Partner bereavement and brain pathologies: a propensity score matching study

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Research

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Abstract

Background: Partner bereavement is one of life's greatest stresses and has been suggested to trigger or accelerate cognitive decline and dementia. However, little information is available about potential brain pathologies underlying the association between partner bereavement and cognitive decline.

Aims: We aimed to test the hypothesis that lifetime partner bereavement is associated with in vivo human brain pathologies underlying cognitive decline.

Method: A total of 319 ever-married older adults between 61 and 90 years of age underwent comprehensive clinical assessments and multimodal brain imaging including [^{11}C] Pittsburgh compound B-positron emission tomography (PET), AV-1451 PET, [^{18}F] fluorodeoxyglucose (FDG)-PET, and magnetic resonance imaging.

Results: Participants were classified as experiencing no partner bereavement or partner bereavement, and comparisons using propensity score matching (59 cases and 59 controls) were performed. Partner bereavement was significantly associated with higher cerebral white matter hyperintensities (WMH) volume compared to no partner bereavement. Interactions and subsequent subgroup analyses showed that partner bereavement was significantly associated with higher WMH in the older (>75 years) subgroup and among those with no- or low-skill occupations. In addition, partner bereavement at 60 years or over affect WMH volume compared to no partner bereavement, whereas partner bereavement at 60 years did not. No group differences were observed in other brain pathologies between partner bereavement categories.

Conclusions: The findings suggest that the partner bereavement may contribute to dementia or cognitive decline by increasing cerebrovascular injury, particularly in older individuals and those with no- or low-skill occupations.

Background

Partner bereavement is a major life event and is regarded as one of life's greatest stresses (1, 2). Extreme stress from partner bereavement has been repeatedly suggested to trigger or accelerate cognitive decline and dementia (3-7). Previous cross-sectional studies reported that bereaved older individuals performed worse on tests of memory, attention, and executive function when compared with non-bereaved individuals (3, 4). One cohort study demonstrated significantly greater cognitive decline among individuals with a history of partner bereavement (5). A meta-analysis of 15 studies also showed that those who had experienced partner bereavement had a 20% greater risk of developing dementia during 3 15 years of follow-up (7).

Nevertheless, little information is available on the neuropathological changes underlying the association between the experience of partner bereavement and cognitive decline. Some studies have suggested that cardiovascular disease or events are a main biological adverse response to partner bereavement (8, 9). Thus, partner bereavement may be associated with other forms of vascular injury including cerebrovascular disease. In addition, a recent study reported that being widowed was associated with accelerated beta-amyloid protein (Ab)-related cognitive decline. However, the relationship of partner bereavement with in vivo brain pathologies underlying cognitive decline has not yet been clarified.

In this context, we aimed to test the hypothesis that partner bereavement is associated with cerebrovascular injury in non-demented older adults. Cerebral white matter hyperintensities (WMH) on magnetic resonance imaging (MRI) were used as a measure of cerebrovascular injury (10, 11). We also tested the hypothetical associations of partner bereavement with in vivo Alzheimer's disease (AD) pathologies including cerebral beta-amyloid protein (Ab) deposition, tau deposition and AD-signature neurodegeneration. Cerebral Aβ deposition and tau deposition were measured by [^{11}C] Pittsburg compound B (PiB) positron emission tomography (PET) and [^{18}F] AV-1451 PET, respectively. The neurodegeneration of AD-signature regions was measured by both MRI and [^{18}F] fluorodeoxyglucose (FDG) PET imaging.

Methods

Participants

The present study was performed as part of the Korean Brain Aging Study for Early Diagnosis and Prediction of Alzheimer's Disease (KBASE), an ongoing prospective cohort study (12). The KBASE study aimed to search for new AD biomarkers and investigate how multi-faceted lifetime experiences and bodily changes contribute to the brain changes related AD. As of November 2016, a total of 319 ever-married older adults between 61 and 90 years of age were initially enrolled in the study. All Participants were not demented, i.e., were cognitively normal (CN) or exhibited mild cognitive impairment (MCI). Participants were recruited through four recruitment sites around Seoul, South Korea. Potentially eligible individuals who participated in a dementia screening program at two public centers for dementia prevention and management or visited memory clinics at two university hospitals [i.e., Seoul National University Hospital (SNUH) and Seoul National University-Seoul Metropolitan Government (SNU-SMG) Boramae Medical Center] around Seoul, South Korea, were informed about study participation and those who volunteered were invited for an assessment of eligibility. In addition, volunteers from the community were recruited through advertisements at an online homepage, posters, and brochures provided at main recruitment sites and word of mouth (recommended by other participants, family members, friends, or acquaintances). The CN group consisted of participants with a Clinical Dementia Rating (CDR)(13) score of 0 and no diagnosis of MCI or dementia. All individuals with MCI met the current consensus criteria for amnestic MCI and had a CDR score of 0.5. The current consensus criteria for amnestic MCI are as follows: 1) memory complaints confirmed by an informant; 2) objective memory impairments; 3) preserved global cognitive function; 4) independence in functional activities; and 5) no dementia. With regard to criterion 2, the age-, education-, and gender-adjusted z-scores for at least one of four episodic memory tests were less than −1.0. The four memory tests were the Word List Memory, Word List Recall, Word List Recognition, and Constructional Recall tests, which are included in the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD-K) neuropsychological battery.(14) The exclusion criteria were as follows: 1) presence of a major psychiatric illness; 2) significant neurological or medical conditions that could affect mental function; 3) contraindications for MRI; 4) illiteracy; 5) the presence of significant visual/hearing difficulties and/or severe communication or behavioral problems that would make clinical examinations or brain scans difficult; and 6) taking an investigational drug. The presence of any item included in the exclusion criteria was determined by research clinicians referring to the results of laboratory examinations and MRI as well as the clinical data collected by trained nurses during systematic interviews of participants and their

reliable informants during the screening period. More detailed information on the recruitment of the KBASE cohort is presented in a previous report from the research group.(12)

