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ORIGINAL RESEARCH

Death of a Partner and Risks of Ischemic Stroke and Intracerebral Hemorrhage: A Nationwide Danish Matched Cohort Study

Morten Fenger-Grøn, PhD; Ida Paulsen Møller, MD; Henrik Schou Pedersen, MSc; Lars Frost, MD; Annelli Sandbæk, MD; Dimitry S. Davydow, MD; Søren P. Johnsen, MD; Nicklas Vinter, MD

BACKGROUND: Stress has been reported to trigger stroke, and the death of a loved one is a potentially extremely stressful experience. Yet, previous studies have yielded conflicting findings of whether bereavement is associated with stroke risk, possibly because of insufficient distinction between ischemic stroke (IS) and intracerebral hemorrhage (ICH). We therefore examined the associations between bereavement and IS and ICH separately in contemporary care settings using nationwide high-quality register resources.

METHODS AND RESULTS: The study cohort included all Danish individuals whose partner died between 2002 and 2016 and a reference group of cohabiting individuals matched 1:2 on sex, age, and calendar time. Cox proportional hazards regression was used to estimate adjusted hazard ratios (aHRs) and corresponding 95% CIs during up to 5 years follow-up. During the study period, 278 758 individuals experienced partner bereavement, of whom 7684 had an IS within the subsequent 5 years (aHR, 1.11; CI, 1.08–1.14 when compared with nonbereaved referents) and 1139 experienced an ICH (aHR, 1.13; CI, 1.04–1.23). For ICH, the estimated association tended to be stronger within the initial 30 days after partner death (aHR, 1.66; CI, 1.06–2.61), especially in women (aHR, 1.99; CI, 1.06–3.75), but the statistical precision was low. In absolute numbers, the cumulative incidence of IS at 30 days was 0.73 per 1000 in bereaved individuals versus 0.63 in their referents, and the corresponding figures for ICH were 0.13 versus 0.08.

CONCLUSIONS: Statistically significant positive associations with partner bereavement were documented for both IS and ICH risk, for ICH particularly in the short term. However, absolute risk differences were small.

Key Words: bereavement ■ brain infarction ■ cerebral hemorrhage ■ loss of a partner ■ stroke

Accumulating evidence indicates that stress and stressful life events increase the risk of stroke,[1–3] possibly because of neuroendocrine, prothrombotic, and immunological mechanisms.[4] The death of a loved one is one of the most stressful life events[5] and affects most people, regardless of differences in coping mechanisms.[6] Nevertheless, earlier studies in the field hold conflicting or ambiguous findings regarding whether bereavement is associated with stroke risk. Li et al found no association between the death of a child and the parents' stroke risk.[7] Hart el al found a slightly elevated stroke risk in individuals exposed to partner death, but not until 2 years after the bereavement event[8]; in contrast, Carey et al found a strong association between partner death and stroke risk in the first months after bereavement, but no long-term association.[9] Two additional studies of partner death[10] and death of a sibling[11] both found only weak associations with stroke risk; yet, for death of a sibling, a slightly stronger association in women was suggested.[11]

Differences in length and completeness of follow-up, degree of confounder control, type of loss, or

Correspondence to: Nicklas Vinter, Diagnostic Centre, University Clinic for Development of Innovative Patient Pathways, Silkeborg Regional Hospital, Falkevej 3, 8600 Silkeborg, Denmark. E-mail: nicvin@rm.dk

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CLINICAL PERSPECTIVE

What Is New?

- Partner bereavement and risks of ischemic stroke (IS) and intracerebral hemorrhage (ICH) were examined separately in a nationwide cohort study that compared all Danish individuals who lost a partner from 2002 to 2016 with a matched reference group.
- The risks of IS and ICH after bereavement were modestly increased during a study period of 5 years, while a more marked short-term excess risk was suggested for ICH.
- Still, the cumulative risks and risk differences for both IS and ICH were low after partner bereavement.

What Are the Clinical Implications?

- Partner bereavement is associated with a statistically significant excess risk of IS and ICH, which suggests that stressful life events may contribute to the development of stroke.
- Because the absolute risk differences for IS and ICH were small, the results document limited need for stroke prevention efforts particularly targeting bereaved individuals.

Nonstandard Abbreviations and Acronyms

aHR	adjusted hazard ratio
ICH	intracerebral hemorrhage
IS	ischemic stroke

stroke prevention–related care setting may account for some of these discrepancies. Furthermore, most of these studies have low statistical precision and make no distinction between ischemic stroke (IS) and hemorrhagic stroke,[8–11] though mechanisms linking psychosocial stress to risk of stroke may act differently, possibly even in opposite directions, for the 2 types of strokes.

Therefore, the present study aimed to assess the associations between partner bereavement and the risks of IS and intracerebral hemorrhage (ICH) separately in a contemporary care setting, capitalizing on data from a large cohort with extensive confounder information and no loss to follow-up. Particular attention was paid to potential differences between men and women and the influence of time since the loss, risk profile, and age of the bereaved individuals, and whether the loss was expected or not.

METHODS

According to applicable legislation, the authors are not allowed to share unaggregated data from the Danish nationwide registries with any third party. However, access to all source data can be permitted to appropriately approved institutions by application directly to Statistics Denmark.

Design, Setting, and Population

In a nationwide registry-based matched cohort design, we compared the incidence of stroke in all individuals who lost a partner with that in a matched reference group of individuals still registered with a partner. The association between bereavement and stroke risk was estimated in several time spans as well as during the full follow-up of up to 5 years. For both groups, the source population was all individuals without a prior diagnosis of stroke in Denmark between January 1, 2002 and December 31, 2016, who were between 40 and 100 years old and who had at least 10 years of uninterrupted residence in Denmark.

Data Sources

The Danish National Patient Register provided information on all diagnoses. This registry contains data on all inpatient and outpatient contacts to somatic and psychiatric public hospitals in Denmark, including dates and primary and secondary diagnoses coded according to the *International Classification of Diseases, Tenth Revision* (*ICD-10*).[12] For supplementary analyses, we retrieved additional information on strokes from the Causes of Death Register, which covers deaths among citizens dying in Denmark.[13] We obtained data on medications from the Danish National Prescription Registry, which contains information on redeemed prescriptions for reimbursable drugs dispensed from all pharmacies in Denmark since 1995 classified according to the Anatomical Therapeutic Chemical Classification System.[14] The Danish Civil Registration System provided information on birthday, sex, cohabitant status, partner, migration, vital status, and date of death.[15] Additionally, we obtained information on education level and household income from Statistics Denmark.[16]

The unique personal identification number, which is assigned to all Danish citizens at the time of birth or immigration, facilitated linkage of all mentioned databases at person level.

