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Spouse bereavement and brain pathologies: A propensity score matching study

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Aim: Spouse 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 the potential brain pathologies underlying the association between spouse bereavement and cognitive decline. We aimed to investigate that lifetime spouse bereavement is associated with in vivo human brain pathologies underlying cognitive decline.

Methods: A total of 319 ever-married older adults between the ages of 61 and 90 years underwent comprehensive clinical assessments and multimodal brain imaging including [^{11}C] Pittsburgh compound B-positron emission tomography (PET), AV-1451 PET, [^{18}F] fluorodeoxyglucose-PET, and magnetic resonance imaging. Participants were classified as experiencing no spouse bereavement or spouse bereavement, and comparisons using propensity score matching (59 cases and 59 controls) were performed.

Results: Spouse bereavement was significantly associated with higher cerebral white matter hyperintensity (WMH) volume compared with no spouse bereavement. Interaction and subsequent subgroup analyses showed that spouse bereavement was significantly associated with higher WMH in the older (>75 years) subgroup and among those with no- or low-skill occupations. In addition, spouse bereavement at 60 years or older affects WMH volume compared with no spouse bereavement, whereas spouse bereavement at younger than 60 years did not. No group differences were observed in other brain pathologies between spouse bereavement categories.

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

Keywords: *neurodegeneration, spouse bereavement, white matter hyperintensities.*

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Spouse bereavement is a major life event and is regarded as one of life's greatest stresses.[1,2] Extreme stress from spouse 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 nonbereaved individuals.[3,4] One cohort study demonstrated significantly greater cognitive decline among individuals with a history of spouse bereavement.[5] A meta-analysis of 15 studies also showed that those who had experienced spouse bereavement had a 20% greater risk of developing dementia during 3 to 15 years of follow-up.[7]

Nevertheless, little information is available on the neuropathological changes underlying the association between the experience of spouse bereavement and cognitive decline. Some studies have suggested that cardiovascular disease or events are a main biological adverse response to spouse bereavement.[8,9] Thus, spouse bereavement may be associated with other forms of vascular injury including cerebrovascular disease.

Therefore, we first aimed to test the hypothesis that spouse bereavement is associated with cerebrovascular injury in nondemented older adults. Cerebral white matter hyperintensities (WMH) on magnetic resonance imaging (MRI) were used as a measure of cerebrovascular injury.[10,11] We additionally explored the relationship of spouse bereavement with in vivo Alzheimer disease (AD) pathologies including cerebral beta-amyloid protein (Aβ) deposition, tau deposition, and AD-signature neurodegeneration because

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some preclinical studies using AD transgenic mouse models also showed that stress elevates Aβ[12–14] or tau pathologies,[15–17] and a recent study reported that being widowed was associated with accelerated Aβ-related cognitive decline.[6] Furthermore, the relationship of spouse bereavement with whole brain and hippocampal volume was explored considering numerous previous reports on association between chronic stress and brain atrophy.[18–20]

Methods

Participants

The present study was performed as part of the KBASE (Korean Brain Aging Study for Early Diagnosis and Prediction of Alzheimer's Disease), an ongoing prospective cohort study.[21] KBASE aimed to search for new AD biomarkers and investigate how multifaceted lifetime experiences and bodily changes contribute to the brain changes related to AD. As of November 2016, a total of 319 ever-married older adults between the ages of 61 and 90 years 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 through 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)[22] 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 sex-adjusted z scores for at least one of four episodic memory tests were <-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.[23] 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.[21]

Since age and sex, which are likely to have prominent confounding effects on the relationship of spouse bereavement with brain pathologies, differed substantially between groups with and without lifetime experience of spouse bereavement (Table 1), we used propensity score–matching methods[24] 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 spouse 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 performed in accordance with the recommendations of the current version of the Declaration of Helsinki. All patients 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.[21] 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.

A CERAD total score (TS) was generated by summing the scores of six tests in the CERAD neuropsychological battery including the Verbal Fluency, modified Boston Naming Test, Word List Memory, Constructional Praxis, Word List Recall, and Word List Recognition.[25] CERAD-TS was selected as a measure of global cognitive function.

Assessment of spouse bereavement and related conditions

Information (yes/no) on lifetime experience of spouse 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 spouse bereavement into subgroups, i.e. spouse bereavement at <60 years versus spouse bereavement at ≥60 years. Information (yes/no) on a death of a close family member and a close friend, divorce, separation, and remarriage was also obtained.

Assessment of potential confounders or modulators

The association between spouse 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 Method S1.

Measurement of WMH

All participants underwent MRI scans with fluid-attenuated inversion recovery using a 3.0T Biograph mMR (PET-MR) scanner (SiemensUSA) according to the manufacturer's guidelines. We followed the validated automatic procedure reported previously.[26] 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 with the original study: (i) 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, (ii) 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

Table 1. Participant characteristics with and without spouse bereavement[†]