As age and sex, which are likely to have prominent confounding effects on the relationship of partner bereavement with brain pathologies differed substantially between groups with and without lifetime experience of partner bereavement (Table 1), we used propensity score matching methods (15) to generate more balanced groups having similar age and sex characteristics. Propensity scores are conditional probabilities of belonging to a particular group, given a set of observed background characteristics (i.e., age and sex in our propensity score matching model). Finally, 59 individuals with and 59 without lifetime experience of partner bereavement were included, as shown in Table 1.

The study protocol was approved by the Institutional Review Boards of SNUH (C-1401-027-547) and SNU-SMG Boramae Medical Center (26-2015-60), Seoul, South Korea, and was carried out in accordance with the recommendations of the current version of the Declaration of Helsinki. All subjects gave written informed consent.

Clinical and neuropsychological assessments

Trained board-certified psychiatrists administered standardized clinical assessments to all participants based on the KBASE clinical assessment protocol, which incorporated the CERAD-K clinical assessment (12). A clinical neuropsychologist or trained psychometrist also administered a comprehensive neuropsychological assessment battery to the participants, following a standardized protocol incorporating the CERAD-K neuropsychological battery.

Assessment of partner bereavement and related conditions

Information (yes / no) on lifetime experience of partner bereavement was obtained from all participants through systematic interviews with the participants and their reliable informants by trained nurses. If the answer was yes, the age of the bereavement experience was also documented. To analyze the effects of the age of the bereavement experience, we divided those with partner bereavement into subgroups, i.e., partner bereavement at 60 years vs. partner bereavement at 60 years of age or over. Information (yes / no) on a death of close family member and a close friend, divorce, separation, and remarriage was also obtained.

Assessment of potential confounders or modulators

The association between partner bereavement and brain pathologies may be influenced or modulated by various other conditions. Therefore, we systematically evaluated all participants for potential confounders or modulators, such as undernutrition, depression, social support, annual income, occupational complexity, vascular risk, body mass index (BMI), alcohol intake, smoking, physical activity, and apolipoprotein E (APOE) genotyping. The detailed procedures for assessment of these potential confounders or modulators are described in the Supplement Method.

Measurement of cerebral Aβ deposition

All participants underwent simultaneous three-dimensional (3D) [^{11}C] Pittsburgh compound B (PiB)-positron emission tomography (PET) and a 3D T1-weighted MRI scan using a 3.0T Biograph mMR (PET-MR) scanner (Siemens; Washington, DC, USA) according to the manufacturer's guidelines. The details of the PiB-PET imaging acquisition and preprocessing were described previously.(16) An automatic anatomical labeling algorithm and a region-combining method(17) were applied to determine regions of interests (ROIs) to characterize the PiB retention levels in the frontal, lateral parietal, posterior cingulate precuneus, and lateral temporal regions. The standardized uptake value ratio (SUVR) values for each ROI was calculated by dividing the mean value for all voxels within each ROI by the mean cerebellar uptake value in the same image. A global cortical ROI consisting of the four ROIs was also defined and a global Aβ retention value was generated by dividing the mean value for all voxels of the global cortical ROI by the mean cerebellar uptake value in the same image.(17, 18) Amyloid positivity was also used as an outcome variable. Participants were classified as Aβ positive (Aβ+) if global Aβ retention was > 1.21, and as Aβ negative (Aβ) if global Aβ retention was ≤ 1.21. (19)

Measurement of cerebral tau deposition

A subset of subjects underwent [^{18}F] AV-1451 PET scans using a Biograph True point 40 PET/CT scanner (Siemens; Washington, DC, USA), in accordance with the manufacturer's guidelines. While all the other neuroimaging scans were performed during the baseline visit, AV-1451 PET imaging was performed at an average of 2.5 years after the baseline visit; all the other neuroimaging scans were performed during the baseline visit. The details of AV-1451 PET imaging acquisition and preprocessing were described previously. (16) To estimate cerebral tau deposition, we quantified the AV-1541 SUVR of an a priori ROI of "AD-signature regions" of tau accumulation, which was composed of a size-weighted average of partial volume-corrected uptake in entorhinal, amygdala, parahippocampal, fusiform, inferior temporal, and middle temporal ROIs in accordance with the method used in a previous report.(20) The AV-1451 SUVR of the abovementioned ROI was used as an outcome variable for cerebral tau deposition.

