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Influence of negative life events and widowhood on risk for dementia

Lotte Gerritsen, PhD^{1,*}, Hui-Xin Wang, PhD³, Chandra A. Reynolds, PhD⁴, Laura Fratiglioni, MD, PhD^{3,5}, Margaret Gatz, PhD^{6,1}, and Nancy L. Pedersen, PhD^{1,6}

¹Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

²Department of Clinical Psychology, Utrecht University, Utrecht the Netherlands ³Aging Research Center, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet-Stockholm University, Stockholm, Sweden ⁴Department of Psychology, University of California–Riverside, Riverside, CA ⁵Stockholm Gerontology Research Center, Stockholm, Sweden ⁶Department of Psychology, University of Southern California, Los Angeles, CA

Abstract

Objective—The aim of the current study was to examine the effect of negative life events and widowhood on the incidence of dementia.

Design and participants—We used data from four Swedish longitudinal cohort studies with a total of nearly 2,000 participants and 8–25 years of follow-up.

Measurements—We examined seven stressful events for which data were available in all cohorts. Clinical dementia diagnoses were made through medical and psychological examinations. Cox proportional hazards models were used to estimate the association between life events and dementia adjusting for lifestyle and cardiovascular risk factors.

Results—The experience of one stressful life event was not associated with dementia incidence, but two or more life events at baseline predicted higher risk for dementia (pooled HR: 2.00). This was most apparent for the incidence of vascular dementia (pooled HR: 3.60) but not of Alzheimer's disease (pooled HR: 1.29). Moreover we found that for persons who were widowed and had experienced one or more events, the risk for dementia 3-fold.

Conclusions—Widowhood augments the effect of life events on dementia incidence and life events specifically increase the risk for vascular dementia.

Keywords

Stress; dementia; Alzheimer's disease; vascular dementia; old age

*corresponding author: lotte.gerritsen@ki.se, Tel: 0031-647128391.

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Introduction

The experience of stressful life events is thought to have a detrimental effect on the brain especially during stages of life when the brain undergoes major changes (e.g. development in early life and decline in late life (1, 2). During the aging process the brain loses its plasticity, and animal studies have shown that it is particularly this lack of plasticity that leads to post stress dendritic atrophy in both the hippocampus and prefrontal cortex(3). Old age encompasses powerful stressors due to important life changes such as retirement, loss of loved ones, and new diseases. While some events such as loss of a spouse have been suggested to be relatively more impactful to younger individuals when the loss is less expected(4), in older ages the exposure to stressful events and accompanying stress responses may affect functioning due to reduced plasticity in the aging brain(3).

So far there is inconclusive evidence on whether psychosocial stress increases the risk for all types of dementia or only for a certain type of dementia. Previous studies reported that taking care of a severely ill spouse(5), work-related stress(6–8), and outcomes associated with experiencing traumatic events such as post-traumatic stress disorder(9), may increase the risk for dementia. Whether negative life events will have a negative impact on health depends amongst other factors on the quality of social support. For instance marital status and widowhood in particular, has frequently been related to dementia risk (10–12). Therefore in the current study we will look specifically at the effect of experiencing life events after being widowed.

Some of the previous studies suggested that psychosocial stress particularly increases the risk for vascular dementia (VaD) (7), while others suggest that it more likely increases the risk for Alzheimer's disease (AD)(8, 13). The experience of stressful life events has been shown to lead to Alzheimer-related pathology in mouse studies(14) and is also associated with increased risk for cardiovascular diseases and aggravation of vascular risk factors (15). Therefore, it could well be that stress contributes to both AD and VaD. These previous studies had either a 100% female population(13), had a cross-sectional design(7) or were done in a relatively small sample.

In the current study, we investigated whether stressful life events experienced in life can predict the incidence of dementia in four separate Swedish cohort studies with a total of nearly 2,000 participants and a follow-up time varying between 8 and 25 years. By combining these studies, we have enough statistical power to examine the effect of life events not only on dementia, but also specifically on AD and VaD, and whether widowhood augments the effect of experiencing new stressful events on the risk for dementia.

Methods

Sample

Data were derived from four separate cohorts, three of which came from the population-based Swedish Twin Registry (STR), namely (1) the Swedish Adoption/Twin Study of

Aging (SATSA)(16), (2) the Origins of Variance in the Oldest Old: Octogenarian Twins (OCTO-Twin) study,(17) and (3) the Aging in Women and Men (GENDER) study (18).