Exposure: Death of a Partner

The exposure of interest was death of a partner, as identified by linking the annually updated data on cohabitant status and possible partner identity for all

individuals in the source population with their partner's vital status data for the subsequent year. Individuals exposed to bereavement were censored if registered with another partner during the follow-up. In supplementary analyses, we aimed to distinguish between sudden and expected losses by stratifying on the deceased partner's Charlson Comorbidity Index[17] (0–2 versus ≥ 3) assessed 60 days before the death date using previously applied register algorithms.[18]

Reference Group

For each exposed individual, we randomly selected 2 age- and sex-matched referents by the following approach: We constructed matching strata comprising all people with the same birth year and sex who became exposed to bereavement within the same calendar year (index year). To each stratum, we sampled the required number of referents among all remaining individuals in the source population who had the same birth year and sex and were cohabiting and stroke-free on a randomly sampled date within the index year, which was assigned to them as the index date. We performed the sampling without replacement within strata, but with replacement between strata.[19] Similar to exposed individuals, referents were censored if they were observed to have changed marital status (ie, when their partner died or the annually updated databases registered them as single-living.

Outcomes: Ischemic Stroke and Intracerebral Hemorrhage

The outcome of interest was diagnosis of stroke, which was categorized into IS (*ICD-10*: I63 or I64, unspecified stroke) or ICH (*ICD-10*: I61) in accordance with earlier studies.[20,21] Thus, we identified the first-time stroke date as the initiation date of a person's first stroke-related inpatient or outpatient hospital visit. To define visits, we merged all inpatient and outpatient contacts with overlapping dates for a given person. We defined a stroke event as a first-time primary stroke diagnosis or a secondary stroke diagnosis linked with a rehabilitation procedure (*ICD-10*: Z50) [20,21]; we excluded stroke registrations identified only in emergency departments, for which we expected low validity. Patients registered with both an IS and an ICH diagnosis on the same day were included in both analyses. If people were registered with stroke-related healthcare contacts without these qualifiers (ie, a contact with any of the above-mentioned diagnoses or with the diagnosis "sequelae of cerebrovascular disease," *ICD-10*: I69), they were censored on the admission date. For the primary analyses, all information on stroke diagnoses was retrieved from the Danish National Patient Register, for which validation studies of stroke diagnoses have documented a high validity (positive predictive value of 88%–97% for IS and 66%–74% for ICH).[22,23] However, in supplementary analyses, we also included stroke diagnoses registered as the primary cause of death in the Causes of Death Registry. In further supplementary analyses, on the other hand, we restricted the outcome definition to include only primary diagnoses from inpatient contacts and/or (for IS) only registrations of the diagnosis code I63.[24,25]

Covariates

In addition to the matching variables, age, sex, and calendar year, several covariates were adjusted for in regression analyses. Covariates included highest attained education level, household income, physical and mental health comorbidities, as well as medical treatments (Table 1). Education level was classified according to the United Nations Educational, Scientific, and Cultural Organization classification as low (≤10 years), medium (11–15 years), and high education (>15 years). Missing information on education level was accepted as a separate category. Household income was categorized into quartiles of the Danish population. People with missing information or registration of a negative income were assigned to a separate category.

For the identification of comorbidities, which were selected based on other studies of the same Danish data sources and outcomes,[20,21] we used a modified version of the approach developed by Prior et al[26] as outlined in Table S1. The following comorbidities were considered: hypertension (hospital-diagnosed), atrial fibrillation, ischemic heart disease, congestive heart failure, peripheral artery occlusive disease, cerebrovascular disease, diabetes mellitus, chronic obstructive pulmonary disease, chronic liver disease, coagulation defects, anemia, cancer, epilepsy, Parkinson disease, alcohol problems, substance abuse, bipolar affective disorders, other mood, stress, and anxiety-related disorder, schizophrenia or schizoaffective disorder, and dementia. All the above-mentioned covariates were evaluated on index date.

We evaluated medicine redemptions within 120 days before index date for the following medication types: antiplatelet agents, anticoagulant agents, antihypertensive agents, statins, NSAIDs, systemic glucocorticoids, and SSRIs. Table S2 presents all Anatomical Therapeutic Chemical codes.

Statistical Analysis

We estimated adjusted hazard ratios (aHRs) for the association between death of a partner and time to first stroke for the 2 different event types (IS and ICH) in separate stratified Cox proportional hazards regression models. We used cluster robust standard errors to estimate the corresponding 95% CIs, accounting for the fact that individuals could be sampled more than once.[27] We used

Table 1. Characteristics of Bereaved Individuals and Their Matched Nonbereaved Referents

Characteristics	Bereaved, No. (%), (n=278 758)	Nonbereaved, No. (%), (n=557 516)
Sex		
Female	187 926 (67.4)	375 852 (67.4)
Male	90 832 (32.6)	181 664 (32.6)
Age (y)		
40–50	12 214 (4.4)	24 462 (4.4)
50–60	34 356 (12.3)	68 690 (12.3)
60–70	72 253 (25.9)	144 797 (26.0)
70–80	93 385 (33.5)	186 397 (33.4)
80–100	66 550 (23.9)	133 170 (23.9)
Calendar time		
2002–2009	154 586 (55.5)	309 172 (55.5)
2010–2016	124 172 (44.5)	248 344 (44.5)
Education level (y)		
<10	129 240 (46.4)	228 834 (41.0)
10–15	98 609 (35.4)	205 435 (36.8)
>15	31 538 (11.3)	85 093 (15.3)
No information	19 371 (6.9)	38 154 (6.8)
Household income (5 y lagged)		
First quartile	89 082 (32.0)	141 453 (25.4)
Second quartile	75 062 (26.9)	134 939 (24.2)
Third quartile	53 801 (19.3)	114 172 (20.5)
Fourth quartile	60 247 (21.6)	165 721 (29.7)
Negative or not registered	566 (0.2)	1 231 (0.2)
Comorbidity		
Hypertension*	45 880 (16.5)	90 024 (16.1)
Atrial fibrillation	13 116 (4.7)	27 609 (5.0)
Other circulatory condition†	42 064 (15.1)	79 129 (14.2)
Other medical condition‡	67 165 (24.1)	122 875 (22.0)
Psychiatric or neurological condition§	10 786 (3.9)	18 792 (3.4)
Medications‖		
Antiplatelet agents	52 431 (18.8)	101 938 (18.3)
Anticoagulant agents	11 749 (4.2)	24 705 (4.4)
Antihypertensive agent	131 154 (47.0)	255 667 (45.9)
Statins	51 146 (18.3)	103 805 (18.6)
Nonsteroidal anti-inflammatory drugs	32 288 (11.6)	60 107 (10.8)
Systemic glucocorticoid	11 057 (4.0)	22 064 (4.0)
Selective serotonin reuptake inhibitors	20 868 (7.5)	32 149 (5.8)

*Note: hospital diagnoses only.
†Minimum 1 of the following: ischemic heart disease, congestive heart failure, peripheral artery occlusive disease, cerebrovascular disease.
‡Minimum 1 of the following: diabetes mellitus, chronic obstructive pulmonary disease, chronic liver disease, coagulation defects, anemia, cancer.
§Minimum 1 of the following: epilepsy, Parkinson disease, mood-, stress-, or anxiety-related disorders, alcohol problems, substance abuse, bipolar affective disorder, schizophrenia or schizoaffective disorder, and dementia.
‖Redeemed prescriptions 4 (120 days) months before index date.

time since index date as the underlying time scale and stratified on matching strata, which implied a detailed adjustment for age, sex, calendar time, and potential interactions among these characteristics. Individuals contributed at-risk time until stroke date, 5 years after index date, change of cohabitation status, their 100th birthday, December 31, 2016, date of death, or date of emigration, whichever came first. To avoid ties, we assumed that bereavement happened before stroke if an individual had a stroke on the same day their partner died.