Measurement of AD-signature neurodegeneration

All participants underwent [^{18}F] fluorodeoxyglucose (FDG)-PET imaging using the abovementioned PET-MR machine. The details of the FDG-PET image acquisition and preprocessing were described previously.(16) AD-signature FDG ROIs, such as the angular gyri, posterior cingulate cortex, and inferior temporal gyri, which are sensitive to changes associated with AD,(21) were determined. AD-signature cerebral glucose metabolism (AD-CM) was defined as the voxel-weighted mean SUVR extracted from the AD-signature FDG ROIs. The details of MRI acquisition and preprocessing were described previously.(16) AD-signature cortical thickness (AD-CT) was defined as the mean cortical thickness values obtained from AD-signature regions, including the entorhinal, inferior temporal, middle temporal, and fusiform gyrus, as described previously.(21)

Measurement of WMH

All participants underwent MRI scans with fluid-attenuated inversion recovery using the abovementioned 3.0T PET-MR scanner. We followed the validated automatic procedure reported previously.(22) Briefly, the procedure

consisted of 11 steps, i.e., spatial coregistration of T1 and FLAIR images, fusion of T1 and FLAIR images, segmentation of T1, attainment of transformation parameters, deformation and obtainment of the white matter mask, obtainment of FLAIR within the white matter mask, intensity normalization of the masked FLAIR, nomination of candidate WMH with a designated threshold, creation of a junction map, and elimination of the junction. The current processing procedure had two modifications compared to the original study: (a) an optimal threshold of 70 was applied, as it was more suitable for our data than the threshold of 65 used in the original study; and, (b) given that individuals with acute cerebral infarcts were not enrolled in our sample, we did not use diffusion weighted imaging in the current automated procedure. Using the final WMH candidate image, the WMH volume was extracted in the native space in each subject. More specifically, the lobar ROIs template was adapted from a previously published minimal deformation template (MDT3).(23) The acquired transformation parameter for each subject from the automated procedure was applied to the template to transform the lobar ROIs template into native space to be used for extracting WMH volumes in each lobe.

Statistical analysis

To test the hypothetical associations between partner bereavement and in vivo brain pathologies, multiple linear regression analysis with partner bereavement group as the independent variable and each neuroimaging biomarker (Ab and tau retention, AD-CM, AD-CT, or WMH) as a dependent variable was performed. In the analysis, global Aβ retention and WMH were used after natural log-transformation to achieve normal distributions. Multiple logistic regression analysis with partner bereavement categories as the independent variable and Ab positivity as the dependent variable was also conducted. Three models were tested for stepwise control of the potential confounders other than age and sex that could affect the relationships between partner bereavement and the biomarkers. The first model (Model I) did not include any covariate. The second model (Model II) included clinical diagnosis (CN vs. MCI), VRS, BMI, APOE4, and undernutrition. The third model (Model III) included the covariates in the second model plus education, GDS score, MOS-SSS score, annual income, occupational complexity, alcohol intake status, and smoking status, which have been considered possible confounders in previous studies.(1, 6, 8, 24, 25) To explore the effects of age of the bereavement experience, the same analyses were separately performed for the two relevant subgroups (i.e., partner bereavement at 60 years vs. partner bereavement at 60 years or over). In all analyses, no partner bereavement was used as a reference. As sensitivity analyses, the same analyses were also performed for 1) the participants without death of close friend, 2) those with neither divorce nor marital separation, and 3) those without remarriage. Additional exploratory analyses were performed for the neuroimaging biomarkers showing significant associations with partner bereavement in the above analyses as follows. To investigate the modulating effects of age (younger [≤ 75 years] vs. older [> 75 years]), sex, APOE4 positivity, clinical diagnosis, education, GDS score, MOS-SSS score, annual income, occupational complexity, VRS, BMI, physical activity, alcohol intake, and smoking on the association between partner bereavement and the neuroimaging biomarker(s), the same regression analyses were repeated including a two-way interaction term between partner bereavement and each of the factors mentioned above as an additional independent variable. Statistical analyses were performed using IBM SPSS Statistics 27 (IBM Corp. Armonk, NY).

Results

Participant characteristics

Participants' demographic and clinical characteristics are presented in Table 1. Before the propensity score matching, 260 of the 319 participants were categorized as the no partner bereavement group and 59 as the partner bereavement group. After the matching, 59 of 118 participants were categorized as the no partner bereavement group, and 59 as the partner bereavement group (29 with partner bereavement at 60 years and 30 with partner bereavement at 60 years or over).

Association of partner bereavement with AD neuroimaging biomarkers

Independent of the models, no differences were observed in Ab positivity, Ab and tau deposition, AD-CM, and AD-CT between the group with and that without partner bereavement (Tables 2 and 3).

Association of partner bereavement with WMH

The partner bereavement group showed greater WMH volume compared to the no partner bereavement group independent of the covariates (Table 2 and Fig. 1A). Furthermore, individuals with partner bereavement at 60 years or over had greater WMH volume than those without partner bereavement, whereas those with partner bereavement at 60 years did not (Table 3 and Fig. 1B).

Sensitivity analyses

The same analyses including only participants with no death of a close friend showed similar results in terms of the association between partner bereavement and each of the neuroimaging markers (Supplementary Table S1). The results were also similar after excluding those with divorce or marital separation (Supplementary Table S2) and those who had remarried (Supplementary Table S3).

Influence of potential modulators on the association between partner bereavement and WMH

The interactions of partner bereavement with age and occupational complexity were significant, indicating that age and occupational complexity independently modulated the association between partner bereavement and WMH volume (Supplementary Table S4). Further subgroup analyses showed that partner bereavement was significantly associated with higher WMH in the older (>75 years) subgroup but not in the younger (≤75 years) one, and in the no- or low- skill occupational subgroup but not in the high-skill group (Supplementary Table S5; Supplementary Fig. 1A and 1B). The interactions of partner bereavement with sex, APOE4 positivity, clinical diagnosis, education, GDS score, MOS-SSS score, annual income, VRS, BMI, physical activity, alcohol intake, and smoking were not significant (Supplementary Table S4).