In brief, SATSA is an ongoing study of same-sex twin pairs (both monozygotic and dizygotic pairs). The first questionnaire was filled out by 2,019 participants in 1984. Immediately after receipt of this questionnaire a second questionnaire, including the life events instrument used for this study, was sent out to and returned by 1736 participants, of whom 1443 responded to the life events items. The first face-to-face examination was conducted between 1986 and 1988 and was only performed on participants 50 years or older, with follow-ups every 3 years (except for 1995 to 1997). Medical and cognitive data were available from the first in-person testing wave, during which 630 participants were included. From these 630, 11 participants were excluded due to prevalent dementia, leaving 619 participants.

The OCTO-Twin study included 702 individuals from same-sex (monozygotic and dizygotic) twin pairs (where both had survived to the age of 80 years, with a baseline examination including questionnaires and face-to-face interviews and cognitive testing, in 1991 to 1994 and 4 follow-ups on a 2 year rolling schedule. Of those participating at baseline, 109 were excluded for current analysis because of prevalent dementia and 75 for incomplete data on lifestyle factors and medical background, leaving 517 participants.

The GENDER study consists of 498 twins from unlike-sex (only dizygotic) pairs born from 1916 to 1925 with both members of the pair alive and willing to participate in 1995. Two follow-up occasions of testing took place in 1999 to 2001 and 2003 to 2004. At baseline 496 participants participated on both questionnaires and face-to-face interviews, 20 were excluded for current analysis because of prevalent dementia and 50 participants for incomplete data on lifestyle factors and medical background, leaving 456 participants.

The fourth study is the Kungsholmen Project, which is a community based cohort study of aging and dementia(19) that includes all inhabitants born in 1912 or earlier, and who lived in one area of Stockholm (Kungsholmen) in October 1987. From the original population, all participants with a Mini-Mental State Examination (MMSE) score less than 24 ($n = 314$) and a random sample of participants with an $MMSE > 23$ ($n = 354$) underwent an extensive medical and psychological examination. During the clinical phase of the project, data on medical history, current health, lifestyle and stressful life events were gathered, clinical follow-ups were performed every 3 years. Of these 668 participants, 128 participants did not participate in any of the follow-up waves, leaving 398 participants for the current analysis.

All of the projects received approval from the ethics committee of Karolinska Institutet.

Dementia ascertainment

STR studies—In all three STR studies, dementia was assessed through a 2-step procedure that entailed, first, a cognitive screening and, second, diagnostic assessment of each suspected case(20). In brief, a combination of Mini-Mental State Examination and overall cognitive performance on the test battery was used to screen for dementia.

All twins who screened positive for suspicion of dementia (and their twin partners) were given a complete clinical work-up including physical and neurologic evaluation, a complete history based on informant interviews, neuropsychological assessment, laboratory tests, and neuroimaging. The diagnostic assessment of dementia was based on reviews of medical records (from both inpatient and outpatient settings), the results on cognitive tests and physician evaluation, biochemical blood values, and informant interviews. The final diagnoses of dementia were set at a multidisciplinary consensus conference.

Kungsholmen—In the Kungsholmen Project, all the participants who participated at the face-to-face interviews underwent an extensive clinical examination, including a structured interview on family and personal history by nurses, clinical (physical and neurological) examination by a physician and the administration of psychological tests by trained personnel to assess cognitive and psychological status.

The diagnosis of dementia and dementia-type followed a three-step approach; first a preliminary diagnosis was made by the examining physician, second all cases were independently reviewed by a specialized clinician and third in case of disagreement between the first and second step a third opinion was sought and the concordant diagnosis was accepted.

In all four studies, dementia was diagnosed according to the criteria in the Diagnostic and Statistical Manual of Mental Disorders, third edition, revised (DSM-III-R) (23) and fourth edition (24) and differentially diagnosed as AD (based on the NINCDS/ADRDA criteria) (25, 26) VaD (based on the NINDS-AIREN criteria) (27).

Life events—For each study we only used life events reported at baseline, different methods were used to assess life events in each study, which will be described in detail below.

In SATSA, life events were measured using a structured questionnaire consisting of 18 pre-defined events (28). Participants indicated, for each event, whether it had happened and, the extent to which the event was perceived as stressful.