We examined the association of partner bereavement with stroke risk in 3 sequentially adjusted regression models. Model 1 included only the adjustment for matching variables. Model 2 additionally included education level, income, and comorbidities, and model 3 also included medications.

To analyze whether time since death of a partner modified the association, we divided this time into 6 prespecified categories (0–1 month, 1–2 months, 2–6 months, 6–12 months, 1–2 years, and 2–5 years after bereavement) and estimated the association in each of the categories for both outcomes and for each sex.

We estimated and plotted the cumulative incidence proportion in the first year after index date by the Aalen-Johansen estimator with ICH and death as competing events for IS, and with death and IS as competing events for ICH. The cumulative incidence curves were smoothed using the Epanechnikov kernel[28] to avoid identification of single individuals.

All analyses were performed with Stata version 15.

Approvals

The study was approved by the Danish Health Data Authority, Statistics Denmark, and the Danish Data Protection Agency. According to Danish law, no further ethical approval or informed consent from the participants was required for this entirely register-based study.

RESULTS

Population Characteristics

The population comprised 278 758 individuals exposed to partner bereavement. Table 1 summarizes their characteristics along with those of their matched referents. Bereaved individuals had modestly higher frequencies of comorbidities and medications. During the subsequent 5 years (mean follow-up time: 3.5 years), 7684 of the exposed individuals had an IS, and 1139 had an ICH (Table 2).

Ischemic Stroke

Partner bereavement was associated with a slightly higher risk of IS during the 5 years of follow-up (aHR, 1.13; 95% CI, 1.10–1.17) when only the matching

Table 2. Associations (Adjusted Hazard Ratios [95% CIs]) Between Loss of a Partner and Risks of Ischemic Stroke and Intracerebral Hemorrhage During 5 Years of Follow-up

	Events, N	Model 1	Model 2	Model 3
Ischemic stroke				
Bereaved individuals	7684	1.13 [1.10-1.17]	1.12 [1.08-1.15]	1.11 [1.08-1.14]
Nonbereaved referents	12 716	Ref	Ref	Ref
Intracerebral hemorrhage				
Bereaved individuals	1139	1.14 [1.05-1.23]	1.14 [1.05-1.23]	1.13 [1.04-1.23]
Nonbereaved referents	1874	Ref	Ref	Ref

Model 1: Adjusted for matching variables (sex, age, and calendar time).
Model 2: Further adjusted for socioeconomic variables and comorbidities.
Model 3: Further adjusted for medications.

characteristics were accounted for (Model 1). This association was virtually unchanged by successive adjustment for comorbidity and even for medications (aHR, 1.11; 95% CI, 1.08–1.14) (Table 2), and it was quite constant over time since bereavement (Figure 1A and Table S3). In women, the association was estimated to be slightly stronger within the first 30 days (aHR, 1.33; 95% CI, 1.06–1.68), but no similar tendency was found among men (aHR in the first 30 days, 0.94; 95% CI, 0.71–1.22) (Table S4).

In absolute numbers, the cumulative incidence after 30 days was 0.73 (95% CI, 0.64–0.84) per 1000 bereaved individuals and 0.63 (95% CI, 0.56–0.69) per 1000 nonbereaved referents (Figure 2A and Table S5). The corresponding figures after 1 year were 7.53 (95% CI, 7.21–7.87) versus 6.75 (95% CI, 6.54–6.98) per 1000.

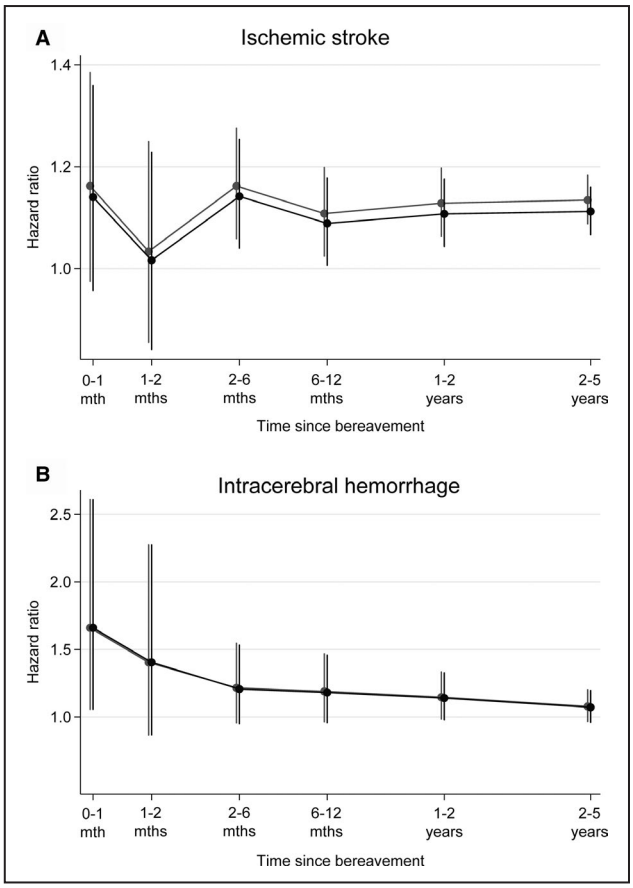

Figure 1. Associations (adjusted hazard ratios [95% CI]) between loss of a partner and risks of ischemic stroke (A) and intracerebral hemorrhage (B) estimated by time since bereavement (index date).
Estimates corresponding to model 1 (only adjusted for matching variables) are presented in gray and fully adjusted estimates (model 3) in black.

Intracerebral Hemorrhage

For the risk of ICH, the association with bereavement was quite similar to the above when assessed over the full study period (aHR, 1.14; 95% CI, 1.05–1.23) according to the simplest model that accounted only for matching characteristics and aHR: 1.13 (95% CI, 1.04–1.23, fully adjusted) (Table 2). However, the estimated association with ICH risk showed some attenuation from a high level (aHR, 1.66; 95% CI, 1.06–2.61) in the initial 30 days (Figure 1B and Table S3). This pattern was most pronounced for women (aHR in the initial 30 days: 1.99; 95% CI, 1.06–3.75), but the statistical precision in these analyses was low (Table S4).