	Before matching			After matching		
	No spouse bereavement	Spouse bereavement	*P*-value	No spouse bereavement	Spouse bereavement	*P*-value
No.	260	59		59	59	
Age (years)	72.32 (6.21)	76.05 (5.76)	<0.001[‡]	75.58 (5.21)	76.05 (5.76)	0.640[‡]
Age at spouse bereavement, No. (%)			<0.001[§]			<0.001[§]
<60 years	0 (0.00)	29 (49.15)		0 (0.00)	29 (49.15)	
≥60 years	0 (0.00)	30 (50.85)		0 (0.00)	30 (50.85)	
Women, No. (%)	126 (48.46)	47 (79.66)	0.001[§]	48 (81.36)	47 (79.66)	0.816[§]
Education (years)			0.001[§]			0.108[§]
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[§]	16 (27.12)	16 (27.59)	0.955[§]
Clinical diagnosis, CN, No. (%)	169 (65.00)	38 (64.41)	0.931[§]	32 (54.24)	38 (64.41)	0.261[§]
Other bereavement, No. (%)						
Close family members	244 (93.85)	55 (93.22)	0.772[¶]	54 (91.53)	55 (93.22)	0.717[¶]
Close friends	115 (44.23)	23 (38.98)	0.463[§]	20 (33.90)	23 (38.98)	0.566[§]
Divorce or separation, No. (%)	13 (5.00)	3 (5.08)	1.000[¶]	2 (3.39)	3 (5.08)	1.000[¶]
Remarriage, No. (%)	1 (0.38)	2 (3.39)	0.089[¶]	0 (0.00)	2 (3.39)	0.496[¶]
MOS-SSS overall score	71.54 (16.32)	71.76 (16.08)	0.924[‡]		71.76 (16.08)	
Physical activity score, No. (%)			0.944[§]			0.737[§]
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[‡]	6.46 (5.47)	7.58 (6.17)	0.300[‡]
BMI	24.50 (3.02)	24.37 (2.93)	0.766[‡]	24.74 (2.80)	24.37 (2.93)	0.489[‡]
Smoking status, No. (%)			0.013[§]			1.000[§]
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 drinking status, No. (%)			0.004[§]			1.000[§]
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[§]			0.116[§]
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[§]			0.732[§]
<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[§]	34 (57.63)	41 (69.49)	0.181[§]
Diabetes, No. (%)	49 (18.85)	12 (20.34)	0.792[§]	8 (13.56)	12 (20.34)	0.326[§]
Coronary artery disease, No. (%)	16 (6.15)	3 (5.08)	1.000[¶]	5 (8.47)	3 (5.08)	0.717[¶]

Table 1. (*Continued*)

	Before matching			After matching		
	No spouse bereavement	Spouse bereavement	*P*-value	No spouse bereavement	Spouse bereavement	*P*-value
Hyperlipidemia, No. (%)	90 (34.62)	29 (49.15)	0.040¶	26 (44.07)	29 (49.15)	0.580¶
Transient ischemic attack, No. (%)	3 (1.15)	0 (0.00)	1.000¶	1 (1.69)	0 (0.00)	1.000¶
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‡	1.25 (0.99)	1.44 (0.90)	0.286‡
Undernutrition	46 (17.69)	11 (18.64)	0.819§	14 (23.73)	11 (18.64)	0.530§
WMH volume, cm^3	12.52 (10.74)	15.72 (13.03)	0.048‡	11.10 (7.67)	15.72 (13.03)	0.021‡
Cerebral Aβ deposition						
Aβ retention, SUVR	1.32 (0.37)	1.31 (0.32)	0.791‡	1.37 (0.37)	1.31 (0.32)	0.348‡
Cerebral tau deposition						
AV-1451, SUVR ($n = 86$)	1.59 (0.69) ($n = 71$)	1.42 (0.29) ($n = 15$)	0.352‡	1.62 (0.92) ($n = 13$)	1.42 (0.29) ($n = 15$)	0.420‡
AD-neurodegeneration						
AD-CM, SUVR	1.39 (0.13)	1.38 (0.13)	0.530‡	1.39 (0.15)	1.38 (0.13)	0.585‡
AD-CT (mm)	2.79 (0.22)	2.73 (0.21)	0.056‡	2.75 (0.21)	2.73 (0.21)	0.491‡
HVa, cm^3	−1.21 (1.06)	−1.34 (1.09)	0.398‡	−1.22 (1.07)	−1.34 (1.09)	0.558‡
WBV, cm^3	0.73 (0.34)	0.74 (0.31)	0.047‡	0.73 (0.03)	0.74 (0.31)	0.580‡
CERAD-NP test						
VF	14.52 (4.52)	12.78 (4.43)‡	0.008	13.56 (4.54)	12.78 (4.43)	0.347‡
BNT	11.43 (2.39)	10.12 (2.59)‡	<0.001	11.17 (2.33)	10.12 (2.59)	0.022‡
CP	9.73 (1.44)	9.54 (1.61)‡	0.385	9.61 (1.46)	9.54 (1.61)	0.811‡
WLM	15.77 (6.41)	14.000 (7.49)‡	0.066	15.56 (6.26)	14.00 (7.49)	0.223‡
WLR	5.05 (2.33)	4.73 (2.45)‡	0.353	4.81 (2.49)	4.73 (2.45)	0.852‡
WLRc	7.98 (2.34)	8.19 (2.23)‡	0.532	7.63 (0.271)	8.19 (2.23)	0.223‡
CR	5.76 (3.56)	4.32 (3.16)‡	0.005	4.80 (3.54)	4.32 (3.16)	0.444‡
MMSE	25.35 (3.30)	24.66 (3.55)‡	0.154‡	24.71 (3.66)	24.66 (3.55)	0.939‡
TS	70.13 (16.52)	63.68 (17.65)‡	0.008	67.03 (16.68)	63.68 (17.65)	0.291‡

†Unless otherwise indicated, data are expressed as mean (standard deviation).
‡By *t* test.
§By chi-square test.
¶By Fisher exact test.
Aβ, beta-amyloid; AD, Alzheimer disease; AD-CM, Alzheimer disease signature cerebral glucose metabolism; AD-CT, Alzheimer disease signature cortical thickness; APOE4, apolipoprotein ε4; BMI, body mass index; BNT, Boston naming test; CERAD-NP, consortium to establish a registry for Alzheimer disease neuropsychological battery; CN, cognitively normal; CP, construction praxis; CR, constructional recall; GDS, Geriatric Depression Scale; HVa, adjusted hippocampal volume; MCL, minimum cost of living; MMSE, Mini-Mental State Examination; MOS-SSS, Medical Outcomes Study-Social Support Survey; SUVR, standardized uptake value ratio; TS, total score of the CERAD-NP; VF, verbal fluency; WBV, whole brain volume; WLM, word list memory; WLR, word list recall; WLRc, word list recognition; WMH, white matter hyperintensity.

in each patient. More specifically, the lobar regions of interest (ROIs) template was adapted from a previously published minimal deformation template.[27] 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.