In GENDER and OCTO-twin, no life events questionnaire was administered. Therefore we constructed a list of life events by using information from the in-person testing interview. The following questions were used to assess life events: ‘how do you rate your current health in comparison to the previous three years?’; ‘Do you have children, if yes how many and how many are still alive?’; ‘How do you rate your current financial situation in comparison to three years ago?’; ‘How many siblings do you have and how many are still alive?’. Additionally, we used data on marital status, changes in living arrangements (e.g. moving to an elderly home) and hospitalization (yes vs. no).

In the Kungsholmen Project, during the clinical phase at baseline, participants were asked the following question: ‘Have you during the last couple of years experienced one or several events that have, respectively, positively or negatively impacted your life?’ Participants could give up to three answers. Their answers were categorized according to the same life

events as assessed in the STR studies and we only used the events reported as negative events.

To make the life event variables comparable over the different four studies, we selected only those seven events on which information was available in all studies (Table 1 shows the frequencies of the reported events).

Covariates—In all four studies comparable methods were used to assess the following variables that were considered as possible confounders for our study: Age at baseline, sex, history of smoking (current, former, never), and level of education (less than elementary school vs. more than elementary school) were based on self-reported data and body mass index (BMI) was based on clinical measurements. Baseline cognitive status was based on the Mini-Mental State Examination(22).

In the STR studies, information on heart diseases was derived from self-report questionnaires and medication use. Information on diabetes from the in-patient register was integrated with self-reports of a doctor's diagnosis of diabetes, use of oral hypoglycemic medication or insulin, or a blood glucose level greater than 11 mmol/liter. Arterial blood pressure was measured at baseline with a mercury sphygmomanometer by trained nurses. If the first reading was abnormal (systolic pressure ≥ 160 mmHg or diastolic pressure ≥ 95 mmHg), two additional readings were made. The mean of the second and third readings was used for analyses.

In the Kungsholmen Project, information on heart diseases was derived from the computerized Stockholm Inpatient Registry System, in which all admission and discharge diagnoses from every hospital in Stockholm are recorded. Diseases were diagnosed according to the *International Classification of Diseases*, Eighth Revision (codes 410–414 for coronary disease, code 428 for heart failure, code 427 for arrhythmia, and code 250 for diabetes mellitus).

Information on alcohol use was collected from relatives or by self-report. Since consumption of alcohol in this elderly population was found to be particularly low we divided the alcohol data into two categories: no use, any use.

Statistical analysis

The relationship between reported life events at baseline and dementia incidence at follow-up was determined using Cox's proportional hazards regression models, separately for each cohort. Time was represented by age of onset of dementia and for those who did not develop dementia we used last recorded age in the cohorts for right censoring. First we examined the overall effect of occurrence of life events (yes vs. no). Second to investigate whether the experience of more events was associated with greater risk, we created dummy variables for the following three categories: no events (reference group); only one event reported; two or more events reported.

Third, separate models were created for dementia, AD, VaD and VaD + mixed type dementia. For these latter models per dementia type, cases with any of the other dementia type were excluded from analysis.

Fourth, to investigate whether being widowed interacts with other negative life events influence the risk of dementia, we first added interaction terms between life event (yes vs. no) and widowhood (yes vs. no) to the models. For these analyses we used widowhood status from marital status, which also included long-time widowers that did not report becoming widow as a life event around the time of baseline measurement and we excluded the event of becoming a widow (N for widowhood status = 354, N for widowhood as life event at baseline = 230). In case of significant interactions we performed stratified analysis by widowhood status and calculated the difference between the widowed and non-widowed groups. Second, for graphic purposes we created a 4-category variable based on the 4 possible combinations of widowhood status with life events (no widowhood + no life events; no widowhood + life events; widowhood + no life events; widowhood + life events) and related it to the incidence of dementia.

Fifth, to further disentangle the effects of life events on dementia we performed the following sensitivity analyses. First we conducted Cox proportional hazard survival analyses per reported life event (widowhood, death of (grand)child etc.). Second, in SATSA we had data on more life events and we had data on the subjective stress experience. We therefore also examined whether using a larger range of life events and the subjective stress experience influenced our results..

We also investigated possible sex and age effects, as the age at which a stressful event occurs may matter and men and women may cope differently with stressful life events. To do this we added interaction terms between life events and sex as well as between life events and age in separate models. In case of significant interactions we performed stratified analysis by sex or age groups.