In absolute numbers, the cumulative incidence of ICH after 30 days was 0.13 (95% CI, 0.09–0.18) per 1000 bereaved individuals and 0.08 (95% CI, 0.06–0.10) per 1000 nonbereaved referents (Figure 2B and Table S5). After 1 year, these figures were 1.15 (95% CI, 1.02–1.28) and 0.91 (95% CI, 0.84–1.00), respectively.

Supplementary Analyses

Including diagnoses registered in death certificates only added ≈10% events of IS and ICH, whereas the restrictions to primary diagnoses from inpatient contacts and/or with diagnosis code I63 (for IS) reduced the number of events by 15% to 20%. Yet, all of these changes of the outcome definitions left the estimated risk associations with bereavement virtually unchanged (Table S6 and Table S7). Likewise, stratifying on the

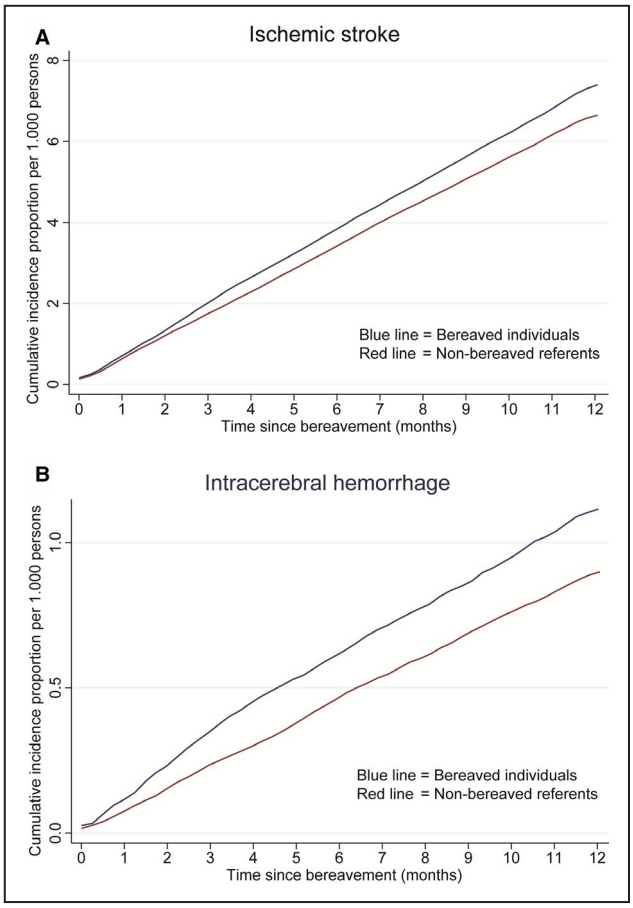

Figure 2. Cumulative incidence of ischemic stroke (A) or intracerebral hemorrhage (B) during the year after bereavement (index date) in bereaved individuals and matched nonbereaved referents

bereaved individuals' risk profiles or on expectedness of loss as assessed from the deceased partner's level of morbidity 60 days before dying had very little impact on the estimated associations (Table S8 and Table S9). In contrast, analyses stratified on age suggested that the associations for both IS and ICH were strongest in those age <70 years at the time of bereavement (Table S10).

DISCUSSION

In this nationwide matched cohort study, we found statistically significant associations between death of a partner and both IS and ICH after adjustment for several covariates. The associations did not seem to depend on the pre-death morbidity level of the deceased partner, but may have been stronger among individuals bereaved at a relatively young age. For ICH, the estimated association was marked in the initial 30 days, but attenuated over time, especially in women. However, for both IS and ICH, the statistical precision of the short-term associations was low, and the absolute risk differences between bereaved individuals and their matched referents were small.

To the best of our knowledge, the present study is by far the largest to examine the associations between a stressful life event such as partner bereavement and risks of IS and ICH separately and with focus on changes in these associations over time. Previous studies of the association between death of a loved one and risk of stroke exist, but their findings are ambiguous.[7–11,29] In another nationwide, population-based study based on Danish registries, Li et al compared >21 000 parents who had lost a child with nearly 300 000 parents who had not and found no statistically significant excess risk of any stroke, neither IS nor nonischemic stroke.[7] However, they found a nearly 20% increased risk of ICH during the initial 7 years (aHR, 1.19; 95% CI, 0.83–1.70). This is fully compatible with our findings, but as the participants in their study were included at a younger age (mean: 33 years) when the risk of stroke is very low, it lacked statistical power and could not assess for short-term changes in risk associations over time, a potentially interesting signal in our data.

A high short-term risk of stroke and attenuation over time was found in other studies, but the associations were generally stronger than in our study. In a case-crossover design, Guiraud et al reported an association between IS and bereavement within the last month before the stroke (odds ratio, 1.86; 95% CI, 1.14–3.10).[29] In a cohort study comparing 31 427 individuals whose partner died with matched nonbereaved referents, Carey et al found higher adjusted incidence rate ratios of any type of stroke within 30 days (2.40; 95% CI, 1.22–4.71) and possibly between 31 and 90 days (1.30; 95% CI, 0.87–1.93) but not between 91 and 365 days (0.89; 95% CI, 0.73–1.10).[9] Furthermore, using a composite of myocardial infarction or stroke within 30 days in a sex-stratified analysis, they observed a stronger association in women than in men (incidence rate ratio, 2.93; 95% CI, 1.71–5.02; versus 1.65; 95% CI, 0.96–2.84), although this difference was not statistically significant. In our study, we estimated a slightly stronger risk association for IS within 30 days among women as well.

For the same composite outcome of myocardial infarction or stroke, the results by Carey et al suggested that the relative risk increase during the first month after bereavement was higher in people with no prior cardiovascular morbidity.[9] The finding that the impact of an additional risk factor, measured on a relative scale, is smallest in people who are already at high risk is common in epidemiological studies and even well known in a specific stroke context.[30] Our finding of a stronger risk association in the youngest age group could be inferred as an

indication of this tendency. However, a similar indication was not obvious from our analyses specifically stratified on cardiovascular risk, although the association for IS 0 to 5 years after bereavement was slightly stronger in people considered at low cardiovascular risk. A part of the background for this potential difference could be that bereaved people in the cohort of Carey et al had a higher prevalence of cardiovascular comorbidity than those in our study cohort; most spectacularly, Carey et al reported a 51% frequency of hypertension,[9] while we found only 16% with (hospital-diagnosed) hypertension. Yet, this discrepancy is likely a matter of definitions more than of true differences in health status, because 47% of our cohort received antihypertensive treatment, which seems fully compatible with the figures by Carey et al.