Discussion

The present study showed that lifetime experience of partner bereavement was associated with increased WMH volume, but not with AD neuroimaging markers, in non-demented older adults. The association of partner bereavement with WMH observed in the present study may be explained by the following potential mechanisms. First, the loss of a partner is considered as one of the most stressful life events (1, 2, 26). The experience of partner bereavement can cause a severe acute or chronic stress reaction and emotional sequalae such as depression, which may subsequently contribute to cerebrovascular changes, resulting in increased WMH. Evidence indicates that stress and depression elicit multifaceted dysfunction in the cerebral

microcirculation, which plays a critical role in brain health and the pathogenesis of stress-related cerebrovascular events (27, 28). Second, a widowed state after partner bereavement may lead to lower socioeconomic status (SES) and poor health care utilization (29). Both may result in poor management of vascular risks, which could contribute to cerebrovascular changes and subsequent increased WMH. However, given the association between partner bereavement and WMH was observed even after controlling the annual income, the degree of social support, nutritional status, and VRS, the possibility appears not so high.

Unlike the association with WMH, the experience of partner bereavement was not associated with any AD neuroimaging biomarkers, indicating that it may not directly affect AD-specific brain changes in older adults. One cohort study reported that widowed adults with higher baseline cortical Ab levels exhibited steeper cognitive decline (6). However, similar to our finding, the authors of that study reported no difference in brain Ab between the groups with and without partner bereavement. As they suggested, partner bereavement may modulate AD pathology-related cognitive decline by affecting the brain or cognitive reserves, but not by affecting AD pathologies themselves. White matter degeneration as indicated by WMH volume can impair the brain or cognitive reserves (30, 31). Therefore, together with our finding for WMH, the decreased reserves associated with white matter degeneration may synergistically aggravate cognitive function in individuals with partner bereavement when AD pathologies are present in the brain.

The individuals who had experienced partner bereavement at 60 years or over had greater WMH than those without partner bereavement, whereas those who had experienced it under 60 years of age did not. This finding implies that the age-related vulnerability of the brain to stress or cerebrovascular changes at the time of bereavement is more important than the time elapsed since bereavement or the chronicity of influence. Similarly, current age also moderated the relationship between bereavement and WMH volume; partner bereavement was significantly associated with higher WMH volume in the older (>75 year) subgroup, but not in the younger (≤75 years) subgroup. This finding additionally indicates that vulnerability to bereavement-related white matter injury depends not only on the age of bereavement but also on current age.

In addition to age, lifetime occupation also moderated the relationship between bereavement and WMH volume, with partner bereavement significantly associated with higher WMH only in individuals with no- or low-skill occupations and not in those with higher skill occupations. Given that the moderation effect of occupational complexity was significant even after annual income and social support were controlled, the association is apparently not simply due to economic difficulty or poorer social support resulting from partner loss. Furthermore, because the National Health Insurance system in Korea covers nearly all people in the country, the lack of access to adequate health care caused by the loss of partner with better health insurance (32) may not clearly explain the moderation effect of occupational level. The brains of those with no- or low-skill occupations may be more venerable to stress or cerebrovascular disease due to lower brain reserves (33).

Strengths And Limitations

The present study had some strengths. First, to our knowledge, this is the first study to elucidate the association of partner bereavement with brain pathologies in living human. Second, the study included a relatively large number of participants who were well-characterized through comprehensive clinical

assessments including systematic interviews for detailed history about partner bereavement, the death of close family members and close friends, divorce, separation, and remarriage, in addition to multimodal brain imaging to assess in vivo AD pathologies and WMH. Third, we used propensity score matching methods to create more balanced groups of similar age and sex and to minimize the potential confounding effect of age and sex on the relationship of partner bereavement with brain pathologies. Additionally, various other potential confounders were systematically controlled in the statistical models to clarify the association between partner bereavement and brain pathologies as clearly as possible. The findings from the present study were not changed even after controlling for all potential confounders and were confirmed by sensitivity analyses conducted after excluding participants with bereavement of close friends, those reporting divorce or marital separation, and those who had remarried.

Nevertheless, the present study had several limitations that should be considered. First, as this was a cross-sectional study, we could not confirm a causal relationship between partner bereavement and brain WMH. Further long-term follow-up studies are required to clarify the causal relationships. Second, our study did not attempt to examine individual psychological reactions to bereavement or the severity of grief (i.e., normal grief vs. complicated grief; unexpected bereavement vs. expected bereavement). Third, information about bereavement and related topics was obtained through clinical interviews, raising some concern about recall bias, especially for participants with MCI. However, although MCI individuals have some problem with recent memory, their remote memory tends to be well preserved (34). Therefore, it is not likely that MCI individuals reported a history of partner bereavement less accurately, as such history mainly depends on remote memory rather than recent memory. Furthermore, even when we controlled for clinical diagnosis (CN vs. MCI) as an additional covariate in Model 2 (Tables 2 and 3; S1-3, 5 Tables), the results were still very similar. Additionally, we interviewed reliable informants as well as the participants. Third, the present study excluded participants with a history of stroke or severe vascular lesions including infarcts and hemorrhages on brain MRI. Therefore, we could not assess the effect of partner bereavement on individuals with severe cerebrovascular disease. Further studies are required to clarify these effects in those with high cerebrovascular burdens. Finally, tau PET was applied at an average of 2.5 years from the baseline visit, whereas other neuroimaging scans were performed at baseline. This temporal gap may have influenced the association between partner bereavement and tau. When we controlled for the temporal gap as an additional covariate, however, the results did not change. In addition, only a subset of participants (n = 13 without partner bereavement vs. n = 15 with partner bereavement after propensity score matching) underwent tau PET. This relatively reduced sample size for tau PET may have decreased the statistical power and contributed to the null result for the relationship between partner bereavement and tau deposition.