For all cohorts, we analyzed two models: the first model was adjusted for age and sex, while the second model was additionally adjusted for educational level, baseline cognitive functioning, blood pressure, BMI, diabetes mellitus, alcohol use, current smoking and coronary heart disease. To adjust for relatedness in the twin studies we corrected the standard errors for pair effects by adding zygosity as a stratum in the *proc phreg* statement. All these analyses were conducted using SAS 9.4 software. For the estimates per cohort we will report Wald's Chi-square, Hazard ratios, 95% confidence intervals and p-values.

Pooled estimates over all studies were calculated using the 'meta' package in 'R' using linear regression with random effects in the function 'metagen' in which between-study variance tau-squared was estimated with restricted maximum likelihood.

For these pooled estimates we will report Z-statistics, Hazard ratios, 95% confidence intervals and p-values. Significance was set at $p < 0.05$.

Results

Table 2 shows baseline characteristics, per cohort study. There are several differences among the four studies; for instance participants from SATSA had the lowest mean age and the percentage of males was highest in GENDER (given its design) whereas in the Kungsholmen Project the participants had the highest mean age and lowest percentage of male participation. Dementia incidence rates per year were as follows: SATSA 1%; OCTO-twin 3%; GENDER 3% and Kungsholmen 2%.

All reported hazard ratios (HR) are estimates from Cox proportional hazard models. We describe cohort specific HR's in the supplementary material and HR's from pooled analysis in the main text.

Life events at baseline and dementia incidence-per study

Table S1a in supplementary material gives the estimates per cohort for all-cause dementia. In all cohorts, except for the SATSA cohort the experience of life events was associated with increased risk for dementia.

Life events and dementia incidence—pooled data across studies

When pooling the data we found that across all studies the experience of one event was not significantly associated with dementia over follow-up (pooled HR=1.18; Table 3). However the experience of two or more events was significantly associated with increased risk for dementia incidence (model 2: pooled HR= 2.00; Table 3). Figure 1 shows the corresponding forest plots. The I^2 -statistic for heterogeneity among the four studies in the meta-analysis reached significance in the one reported life event category (test of heterogeneity: $Q=10.9$, $df=3$, $p=0.01$), but not in the two or more events reported category (test of heterogeneity : $Q=7.05$ ($df=3$), $p=0.07$). This suggested that we should be cautious with interpreting the results of one reported life event, as the studies may have been too heterogeneous to pool.

Alzheimer's Disease

Table S1b in supplementary material gives the estimates per cohort for Alzheimer's disease (AD).

After pooling the data across all studies, we found that life events at baseline were not significantly associated with incidence of AD (all Z-statistics <1.60 ; $p >0.05$). See table 3 for more detailed information on pooled estimates. Figure 2a shows the corresponding forest plots. None of the I^2 -statistics reached significance (test of heterogeneity : all Q ($df=3$) <6 ; $p >0.05$), suggesting that the cohorts did not differ too much to pool the single estimates together.

Vascular Dementia

Table S1c in supplementary material gives the estimates per cohort for Vascular dementia (VaD). Figure 2b shows the corresponding forest plots. None of the I^2 -statistics reached significance (test of heterogeneity: all Q ($df=3$) <6 ; $p >0.05$), suggesting that the cohorts did

not differ too much to pool the single estimates together. These analyses showed that one life event at baseline was not significantly associated with greater risk for VaD (pooled HR: 1.61; $p=0.38$), but the experience of two or more life events was associated with greater risk for VaD (pooled HR: 3.10; Table 3).

Vascular Dementia + mixed-type dementia

The number of VaD cases was rather low and to increase statistical power we added cases with mixed-type dementia to the VaD cases. Table S1d in supplementary material gives the estimates per cohort for VaD+mixed type dementia and Figure 2c shows the corresponding forest plots. None of the I^2 -statistics reached significance (test of heterogeneity : all Q ($df=3$) <6 ; $p >0.05$), suggesting that the cohorts did not differ too much to pool the single estimates together.

These analyses showed that one life event at baseline (pooled HR: 2.46; Table 3) and two or more life events (pooled HR= 3.60; Table 3) were associated with greater risk for VaD and mixed typed dementia.

Figures S1 A–C in supplementary material shows the incidence of dementia over time for reporting stressful life events (none, one and two or more) for all types of dementia (Figure S1; Chi-square ($df=2$) was 4.4; $p=0.11$), for AD (Figure S1; Chi-square ($df=2$) was 2.1; $p=0.35$) and for Vascular dementia+mixed type dementia (Figure S1; Chi-square ($df=2$) was 10.8; $p=0.005$).

