이학박사 학위논문

Effect of controlled hypertension on cerebral white matter hyperintensity and cognitive function in older adults

노인에서 조절 중인 고혈압이 대뇌백질고강도신호와 인지기능에 미치는 영향

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서울대학교 대학원

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이 논문을 이학박사학위논문으로 제출함

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2021년 7월

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Abstract

Effect of controlled hypertension on cerebral white matter hyperintensity and cognitive function in older adults

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Background and Objectives: Hypertension, even when controlled, is associated with cognitive impairment. Although hypertension is also associated with white matter hyperintensity (WMH) and WMH is associated with cognitive impairments, the mediation role of WMH in the association of hypertension with cognitive impairments has never been directly investigated. If WMH shows to mediate the cognitive impairments in participants with controlled hypertension, presence or volume of WMH may be a good biomarker of those who are at risk of cognitive impairments. However, neither the WMH probability map (WMHPM) of healthy older adults nor the predictive validity of WMH age estimated by WMHPM for cognitive impairments has been investigated. This study examined two main hypotheses; 1) Does cerebral WMH mediate the effect of controlled hypertension on cognitive function in nondemented older adults?; 2) Does WMH age estimated using the WMHPM predict current cognitive impairment and future cognitive decline in older adults with controlled hypertension?

Methods: We recruited 890 community-dwelling nondemented Koreans aged 60 years or older; 505 from the participants of the Korean Longitudinal Study on Cognitive Aging and Dementia and 385 from the visitors to the Dementia Clinic of the Seoul National University Bundang

Hospital. Among them, 368 participants completed 2-year follow-up assessment. We constructed WMHPM using 300 community-dwelling cognitively and physically healthy Koreans aged 60 years or older; 228 from the KLOSCAD and 72 from the Gwangju Alzheimer's & Related Dementias Study. We defined controlled hypertension (cHT) as having history of hypertension, however, office-measured systolic blood pressure (SBP) less than 140 mm Hg and office-measured diastolic blood pressure (DBP) less than 90 mm Hg; low systolic blood pressure (LSBP) as having office-measured SBP of 110 mm Hg or below; low diastolic blood pressure (LDBP) as having office-measured DBP of 60 mm Hg or below. We measured blood pressure three times in a sitting position using an automated blood pressure monitoring device. We evaluated cognitive performance using the CERAD-K Neuropsychological Assessment Battery, Frontal Assessment Battery and Digit Span Test. We calculated Consortium to Establish a Registry for Alzheimer Disease neuropsychological battery total score (CERAD-TS). We segmented and quantified WMH from 3.0 Tesla fluid attenuated inversion recovery magnetic resonance images. We estimated WMH age using the WMHPM by calculating the lowest deviance between individual's WMH and each of the 5 age-banded WMHPMs. We classified the participants into three WMH age group; normal WMH age group whose WMH age is equal to their chronological age, younger WMH age group whose WMH age is younger than their chronological age, and the older WMH age group whose WMH age is older than their chronological age. We analyzed the mediation role of WMH on the effect of controlled hypertension on cognitive function using Baron and Kenny method of mediation analysis. We examined the effect of controlled hypertension and WMH age on the risk of incident mild cognitive impairment (MCI) using logistic regression analysis.

Results: cHT ($p < .001$), LSBP ($p = .018$), and their interaction ($p < .001$) were associated with WMH volume, and WMH volume was associated with negative cognitive performance ($p < .001$ for all cognitive performance). WMH mediated the association of LSBP on the

performance of neuropsychological tests with 1 mm Hg decrease of SBP affect 0.016 to 0.030 points decrease in various cognitive tests. Compared to the younger or normal WMH age groups, the older WMH age group performed worse in all neuropsychological tests (p = .002 for DST; p < .001 for other tests). cHT (p = .002), LSBP (p = .003), LDBP (p = .013) and their interaction (p = .010) were associated with older WMH age. The cHT with the older WMH age group showed the faster cognitive decline and 8 times higher risk of incident MCI after two years than normotensive participants with the normal or younger WMH age.

Conclusion: In the cHT patients, LSBP was associated with worse cognitive performance by increasing WMH volume. If we use WMHPM of healthy older adults, we can identify older adults with controlled hypertension who are at risk of cognitive decline by estimating their WMH age in clinical settings.

Keywords: cerebral white matter hyperintensity, hypertension, cognitive performances, magnetic resonance imaging, elderly

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List of Abbreviations

ANOVA	Analysis of Variance
BBB	Blood Brain Barrier
BNT	15-item Boston Naming Test
CBF	Cerebral Blood Flow
CERAD-TS	Consortium to Establish a Registry for Alzheimer Disease neuropsychological battery Total Score
cHT	Controlled Hypertension
CPT	Constructional Praxis Test
CRT	Constructional Recall Test
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
DM	Diabetes Mellitus
DST	Digit Span Test
DWMH	Deep White Matter Hyperintensity
FAB	Frontal Assessment Battery
FLAIR	Fluid-Attenuated Inversion Recovery
FS	Fazekas' Scale
GARD	Gwangju Alzheimer's & Related Dementias
KLOSCAD	Korean Longitudinal Study on Cognitive Aging and Dementia
KNE	Korean Normal Elderly template
LDBP	Low Diastolic Blood Pressure group
LSBP	Low Systolic Blood Pressure group
MCI	Mild Cognitive Impairment
MMSE	Mini Mental Status Examination
MRI	Magnetic Resonance Imaging

NDBP	Normal Diastolic Blood Pressure group
nHT	Without history of Hypertension
NSBP	Normal Systolic Blood Pressure group
PVWMH	Periventricular White Matter Hyperintensity
rmANOVA	Repeated Measure Analysis of Variance
SBP	Systolic Blood Pressure
SNUBH	Seoul National University Bundang Hospital
TMT-A	Trail Making Test A
TMT-B	Trail Making Test B
VFT	Verbal Fluency Test
VM	Verbal Memory
WLMT	Word List Memory Test
WLRT	Word List Recall Test
WLRcT	Word List Recognition Test
WMH	White Matter Hyperintensity
WMHPM	White Matter Hyperintensity Probability Map

1. Introduction

1.1. Study Background

Hypertension is one of the major contributors to premature morbidity and mortality and affects approximately 1 billion individuals worldwide [1]. According to the Korean National Health and Nutrition Examination Survey, about two thirds of older Koreans had hypertension and the number of those with hypertension has been increasing in the last decade [2].

Hypertension is a well-known risk factor for cognitive disorders including cognitive decline [3-5], mild cognitive impairment (MCI) [3, 6, 7] and dementia [8-10]. Prehypertension, which considered as not meeting hypertension criteria but systolic blood pressure (SBP) ≥ 120 mm Hg, and diastolic blood pressure (DBP) ≥ 80 mm Hg, as well was reported to increase the risk of cognitive disorders [8]. In the Atherosclerosis Risk in Communities cohort study, people with hypertension or prehypertension in their midlives showed about 40 % higher risk of dementia than people with normotension [8]. Although endothelial dysfunction [11], reduced amyloid β clearance [12] and excessive blood pressure dipping during sleep [13] have been proposed the potential mechanisms that underlie the effect of hypertension on the risk of cognitive disorders, it has not been fully understood how hypertension increases the risk of cognitive disorders.