Conclusions

The findings from the present study suggest that the experience of partner bereavement may contribute to dementia or cognitive decline by increasing cerebrovascular injury rather than by aggravating AD pathologies, particularly in older individuals and no- or low-skill occupations. More attention should be paid to partner bereavement-related brain health problems.

Declarations

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Author Contributions

JWK and DYL conceived and designed the study. MSB, DY, JHL, MJK, GJ, J-YL, KMK, C-HS, Y-SL, YKK, and DYL were involved in acquisition, or analysis and interpretation of the data and helped to draft the manuscript. JWK, MSB, DY, JHL, and DYL were major contributors in writing the manuscript and critically revising the manuscript for intellectual content. DYL served as principal investigator and supervised the study. All authors read and approved the final manuscript.

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Availability of data and materials

The data of the current study are not freely accessible because the Institutional Review Board (IRB) of Seoul National University Hospital prohibits public data-sharing for privacy reasons. However, the data may be available from the independent data-sharing committee of the KBASE research group on reasonable request, after approval by the IRB. Requests for data access can be submitted to the administrative coordinator of the KBASE group by e-mail (kbasecohort@gmail.com); the coordinator is independent of the authors.

Ethics approval and consent to participate

This study protocol was approved by the Institutional Review Boards of Seoul National University Hospital (SNUH) (C-1401-027-547) and Seoul Metropolitan Government-Seoul National University (SMG-SNU) Boramae Medical Center (26-2015-60), Seoul, South Korea, and was conducted in accordance with the recommendations in the current version of the Declaration of Helsinki. The subjects or their legal representatives gave written informed consent.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1 Participant characteristics with and without partner bereavement [a]

	Before matching			*After matching*		
	No partner bereavement	Partner bereavement	*P*	No partner bereavement	Partner bereavement	*P*
n	260	59		59	59	
Age, yrs	72.32 (6.21)	76.05 (5.76)	<0.001 [b]	75.58 (5.21)	76.05 (5.76)	0.640 [b]
Age at partner bereavement, No. (%)			<0.001 [c]			<0.001 [c]
Under 60 years	0 (0.00)	29 (49.15)		0 (0.00)	29 (49.15)	
60 years or over	0 (0.00)	30 (50.85)		0 (0.00)	30 (50.85)	
Female, No. (%)	126 (48.46)	47 (79.66)	0.001 [c]	48 (81.36)	47 (79.66)	0.816 [c]
Education, yrs			0.001 [c]			0.108 [c]
0-6	59 (22.69)	25 (42.37)		18 (30.51)	25 (42.37)	
7-12	101 (38.85)	26 (44.07)		24 (40.68)	26 (44.07)	
13-	100 (38.46)	8 (13.56)		17 (28.81)	8 (13.56)	
APOE4 positivity, No. (%)	58 (22.31)	16 (27.59)	0.390 [c]	16 (27.12)	16 (27.59)	0.955 [c]
Clinical diagnosis, CN, No. (%)	169 (65.00)	38 (64.41)	0.931 [c]	32 (54.24)	38 (64.41)	0.261 [c]
Other bereavement, No. (%)						
Close family members	244 (93.85)	55 (93.22)	0.772 [d]	54 (91.53)	55 (93.22)	0.717 [d]
Close friends	115 (44.23)	23 (38.98)	0.463 [c]	20 (33.90)	23 (38.98)	0.566 [c]
Divorce or separation, No. (%)	13 (5.00)	3 (5.08)	1.000 [d]	2 (3.39)	3 (5.08)	1.000 [d]
Remarriage, No. (%)	1 (0.38)	2 (3.39)	0.089 [d]	0 (0.00)	2 (3.39)	0.496 [d]
MOS-SSS overall score	71.54 (16.32)	71.76 (16.08)	0.924 [b]		71.76 (16.08)	
Physical activity score, No. (%)			0.944 [c]			0.737 [c]