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 the abovementioned 3.0T PET-MR scanner (Siemens). The details of the PiB-PET imaging acquisition and preprocessing were previously described.[28] An automatic anatomical labeling algorithm and a region-combining method[29] were applied to determine 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) 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.[29,30]

Measurement of cerebral tau deposition

A subset of patients underwent [^{18}F] AV-1451 PET scans using a Biograph TruePoint 40 PET/CT scanner (Siemens), in accordance with the manufacturer's guidelines. While all of 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. The details of AV-1451 PET imaging acquisition and preprocessing were previously described.[28] 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.[31] The AV-1451 SUVR of the abovementioned ROI was used as an outcome variable for cerebral tau deposition.

Measurement of AD-signature neurodegeneration and brain volume

All participants underwent [^{18}F] fluorodeoxyglucose (FDG)-PET imaging using the abovementioned PET-MRI machine. The details of the FDG-PET image acquisition and preprocessing were previously described.[28] AD-signature FDG ROIs, such as the angular gyri, posterior cingulate cortex, and inferior temporal gyri, which are sensitive to changes associated with AD,[32] 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 previously described.[28] 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 previously described.[32] An adjusted hippocampal volume (HVa) was calculated as the unstandardized residual from the linear regression of total hippocampal volume versus the total intracranial volume of the reference group (the young CN group of the study cohort).[33] HVa indicates the volume deviated from the expected total hippocampal volume according to the ICV in young CN individuals. For the whole brain volume (WBV), we chose to use the "ratio of brain segmentation volume to estimated ICV" variable output from FreeSurfer recon-all segmentation with manual correction.

Statistical analysis

To test the hypothetical associations between spouse bereavement and WMH, multiple linear regression analysis with the spouse bereavement group as the independent variable and WMH volume as a dependent variable was performed. In the analysis, WMH volume was used after natural log-transformation to achieve normal distributions. Three models were tested for stepwise control of the potential confounders other than age and sex that could affect the relationships between spouse bereavement and the biomarkers. The first model (model I) did not include any covariate. The second model (model II) included clinical diagnosis (CN versus MCI), vascular risk score (VRS), BMI, APOE4, and undernutrition. The third model (model III) included the covariates in the second model plus education, Geriatric Depression Scale (GDS) score, Medical Outcomes Study-Social Support Survey (MOS-SSS) score, annual income, occupational complexity, alcohol intake status, and smoking status, which have been considered possible confounders in previous studies.[1,6,8,34,35] To explore the effects of age of the bereavement experience, the same analyses were separately performed for the two relevant subgroups (i.e. spouse bereavement at <60 years versus spouse bereavement at ≥60 years). In all analyses, no spouse bereavement was used as a reference. As sensitivity analyses, the same analyses were also performed for: (i) participants without death of a close friend, (ii) those with neither divorce nor marital separation, and (iii) those without remarriage. Additional exploratory analyses were performed for the neuroimaging biomarkers showing significant associations with spouse bereavement in the above analyses as follows. To investigate the modulating effects of age (younger [≤75 years] versus 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 spouse bereavement and the neuroimaging biomarker(s), the same regression analyses were repeated including a two-way interaction term between spouse bereavement and each of the factors mentioned above as an additional independent variable. We additionally investigated the association between spouse bereavement and cognitive performance using a multiple linear regression model with spouse bereavement as an independent variable, cognitive test as a dependent variable, and the potential covariates. Then, the same regression model was analyzed again while controlling for WMH volume as additional covariates in order to examine whether the relationship between spouse bereavement and cognitive impairment was mediated by WMH. For the purpose of exploration, we additionally analyzed the association between spouse bereavement and other neuroimaging biomarkers (Aβ and tau retention, AD-CM, AD-CT, HVa, or WBV) using the same multiple regression models used for WMH. Global Aβ retention was used after natural log-transformation to achieve normal distributions. Statistical analyses were performed using SPSS Statistics version 27 (IBM).

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 spouse bereavement group and 59 as the spouse bereavement group. After the matching, 59 of 118 participants were categorized as the no spouse bereavement group and 59 as the spouse bereavement group (29 with spouse bereavement at <60 years and 30 with spouse bereavement at ≥60 years).

Table 2. Results of multiple linear regression analyses for assessing the relationships between stratified spouse bereavement and WMH volume (N = 118)

	No spouse bereavement $n = 59$	Spouse bereavement $n = 59$	
		B (95% CI)	*P*-value
WMH volume, cm^3			
Model I[†]	Reference	0.074 (0.006–0.142)	0.034
Model II[‡]	Reference	0.082(0.012–0.152)	0.021
Model III[§]	Reference	0.090 (0.016–0.164)	0.018

[†]Unadjusted.
[‡]Adjusted for clinical diagnosis, vascular risk score (VRS), body mass index (BMI), apolipoprotein ε4 (APOE4), and undernutrition.
[§]Adjusted for clinical diagnosis, VRS, BMI, APOE4, undernutrition, education, occupational complex, annual income, Geriatric Depression Scale (GDS) score, Medical Outcomes Study-Social Support Survey (MOS-SSS) score, alcohol intake status, and smoking status.
CI; confidence interval; WMH, white matter hyperintensity.