Death of a partner and sex-specific risks of mortality caused by stroke or other cerebrovascular events were examined in a US setting by Elwert et al, who reported an elevated risk among both men (aHR, 1.12; 95% CI, 1.08–1.18) and women [aHR, 1.09; 95% CI, 1.04–1.14), but no statistical difference between the sexes.[10] However, these authors did not consider shorter follow-up periods in the analyses and may have missed a potential higher short-term risk.

While none of the above-mentioned studies examined a short-term risk for ICH as seen in our study, Henderson et al demonstrated that high levels of distress are associated with incident hemorrhagic strokes (aHR, 1.70; 95% CI, 1.28–2.25) but not IS (aHR, 1.02; 95% CI, 0.91–1.15) in the Chicago Health and Aging Project.[31] These results seem to agree well with ours, although Henderson et al established exposure status from detailed subjective information on psychological distress, whereas our exposure, loss of a partner, was objective, but unspecific from a psychological point of view.

Several pathophysiological mechanisms linking psychological stress to IS have been suggested.[4] For instance, acute psychosocial stress activates the hypothalamic–pituitary–adrenal axis and the autonomic nervous system, resulting in net hypercoagulability, plasma volume concentration, and endothelial dysfunction.[32–34] Kajantie et al have suggested that these pathophysiological stress responses are weaker in women than men,[33] which was not confirmed in our data. However, these authors emphasize that the sex differences in response are smaller once women have passed menopause, and most of our participants are >60 years old.

In contrast, the mechanisms linking psychological stress to development of ICH are less known and require further evaluation. However, psychological stress may lead to ICH by a sudden rise in blood pressure/cerebral blood flow as well as small-vessel fibrinoid necrosis and rupture.[35] Perhaps the most likely causal explanation for the increased short-term risk of ICH is that stressful life events might entail changes in health behavior that could increase stroke risk, such as excessive intake of alcohol, unhealthy diet or sleeping habits, decreased adherence to antihypertensive medication, physical inactivity, and/or use of sympathomimetic drugs. However, because such modifiable risk factors for IS and ICH show substantial overlap,[36] this does not fully explain the observed differences between the stress responses in IS and ICH.

Limitations

We used nationwide registers to define our study population, and no individuals were lost to follow-up. Because the Danish Civil Registration System contains updated vital statistics on all Danish citizens, misclassification of death of a partner is unlikely, and detailed knowledge of pre-death morbidity of the deceased partners could suggest whether their deaths were expected or not. Nevertheless, we were not able to quantify the level of psychological stress nor the exact timing of psychological stress among the exposed participants. Thus, the death of a partner could induce severe acute psychological stress in some cases, whereas in others, a long course of disease in the partner may have produced chronic stress, which could be unchanged or even relieved by the partner's eventual dying. This could be a part of the explanation that we observe stronger risk associations for bereavement at younger ages. Furthermore, we lacked information about other stressful life events, which could have blurred the contrast between the exposed group and the referents in our study. However, there is no reason to believe that the occurrence of non-bereavement-related stressful events would differ between the exposure groups.

The potential influence of both over- and underdiagnosis should be acknowledged. In this study, such misclassification is not likely differential because all data registration was prospective and independent of our study hypothesis, but it could still have weakened the estimated association. Moreover, granular data on stroke severity, such as results of neuroimaging and symptom scales, would be of interest, but were unavailable.

In the present study, we adjusted for several potentially important confounders, including sex, age, education level, comorbidities, and medication treatments. However, a risk of residual confounding remains, especially from unregistered lifestyle characteristics. For characteristics such as obesity or genetic disposition that are relatively constant over

time, the risk of residual confounding seems limited because both the exposed people and the referents were recruited from the same population although at different times in life. Still, we cannot completely rule out that the risk profile of people bereaved of a partner differs from that of their contemporaries whose partner lived a little longer, even after adjustment for known conditions and medications. Presumably, this would imply an upward bias on the estimated long-term associations, which are still weak. Yet, we would anticipate this upward bias to be most pronounced for those who are bereaved earliest in life, and this could be a contributory explanation of our observation of stronger risk associations with bereavement at younger ages. For residual confounding to explain the observed fluctuations in the associations for ICH, potentially confounding characteristics would have to exhibit marked changes shortly after the bereavement experience. As discussed above, such fluctuations in risk profiles are plausible. However, to the extent that high-risk characteristics are especially frequent in the weeks after a bereavement experience, they must be considered mediators rather than confounders for the associations with IS and ICH and, hence, should not be corrected for.

Finally, both biological and cultural/sociological characteristics of our study setting could have limited the generalizability of our findings. The Danish population is almost exclusively White and has access to a relatively high level of social security, which could limit the practical consequences of losing a partner. These factors may partially explain the relatively weak associations found between partner loss and stroke in our study.

CONCLUSIONS

People exposed to partner bereavement had modestly increased risks of both IS and ICH, for ICH especially in the immediate period after their partner's death. However, the absolute risks were low.

ARTICLE INFORMATION

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Affiliations

From the Research Unit for General Practice, Aarhus, Denmark (M.F.-G., H.S.P.); Diagnostic Centre, University Research Clinic for Innovative Patient Pathways, Silkeborg Regional Hospital, Silkeborg, Denmark (I.P.M., L.F., N.V.); Department of Clinical Medicine (L.F., N.V.)and Steno Diabetes Center, Aarhus and Department of Public Health (A.S.), Aarhus University, Aarhus, Denmark; Comprehensive Life Resources, Tacoma, WA (D.S.D.); and Danish Center for Clinical Health Services Research, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark (S.P.J., N.V.).

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Disclosures

Outside the submitted work, DD has received an associate editor fee from Elsevier Science. LF has been an advisory board member for Bristol-Myers Squibb, Pfizer, and MSD and has served on the speakers' bureau for Bayer, Bristol-Myers Squibb, Pfizer, MSD, and Boehringer Ingelheim. SPJ has been an advisory board member for Bristol-Myers Squibb, Pfizer, and Bayer and has served on the speakers' bureau for Bristol-Myers Squibb, Pfizer, Bayer, and Sanofi. The remaining authors have no disclosures to report.

Supplementary Material

Tables S1-S10

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Supplemental Material

Table S1. Information on comorbidity by the Multimorbidity Index obtained from the Danish National Patient Register and the Danish National Prescription Registry[26].