High	77 (36.32)	14 (34.15)		19 (42.22)	14 (34.15)	
Medium	68 (32.08)	13 (31.71)		13 (28.89)	13 (31.71)	
Low	67 (31.60)	14 (34.15)		13 (28.89)	14 (34.15)	
GDS score	6.62 (6.22)	7.58 (6.17)	0.286 [b]	6.46 (5.47)	7.58 (6.17)	0.300 [b]
BMI	24.50 (3.02)	24.37 (2.93)	0.766 [b]	24.74 (2.80)	24.37 (2.93)	0.489 [b]
Smoking status, No. (%)			0.013 [c]			1.000 [c]
Never	171 (66.02)	50 (84.75)		51 (86.44)	50 (84.75)	
Former	76 (29.34)	9 (15.25)		8 (13.56)	9 (15.25)	
Smoker	12 (4.63)	0 (0.00)		0 (0.00)	0 (0.00)	
Alcohol drink status, No. (%)			0.004 [c]			1.000 [c]
Never	137 (52.90)	45 (76.27)		45 (76.27)	45 (76.27)	
Former	40 (15.44)	3 (5.08)		4 (6.78)	3 (5.08)	
Drinker	82 (31.66)	11 (18.64)		10 (16.95)	11 (18.64)	
Occupational complexity, No. (%)			0.044 [c]			0.116 [c]
None	47 (18.15)	14 (23.73)		19 (32.20)	14 (23.73)	
Skill level 1	16 (6.18)	6 (10.17)		4 (6.78)	6 (10.17)	
Skill level 2	76 (29.34)	23 (38.98)		15 (25.42)	23 (38.98)	
Skill level 3	33 (12.74)	8 (13.56)		4 (6.78)	8 (13.56)	
Skill level 4	87 (33.59)	8 (13.56)		17 (28.81)	8 (13.56)	
Annual income, No. (%)			0.100 [c]			0.732 [c]
<MCL	24 (9.23)	5 (8.47)		5 (8.47)	5 (8.47)	
MCL, <2 MCL	115 (44.23)	35 (59.32)		31 (52.54)	35 (59.32)	
2 MCL	121 (46.54)	19 (32.20)		23 (38.98)	19 (32.20)	
Vascular risk						
Hypertension, No. (%)	128 (49.23)	41 (69.49)	0.005 [c]	34 (57.63)	41 (69.49)	0.181 [c]
Diabetes mellitus, No. (%)	49 (18.85)	12 (20.34)	0.792 [c]	8 (13.56)	12 (20.34)	0.326 [c]
Coronary artery ds, No. (%)	16 (6.15)	3 (5.08)	1.000 [d]	5 (8.47)	3 (5.08)	0.717 [d]

Hyperlipidemia, No. (%)	90 (34.62)	29 (49.15)	0.040 [d]	26 (44.07)	29 (49.15)	0.580 [d]
Transient ischemic attack, No. (%)	3 (1.15)	0 (0.00)	1.000 [d]	1 (1.69)	0 (0.00)	1.000 [d]
Stroke, No. (%)	0 (0.00)	0 (0.00)	NA	0 (0.00)	0 (0.00)	NA
Vascular risk score	1.10 (1.00)	1.44 (0.90)	0.017 [b]	1.25 (0.99)	1.44 (0.90)	0.286 [b]
Undernutrition	46 (17.69)	11 (18.64)	0.819 [c]	14 (23.73)	11 (18.64)	0.530 [c]
Cerebral Aβ deposition						
Aβ positivity, No. (%)	72 (27.69)	17 (28.81)	0.862 [c]	21 (35.59)	17 (28.81)	0.431 [c]
Aβ retention, SUVR	1.32 (0.37)	1.31 (0.32)	0.791 [b]	1.37 (0.37)	1.31 (0.32)	0.348 [b]
Cerebral tau deposition						
AV-1451, SUVR (n = 86)	1.59 (0.69) (n = 71)	1.42 (0.29) (n = 15)	0.352 [b]	1.62 (0.92) (n = 13)	1.42 (0.29) (n = 15)	0.420 [b]
AD-neurodegeneration						
AD-CM, SUVR	1.39 (0.13)	1.38 (0.13)	0.530 [b]	1.39 (0.15)	1.38 (0.13)	0.585 [b]
AD-CT, mm	2.79 (0.22)	2.73 (0.21)	0.056 [b]	2.75 (0.21)	2.73 (0.21)	0.491 [b]
WMH volume, cm^3	12.52 (10.74)	15.72 (13.03)	0.048 [b]	11.10 (7.67)	15.72 (13.03)	0.021 [b]
CERAD-NP test						
VF	14.52 (4.52)	12.78 (4.43) [b]	0.008	13.56 (4.54)	12.78 (4.43)	0.347 [b]
BNT	11.43 (2.39)	10.12 (2.59) [b]	<0.001	11.17 (2.33)	10.12 (2.59)	0.022 [b]
CP	9.73 (1.44)	9.54 (1.61) [b]	0.385	9.61 (1.46)	9.54 (1.61)	0.811 [b]
WLM	15.77 (6.41)	14.000 (7.49) [b]	0.066	15.56 (6.26)	14.00 (7.49)	0.223 [b]
WLR	5.05 (2.33)	4.73 (2.45) [b]	0.353	4.81 (2.49)	4.73 (2.45)	0.852 [b]

WLRc	7.98 (2.34)	8.19 (2.23) [b]	0.532	7.63 (0.271)	8.19 (2.23)	0.223 [b]
CR	5.76 (3.56)	4.32 (3.16) [b]	0.005	4.80 (3.54)	4.32 (3.16)	0.444 [b]
MMSE	25.35 (3.30)	24.66 (3.55) [b]	0.154 [b]	24.71 (3.66)	24.66 (3.55)	0.939 [b]
TS	70.13 (16.52)	63.68 (17.65) [b]	0.008	67.03 (16.68)	63.68 (17.65)	0.291 [b]