White matter hyperintensity (WMH) is cerebral white matter lesions which appear hyperintense in T2-weighted or fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI). Although WMH is commonly found in healthy older adults [14, 15], it is usually associated with various geriatric disorders [16, 17] including cognitive disorders [18, 19] and cognitive impairments [20, 21]. Hypertension increases the risk of WMH by inducing cerebral hypoperfusion because it thickens the cerebral vessel wall [22] and increases systemic vascular resistance [23]. In addition, hypertension damages brain endothelial cells which release nitric oxide which is an important vasodilator [24, 25], and causes cerebral small vessel disease (SVD) by increasing vascular stiffness [26, 27]. In previous research, hypertension has been consistently found to increase WMH [28-31]. In

addition, older adults with poorly controlled hypertension have higher prevalence of severe WMH than adults without hypertension or with controlled hypertension [32, 33]. Moreover, older adults with treated, controlled hypertension have lower prevalence of WMH than both untreated hypertension and treated but uncontrolled hypertension [32].

However, it has been barely investigated whether the effect of WMH may remain on the effects of hypertension on cognitive function when hypertension is under controlled. In the older adults with controlled hypertension, hypotension is common. One in three older adults with controlled hypertension in usual clinical practice were at risk of hypotension and more than half of them had masked hypotension [34]. Since hypotension is risk factor of both cognitive impairment [35, 36] and WMH [37] as well, older adults with hypertension, even if controlled, may be still at higher risk of cognitive disorders or cognitive impairments and WMH. Furthermore, the mediating role of WMH in the effect of hypertension on cognitive function has been barely investigated. Since hypertension increases the risks of both cognitive impairments and WMH and WMH increases the risk of cognitive impairments, WMH may mediate the effect of hypertension on the risk of cognitive disorders or cognitive impairments. If WMH mediates the effect of controlled hypertension on the risks of cognitive disorders or cognitive impairments, presence of WMH may be a useful biomarker for predicting cognitive disorders or impairments in older adults with hypertension.

WMH can be found in healthy older adults without any disorders including hypertension [14, 15]. Therefore, it is important to develop a reference for differentiating WMH attributable to hypertension from the age-associated WMH. A probability map provides probabilistic information about the voxel-wise distribution of certain neuroanatomical or pathological structures of interest [38]. They have been used in various contexts to obtain information about the neuroanatomic complexity and inter-individual variability within a specific population in a common stereotaxic system [39, 40]. In particular, population-level lesion probability maps, in which the value at each voxel reflects the probability of finding a lesion in a specific population, can provide essential information about pathology-specific spatial variations and can be used to study differences between normal and

pathological groups [41, 42] or detect lesions associated with neurodegenerative disorders [43]. Therefore, cerebral WMH probability map (WMHPM) in healthy older adults may provide such reference for defining morbid WMH in each individual. Although there were several previous studies that reported WMHPM, all [44-49] but two [50, 51] were disease-specific probability maps. The two previous WMHPMs that were constructed from normal populations also had several limitations in terms of age, size and normality of study samples. Furthermore, the two WMHPMs would not be applicable to Asian populations because they were constructed from Caucasians whose shape of brain [52] and risk of cerebrovascular diseases [53] are quite different from those of Asians.

1.2. Purpose of Research

In this study, we examined two main hypotheses with 6 sub-hypotheses to identify the mediating role of cerebral WMH in the effect of controlled hypertension on cognitive impairment and to identify older adults with controlled hypertension who are at risk of future cognitive decline. The first main hypothesis was that WMH mediates the effect of controlled hypertension on cognitive impairments in nondemented older adults. To answer this hypothesis, we sequentially tested three sub-hypotheses: 1) controlled hypertension is associated with the more cerebral WMH; 2) controlled hypertension is associated with the lower cognitive performance; 3) cerebral WMH mediates the association of controlled hypertension with lower cognitive performance. The second main hypothesis was that cerebral WMH age estimated using the WMHPM of healthy older adults predicts current cognitive impairments and future cognitive decline in older adults with controlled hypertension. To answer this hypothesis, we sequentially tested three sub-hypotheses: 1) controlled hypertension is associated with the older WMH age estimated using WMHPM of healthy older adults; 2) older WMH age is associated with lower cognitive performance; 3) older WMH age predicts risks of current cognitive impairments and future cognitive decline in older adults with controlled hypertension.

2. Methods

2.1. Study population

2.1.1. Hypothesis 1. Does cerebral WMH mediate the effect of controlled hypertension on cognitive function in nondemented older adults?

We recruited 890 community-dwelling Koreans aged 60 years or older, including 385 patients from the Dementia Clinic of the Seoul National University Bundang Hospital (SNUBH) from 2011 to 2020 and 505 participants of the Korean Longitudinal Study on Cognitive Aging and Dementia (KLOSCAD). The KLOSCAD is an ongoing, nationwide, population-based, prospective cohort study on cognitive aging and dementia in the elderly [54]. In the KLOSCAD, 6,818 community-dwelling Koreans, aged 60 years or older, who were randomly sampled from 30 villages or towns across South Korea, completed the baseline assessment, which was conducted from November 2010 through October 2012. We excluded participants with any of the following conditions: uncontrolled hypertension with an office-measured SBP $\geq$ 140 mm Hg or DBP $\geq$ 90 mm Hg; major neurologic or psychiatric disorders; dementia; time gap between the clinical assessment and the brain MRI acquisition > 1 year. The demographic and clinical characteristics of the participants are summarized in Table 1.

2.1.2. Hypothesis 2. Does WMH age estimated using the WMH probability map (WMHPM) predict current cognitive impairment and future cognitive decline in older adults with controlled hypertension?

To construct a WMHPM, we enrolled 300 community-dwelling healthy Koreans aged 60 years or older from the participants of two ongoing population-based prospective cohort studies; 228 from the KLOSCAD and 72 from the Gwangju Alzheimer's & Related Dementias (GARD) Study [55]. They consisted of five age groups (60–64 years, 65–69 years, 70–74 years, 75–79 years, and 80 years or

above), and each age group included 30 men and 30 age-matched women. We diagnosed the participants as 'healthy' if they met the following criteria: 1) The participant was functioning independently in the community without impaired activities of daily living; 2) had a Mini Mental Status Examination (MMSE) point of above -1.0 standard deviation of age-, gender-, and education adjusted norm of elderly Koreans; 3) had a Clinical Dementia Rating of 0; and 4) did not have any of the conditions, such as major psychiatric disorders including depressive disorders and substance use disorders, cognitive disorders including dementia and other axis I mental disorders according to the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition [56], and mild cognitive impairment according to the consensus criteria proposed by the International Working Group on MCI [57], major neurologic disorders including movement disorders and strokes, cardiovascular and metabolic diseases including hypertension and diabetes mellitus (DM), and other severe medical conditions that may influence mood and cognition. Their demographic and clinical characteristics are summarized in Table 2.