Category	Coding definition	Diagnoses codes (ICD-10)	Diagnosis time frame	Drug codes (ATC)	Prescription time frame
Hypertension*	Diagnosis	I10-I13, I15	Since 1995		
Atrial fibrillation	Diagnosis	I48	Since 1995		
Other circulatory conditions:					
Ischemic heart disease	Diagnosis AND/OR prescriptions for antianginal drug	I20-I25	Since 1995	C01DA	Twice last year
Congestive heart failure	Diagnosis	I50	Since 1995		
Peripheral artery occlusive diseases	Diagnosis	I70-I74	Since 1995		
Cerebrovascular disease†	Diagnosis	I60, I62	Since 1995		
Other medical conditions:					
Diabetes mellitus	Diagnosis AND/OR prescription of antidiabetics	E10-E14	Since 1995	A10A, A10B	Twice last year
Chronic obstructive pulmonary disease	Prescriptions for obstructive airway disease drugs			R03	Twice last year
Chronic liver disease	Diagnosis	B16-B19, K70-K74, K766, I85	Since 1995		
Coagulation defects‡	Diagnosis	D66-D69	Since 1995		
Anemias	Diagnosis	D50-D53, D55-D61, D63-D64	Last two years		
Cancer	Diagnosis	C00-C43, C45-C97	Last five years		
Psychiatric or neurological conditions:					
Epilepsy§	Diagnosis AND prescriptions of anti-epileptics	G40-G41	Since 1995	N03	Twice last year
Parkinson's disease	Diagnosis	G20-G22	Since 1995		
Alcohol problems	Diagnosis	F101-F109	Last two years		
Substance abuse	Diagnosis	F11-F16, F18-F19	Last two years		
Bipolar affective disorder	Diagnosis AND/OR prescriptions of lithium salts	F30-F31	Since 1995	N05AN	Twice last year
Other mood-, stress-, or anxiety-related disorder	Diagnosis	F32-F34, F40-F48	Last two years		
Schizophrenia or schizoaffective disorder	Diagnosis	F20, F25	Since 1995		
Dementia	Diagnosis AND/OR prescriptions for antidementia drugs	F00-F03, F051, G30	Since 1995	N06D	Twice last year

* Modified from original index by not including prescriptions for antihypertensive drugs from the definition of this category.

† Modified from original index by not including stroke diagnoses (i.e. ICH and IS: I61+I63+I64) from the definition of the category 'Stroke' (now renamed 'cerebrovascular disease').

‡ Modified from original index by adding a new category including coagulation defects.

§ Modified from the original index by including epilepsy diagnoses only in the definition of the category 'Epilepsy'.

Table S2. Information on prescriptions redeemed for selected agents that may influence the risk of stroke obtained from the Danish National Prescription Register.

Drug category	Drug name	ATC codes
Antithrombotic agents		
Antiplatelet agents		
	Acetylsalicylic acid	B01AC06, B01AC30
	Dipyridamole	B01AC07
	Clopidogrel	B01AC04
	Other APD (Prasugrel and Ticagrelor)	B01AC22, B01AC24
Anticoagulant agents		
Vitamin K antagonists	Vitamin K antagonists	B01AA
Direct oral anticoagulants (DOAC)	Dabigatran etexilate	B01AE07
	Rivaroxaban	B01AF01/B01AX06
	Apixaban	B01AF02
	Edoxaban	B01AF03
Antihypertensive agents		
	Antihypertensives	C02
	Diuretics	C03
	Peripheral vasodilators	C04
	Beta blockers	C07
	Calcium channel blockers	C08
	Agents acting on the renin-angiotensin system	C09
Other selected agents that may influence risk of stroke		
Statins	Simvastatin, Lovastatin, Pravastatin, Fluvastatin, Atorvastatin, Cerivastatin, Rosuvastatin	C10AA
Non-steroidal anti-inflammatory drugs (NSAID)	Butylpyrazolidines, acetic acid derivatives, oxicams, propionic acid derivatives, coxibs, nabumetone	M01AA-M01AH, M01AX01
Systemic glucocorticoids	Betamethasone, methylprednisolone, prednisolone, prednisone, triamcinolone, hydrocortisone	H02AB01, H02AB04, H02AB06-09
Selective serotonin reuptake inhibitors (SSRI)	Zimeldine, fluoxetine, citalopram, paroxetine, sertraline, alaproclate, fluvoxamine, etoperidone, escitalopram	N06AB

Table S3. Associations (adjusted hazard ratios [95% confidence intervals]) between loss of a partner and risks of ischemic stroke and intracerebral hemorrhage by time since bereavement (index date).

Time after bereavement	Events in exposed group, n	Model 1	Model 2	Model 3
Ischemic stroke:				
0-1 month	197	1.16 [0.98-1.39]	1.15 [0.96-1.37]	1.14 [0.96-1.36]
1-2 months	162	1.03 [0.86-1.25]	1.02 [0.85-1.24]	1.02 [0.84-1.23]
2-6 months	697	1.16 [1.06-1.28]	1.15 [1.05-1.26]	1.14 [1.04-1.25]
6 months – 1 year	970	1.11 [1.02-1.20]	1.09 [1.01-1.18]	1.09 [1.01-1.18]
1-2 years	1727	1.13 [1.06-1.20]	1.11 [1.05-1.18]	1.11 [1.04-1.18]
2-5 years	3931	1.13 [1.09-1.18]	1.12 [1.07-1.17]	1.11 [1.07-1.16]
Intracerebral hemorrhage:				
0-1 month	34	1.66 [1.06-2.61]	1.67 [1.06-2.62]	1.66 [1.06-2.61]
1-2 months	28	1.40 [0.87-2.27]	1.40 [0.86-2.27]	1.40 [0.87-2.27]
2-6 months	107	1.22 [0.96-1.55]	1.21 [0.95-1.54]	1.21 [0.95-1.53]
6 months – 1 year	138	1.19 [0.96-1.47]	1.19 [0.96-1.46]	1.18 [0.96-1.46]
1-2 years	267	1.15 [0.98-1.33]	1.14 [0.98-1.33]	1.14 [0.98-1.33]
2-5 years	565	1.08 [0.97-1.20]	1.07 [0.96-1.20]	1.07 [0.96-1.20]

Model 1: adjusted for matching variables (sex, age, and calendar time).

Model 2: further adjusted for socioeconomic variables and comorbidities.

Model 3: further adjusted for medications.

Table S4. Associations (adjusted hazard ratios [95% confidence intervals]) between loss of a partner and risks of ischemic stroke and intracerebral hemorrhage in bereaved individuals by sex.