When comparing the effect of life events on AD versus the effect of life events on VaD and mixed type dementia, we found that the z-statistic for difference in HR for 1 life event was not significant (z-statistic for difference=1.10; p-value =0.16) but the difference for 2 or more life events was significant (z-statistic for difference=2.14; $p=0.03$).

Moderation by widowhood status

In total among all four studies, 607 (30%) participants were widowed, of these 211 (35%) participants were widowed within 3 years prior to baseline. In two of our four cohort studies the interaction term between widowhood status and life events reached significance and in one study (SATSA) it reached borderline significance on the incidence of dementia (p-value for interaction terms: SATSA=0.07; GENDER=0.001; OCTO-twin=0.002; Kungsholmen=0.23).

In further analyses we pooled the results of the four cohort studies and stratified the data on widowhood (and excluded becoming a widow from the reported life events). We found a pooled HR for reporting one or more life events of 2.86 (95% CI: 1.16 to 4.40; $p=0.01$) in participants who were widowed and no effect of reported life events in persons who were not widowed (pooled HR= 0.85, 95%CI=0.63 to 1.15; $p=0.30$). None of the I^2 -statistics reached significance (test of heterogeneity: all Q ($df=3$) <6 ; $p >0.05$). The z-statistic for difference between the widowed and non-widowed group was 2.98 with a p-value of 0.002, indicating that the interaction between widowhood and life events on dementia risk was significant. Figure 4 shows the proportion without dementia over time for reporting one or

more stressful life event (yes vs. no) and being widowhood (yes vs. no), here the Chi-square (df=3) was 9.3 (p=0.02).

Numbers got too small to investigate the effect on type of dementia.

Interaction with age and sex

None of the interaction terms between age and life events nor between sex and life events reached significance in any of the four studies, nor in pooled analyses (all p for interaction terms > 0.05).

Sensitivity analyses

The sensitivity analyses per life event on all-cause dementia incidence showed that only forced move to a care facility was significantly associated (HR=1.73, z-statistic= 3.61, p-value= 0.0003) and death of a (grand)child was borderline significantly associated (HR= 1.51, z-statistic=1.66, p=0.09) with increased risk for dementia (Figure S2 in supplementary material shows the corresponding forest plot).

When we examined the total number of life events reported in the SATSA cohort (maximum of events reported: 15) the associations did not change compared to the results based on the 7 events. Moreover, when restricted to the selection of 7 events we captured 87 % of the reported events from the total of reported events.

We also found no evidence that the subjective experience of reported events had any additional effect on dementia risk (all p > 0.05).

Discussion

In this study we combined the data of four Swedish cohort studies to investigate whether life events experienced prior to baseline could predict occurrence of dementia over 8 to 25 years of follow-up. Despite some differences among cohorts on mean age, sex distribution and assessment of life events, we found a more or less consistent pattern across all four studies showing that experiencing two or more negative life events prior to baseline was associated with increased risk for incident dementia; specifically, it was significant for one of the studies and for the pooled results in the meta-analysis. The effect of stressful life events was strongest and most consistent for vascular dementia and combined VaD and mixed-type dementia (even after controlling for vascular risk factors).

Furthermore, when we stratified our participants on either being widowed or not, we found that the experience of one or more additional negative life events was associated with increased dementia risk only for widows. This latter finding builds on preceding studies that reported increased dementia risk after widowhood (10, 11) and suggest that without a proper social support dealing with life events can lead to increased dementia risk (12).

Our findings are supported by a few comparable epidemiological studies reporting that psychological stress (7, 8), post-traumatic stress disorder (9) or having a stress-prone personality are associated with the development of dementia (29).

The specific effect of negative life events on VaD incidence is in line with a recent study on post-traumatic stress disorder (PTSD) that showed a larger effect of PTSD on VaD than on AD incidence(9). However another study reported opposite associations; namely, that high levels of stress are related to increased risk for AD, but not for VaD (13). A large difference with our study is that the study by Johansson et al. only investigated females and had a younger population than our study. And more importantly, Johansson et al looked at subjective stress unlike our study in which we looked at number of reported negative life events. However within the SATSA cohort we did have data on subjective stress experience, but by adding the subjective experience to the number of reported events the results did not change. When looking solely at the SATSA study, none of the studied associations reached significance, so it could still be that in the other studies subjective stress experience could explain part of the associations. Compared to the other three studies, SATSA has relatively young participants and lowest dementia incidence rate (1% per year) this could explain why we did not find any significant associations. It should be noted that the direction of the association was often in the same direction as the pooled estimates, thus SATSA contributed significantly to the pooled results. Possibly due to lack of statistical power none of the tested associations reached significance within this one study.