We investigated whether WMH age estimated using the WMHPM is associated with current cognitive impairment or not using the same participants as enrolled for investigating the first hypothesis (Table 1). Then we investigated the interactive effect of current controlled hypertension and WMH age group on the cognitive decline over 2 year follow up period in the 368 out of 890 participants who completed 2 year follow up assessment. Their demographic and clinical characteristics are summarized in Table 3.

2.2. Research ethics

All participants and/or their legal guardians provided written informed consent for participation in this study. The SNUBH (B-2005-615-001), KLOSCAD (B-0912-089-010) and GARD (CHOSUN 2013-12-018-070) were approved by the Institutional Review Board of the Seoul National University Bundang Hospital for SNUBH and KLOSCAD, and the Chosun University Hospital for GARD.

2.3. Assessments

Geriatric psychiatrists or neurologists with expertise in dementia research performed face-to-face, standardized diagnostic interviews; physical and neurological examinations; laboratory tests including complete blood counts, chemistry profiles, serological tests for syphilis, echocardiography, and chest X-ray. Research neuropsychologists or trained research nurses administered the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease neuropsychological battery (CERAD-K-N), which comprises the following neuropsychological tests: verbal fluency test (VFT), 15-item Boston Naming Test (BNT), MMSE, word list memory test (WLMT), Constructional Praxis Test (CPT), word list recall test (WLRT), word list recognition test (WLRcT), Constructional Recall Test (CRT), Trail Making Test A/B (TMT-A/B), Digit Span Test (DST), and Frontal Assessment Battery (FAB) [58, 59]. We calculated CERAD total score (CERAD-TS) [60] by adding the points of VFT, BNT, WLMT, WLRT, WLRcT and CPT. We derived the Verbal Memory (VM) [61] by calculating weighted average of the points of WLMT, WLRT and WLRcT. The CERAD-TS and VM range from 0 to 100 and 0 to 30, respectively, and higher points represent better cognitive function.

A trained research nurse measured the blood pressure thrice with a 5 min interval, when the participants visited the hospital over the participants' right brachial artery, in a sitting position, using an automated blood pressure monitoring device (OMRON HBP-9020, Omron healthcare Co. Ltd., Kyoto, Japan). To reduce bias, the mean value of the three measurements was used for the analysis.

2.4. Diagnoses

We diagnosed dementia and other axis I mental disorders according to the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, for dementia [56], and MCI according to the consensus criteria proposed by the International Working Group on MCI [57].

We defined controlled hypertension (cHT) as having a history of hypertension but current SBP

of below 140 mm Hg and DBP of below 90 mm Hg and normotension (nHT) as having no history of hypertension and the current SBP of greater than or equal to 90 mm Hg and below 140 mm Hg and DBP of greater than or equal to 60 mm Hg and below 90 mm Hg. Then we further classified the participants into the low SBP group (LSBP) and normal SBP group (NSBP) using current SBP, and into the low DBP group (LDBP) and normal DBP group (NDBP) using current DBP. We defined the LSBP as having current SBP of 110 mm Hg or below, and the LDBP as having current DBP of 60 mm Hg or below.

2.5. Acquisition of brain MRI

The participants from the SNUBH and the KLOSCAD underwent MRI on a 3.0 Tesla Achieva Scanner (Philips Medical Systems; Eindhoven, NL) using the following protocol, T1: acquired voxel size = 1.0 mm × 0.5 mm × 0.5 mm, echo time = 4.6 ms, repetition time = 8.1 ms, acquisition axial plane matrix size = 240 mm × 240 mm, number of excitation = 1, flip angle = 8°, inversion time = not applied and FLAIR: acquired voxel size = 0.47 mm × 0.47 mm × 3.0 mm, slice thickness = 3 mm, spacing between slices = 3 mm, echo time = 125 ms, repetition time = 9,900 ms, acquisition axial plane matrix size = 256 mm × 256 mm, number of excitations = 1, flip angle = 90°, and inversion time = 2,800 ms. The participants from the GARD underwent MRI on 3.0 Tesla Skyra Scanner (SIEMENS Healthineers; Erlangen, DE) using the following protocol, T1: acquired voxel size = 0.8 mm × 0.8 mm × 0.8 mm, echo time = 2.14 ms, repetition time = 2.3 ms, acquisition sagittal plane matrix size = 320 mm × 320 mm, number of excitations = 1, flip angle = 9°, inversion time = 900 ms and FLAIR: acquired voxel size = 0.63 mm × 0.63 mm × 7.5 mm, slice thickness = 5 mm, spacing between slices = 7.5 mm, echo time = 96 ms, repetition time = 8,000 ms, acquisition axial plane matrix size = 218 mm × 384 mm, number of excitations = 1, flip angle = 150°, and inversion time = 2,500 ms.

2.6. Processing of brain MRI

We conducted all image preprocessing and registration using the Statistical Parametric Mapping

software (version 8, SPM8; Wellcome Trust Centre for Neuroimaging, London). First, we spatially normalized each individual's T1 image to a previously developed standard template for Korean normal elderly (KNE200 template) [52]. The normalization process involves estimating an optimum 12-parameter affine transformation that matches the head orientation of the individual image to the template, followed by estimating a nonlinear deformation which further minimizes the residual squared difference between the individual image and the template [62]. Through normalization to a common stereotaxic space (voxel size 1x1x1 mm, slice thickness 1 mm), we aimed to correct for inter-individual differences in brain size and shape. Meanwhile, we applied bias correction on the FLAIR images to correct for non-uniformities caused by the bias field due to different tissue properties and physics of MR scanning, using the "Segment" tool from SPM8. The bias correction method in SPM8 uses a Bayesian model to accurately estimate a smooth function that is multiplied with the image using prior knowledge about field distributions likely to be encountered [63]. Next, we coregistered the bias corrected FLAIR images to native T1 images. We then applied the transformation parameters produced from the normalization step of T1 images to the bias corrected, T1-coregistered FLAIR images to produce spatially KNE-normalized FLAIR images.

2.7. Segmentation of WMH

We segmented WMH from the spatially KNE-normalized FLAIR images by using a fully automated in-house code run on MATLAB 2014a (MATLAB and statistics Toolbox Release 2014a, MathWorks, Inc., Natick, MA) which has been previously shown to work on different protocols from different scanners without any parameter adjustment [64]. Each voxel of the segmented WMH mask has values of 1 or 0, indicating the presence or absence of WMH respectively. We calculated the volume of overall cerebral WMH using in-house code run on MATLAB 2014a.