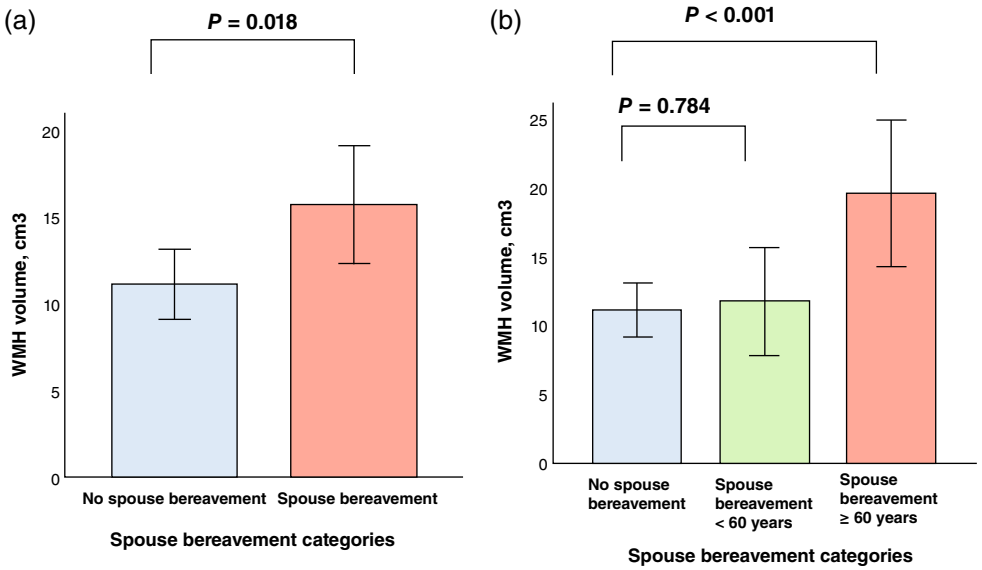

Fig. 1 Bar plots of the associations of spouse bereavement categories. (a) No spouse bereavement vs spouse bereavement, and (b) no spouse bereavement vs spouse bereavement aged <60 years vs spouse bereavement at ≥60 years with white matter hyperintensity (WMH) volume in participants. Multiple linear 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.

Association of spouse bereavement with WMH

The spouse bereavement group showed greater WMH volume compared with the no spouse bereavement group independent of the covariates (Table 2 and Fig. 1a). Furthermore, individuals with spouse bereavement at ≥60 years had greater WMH volume than those without spouse bereavement, whereas those with spouse bereavement at <60 years did not (Table 3 and Fig. 1b). The same analyses including only participants with no death of a close friend showed similar results in terms of the association between spouse bereavement and WMH volume (Table S1). The results were also similar after excluding those with divorce or marital separation (Table S2) and those who had remarried (Table S3).

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

The interactions of spouse bereavement with age and occupational complexity were significant, indicating that age and occupational complexity independently modulated the association between spouse bereavement and WMH volume (Table S4). Further subgroup analyses showed that spouse 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 (Table S5; Fig. 2a,b). The interactions of spouse 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 (Table S4).

Association between spouse bereavement, WMH, and cognitive performance

The spouse bereavement group was associated with lower cognitive performance as assessed by CERAD-TS compared with no spouse bereavement (Table S6). In addition, WMH volume was inversely associated with CERAD-TS (Table S7). When WMH volume was controlled as an additional covariate, the relationship between spouse bereavement and CERAD-TS was not significant any more (Table S6).

Association of spouse bereavement with other neuroimaging biomarkers

Independent of the models, no differences were observed in Aβ and tau deposition, AD-CM, AD-CT, HVa, and WBV between the group with and that without spouse bereavement (Tables 4 and 5).

Table 3. Results of multiple linear regression analyses for assessing the relationships between stratified spouse bereavement and WMH volume (N = 118)

	No spouse bereavement	Spouse bereavement at <60 years		Spouse bereavement at ≥60 years	
	$n = 59$	$n = 29$		$n = 30$	
		B (95% CI)	*P-value*	B (95% CI)	*P*-value
WMH volume, cm^3					
Model I[†]	Reference	0.006 (−0.075 to 0.087)	0.880	0.141 (0.061 to 0.222)	0.001
Model II[‡]	Reference	0.011 (−0.070 to 0.093)	0.787	0.157 (0.074 to 0.240)	<0.001
Model III[§]	Reference	0.012 (−0.076 to 0.101)	0.784	0.160 (0.075 to 0.246)	<0.001

[†]Unadjusted.
[‡]Adjusted for clinical diagnosis, vascular risk score (VRS), body mass index (BMI), apolipoprotein ε4 (APOE4), and undernutrition.
[§]Adjusted for clinical diagnosis, VRS, BMI, APOE4, undernutrition, education, occupational complex, annual income, Geriatric Depression Scale (GDS) score, Medical Outcomes Study-Social Support Survey (MOS-SSS) score, alcohol intake status, and smoking status.
BMI, body mass index; CI, confidence interval; WMH, white matter hyperintensity.