Abbreviations: APOE4, apolipoprotein ε4; CN, cognitive normal; MOS-SSS, Medical Outcomes Study-Social Support Survey; GDS, geriatric depression scale; BMI, body mass index; MCL, minimum cost of living; Aβ, beta-amyloid; AD, Alzheimer's disease; AD-CM, Alzheimer's disease signature cerebral glucose metabolism; AD-CT, Alzheimer's disease signature cortical thickness; SUVR, standardized uptake value ratio; WMH, white matter hyperintensities; CERAD-NP, consortium to establish a registry for Alzheimer disease neuropsychological battery; VF, verbal fluency, BNT, Boston naming test; CP, construction praxis; WLM, word list memory; WLR, word list recall; WLRc, word list recognition; CR, constructional recall; MMSE, mini-mental state examination; TS, total score of the CERAD-NP

[a] Unless otherwise indicated, data are expressed as mean (standard deviation).

[b] by t-test

[c] by chi-square test.

[d] by fisher's exact test.

Table 2 Results of multiple logistic and linear regression analyses for assessing the relationships between stratified partner bereavement and Aβ, AV-1451, AD-CM, AD-CT, or WMH volume (N = 118).

	No partner bereavement n = 59	Partner bereavement n = 59	
		OR (95% CI)	p
Aβ positivity			
Model I [a]	Reference	0.807 (0.384 to 1.695)	0.571
Model II [b]	Reference	0.926 (-.363 to 2.361)	0.871
Model III [c]	Reference	0.989 (0.352 to 2.777)	0.983
		B (95% CI)	p
Aβ retention, SUVR			
Model I [a]	Reference	-0.049 (-0.130 to 0.032)	0.231
Model II [b]	Reference	-0.030 (-0.094 to 0.035)	0.366
Model III [c]	Reference	-0.025 (-0.092 to 0.041)	0.456
AV-1451, SUVR			
Model I [a]	Reference	-0.204 (-0.717 to 0.308)	0.420
Model II [b]	Reference	-0.181 (-0.720 to 0.359)	0.493
Model III [c]	Reference	0.053 (-0.563 to 0.669)	0.856
AD-CM, SUVR			
Model I [a]	Reference	-0.011 (-0.064 to 0.041)	0.664
Model II [b]	Reference	-0.021 (-0.070 to 0.029)	0.411
Model III [c]	Reference	-0.024 (-0.076 to 0.028)	0.359
AD-CT, mm			
Model I [a]	Reference	-0.026 (-0.105 to 0.053)	0.518
Model II [b]	Reference	-0.044 (-0.117 to 0.029)	0.233
Model III [c]	Reference	-0.052 (-0.125 to 0.021)	0.061
WMH volume, cm^3			
Model I [a]	Reference	0.074 (0.006 to 0.142)	0.034
	Reference	0.082(0.012 to 0.152)	0.021

Model II [b]			
Model III [c]	Reference	0.090 (0.016 to 0.164)	0.018

Abbreviations: Aβ, beta-amyloid; AD-CM, Alzheimer's disease signature cerebral glucose metabolism; AD-CT, Alzheimer's disease signature cortical thickness; WMH, white matter hyperintensities; SUVR, standardized uptake value ratio; OR; odds ratio; CI; confidence interval; VRS; vascular risk score; BMI, body mass index; GDS, geriatric depression scale; MOS-SSS, Medical Outcomes Study-Social Support Survey.

[a] Unadjusted.

[b] Adjusted for clinical diagnosis, VRS, BMI, and undernutrition.

[c] Adjusted for clinical diagnosis, VRS, BMI, undernutrition, education, occupational complex, annual income, GDS score, MOS-SSS score, alcohol intake status, and smoking status.

Table 3 Results of multiple logistic and linear regression analyses for assessing the relationships between stratified partner bereavement and Aβ, AV-1451, AD-CM, AD-CT, or WMH volume (N = 118).

	No partner bereavement n = 59	Partner bereavement under their 60 years n = 29		Partner bereavement of their 60 years or over n = 30	
		OR (95% CI)	p	OR (95% CI)	p
Aβ positivity					
Model I [a]	Reference	0.503 (0.191 to 1.321)	0.163	1.232 (0.504 to 3.014)	0.648
Model II [b]	Reference	0.411 (0.120 to 1.410)	0.157	1.910 (0.608 to 5.998)	0.268
Model III [c]	Reference	0.341 (0.083 to 1.402)	0.136	2.305 (0.658 to 8.079)	0.192
		B (95% CI)	p	B (95% CI)	p
Aβ retention, SUVR					
Model I [a]	Reference	-0.088 (-0.186 to 0.010)	0.079	-0.010 (-0.108 to 0.088)	0.840
Model II [b]	Reference	-0.072 (-0.149 to 0.005)	0.068	0.015 (-0.064 to 0.093)	0.708
Model III [c]	Reference	-0.074 (-0.156 to 0.007)	0.074	0.020 (-0.059 to 0.099)	0.624
AV-1451, SUVR					
Model I [a]	Reference	-0.265 (-0.992 to 0.461)	0.459	-0.174 (-0.754 to 0.407)	0.544
Model II [b]	Reference	-0.431 (-1.214 to 0.353)	0.265	-0.069 (-0.668 to 0.529)	0.811
Model III [c]	Reference	-0.234 (-1.166 to 0.699)	0.597	0.156 (-0.516 to 0.828)	0.624
AD-CM, SUVR					
Model I [a]	Reference	-0.014 (-0.078 to 0.050)	0.671	-0.009 (-0.073 to 0.055)	0.779
Model II [b]	Reference	-0.019 (-0.079 to 0.041)	0.539	-0.023 (-0.084 to 0.039)	0.467
Model III [c]	Reference	-0.021 (-0.085 to 0.044)	0.530	-0.027 (-0.090 to 0.035)	0.390
AD-CT, mm					