2.8. Visual rating of WMH

Geriatric psychiatrists graded the severity of periventricular WMH (PVWMH) and deep WMH

(DWMH) according to the Fazekas' scale (FS) [65], which is widely used method to visually rate hyperintense white matter signal abnormalities in brain MRI. In the FS, WMH was scored from 0 to 3 (0 = absence, 1 = 'caps' or pencil-thin lining, 2 = smooth 'halo' and 3 = irregular PVWMH extending into the deep white matter for PVWMH; 0 = absence, 1 = punctuate foci, 2 = beginning confluence of foci and 3 = large confluent areas for DWMH).

2.9. Construction of WMHPM

We overlapped the segmented WMH masks of each of five age banded groups. We then created a map that represent the probability of the presence of WMH in each voxel by dividing the values of each voxel by the total number of participants in each age banded group which is 60. We reduced the noises associated with individual anatomical details or other imaging artifacts by smoothing with a Gaussian filter with a full with at half maximum of 1 [66] and excluding the voxels with the probability of 0.1 or below [67].

2. 10. Estimation of WMH age

We overlaid the segmented WMH mask of each participant to the five age-band WMHPMs. Subsequently, we subtracted the voxel value of the segmented WMH mask (0 and 1, reflecting absence and presence, respectively) from the voxel value of the WMHPMs (0 to 1). We summed the absolute values of the subtracted values from all voxels. We obtained the deviance value by dividing the sum by the total number of voxels. We defined the estimated WMH age of each participant as the age range of the WMHPM which showed the lowest deviance value from his or her segmented WMH mask. Finally we classified the participants into three groups using the estimated WMH age group: the normal WMH age group whose estimated WMH age range included his or her chronological age, the younger WMH age group whose estimated WMH age range is below his or her chronological age, and the older WMH age group whose estimated WMH age range is above his or her chronological age.

2. 11. Statistical analyses

We compared continuous variables using independent samples t-test or one-way analysis of variance (ANOVA) and categorical variables using chi-square test between groups.

We examined the association of different hypertension groups with cerebral WMH volume, cognitive performances using ANOVA that adjusted for education, hyperlipidemia, DM and other cardiovascular disease as covariates.

We then performed mediation analysis to investigate the mediation effect of cerebral WMH volume on the effect of cHT on the cognitive performance. We analyzed the mediation effect using the Baron and Kenny method [68]. This method is to test mediation effect which have two paths to the dependent variable. The independent variable must predict the dependent variable and the independent variable must predict the mediator. We tested mediation effects through three linear regression processes, first, independent variable predicting the dependent variable; second, independent variable predicting the mediator; and third, independent variable and mediator predicting the dependent variable. Then we analyzed the association of cHT, LSBP, LDBP, and their interactions on the cerebral WMH volume and cognitive performance using ANOVA that adjusted education, DM and hyperlipidemia as covariates. Then we analyzed the association of SBP on cerebral WMH volume and cognitive performance in cHT and nHT groups separately using ANOVA that adjusted education, DM, hyperlipidemia and DBP as covariates. We examined the association of log-transformed cerebral WMH volume on the cognitive performances and cognitive domains of cHT participants using linear regression analysis that computed log-transformed cognitive test points as dependent variables and education, DM and hyperlipidemia as covariates. We performed mediation analysis to investigate the mediation effect of cerebral WMH volume on the effect of SBP on the cognitive performances in cHT participants. We analyzed the mediation effect using the Baron and Kenny method [68].

For the constructed WMHPM, we calculated the total volume, hemispheric volume, and regional volumes and proportions of total WMH, PVWMH and DWMH. We obtained hemispheric volumes by dividing the WMH labels into those corresponding to the left and right hemispheres by

referencing the longitudinal fissure, and anterior and posterior regions as specified in a white matter atlas proposed by Murray et al [69].

We examined the association of cHT, LSBP, LDBP, and their interactions with the older WMH age using ANOVA that adjusted education, DM and hyperlipidemia as covariates. We then compared cognitive performance between different WMH age groups using ANOVA that adjusted chronological age, hypertension and DM as covariates.

We examined the effects of cHT and WMH age on the changes of cognitive performance during 2-year follow-up period using repeated measure ANOVA (rmANOVA) adjusting for chronological age and DM as covariates, and the risk of incident MCI during 2-year follow-up period using logistic regression analysis adjusting for chronological age and DM.

For all analyses, we used SPSS for Windows version 20.0 (IBM Co., Armonk, NY, USA) and considered 2-sided *p* value below .05 as statistically significant.

3. Results

3.1. Hypothesis 1. Does cerebral WMH mediate the effect of controlled hypertension on cognitive function in nondemented older adults?

Compared to the nHT group, the cHT group was less educated, more likely to have DM, hyperlipidemia and MCI and higher SBP and cerebral WMH volume. LSBP had higher SBP, DBP and cerebral WMH volume and more likely to have MCI than NSBP while age, sex, education, DM, hyperlipidemia, other CVD, drinking and smoking were comparable between groups. LDBP had higher SBP and DBP and more likely to have MCI than NDBP while other variables were comparable to NDBP (Table 1). Compared to the nHT group, the cHT group was less educated and more likely to have DM, hyperlipidemia, other CVD, cerebral WMH volume and MCI. When we analyzed the NSBP and LSBP groups separately in cHT group, LSBP was less educated and more likely to have other CVD than nHT. Both LSBP and NSBP were likely to have DM while only NSBP was more likely to have hyperlipidemia than nHT. SBP and DBP were least in LSBP, followed by nHT and NSBP, while cerebral WMH volume and MCI were least in nHT, followed by NSBP and LSBP. When we analyzed the NDBP and LDBP groups separately in cHT group, NDBP and LDBP were more likely to have hyperlipidemia and other CVD than nHT, respectively. LDBP and NDBP were more likely to have DM and less educated than nHT. SBP was least in LDBP, followed by nHT and NDBP. DBP was comparable between nHT and NDBP, however they were higher than LDBP. WMH volume was larger in LDBP and NDBP than nHT, while MCI was more likely to have in LDBP, followed by NDBP and nHT (Table 4).

As summarized in Table 5 and Supplementary table 1, LSBP of cHT have higher cerebral WMH volume ($p < .001$), more likely to have MCI ($p < .001$) and showed lower performance in all cognitive test except CRT ($p = .945$) and TMT-A ($p = .492$) than nHT. LDBP of cHT have higher cerebral WMH volume ($p < .001$), more likely to have MCI ($p = .007$) and showed lower performance in BNT ($p < .001$), MMSE ($p = .001$), WLMT ($p = .005$), CPT ($p = .020$), TMT-B ($p = .025$), CERAD-TS ($p = .003$) and VM ($p = .019$) than nHT, while the cognitive performance of NSBP and NDBP of

cHT were comparable to nHT.