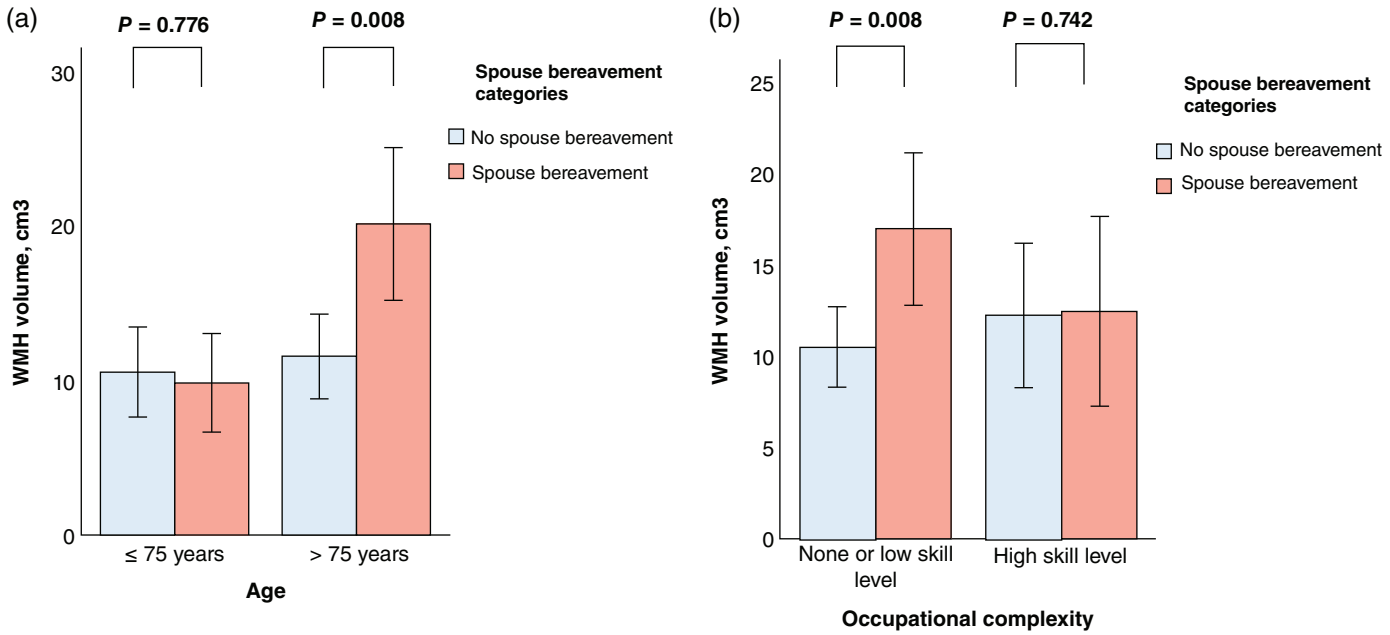

Fig. 2 Bar plots of the associations of spouse bereavement categories with white matter hyperintensity (WMH) volume according to (a) age and (b) occupational complexity. Multiple linear regression analyses were performed after adjusting for all potential covariates. Values are presented as the mean of WMH volume, and error bars represent standard errors. [Correction added on Aug 01, 2022, after first online publication: "<75 years" has been amended to ">75 years".]

Discussion

The present study shows that lifetime experience of spouse bereavement was associated with increased WMH volume, but not with AD neuroimaging markers, in nondemented older adults. The association of spouse bereavement with WMH observed in the present study may be explained by the following potential mechanisms. First, the loss of a spouse is considered one of the most stressful life events.[1,2,36] The experience of spouse 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.[37,38] Second, a widowed state after spouse bereavement may lead to lower socioeconomic status and poor health care utilization.[39] Both may result in poor management of vascular risks, which could contribute to cerebrovascular changes and subsequent increased WMH. However, given the association between spouse 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, additional exploratory analyses showed that the experience of spouse bereavement was not associated with any other neuroimaging biomarkers including AD-related ones, 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 Aβ levels exhibited steeper cognitive decline.[6] However, similar to our finding, the authors of that study reported no difference in brain Aβ between the groups with and without spouse bereavement. As they suggested, spouse bereavement may modulate AD pathology-related cognitive decline by affecting the brain or cognitive reserves, but not by affecting AD pathologies themselves. Although WBV was not related to spouse bereavement, white matter degeneration as indicated by WMH volume can impair the cognitive reserves.[40,41] Therefore, together with our finding for WMH, the decreased reserves associated with white matter degeneration may synergistically aggravate cognitive function in individuals with spouse bereavement when AD pathologies are present in the brain.

The individuals who had experienced spouse bereavement at ≥60 years had greater WMH than those without spouse bereavement, whereas those who had experienced it <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; spouse 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 spouse 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 attributable to economic difficulty or poorer social support resulting from spouse 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 a spouse with better health insurance[42] may not clearly explain the moderation effect of occupational level. The brains of those with no- or low-skill occupations may be more vulnerable to stress or cerebrovascular disease because of lower brain reserves.[43]

We additionally observed a significant relationship between spouse bereavement and poorer cognitive performance, replicating previous reports.[3,4] When WMH volume was adjusted as an additional covariate, the relationship between spouse bereavement and cognitive impairment was not significant any more, further supporting the possibility that spouse bereavement may contribute to the development of dementia or cognitive decline via cerebrovascular injury in older adults.

Table 4. Results of multiple linear regression analyses for assessing the relationships between stratified spouse bereavement and Aβ, AV-1451, AD-CM, AD-CT, HVa, or WBV (N = 118)

	No spouse bereavement $n = 59$	Spouse bereavement $n = 59$	
		B (95% CI)	*P*-value
Aβ retention, SUVR			
Model I†	Reference	−0.049 (−0.130 to 0.032)	0.231
Model II‡	Reference	−0.030 (−0.094 to 0.035)	0.366
Model III§	Reference	−0.025 (−0.092 to 0.041)	0.456
AV-1451, SUVR			
Model I†	Reference	−0.204 (−0.717 to 0.308)	0.420
Model II‡	Reference	−0.181 (−0.720 to 0.359)	0.493
Model III§	Reference	0.053 (−0.563 to 0.669)	0.856
AD-CM, SUVR			
Model I†	Reference	−0.011 (−0.064 to 0.041)	0.664
Model II‡	Reference	−0.021 (−0.070 to 0.029)	0.411
Model III§	Reference	−0.024 (−0.076 to 0.028)	0.359
AD-CT, mm			
Model I†	Reference	−0.026 (−0.105 to 0.053)	0.518
Model II‡	Reference	−0.044 (−0.117 to 0.029)	0.233
Model III§	Reference	−0.052 (−0.125 to 0.021)	0.061
HVa, cm^3			
Model I†	Reference	−0.114 (−0.519 to 0.290)	0.577
Model II‡	Reference	−0.213 (−0.565 to 0.139)	0.232
Model III§	Reference	−0.284 (−0.634 to 0.067)	0.111
WBV			
Model I†	Reference	0.002 (−0.010 to 0.015)	0.707
Model II‡	Reference	0.001 (−0.011 to 0.013)	0.881
Model III§	Reference	−0.002 (−0.014 to 0.010)	0.775

†Unadjusted.
‡Adjusted for clinical diagnosis, vascular risk score (VRS), body mass index (BMI), apolipoprotein ε4 (APOE4), and undernutrition.
§Adjusted for clinical diagnosis, VRS, BMI, APOE4, undernutrition, education, occupational complex, annual income, Geriatric Depression Scale (GDS) score, Medical Outcomes Study-Social Support Survey (MOS-SSS) score, alcohol intake status, and smoking status.
Aβ, beta-amyloid; AD-CM, Alzheimer disease signature cerebral glucose metabolism; AD-CT, Alzheimer disease signature cortical thickness; CI; confidence interval; HVa, adjusted hippocampal volume; SUVR, standardized uptake value ratio; WBV, whole brain volume.