How stress can lead to dementia remains unclear; among the most often proposed explanations is dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis(30). When a stressor is perceived the HPA axis is activated and the end product of this activation is the release of glucocorticoid hormones, such as cortisol. In the brain, excessive exposure to glucocorticoids have been related to markers of AD such as deposition of β -amyloid peptide and tau-protein in the brain (14) and reduced hippocampal volume (31). The hippocampus, which is a structure in the medial part of the temporal lobe, plays a key role in the regulation of the HPA axis(3) by sending inhibitory feedback to the hypothalamus, which leads to deactivation of the HPA-axis. Furthermore, the hippocampus is responsible for processing of stress(32), spatial information and memory functioning(33). The hippocampus is among the first structures of the brain to be affected by AD pathology and is very sensitive to vascular pathology(34). The distinction between AD and vascular dementia is becoming less discrete, as it is becoming clear that vascular risk factors may also accelerate A β 40–42 production/aggregation/deposition and that during a neuropathological exam many patients have both AD-related neuropathology and vascular pathology(35).

Along the same lines, high levels of cortisol are found in AD, VaD and stroke patients(36); HPA axis dysregulation is also a common finding in cardiovascular diseases (15); and several vascular risk factors, including obesity(37), insulin resistance(38) and atherosclerosis(39), are associated with HPA axis dysregulation. Thus, the experience of stressful life events may lead to vascular dementia by increase in vascular risk factors, increase in cytokines and/or increase of cortisol levels.

The major strength of this study is that we combined data from four large cohort studies, enabling us to pool the data to increase the statistical power and external validity. The heterogeneity among the studies played a significant role when we examined the incidence of AD where rates varied among the studies, with the highest rates in the Kungsholmen Project. Only in this study we found a significant association between two or more life

events at baseline and increased AD incidence. The participants of the Kungsholmen Project were significantly older, with higher levels of education, lower BMI, fewer smokers, and many more women than in the other three cohorts. All these characteristics might partly explain the difference in AD incidence rate because cardiovascular factors are particularly related to increased risk of VaD. Moreover a preceding study among elderly women also found a higher risk for AD associated with stress than for VaD (13). However, it should be noted that in Kungsholmen there was also a strong association of life events with vascular dementia, suggesting that within this cohort there was a less distinct effect of life events on type of dementia.

The follow-up time varied across the studies, from 8 to a maximum of 25 years of follow-up. The SATSA study had the longest follow-up time and also had the youngest participants and the lowest incidence of dementia. Because age is the main risk factor for dementia incidence, by using age as the time variable in our survival analyses instead of follow-up time we should have appropriately taken care of the differences in follow-up time.

It has previously been found that stressful events before the age of 16 (40, 41) and after the age of 65 were associated with cognitive impairment and increased dementia incidence (40). Unfortunately we did not have data on the time of event occurrence and thus we were not able to dissect the effect of mid-life (adulthood before 65 years) and late-life events. We however expect that most events that were reported were late-life events (e.g. widowhood; severe illness; moving to care facility).

Among the four cohorts, different methods were used to assess life events; in SATSA a structured life event questionnaire was used, whereas in the Kungsholmen project an open question on life stress was asked and in the other two cohorts we gathered life event data by combining answers on questions about living situation, family and health issues. This variety in assessment could result in information bias and specifically in under reporting of events in the two cohorts in which no direct life event question was asked. However, the mean of events was similar across the four cohorts and when looking into single effects of each event on dementia incidence, we found comparable findings for each event on dementia incidence. This suggests that even though different life event assessments were used, the data gave consistent and thus reliable results across all cohorts. Because we were not necessarily interested in the physiological effect of health problems on dementia incidence, we adjusted for blood pressure, BMI, diabetes mellitus and coronary heart disease in the analyses, as vascular risk factors and diseases are the most frequent health-related risk factors for dementia (42). By pooling each study's results into a meta-analysis our results may generalize further to other studies, as usually many different measures of psychosocial stress are used.