In the mediation analysis, cerebral WMH was found to mediate the effect of cHT on the points of all cognitive tests. We analyzed the relationships between cHT and cognitive performance mediated by WMH volume. As Figure 1 illustrates, the standardized regression coefficient between cHT and WMH volume was statistically significant (β = 0.158, $p < .001$), as was the standardized regression coefficient between WMH volume and cognitive performances were following, of MMSE (β = -0.214, $p < .001$), FAB (β = -0.221, $p < .001$) and CERAD-TS (β = -0.302, $p < .001$). We analyzed indirect effect of cHT on each cognitive tests by using Sobel product of coefficients approach proposed by Sobel [70] which calculates the indirect effect by multiplying two regression coefficients. We calculated 2-sided *p*-value using Sobel test [70] to find significance of indirect effect. The indirect effect of cHT on MMSE was 0.034 ($p < .001$), FAB was 0.035 ($p < .001$) and CERAD-TS was 0.048 ($p < .001$).

The interaction between cHT and LSBP was associated with the cerebral WMH volume ($F_{1, 877} = 11.005$, $p = .001$), MMSE ($F_{1, 877} = 5.662$, $p = .011$), FAB ($F_{1, 877} = 5.556$, $p = .009$) and marginally with CERAD-TS ($F_{1, 877} = 3.579$, $p = .059$), while none of the above were associated with the interaction between cHT and LDBP (Table 6). We then analyzed the association of LSBP with cerebral WMH volume and cognitive performance in the nHT and cHT groups separately. As summarized in Table 7, the LSBP group was associated with lower MMSE ($p = .031$), FAB ($p = .005$) and CERAD-TS ($p = .005$) performance in the cHT group, while only MMSE ($p = .032$) was associated in the nHT group. In the cHT group, the LSBP group had approximately 1.6 times larger cerebral WMH volume than did those the NSBP group ($p = .001$). However, in the nHT group, the WMH volume was comparable between the LSBP and NSBP groups ($p = .499$).

Log-transformed cerebral WMH volume was associated with the log-transformed points of all cognitive tests. MMSE point decreases 0.16, FAB point decreases 0.18 and CERAD-TS point decreases 1.08 for each cc of WMH volume increases in cHT group ($p < .001$ for all cognitive performance, Figure 2); VFT point decreases 0.18, BNT point decreases 0.17, WLMT point decreases 0.21, WLRT point decreases 0.19, WLRT point decreases 0.14, CPT point decreases 0.16, CRT point

decreases 0.16, TMT-A time increases 0.25, TMT-B time increases 0.21, DST point decreases 0.18 and VM point decreases 0.54 for each cc of WMH volume increases ($p < .001$ for all cognitive performances, Supplementary figure 1)

In the Baron and Kenny method, cerebral WMH was found to mediate the effect of SBP on the points of all cognitive tests in the cHT. We analyzed the relationships between SBP and cognitive performance mediated by WMH volume in cHT group. As Figure 3 illustrates, the standardized regression coefficient between SBP and WMH volume was statistically significant ($\beta = -0.090$, $p = .048$), as was the standardized regression coefficient between WMH volume and cognitive performances were following, of MMSE ($\beta = -0.214$, $p < .001$), FAB ($\beta = -0.221$, $p < .001$) and CERAD-TS ($\beta = -0.302$, $p < .001$); of VFT ($\beta = -0.193$, $p < .001$), BNT ($\beta = -0.217$, $p < .001$), WLMT ($\beta = -0.281$, $p < .001$), WLRT ($\beta = -0.242$, $p < .001$), WLRcT ($\beta = -0.330$, $p < .001$), CPT ($\beta = -0.202$, $p < .001$), CRT ($\beta = -0.268$, $p < .001$), TMT-A ($\beta = 0.196$, $p < .001$), TMT-B ($\beta = 0.238$, $p < .001$), DST ($\beta = -0.176$, $p < .001$) and VM ($\beta = -0.310$, $p < .001$) (Supplementary figure 2). While the indirect effect of SBP on MMSE was 0.019 ($p = .038$), FAB was 0.020 ($p = .038$) and CERAD-TS was 0.027 ($p = .037$) (Figure 3); VFT was 0.017 ($p = .039$), BNT was 0.020 ($p = .038$), WLMT was 0.025 ($p = .038$), WLRT was 0.022 ($p = .038$), WLRcT was 0.030 ($p = .038$), CPT was 0.018 ($p = .038$), CRT was 0.024 ($p = .038$), TMT-A was -0.018 ($p = .346$), TMT-B was 0.021 ($p = .414$), DST was 0.016 ($p = .039$) and VM was 0.028 ($p = .035$) (Supplementary figure 2).

3.2. Hypothesis 2. Does WMH age estimated using the WMH probability map (WMHPM) predict current cognitive impairment and future cognitive decline in older adults with controlled hypertension?

We first develop the WMHPM of older Koreans which will be a reference for estimating WMH age. The participants included in the dataset for developing the WMHPM were aged 72.3 ± 7.5 years and educated for 12.1 ± 4.5 years on average. Compared to the male participants, the female participants

showed the higher volume and proportion of WMH (p = .009) despite that age, MMSE points, and FS points were comparable. The volume and proportion of WMH gradually increased with advancing age (p < .001). The volume of WMH in the 80+ group was more than six folds higher than that in the 60–64 age group (Table 2). These age-associated differences in the volume and proportion of the WMH were observed in both hemispheres (p < 0.001) and regions (p < 0.001, Table 8). The ratios of the hemispheric WMH volumes and proportions between right and left hemispheres and those of regional WMH volumes and proportions between anterior and posterior regions were comparable in all the age groups (Table 8). Figure 4 demonstrated the WMHPM in three representative brain slices, including the centrum semiovale, corona radiata, and striatocapsular region.

Then we calculated estimated WMH age of every participants. As summarized in Table 9, the older WMH age group was more likely to have hypertension (p = .013) and DM (p < .001) than the normal or younger WMH age groups. The younger WMH age group was older than normal WMH age followed by older WMH age group. The older WMH age group have larger WMH volume and more likely to have MCI than normal WMH age followed by younger WMH age group. Sex, education, hyperlipidemia, other CVD, drinking, smoking, SBP and DBP were comparable between groups.

As summarized in Table 10, the cHT ($F_{1, 877}$ = 9.835, p = .002), LSBP ($F_{1, 877}$ = 8.944, p = .003), LDBP ($F_{1, 877}$ = 6.231, p = .013), interaction between cHT and LSBP ($F_{1, 877}$ = 7.965, p = .005), interaction between cHT and LDBP ($F_{1, 877}$ = 4.971, p = .026) and interaction between cHT, LSBP and LDBP ($F_{1, 877}$ = 6.684, p = .010) were associated with having older WMH age. As shown in Table 11 and Supplementary table 2, the older WMH showed lower cognitive test points than the younger WMH age (p < .001 for all cognitive performance). Although the older WMH age group performed worse than the normal WMH age group in all cognitive tests, the differences were not statistically significant. MCI was most prevalent in the older WMH age group, followed by the normal WMH age group. MCI was more than twice as common in the older WMH age group as in the younger WMH age group. Although the older WMH age group performed worse than the normal WMH age group in all cognitive performance, the differences were not statistically significant. In the logistic regression analysis adjusting for chronological age, hypertension and DM, the older WMH age group was 1.51 (95% CI =

1.06 – 2.14, p = .023) times more likely to have MCI while the younger WMH age group was 0.50 (95% CI = 0.34 – 0.72, p < .001) times less likely to have MCI than the normal WMH age group.