Strengths and Limitations

The present study had some strengths. First, to our knowledge, this is the first study to elucidate the association of spouse 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 spouse 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 spouse bereavement with brain pathologies. Additionally, various other potential confounders were systematically controlled in the statistical models to clarify the association between spouse 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 spouse bereavement and brain WMH. Further long-term follow-up studies are required to clarify the causal relationships. Second, we did not consider the duration or severity of bereavement reaction and other family members who lived with the patients, although those factors may have an impact on the relationship between spouse bereavement and brain change. 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 individuals with MCI have some problem with recent memory, their remote memory tends to be well preserved.[44] Therefore, it is not likely that individuals with MCI reported a history of spouse bereavement less accurately, as such history mainly depends on remote memory rather than recent memory. Furthermore, even when we controlled for clinical diagnosis (CN versus MCI) as an additional covariate (Tables 2–5; Tables S1–S7), the results were still 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 spouse 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

Table 5. Results of multiple linear regression analyses for assessing the relationships between stratified spouse bereavement and Aβ, AV-1451, AD-CM, AD-CT, Hva, or WBV (N = 118)

	No spouse bereavement $n = 59$	Spouse bereavement at <60 years $n = 29$		Spouse bereavement at ≥60 years $n = 30$	
		B (95% CI)	*P*-value	B (95% CI)	*P*-value
Aβ retention, SUVR					
Model I[†]	Reference	−0.088 (−0.186 to 0.010)	0.079	−0.010 (−0.108 to 0.088)	0.840
Model II[‡]	Reference	−0.072 (−0.149 to 0.005)	0.068	0.015 (−0.064 to 0.093)	0.708
Model III[§]	Reference	−0.074 (−0.156 to 0.007)	0.074	0.020 (−0.059 to 0.099)	0.624
AV-1451, SUVR					
Model I[†]	Reference	−0.265 (−0.992 to 0.461)	0.459	−0.174 (−0.754 to 0.407)	0.544
Model II[‡]	Reference	−0.431 (−1.214 to 0.353)	0.265	−0.069 (−0.668 to 0.529)	0.811
Model III[§]	Reference	−0.234 (−1.166 to 0.699)	0.597	0.156 (−0.516 to 0.828)	0.624
AD-CM, SUVR					
Model I[†]	Reference	−0.014 (−0.078 to 0.050)	0.671	−0.009 (−0.073 to 0.055)	0.779
Model II[‡]	Reference	−0.019 (−0.079 to 0.041)	0.539	−0.023 (−0.084 to 0.039)	0.467
Model III[§]	Reference	−0.021 (−0.085 to 0.044)	0.530	−0.027 (−0.090 to 0.035)	0.390
AD-CT, mm					
Model I[†]	Reference	0.006 (−0.092 to 0.105)	0.899	−0.056 (−0.152 to 0.040)	0.251
Model II[‡]	Reference	−0.008 (−0.098 to 0.081)	0.856	−0.080 (−0.168 to 0.009)	0.079
Model III[§]	Reference	−0.022 (−0.113 to 0.070)	0.639	−0.077 (−0.164 to 0.009)	0.080
HVa, mm^3					
Model I[†]	Reference	0.146 (−0.396 to 0.689)	0.594	−0.237 (−0.773 to 0.299)	0.382
Model II[‡]	Reference	−0.009 (−0.488 to 0.469)	0.969	−0.406 (−0.903 to 0.092)	0.109
Model III[§]	Reference	−0.066 (−0.554 to 0.422)	0.789	−0.483 (−0.971 to 0.006)	0.053
WBV					
Model I[†]	Reference	0.001 (−0.014 to 0.017)	0.850	0.003 (−0.012 to 0.018)	0.678
Model II[‡]	Reference	0.001 (−0.015 to 0.016)	0.928	0.001 (−0.014 to 0.016)	0.879
Model III[§]	Reference	−0.004 (−0.09 to 0.012)	0.652	<0.001 (−0.015 to 0.014)	0.971

[†]Unadjusted.
[‡]Adjusted for clinical diagnosis, vascular risk score (VRS), body mass index (BMI), apolipoprotein ε4 (APOE4), and undernutrition.
[§]Adjusted for clinical diagnosis, VRS, BMI, APOE4, undernutrition, education, occupational complex, annual income, Geriatric Depression Scale (GDS) score, Medical Outcomes Study-Social Support Survey (MOS-SSS) score, alcohol intake status, and smoking status.
Aβ, beta-amyloid; AD-CM, Alzheimer disease signature cerebral glucose metabolism; AD-CT, Alzheimer disease signature cortical thickness; CI, confidence interval; HVa, adjusted hippocampal volume; SUVR, standardized uptake value ratio; WBV, whole brain volume.

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 spouse 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 (13 without spouse bereavement versus 15 with spouse 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 spouse bereavement and tau deposition.

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

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Disclosure statement

The authors declare that they have no competing interests.

Author contributions

J.W.K. and D.Y.L. conceived and designed the study. J.W.K., M.S.B., D.Y., J.H.L., M.J.K., G.J., J.Y.L., K.M.K., C.H.S., Y.S.L., Y.K.K., and D.Y.L. were involved in acquisition, or analysis and interpretation of the data and helped to draft the manuscript. J.W.K., M.S.B., D.Y., J.H.L., and D.Y.L. were major contributors in writing the manuscript and critically revising the manuscript for intellectual

content. D.Y.L, served as principal investigator and supervised the study. All authors read and approved the final manuscript.

Data Availability Statement

The data of the current study are not freely accessible because the institutional review board 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 institutional review board. 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.