Model I [a]	Reference	0.006 (-0.092 to 0.105)	0.899	-0.056 (-0.152 to 0.040)	0.251
Model II [b]	Reference	-0.008 (-0.098 to 0.081)	0.856	-0.080 (-0.168 to 0.009)	0.079
Model III [c]	Reference	-0.022 (-0.113 to 0.070)	0.639	-0.077 (-0.164 to 0.009)	0.080
WMH volume, cm^3					
Model I [a]	Reference	0.006 (-0.075 to 0.087)	0.880	0.141 (0.061 to 0.222)	0.001
Model II [b]	Reference	0.011 (-0.070 to 0.093)	0.787	0.157 (0.074 to 0.240)	<0.001
Model III [c]	Reference	0.012 (-0.076 to 0.101)	0.784	0.160 (0.075 to 0.246)	<0.001

Abbreviations: Aβ, beta-amyloid; AD-CM, Alzheimer's disease signature cerebral glucose metabolism; AD-CT, Alzheimer's disease signature cortical thickness; WMH, white matter hyperintensities; OR, odds ratio; CI, confidence interval; VRS, vascular risk score; BMI, body mass index; GDS, geriatric depression scale; MOS-SSS, Medical Outcomes Study-Social Support Survey.

[a] Unadjusted.

[b] Adjusted for clinical diagnosis, VRS, BMI, and undernutrition.

[c] Adjusted for clinical diagnosis, VRS, BMI, undernutrition, education, occupational complex, annual income, GDS score, MOS-SSS score, alcohol intake status, and smoking status.

Figures

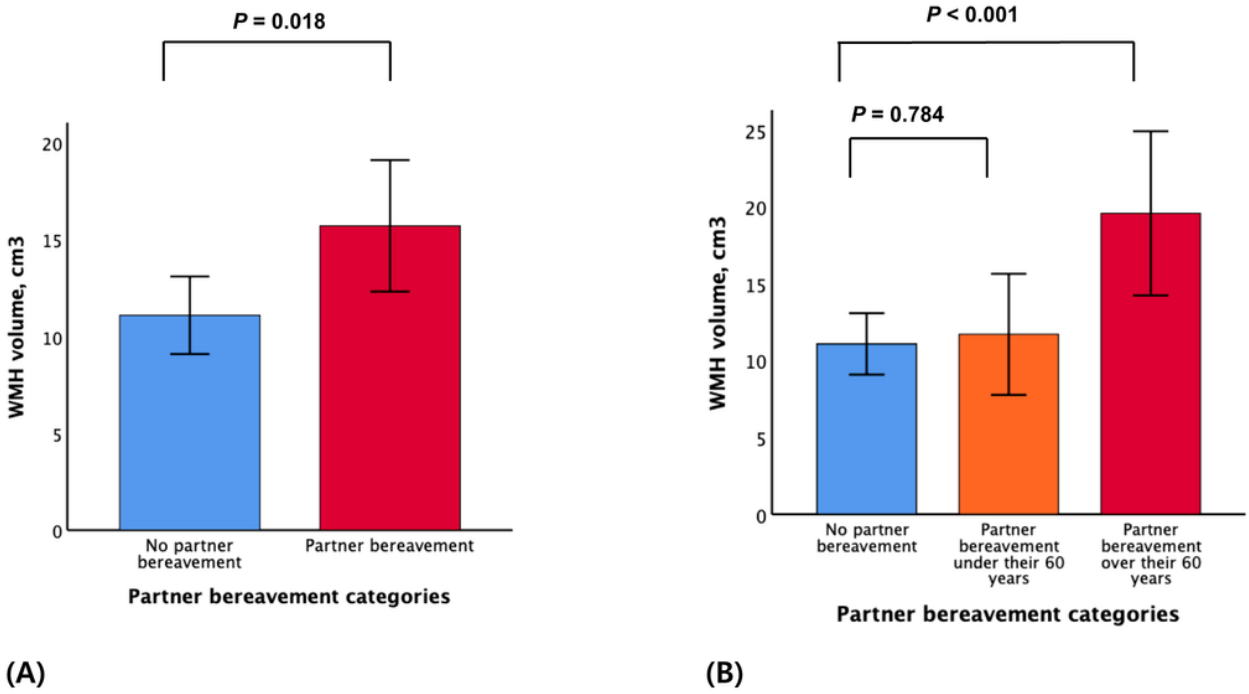

Figure 1

Bar plots of the associations of partner bereavement categories [(A) No partner bereavement vs. partner bereavement] and (B) No partner bereavement vs. partner bereavement aged < 60 years vs. partner bereavement at 60 years or over] with WMH volume in participants. WMH white matter hyperintensities. Multiple linear regression analyses were performed after adjusting for all potential covariates. Values are presented as the mean of WMH volume and error bars represent standard errors.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- PartnerBereavementSupplementsR0.docx
- STROBEchecklistcasecontrol.doc