Among the 890 participants presented in Table 1, 368 completed two-year follow-up assessment. We classified these participants into four groups using the hypertension and the WMH age; cHT with older WMH age (cHTO), cHT with normal or younger WMH age (cHTNY), nHT with older WMH age (nHTO) and nHT with normal or younger WMH age (nHTNY). As summarized in Table 3, compared to the nHTNY group, the cHTO and nHTO groups showed higher WMH volume while the cHTNY group showed comparable WMH volume. The cHTO group was more likely to have MCI than the other three groups (p < .001). As summarized in Table 12 and Supplementary table 3, the declines over two-year follow-up period in the points of all cognitive tests except WLMT, WLRcT, TMT-A and VM were different between the four groups. The cHTO group showed faster decline in the VFT, BNT, MMSE, WLRT, CPT, DST, FAB and CERAD-TS than the nHTNY group. In addition, the cHTO group showed more than eight times higher risk of MCI at the two-year follow-up assessment than the nHTNY group (Table 13).

4. Discussions

This study revealed that LSBP was associated with a larger volume of WMH in the cHT group, and the larger volume of WMH mediated the cognitive impairments associated with cHT. We also successfully replicated the association using newly introduced concept of estimated WMH age defined using WMHPM. We demonstrated that the cHT participants with older WMH age were at higher risk of cognitive decline and cognitive disorder.

The relationship between hypertension and different pathologies associated WMH has been repeatedly reported in many previous studies. Hypertensive condition give rise to the structural changes such as vessel wall remodeling of hypertrophic remodeling [71] and/or eutrophic remodeling [72] to reduce the mechanical stress on the arterial wall and to protect microvessels from pulsatile stress [73]. Hypertension is also a leading risk factor for atherosclerosis. Stroke Prevention: Assessment of Risk in a Community study [74] examined the association between hypertension and aortic atherosclerosis among 581 participants and reported that 10 mm Hg increase of SBP increased 43% the odds of complex aortic atherosclerosis. Hypertension also promotes SVD which gives distinctive alterations in small arteries and arterioles supplying blood to deep white matter. The sensitivity of these vessels to SVD may be due to their short pathway from larger vessels at the base of the brain which may provide them more vulnerable to the mechanical stress due to hypertension [75], and usually demonstrated as arteriolosclerosis [76]. The study of Ighodaro et al [77] studied the clinical and neuropathological data from 2390 elderly participants. They reported that less than 80 years old participants were showing the relationship between hypertension and cerebral arteriolosclerosis. These structural changes induced by hypertension were reported to increase WMH [78-80]. The hemodynamic flow changes of the arterial remodeling and SVD produce more WMH [79].

In addition to structural changes altered by hypertension, functional changes also occurs after hypertension. Cerebral endothelial cell strongly regulates cerebral blood flow (CBF) by releasing vasodilators such as nitric oxide and prostacyclin, and vasoconstrictors such as endothelium-derived constrictor factor and endothelin-1 [81]. Another significant function of cerebral endothelial cell is to

regulate blood-brain barrier (BBB). Cerebral endothelial cells are tightly linked to each other and have a low vesicular transport [82]. However, hypertension stimulates cerebral endothelial dysfunction [11, 72]. Numerous studies confirmed the relationship between hypertension and cerebral endothelial dysfunction. Huang et al [83] studied endothelial nitric oxide syntheses in hypertensive mice and found out that the mice with less endothelial nitric oxide syntheses had elevated SBP approximately 30 mm Hg than wild type mice. The study of Panza et al [84] also reported that the endothelial vasodilation is impaired in the participants with hypertension. The association of endothelial dysfunction on WMH can be found in previously announced reports such that the decreased cerebrovascular dilatory capacity increased WMH [85, 86]. The Rotterdam Scan Study examined the association between vasomotor reactivity and WMH among 73 participants and confirmed that less vasomotor reactivity was associated with WMH [85].

When hypertension was controlled, the risk of WMH due to hypertension also reduced [87, 88]. However, in the CASCADE study, 1625 participants were examined to associate the different status of hypertension such as controlled, untreated or poorly controlled hypertension and the WMH, and concluded that the participants with poorly controlled hypertension recorded higher risk of severe WMH than those with controlled or untreated hypertension. This may be in line with our observation that larger WMH was observed with LSBP of cHT. Though hypotension can results cerebral hypoperfusion, more severe cerebral hypoperfusion can be observed in the participants with hypertension [24], which, even if controlled, may adversely influenced by damaged cerebral autoregulation [89, 90]. Earlier studies have found out that patients with hypertension were found to have shifted the limits of cerebral autoregulation toward higher blood pressure levels [91, 92] and a higher cerebrovascular resistance compared with the normotensive controls, despite their global resting CBF and cerebral oxygen consumption being comparable to those in the normotensive controls [93, 94]. Cerebral autoregulation is the innate capacity of the cerebral vasculature to maintain a constant CBF [95], which allows adequate blood supply to the brain to meet the ample metabolic demands [96]. Cerebral autoregulation in normotensive individuals is relatively constant, maintaining a fixed range of mean arterial pressure between 60 mm Hg and 150 mm Hg [97]. This adaptive mechanism helps to

protect brain from hypertension in some degrees but it can also make brain more vulnerable to cerebral hypoperfusion which resulted from poorly controlled hypertension that induces hypotension [98] and increase the risk of WMH [99-101] in which Liu et al [100] revealed that the decreased posterior and global cerebral autoregulation were associated with the large volume of WMH. .

The association of WMH with cognitive impairments and cognitive disorders has been consistently replicated in numerous previous studies as was in the current study. WMH was associated with the impairments in a wide range of cognitive function including executive function, processing speed, attention, visuospatial memory and organization, visual scanning and new learning in many retrospective studies [20, 102-104]. In the Cardiovascular Health Study Cognition Study, the older adults with MCI showed more WMH than those with normal cognition [6]. WMH was also associated with the future risks of cognitive decline and cognitive disorders in many prospective studies. In cognitively normal older adults, WMH predicted the accelerated decline in many cognitive tests including TMT-A, TMT-B, Digit Symbol Coding, Logical Memory Immediate Recall, and Semantic Fluency Test [105] and the progression to MCI [21]. We assessed MMSE, FAB and CERAD-TS which CERAD-TS reveals high correlation not only to the global cognitive scales but also to the clinical severity scale such as Clinical Dementia Rating Sum of Box and functional scale such as Blessed Dementia Scale-Activity of Daily Living, thus serve as a valid indicator for dementia or MCI progression [60]. Study of Seo et al [60] reported that the cut-off CERAD-TS point of discrimination between normal cognition and MCI was 59.5 points, which is similar to our study that LSBP of cHT and cHTO recorded CERAD-TS of 59.7 points and 60.6 points, respectively, which we considered the groups as cognitively impaired.

