz, has no financial or personal conflicts of interest.

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References


SIR—Measuring the quality of life of people with dementia is overwhelmingly important in ageing research [1, 2]. However, there is remarkably little systematic data available regarding the applicability and inter-rater reliability of the available tools. What little data is available is often gathered by research teams with significant experience in rating the quality of life of people with dementia. Applicability of tools to assess the quality of life of people with dementia in routine research remains uncertain. Although there is evidence that even people with moderate to severe cognitive impairment can reliably rate their quality of life [3], there is little data regarding the effect of different interviewers on the reliability of those assessments.

The Quality of Life in Alzheimer’s Disease (QOL-AD) scale is a brief (generally administered in ∼10 min), dementia-specific tool [4]. Versions are available for use both with the person with dementia and an informant. The available data suggest that the QOL-AD has good inter-rater and test–retest reliability [4, 5]. The QOL-AD also appears to be suitable for use to assess the quality of life of people with severe dementia [3].

Rating the quality of life of people with dementia living in residential care facilities in routine research practice

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