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APPENDIX A

A.1. Authors

Name	Location	Role	Contribution
Jee Wook Kim, MD, PhD	Hallym University Dongtan Sacred Heart Hospital, Hwaseong, Republic of Korea	First author	Study concept and design; analysis, and interpretation of data; and drafting and critically revising the manuscript for intellectual content
Min Soo Byun, MD, PhD	Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Republic of Korea	Author	Acquisition, analysis, and interpretation of data; and critically revising the manuscript for intellectual content
Jun Ho Lee, MD	National Center for Mental Health, Seoul, Republic of Korea	Author	Acquisition, analysis, and interpretation of data; and critically revising the manuscript for intellectual content
Dahyun Yi, PhD	Medical Research Center Seoul National University, Seoul, Republic of Korea	Author	Acquisition, analysis, and interpretation of data; and critically revising the manuscript for intellectual content
Min Jung Kim, MD	Eulji University Nowon Eulji Medical Center, Seoul, Republic of Korea	Author	Acquisition, analysis, and interpretation of data; and critically revising the manuscript for intellectual content
Gijung Jung, RN, PhD	Seoul National University Hospital, Seoul, Republic of Korea	Author	Acquisition, analysis, and interpretation of data; and critically revising the manuscript for intellectual content
Jun-Young Lee, MD, PhD	SMG-SNU Boramae Medical Center, Seoul National University College of Medicine, Seoul, Republic of Korea	Author	Acquisition, analysis, and interpretation of data; and critically revising the manuscript for intellectual content
Yun-Sang Lee, PhD	Seoul National University College of Medicine, Seoul, Republic of Korea	Author	Acquisition, analysis, and interpretation of data; and critically revising the manuscript for intellectual content
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Chul-Ho Sohn, MD, PhD	Seoul National University Hospital, Seoul, Republic of Korea	Author	Acquisition, analysis, and interpretation of data; and critically revising the manuscript for intellectual content
Dong Young Lee, MD, PhD	Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Republic of Korea	Corresponding author	Study concept and design; acquisition, analysis, and interpretation of data; and drafting and critically revising the manuscript for intellectual content

A.2. Coinvestigators

Coinvestigators are listed in elsewhere (http://kbase.kr).

Name	Location	Role	Contribution
Dong Young Lee, MD, PhD	Seoul National University College of Medicine	Principal investigator	Designed and conceptualized the cohort study, led and supervised the cohort study, coordinated communication among study cores and study sites, acquired funding
Min Soo Byun, MD, PhD	Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Republic of Korea	Core PI Clinical & Executive	Supervised and coordinated the Clinical and Executive core of the cohort study
Dahyun Yi, PhD	Medical Research Center Seoul National University	Core PI Neuropsychology	Supervised and coordinated the Neuropsychological Core of the cohort study
Yu Kyeong Kim, MD, PhD	SMG-SNU Boramae Medical Center	Core PI PET	Supervised and coordinated the PET Core of the cohort study
Chul-Ho Sohn, MD, PhD	Seoul National University College of Medicine	Core PI MRI	Supervised and coordinated the MRI Core of the study
Inhee Mook-Jung, PhD	Seoul National University College of Medicine	Core PI Biomarker	Supervised and coordinated the Biomarker Core of the study
Murim Choi, PhD	Seoul National University	Core PI Genetics	Supervised and coordinated the Genetic Core of the study
Yu Jin Lee, MD, PhD	Seoul National University College of Medicine	Core PI Sleep	Supervised and coordinated the Sleep Core of the study
Seokyung Hahn, PhD	Seoul National University College of Medicine	Core PI Biostatistics	Supervised and coordinated the Biostatistics Core of the study
Hyun Jung Kim, MD	Changsan Convalescent Hospital	Coinvestigator	Performed clinical assessment of participants and quality control of the clinical data
Mun Young Chang, MD	Chung-Ang University College of Medicine	Coinvestigator	Coordinated an add-on study of the main cohort study
Seung Hoon Lee, MD	Daerim St. Mary's Hospital	Coinvestigator	Performed clinical assessment of participants and quality control of the clinical data
Na Young Han, MD	Dongrae Medical Center	Coinvestigator	Performed clinical assessment of participants and quality control of the clinical data
Jisoo Pae, MD, PhD	Genome & Company	Coinvestigator	Coordinated an add-on study of the main cohort study
Hansoo Park, MD, PhD	Genome & Company	Coinvestigator	Coordinated an add-on study of the main cohort study
Jee Wook Kim, MD, PhD	Hallym University Dongtan Sacred Heart Hospital	Coinvestigator	Coordinated a study site and performed participants recruitment and quality control of the clinical data
Young Min Choe, MD	Hallym University Dongtan Sacred Heart Hospital	Coinvestigator	Performed recruitment and clinical assessment of participants and monitoring of the clinical data
Jong-Min Lee, PhD	Hanyang University	Coinvestigator	Coordinated an add-on study of the main cohort study
Dong Woo Lee, MD, PhD	Inje University Snaggye Paik Hospital	Coinvestigator	Coordinated a study site and recruited participants of the cohort study
Bo Kyung Sohn, MD	Inje University Snaggye Paik Hospital	Coinvestigator	Coordinated a study site and recruited participants of the cohort study, performed clinical data analysis
Seok Woo Moon, MD, PhD	Konkuk University Chungju Hospital	Coinvestigator	Coordinated a study site and performed clinical data analysis
Seung-Ho Ryu, MD, PhD	Konkuk University Medical Center	Coinvestigator	Coordinated a study site and recruited participants