In this study, LDBP was not associated with the cerebral WMH volume, which is in line with the findings of previous research on the association of BPs on cerebral perfusion. The Framingham Heart Study reported that SBP is a more important vascular risk factor than DBP in subjects aged over 60 years [106]. Glodzik et al. [107] found that the cortical and hippocampal blood flows were negatively associated with the SBP, but not with the DBP. In addition, they found that the cortical and hippocampal

blood flows decreased as the SBP decreased during a 2-year follow-up period, whereas the same were not influenced by the decrease of DBP in the same period [107].

Therefore, hypertension, if not properly controlled, may increase the risk of cognitive impairments and cognitive disorders by increasing cerebral WMH. The Maracaibo Aging Study reported that the effect of nocturnal blood pressure on the decline in memory function was mediated by cerebral WMH in older adults with hypertension but not in those without hypertension [108]. The Cardiovascular Health Study also found that cerebral WMH mediated the adverse effect of hypertension on the mobility, cognition and mood [109]. Although a couple of previously mentioned studies demonstrated the mediating role of cerebral WMH in the effect of hypertension on cognition, to our best knowledge, our study is the first study that clearly demonstrated WMH mediation effect of hypotension on cognitive functions among hypertensive participants.

As results of our hypothesis 1, we concluded that LSBP among cHT is associated with large WMH volume affecting cognitive function. However, there are various different risk factors that increase WMH [110-112]. While WMH enlarges naturally with age [14, 15], it sometimes develops pathologically and affect cognitive function as mentioned earlier. Standard criteria are needed to determine this morbid increase in WMH, which is why we constructed standardized WMHPM using well- balanced, healthy, age stratified and sex matched elderly Koreans.

As far as we know, our WMHPM is the first that comes from an Asian population and covers the entire age range of older adults from 60 years and above. Furthermore, we strictly balanced gender and age ratios of the sample and rigorously excluded the conditions from the sample that could have influenced the risk and prevalence of the WMH. Although different studies reported WMHPMs [44-51], most of them were disease-specific WMHPMs, such as the cerebrovascular disease WMHPMs [44, 47-49] or WMHPMs of MCI [46] or AD [45]. There were two WMHPMs of healthy elderly participants; one from the Austrian Stroke Prevention Study (ASPS) using proton density weighted images [50] and the other from the Path Through Life (PTL) project using FLAIR images [51]. The ASPS WMHPM was constructed from 189 community-dwelling volunteers (95 men and 94 women) aged 50–75 years

(mean = 60.8, standard deviation = 6.2) without neuropsychiatric disorders. The PTL WMHPM was constructed from 477 randomly selected healthy residents (251 men and 226 women) aged 60-64 (mean = 62.6, standard deviation = 1.5). However, these two WMHPMs had some limitations to represent the probability of WMH of healthy elderly population; the ASPS WMHPM was constructed from a small number of subjects and the PTL WMHPM was constructed from subjects in their early 60s only, and did not exclude the subjects with a history of stroke, head injury, epilepsy, and heart disease. Furthermore, both WMHPMs were constructed from Caucasian populations, which the brain shape [52] and the risk of cerebrovascular diseases and WMH are different between Caucasians and Asians [53], that may not be directly applicable to Asian population.

We introduced new concept of WMH age using constructed WMHPM in answer to the question on how we apply the cerebral WMH volume causing cognitive impairment in the participants with controlled hypertension in clinical field. Quantitative assessment and measurement of WMH is a crucial requirement for sufficient analysis of associated clinical deficits for clinical research. However, common methods currently used to assess and measure WMH [65, 113, 114] ignore the effect of WMH affected by age. In our WMHPM, the volume, proportion and severity of WMH increased continuously with advancing age which is in line with previous studies reported that the prevalence and severity of WMH have been consistently increased with age regardless of ethnicities [15, 115]. Across the human lifespan, cerebral metabolic rates for oxygen and glucose decreased by approximately 6% per decade [116] and CBF decreased by 4.8 mL/min per year [117]. The reduction in cerebral metabolic rates was coupled to the concurrent hemodynamic insufficiency [118, 119]. In addition, atrial fibrillation [120] and carotid atherosclerosis [121] became more prevalent with advancing age. All these age-associated changes may contribute to the development and progression of cerebral WMH with advancing age in late life. Our concept fully accepted the age which has not yet been implied in quantitative assessment of WMH in other studies. Through our proposed WMH age, researcher can differentiate pathological WMH from non-pathological WMH and concentrate on clinical deficits caused by WMH.

There are several limitations in the current study. First, we did not conduct a 24-hour ambulatory blood pressure monitoring in the current study despite that blood pressure is highly dynamic. Second, although there are no standard values for defining low SBP and DBP, we defined LSBP as below 110 mm Hg and LDBP as below 60 mm Hg in the current study. In the 81,134 participants from National Trauma Data Bank 5.0, the annual mortality rate increased 4.8% for every decrement of 10 mm Hg in the baseline SBP from 110 mm Hg [122]. In the 2,071 participants with gastrointestinal diseases, the mortality was higher in those whose SBP was below 110 mm Hg [123]. We defined LDBP as below 60 mm Hg. In 5,376 older adults from The Cardiovascular Health Study, isolated diastolic hypotension defined as DBP of below 60 mm Hg was associated with the risk of heart failure [124]. In the 477 participants from Oxford Project to Investigate Memory and Aging that includes cognitive healthy control, MCI and Alzheimer's disease, LDBP of below 60 mm Hg was associated with the faster cognitive decline [125]. Third, the other factors associated between hypertension and cognition should be considered. The antihypertensive drugs, such as calcium channel blocker [126], angiotensin II receptor blocker [127] and β-blocker [128] were reported as preserving agents for cognitive decline among participants with hypertension [126-130]. In addition, the study of Jaiswal et al [129] revealed that the cognitive test points of participants with hypertension were increased after 3 months of antihypertensive therapy which were found declined at the baseline. This suggest that not only antihypertensive drugs but also the duration of antihypertensive treatment may important in the association between hypertension and cognition. Moreover, duration of hypertension [131, 132] and blood pressure fluctuation [133, 134] may also affect the cognition. In this study, we could not perfectly control the underneath factors affecting hypertension and cognition. However, we considered the direct effect of path analysis we investigated, includes all the remaining effects which were not transmitted via mediating variable [135]. Thus further study need to carefully consider the factors affecting the association between hypertension and cognition. Fourth, our multivariable analyses may not have fully adjusted all potential factors that may confound the association of blood pressure and WMH. Further studies need to consider variables that may affect the blood pressure or WMH. Fifth, it is unknown

whether the LSBP in the participants with cHT is attributable to overtreatment of the hypertension or to underlying structural or functional abnormalities that are associated with predisposition to WMH.