	Women		Men		Women vs. men
Time after bereavement	**Events in exposed group, n**	**aHR* [95% CI]**	**Events in exposed group, n**	**aHR* [95% CI]**	**aHRR† [95% CI]**
Ischemic stroke:					
0-1 month	119	1.33 [1.06-1.68]	78	0.94 [0.71-1.22]	1.42 [1.00-2.03]
1-2 months	94	1.02 [0.80-1.31]	68	1.01 [0.75-1.35]	1.02 [0.69-1.49]
2-6 months	411	1.11 [0.98-1.25]	286	1.19 [1.03-1.38]	0.93 [0.77-1.12]
6 months – 1 year	574	1.13 [1.02-1.25]	396	1.04 [0.92-1.17]	1.09 [0.93-0.28]
1-2 years	1057	1.14 [1.05-1.23]	670	1.07 [0.97-1.17]	1.07 [0.94-1.20]
2-5 years	2461	1.09 [1.03-1.15]	1470	1.15 [1.08-1.23]	0.95 [0.87-1.03]
Full period: 0-5 years	4716 ‡	1.11 [1.07-1.16]	2968 §	1.11 [1.06-1.16]	1.00 [0.94-1.07]
Intracerebral hemorrhage:					
0-1 month	19	1.99 [1.06-3.75]	15	1.37 [0.72-2.63]	1.45 [0.59-3.60]
1-2 months	16	1.28 [0.68-2.39]	12	1.62 [0.76-3.46]	0.79 [0.29-2.10]
2-6 months	58	1.13 [0.82-1.56]	49	1.30 [0.91-1.87]	0.87 [0.54-1.41]
6 months – 1 year	87	1.23 [0.94-1.61]	51	1.11 [0.79-1.56]	1.11 [0.72-1.71]
1-2 years	167	1.14 [0.94-1.38]	100	1.14 [0.89-1.46]	1.00 [0.73-1.36]
2-5 years	362	1.04 [0.90-1.19]	203	1.13 [0.95-1.35]	0.92 [0.73-1.15]
Full period: 0-5 years	709 ‖	1.11 [1.00-1.23]	430 ¶	1.17 [1.03-1.32]	0.95 [0.81-1.12]

*Fully adjusted hazard ratio (aHR) for bereaved persons versus references as in model 3.

†Ratio between associations estimated in the two strata.

‡Events in reference group: 7379.

§Events in reference group: 5337.

‖Events in reference group: 1128.

¶Events in reference group: 746.

Table S5. Cumulative incidence proportion (CIP) of ischemic stroke[*] and intracerebral hemorrhage[†] (per 1000 persons).

	Months after bereavement (index date)	Bereaved individuals CIP [95% CI]	Non-bereaved referents CIP [95% CI]
Ischemic stroke	1	0.73 [0.64-0.84]	0.63 [0.56-0.69]
	2	1.31 [1.18-1.45]	1.18 [1.10-1.28]
	6	3.88 [3.65-4.12]	3.42 [3.27-3.58]
	12	7.53 [7.21-7.87]	6.75 [6.54-6.98]
Intracerebral hemorrhage	1	0.13 [0.09-0.18]	0.08 [0.06-0.10]
	2	0.23 [0.18-0.29]	0.15 [0.12-0.19]
	6	0.62 [0.54-0.72]	0.47 [0.42-0.53]
	12	1.15 [1.02-1.28]	0.91 [0.84-1.00]

[*]Adjusted for competing risks of death and intracerebral hemorrhage.

[†]Adjusted for the competing risks of death and ischemic stroke.

Table S6. Associations (adjusted hazard ratios [95% confidence intervals]) between loss of a partner and risks of ischemic stroke and intracerebral hemorrhage estimated including events from death certificates only.

Time after bereavement	Events in exposed group, n	aHR* [95% CI]
Ischemic stroke:		
0-1 month	218	1.18 [1.00-1.39]
1-2 months	179	1.07 [0.89-1.29]
2-6 months	746	1.14 [1.04-1.25]
6 months – 1 year	1038	1.10 [1.02-1.19]
1-2 years	1862	1.11 [1.05-1.18]
2-5 years	4260	1.12 [1.08-1.17]
Full period: 0-5 years	8303 †	1.12 [1.09-1.15]
Intracerebral hemorrhage:		
0-1 month	37-41 ‡	1.81 [1.18-2.79]
1-2 months	29-33 ‡	1.25 [0.79-1.97]
2-6 months	113	1.12 [0.89-1.41]
6 months – 1 year	156	1.14 [0.93-1.38]
1-2 years	299	1.12 [0.97-1.30]
2-5 years	631	1.04 [0.93-1.15]
Full period: 0-5 years	1268 §	1.10 [1.02-1.18]

* Fully adjusted hazard ratio (aHR) as in model 3

† Events in reference group: 13515.

‡ Numbers cannot be stated precisely due to discretion issues.

§ Events in reference group: 2140.

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Table S7. Associations (adjusted hazard ratios [95% confidence intervals]) between loss of a partner and risks of ischemic stroke and intracerebral hemorrhage estimated under restrictions of the diagnosis criteria and/or type of health care contact.

Time after bereavement	Events in exposed group, n	aHR* [95% CI]
Ischemic stroke, not including unspecified strokes (i.e. ICD10: I63 only):		
0-1 month	139	1.13 [0.91-1.39]
1-2 months	109	0.98 [0.78-1.23]
2-6 months	489	1.16 [1.04-1.30]
6 months – 1 year	688	1.08 [0.98-1.19]
1-2 years	1239	1.09 [1.01-1.17]
2-5 years	2995	1.11 [1.06-1.17]
Full period: 0-5 years	5659 †	1.10 [1.06-1.14]
Ischemic stroke, primary diagnoses from inpatient contacts only and not including unspecified strokes (i.e. ICD10: I63 only):		
0-1 month	113	1.08 [0.86-1.36]
1-2 months	93	0.98 [0.77-1.26]
2-6 months	408	1.17 [1.03-1.32]
6 months – 1 year	572	1.09 [0.98-1.21]
1-2 years	1045	1.10 [1.02-1.19]
2-5 years	2487	1.12 [1.06-1.18]
Full period: 0-5 years	4718 ‡	1.11 [1.07-1.16]
Intracerebral hemorrhage, primary diagnoses from inpatient contacts only:		
0-1 month	29	1.57 [0.97-2.54]
1-2 months	22	1.30 [0.76-2.22]
2-6 months	85	1.20 [0.92-1.57]
6 months – 1 year	127	1.25 [1.00-1.56]
1-2 years	231	1.14 [0.97-1.34]
2-5 years	461	1.02 [0.90-1.15]
Full period: 0-5 years	955 §	1.11 [1.02-1.21]

*Fully adjusted hazard ratio (aHR) as in model 3

†Events in reference group: 9397.

‡Events in reference group: 7805.

§ Events in reference group: 1602.

Table S8. Associations (adjusted hazard ratios [95% confidence intervals]) between loss of a partner and risks of ischemic stroke and intracerebral hemorrhage by level of cardiovascular risk in bereaved individuals.