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Name	Location	Role	Contribution
Man Ho Choi, PhD	Korea Institute of Science and Technology	Coinvestigator	Supervised and coordinated the MRI Core of the study
Hyewon Baek, MD	Kyunggi Provincial Hospital for the Elderly	Coinvestigator	Performed clinical assessment of participants and quality control of the clinical data
Yoon-Keun Kim, MD, PhD	MD Healthcare Inc.	Coinvestigator	Coordinated an add-on study of the main cohort study
Kang Ko, MD	National Center for Mental Health	Coinvestigator	Performed clinical assessment of participants and quality control of the clinical data
Jong-Won Kim, MD, PhD	Samsung Medical Center	Coinvestigator	Supervised and performed genetic analysis
Shin Gyeom Kim, MD, PhD	Soonchunhyang University Hospital Bucheon	Coinvestigator	Coordinated a study site and performed clinical data analysis
Sun-Ho Han, PhD	Seoul National University	Coinvestigator	Coordinated blood sample repository, performed blood-biomarker-related analysis
Joo-Youn Cho, PhD	Seoul National University	Coinvestigator	Coordinated and performed blood-biomarker-related analysis
Jae Sung Lee, PhD	Seoul National University	Coinvestigator	Coordinated and performed PET image data-related analysis
Yun-Sang Lee, PhD	Seoul National University	Coinvestigator	Coordinated the acquisition of the PET data and related logistics
Jong Inn Woo, MD, PhD	Seoul National University	Coinvestigator	Supervised and advised the cohort study
Sang Eun Kim, MD, PhD	Seoul National University Bundang Hospital	Coinvestigator	Coordinated the production of PET radiotracer
Byung Chul Lee, PhD	Seoul National University Bundang Hospital	Coinvestigator	Coordinated the production of PET radiotracer
Gi Jeong Cheon, MD, PhD	Seoul National University Hospital	Coinvestigator	Coordinated the acquisition of the PET data
Koung Mi Kang, MD	Seoul National University Hospital	Coinvestigator	Participated in the acquisition and clinical interpretation of the MRI/MRA data
Jee-Eun Park, MD, PhD	Seoul National University Hospital	Co-investigator	Performed clinical and sleep-related data analysis
Hyeong Gon Yu, MD, PhD	Seoul National University Hospital	Coinvestigator	Coordinated an add-on study of the main cohort study
Jun-Young Lee, MD, PhD	SMG-SNU Boramae Medical Center	Coinvestigator	Coordinated a study site and performed participants recruitment
Hyo Jung Choi, MD		Coinvestigator	Performed clinical assessment of participants and quality control of the clinical data
Kwangsoo Kim, Ph.D	Seoul National University Hospital	Coinvestigator	Supervised and performed biostatistics data analysis
Jun Ho Lee, MD	Seoul National University Hospital	Coinvestigator	Coordinated participant recruitment and follow-up, performed clinical assessment of participants, quality control of the clinical data analysis
Sung Wook Park, MD, PhD	Seoul National University Hospital	Research fellow	Performed an add-on study and data analysis
So Yeon Jeon, MD	Seoul National University Hospital	Research fellow	Coordinated participant recruitment and follow-up, performed clinical assessment of participants, quality control of the clinical data
Woo Jin Kim, MD, PhD	Seoul National University Hospital	Research fellow	Performed clinical assessment of participants and quality control of the clinical data

(continued)

Name	Location	Role	Contribution
Hak Young Kim	Seoul National University Hospital	Psychologist	Performed neuropsychological assessment of participants, quality control. and preprocessing of the data
Haejung Joung	Seoul National University Hospital	Psychologist	Performed neuropsychological assessment of participants. Quality control and preprocessing of the data
Younghwa Lee	Seoul National University Hospital	Psychologist	Performed neuropsychological assessment of participants, quality control, and preprocessing of the data
Donghwi Hwang	Seoul National University	Image analyst	Performed PET data analysis
Seung Kwan Kang	Seoul National University	Image analyst	Performed PET data analysis
Seong A Shin	Seoul National University	Image analyst	Performed PET data pre-processing
Jeong Yeon Hwang, MD	Seoul National University	Data analyst	Performed sleep-related data analysis
Jong-Chan Park	Seoul National University	Data analyst	Performed blood-biomarker related analysis
Jong-Ho Park	Samsung Medical Center	Genetic data analyst	Performed genetic data analysis
Jieun Seo	Seoul National University	Genetic data analyst	Performed genetic data analysis
Gi Jung Jung	Seoul National University Hospital	Research coordinator	Coordinated participants recruitment, follow-up and assessment among sites, performed clinical assessment of participants and data monitoring
Min Jeong Kim	Seoul National University Hospital	Research coordinator	Coordinated participants recruitment, performed clinical assessment of participants
Han Na Lee	Seoul National University Hospital	Research coordinator	Coordinated participants recruitment, follow-up and assessment among sites, performed clinical assessment of participants and data monitoring
Yun Jung Hwang	Seoul National University Hospital	Researcher	Performed the clinical data analysis
Joon Hyung Jung, MD	Seoul National University Hospital	Researcher	Performed the clinical data analysis
Kiyoung Sung, MD	Seoul National University Hospital	Researcher	Performed the clinical data analysis
Eun Hye Kim	Seoul National University	Research assistant	Coordinated and performed the collection and preprocessing of blood samples
Han Byul Choi	National Research Center for Dementia	Administrative staff	Coordinated participant recruitment and provided administrative support

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Appendix S1. Supporting Information

Method S1. Assessment of potential confounders or modulators.

Table S1. Results of multiple logistic and linear regression analyses for assessing the relationships between stratified spouse bereavement and WMH volume in participants without death of close friend(s) ($n = 75$).

Table S2. Results of multiple logistic and linear regression analyses for assessing the relationships between stratified spouse bereavement and WMH volume in participants with neither divorce nor separation ($n = 113$).

Table S3. Results of multiple logistic and linear regression analyses for assessing the relationships between stratified spouse bereavement and WMH volume in participants without remarriage ($n = 116$).

Table S4. Results of multiple linear regression analyses including the interaction term between spouse bereavement and age (or sex or APOE4 positivity or clinical diagnosis or VRS or BMI or undernutrition or education or GDS score or occupational complexity or annual income or physical activity or MOS-SSS score or alcohol intake or smoking) status predicting WMH volume (N = 118).

Table S5. Results of the multiple linear regression analysis for assessing the relationships between spouse bereavement and WMH volume according to participants' age and occupational complexity (N = 118).

Table S6. Results of the multiple linear regression analyses for assessing the relationships between stratified spouse bereavement and cognitive performance (N = 118).

Table S7. Results of multiple linear regression analyses for assessing the relationships between WMH volume and cognitive performance (N = 118).