To conclude, we showed across four separate studies that the experience of negative life events is associated with increased risk for dementia particularly in persons who are widowed and specifically for vascular dementia. Furthermore, widowhood augments the increased risk for dementia due to negative life events. Extra support should therefore be given to elderly who are widowed and who experience other stressful life events.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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1A. All-cause dementia - model I

1B. All-cause dementia - model II

Figure 1.

Forest plots showing association between life events and all-cause dementia

Model 1: adjusted for age and sex

Model 2: adjusted for age, sex, educational level, baseline cognitive functioning, blood pressure, BMI, diabetes mellitus, alcohol use, current smoking and coronary heart disease

No. of total participants = no of participant that report 0, 1 or 2+ events and Dementia cases show the new cases with dementia per life event category.

Figure 2.

Forest plots showing association between life events and types of dementia adjusted for age, sex, educational level, baseline cognitive functioning, blood pressure, BMI, diabetes mellitus, alcohol use, current smoking and coronary heart disease. No. of total participants = no of participant that report 0, 1 or 2+ events and Dementia cases show the new cases with dementia per life event category.

no widowhood and no life events: —

no widowhood and life events: - - - - -

widowhood and no life events: —

widowhood and life events: - - - - -

Figure 3.

Risk for dementia incidence after widowhood and experiencing one or more life events

no widowhood and no life events: —

no widowhood and life events: - - - - -

widowhood and no life events: —

widowhood and life events: - - - - -

Table 1

Frequencies of reported life events at baseline per cohort

	SATSA	GENDER	OCTO-twin	Kungsholmen
Widowhood	37 (8%)	24 (5%)	117 (20%)	52 (13%)
Divorce & marital problems	26 (6%)	28(6%)	0	1 (0.3%)
Severe health problems self	104 (23%)	147 (31%)	268 (46%)	82 (21%)
Forced move to care facility	41 (9%)	6 (1%)	115 (20%)	3 (1%)
Death of (grand)child	10 (2%)	30 (6%)	9 (2%)	9 (2%)
Death of sibling/friend	120 (26%)	NA	229 (39%)	75 (19%)
Financial problems	55 (12%)	29 (6%)	16 (3%)	4 (1%)

NA: not available

Table 2

Baseline characteristics of the dementia-free participants with available information on lifespan stressful life events in the four Swedish cohorts

	SATSA	GENDER	OCTO-twin	Kungsholmen
N	619	456	517	398
Age				
Mean (SD)	66.3 (7.5)	74.5 (2.6)	83.3 (3.0)	84.1 (5.2)
Range (years)	50–87	70–81	79–97	74–96
Male %	40	48	34	17
Educational level %				
Elementary school or less	64	81	74	58
More than elementary school	36	19	26	42
BMI Mean (SD)	25.4 (3.7)	26.5 (3.9)	24.7 (3.7)	23.2 (3.5)
Smoking %				
Never	56	46	61	66
Former	24	42	31	19
Current	20	11	8	15
Alcohol any use %	72	85	67	84
Reported stressful life events				
Mean (SD)	1.01 (2.1)	1.0 (0.9)	1.0 (0.8)	0.6 (0.7)
Range	0–6	0–4	0–3	0–3
2 or more events (%)	30	27	27	11
Mean MMSE score (SD)	27.9 (1.8)	27.8 (2.3)	26.1 (2.9)	23.1 (7.6)
Cumulative dementia incidence (%)	15	15	21	27
Follow-up time (years)				
Mean (SD)	16.0 (7.4)	5.1 (3.2)	4.8 (2.9)	4.5 (3.6)
Range	0–25	0–8	0–8	0–12

Table 3

Pooled Hazard Ratios for life events and dementia risk

Dementia type	Life events	z-statistic	HR*	95% CI	p-value
All cause	0	Ref			
	1	0.64	1.18	0.71–1.97	0.52
	2+	3.20	2.00	1.31–3.07	0.001
Alzheimer's disease	0	Ref			
	1	-0.23	0.95	0.64–1.43	0.82
	2+	1.19	1.29	0.85–1.96	0.23
Vascular dementia	0	Ref			
	1	0.87	1.61	0.55–4.72	0.38
	2+	2.78	3.10	1.39–6.82	0.005
Vascular+mixed dementia	0	Ref			
	1	2.33	2.46	1.16–5.26	0.020
	2+	4.65	3.60	2.10–6.19	<0.0001

* All estimates from Cox proportional Hazard analyses, using Wald Chi-square tests (df=3)