	Low risk		High risk		Low vs High
Time after bereavement	**Events in exposed group, n**	**aHR* [95 CI]**	**Events in exposed group, n**	**aHR* [95 CI]**	**aHRR† [95% CI]**
Ischemic stroke:					
0-1 month	117	1.16 [0.94-1.44]	80	1.11 [0.86-1.42]	1.05 [0.78-1.41]
1-2 months	85	0.94 [0.74-1.19]	77	1.12 [0.87-1.44]	0.84 [0.61-1.15]
2-6 months	385	1.09 [0.97-1.22]	312	1.21 [1.07-1.38]	0.90 [0.77-1.05]
6 months – 1 year	590	1.15 [1.04-1.26]	380	1.01 [0.90-1.13]	1.14 [0.99-1.30]
1-2 years	1058	1.13 [1.05-1.21]	669	1.07 [0.98-1.17]	1.05 [0.95-1.17]
2-5 years	2598	1.16 [1.10-1.22]	1333	1.03 [0.96-1.10]	1.12 [1.04-1.21]
Full period: 0-5 years	4833	1.14 [1.10-1.18]	2851	1.06 [1.01-1.11]	1.08 [1.01-1.14]
Intracerebral hemorrhage:					
0-1 month	18	1.45 [0.84-2.51]	16	1.98 [1.08-3.61]	0.73 [0.36-1.49]
1-2 months	20	1.67 [0.97-2.86]	8	1.00 [0.46-2.18]	1.66 [0.71-3.91]
2-6 months	68	1.16 [0.87-1.56]	43	1.27 [0.90-1.79]	0.92 [0.61-1.38]
6 months – 1 year	94	1.15 [0.89-1.48]	53	1.23 [0.90-1.67]	0.94 [0.65-1.35]
1-2 years	187	1.07 [0.89-1.28]	106	1.27 [1.01-1.59]	0.84 [0.64-1.10]
2-5 years	438	1.10 [0.96-1.25]	169	1.01 [0.84-1.22]	1.08 [0.88-1.34]
Full period: 0-5 years	744	1.12 [1.01-1.24]	395	1.15 [1.01-1.32]	0.97 [0.82-1.14]

*Fully adjusted hazard ratio (aHR) as in model 3.

†Ratio between associations estimated in the two strata.

High risk was defined as at least one of the conditions: hypertension (hospital-diagnosed), atrial fibrillation, ischemic heart disease, congestive heart failure, peripheral artery occlusive disease, cerebrovascular disease, or diabetes mellitus.

Table S9. Associations (adjusted hazard ratios [95% confidence intervals]) between loss of a partner and risks of ischemic stroke and intracerebral hemorrhage by level of expectedness as assessed from the diseased partners' Charlson Comorbidity Index (CCI) 60 days before death.

	Most expected (CCI score ≥3)		Least expected (CCI score 0-2)		Most vs least
Time after bereavement	**Events in exposed group, n**	**aHR* [95% CI]**	**Events in exposed group, n**	**aHR* [95% CI]**	**aHRR† [95% CI]**
Ischemic stroke:					
0-1 month	84	1.08 [0.85-1.38]	113	1.19 [0.96-1.47]	0.91 [0.69-1.21]
1-2 months	82	1.16 [0.91-1.48]	80	0.90 [0.71-1.15]	1.28 [0.94-1.74]
2-6 months	301	1.11 [0.97-1.25]	396	1.17 [1.05-1.31]	0.94 [0.81-1.10]
6 months – 1 year	422	1.06 [0.95-1.18]	548	1.11 [1.01-1.22]	0.96 [0.84-1.09]
1-2 years	779	1.12 [1.03-1.21]	948	1.10 [1.02-1.18]	1.01 [0.92-1.12]
2-5 years	1745	1.11 [1.05-1.17]	2186	1.12 [1.06-1.17]	0.99 [0.93-1.06]
Full period: 0-5 years	3413	1.10 [1.06-1.15]	4271	1.11 [1.07-1.16]	0.99 [0.95-1.04]
Intracerebral hemorrhage:					
0-1 month	15	1.75 [0.96-3.16]	19	1.60 [0.93-2.75]	1.09 [0.55-2.16]
1-2 months	16	1.77 [0.99-3.19]	12	1.10 [0.58-2.09]	1.61 [0.76-3.44]
2-6 months	53	1.33 [0.98-1.81]	54	1.10 [0.81-1.50]	1.20 [0.82-1.77]
6 months – 1 year	68	1.27 [0.97-1.67]	70	1.10 [0.85-1.44]	1.15 [0.83-1.61]
1-2 years	114	1.07 [0.87-1.32]	153	1.19 [0.99-1.44]	0.90 [0.70-1.15]
2-5 years	240	1.02 [0.88-1.18]	325	1.12 [0.98-1.27]	0.91 [0.77-1.08]
Full period: 0-5 years	506	1.12 [1.01-1.24]	633	1.14 [1.04-1.26]	0.98 [0.87-1.10]

*Fully adjusted hazard ratio (aHR) as in model 3.

†Ratio between associations estimated in the two strata.

Table S10. Associations (adjusted hazard ratios [95% confidence intervals]) between loss of a partner and risks of ischemic stroke and intracerebral hemorrhage by age group.

	40-70 years old		70-100 years old		Young vs old
Time after bereavement	**Events in exposed group, n**	**aHR* [95 CI]**	**Events in exposed group, n**	**aHR* [95 CI]**	**aHRR† [95% CI]**
Ischemic stroke:					
0-1 month	41	1.08 [0.74-1.58]	156	1.16 [0.95-1.41]	0.93 [0.61-1.43]
1-2 months	31	1.15 [0.74-1.79]	131	0.99 [0.80-1.22]	1.16 [0.71-1.90]
2-6 months	142	1.38 [1.11-1.71]	555	1.09 [0.99-1.21]	1.26 [0.99-1.60]
6 months – 1 year	203	1.40 [1.17-1.68]	767	1.03 [0.94-1.12]	1.36 [1.12-1.67]
1-2 years	388	1.29 [1.13-1.46]	1339	1.06 [0.99-1.14]	1.21 [1.05-1.40]
2-5 years	975	1.28 [1.18-1.39]	2956	1.06 [1.01-1.12]	1.20 [1.09-1.32]
Full period: 0-5 years	1780	1.29 [1.22-1.37]	5904	1.06 [1.03-1.10]	1.22 [1.14-1.31]
Intracerebral hemorrhage:					
0-1 month	6	2.35 [0.72-7.62]	28	1.56 [0.96-2.55]	1.50 [0.42-5.38]
1-2 months	5	1.41 [0.45-4.45]	23	1.40 [0.83-2.39]	1.00 [0.28-3.56]
2-6 months	26	1.76 [1.04-2.97]	81	1.10 [0.84-1.44]	1.60 [0.88-2.89]
6 months – 1 year	28	0.97 [0.62-1.52]	110	1.25 [0.99-1.59]	0.78 [0.47-1.29]
1-2 years	57	1.30 [0.93-1.82]	210	1.10 [0.93-1.31]	1.18 [0.81-1.72]
2-5 years	146	1.36 [1.10-1.68]	419	0.99 [0.87-1.13]	1.37 [1.07-1.75]
Full period: 0-5 years	268	1.33 [1.14-1.56]	871	1.08 [0.98-1.18]	1.24 [1.03-1.48]

*Fully adjusted hazard ratio (aHR) as in model 3.

†Ratio between associations estimated in the two strata.