5. Conclusions

This study provides the evidence that LSBP after hypertensive condition, may increase the cerebral WMH volume and worsen the cognitive function. Moreover, WMH mediates the effect of LSBP on cognitive function among cHT of nondemented older adults. The study also proposed new method which is the estimated WMH age, to assess and measure WMH quantitatively, using constructed WMHPM. We expect WMH age would be standard method to study pathological features of WMH and use as the method to differentiate the high risk group of cognitive decline in cHT.

Table 1. Demographic and clinical characteristics of the participants

	All (N = 890)	Controlled hypertension			Current SBP			Current DBP		
		nHT (n = 445)	cHT (n = 445)	p*	NSBP (n = 741)	LSBP (n = 149)	p*	NDBP (n = 821)	LDBP (n = 69)	p*
Age, years†	73.6 ± 5.8	73.3 ± 6.3	74.0 ± 5.3	.057	73.7 ± 5.8	73.3 ± 6.2	.424	73.5 ± 5.9	74.9 ± 5.3	.054
Women, %	60.4	58.2	62.7	.170	60.7	59.1	.704	60.9	55.1	.342
Education, years†	11.7 ± 4.9	12.1 ± 4.7	11.2 ± 5.0	.006	11.8 ± 4.9	11.2 ± 4.9	.205	11.7 ± 4.9	10.9 ± 5.1	.159
DM, %	21.2	15.3	27.3	< .001	20.9	22.8	.605	21.0	24.6	.472
Hyperlipidemia, %	44.9	37.7	52.5	< .001	46.3	38.3	.072	45.8	34.8	.077
Other CVD, %	4.4	5.2	3.6	.252	4.3	4.7	.836	4.4	4.3	.988
Drinking, unit/week†	4.5 ± 11.2	4.0 ± 10.0	5.0 ± 12.3	.211	4.5 ± 10.9	4.4 ± 12.7	.909	4.4 ± 11.2	5.7 ± 11.4	.371
Smoking, pack/day†	0.3 ± 0.5	0.3 ± 0.5	0.3 ± 0.5	.528	0.3 ± 0.5	0.3 ± 0.5	.868	0.3 ± 0.5	0.3 ± 0.5	.324
SBP, mm Hg†	122.4 ± 10.0	121.6 ± 10.0	123.2 ± 9.9	.014	125.7 ± 7.0	106.1 ± 5.5	< .001	123.5 ± 9.1	109.3 ± 11.1	< .001
DBP, mm Hg†	73.1 ± 7.6	73.1 ± 7.5	73.0 ± 7.6	.825	74.6 ± 6.8	65.4 ± 6.3	< .001	74.4 ± 6.4	57.9 ± 2.8	< .001
WMH, cc†	10.2 ± 12.6	8.2 ± 10.8	12.2 ± 13.9	< .001	9.8 ± 12.6	12.2 ± 12.6	.003	10.1 ± 12.6	11.5 ± 12.1	.382
MCI, %	35.6	26.5	44.7	< .001	30.9	59.1	< .001	34.2	52.2	.003

nHT, the participants without a history of hypertension whose ages were matched to cHT; cHT, participants with current controlled hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure; NSBP, normal SBP which SBP is greater than 110 mm Hg and less than 140 mm Hg; LSBP, low SBP which SBP is less than or equal to 110 mm Hg; NDBP, normal DBP which DBP is greater than 60 mm Hg and less than 90 mm Hg; LDBP, low DBP which DBP is less than or equal to 60 mm Hg; DM, diabetes mellitus; CVD, cardiovascular disease; WMH, volume of cerebral white matter hyperintensity; MCI, mild cognitive impairment

*Student t test for continuous variables and chi-square test for categorical variables

†Presented as mean ± standard deviation

Table 2. Characteristics of the participants included in the development of the white matter hyperintensity probability map of older Koreans

	Age (years) *							Sex †		
	60 – 64[1]	65 - 69[2]	70 - 74[3]	75 - 79[4]	80 +[5]	*p*§	posthoc	Men	Women	*p* ¶
Age, years	62.0 ± 1.3	67.7 ± 1.2	72.1 ± 1.5	76.6 ± 1.3	83.0 ± 3.1	< .001	1 < 2 < 3 < 4 < 5	72.5 ± 7.8	72.1 ± 7.1	.677
Education, years	12.3 ± 4.7	12.4 ± 3.8	13.8 ± 3.8	12.0 ± 4.2	10.1 ± 5.0	< .001	5 < 3	12.8 ± 4.3	11.4 ± 4.6	.009
MMSE, point	27.6 ± 2.2	27.9 ± 1.5	27.6 ± 1.7	27.2 ± 1.9	26.7 ± 2.1	.004	5 < 2	27.5 ± 1.8	27.3 ± 2.1	.494
FS, score										
PVWMH	0.6 ± 0.5	0.8 ± 0.5	1.0 ± 0.6	1.3 ± 0.7	1.6 ± 0.8	< .001	1 < 3, 4, 5; 2 < 4, 5; 3 < 5	1.1 ± 0.6	1.0 ± 0.8	.575
DWMH	0.5 ± 0.6	0.7 ± 0.6	0.8 ± 0.7	1.1 ± 0.8	1.5 ± 0.9	< .001	1, 2 < 4, 5; 3 < 5	0.9 ± 0.8	1.0 ± 0.8	.348
V_{WMH}, cc	2.5 ± 2.7	4.3 ± 3.2	8.8 ± 11.4	9.8 ± 8.7	16.5 ± 17.1	< .001	1 < 3, 4, 5; 2 < 4, 5; 3, 4 < 5	6.7 ± 8.7	10.1 ± 13.0	.009
P_{WMH}, %	0.6 ± 0.6	1.0 ± 0.8	2.1 ± 2.7	2.4 ± 2.1	4.0 ± 4.1	< .001	1 < 3, 4, 5; 2 < 4, 5; 3, 4 < 5	1.6 ± 2.1	2.4 ± 3.1	.009

All values are presented as mean ± standard deviation

MMSE, Mini Mental Status Exam; FS, Fazekas' scale; PVWMH, periventricular white matter hyperintensity; DWMH, deep white matter hyperintensity; V_{WMH}, total volume of white matter hyperintensity; P_{WMH}, proportion of total white matter hyperintensity in total brain white matter

* Each age group includes 30 men and 30 age-matched women

† Each sex group includes 30 from each age group

§ One-way analysis of variance with Bonferroni posthoc comparisons

¶ Student t-test

Table 3. Baseline demographics and clinical characteristics of the participants who completed two-year follow-up assessment

	All (n = 368)	Hypertension and WMH age group[*]					
		cHTO (n = 76)[1]	cHTNY (n = 125)[2]	nHTO (n = 52)[3]	nHTNY (n = 115)[4]	Statistics[†]	
						p	posthoc
Age, years[§]	73.0 ± 6.5	70.9 ± 4.5	75.1 ± 6.4	69.1 ± 5.2	74.0 ± 7.2	< .001	1, 3 < 2, 4
Women, %	64.9	67.1	65.6	73.1	59.1	.334	-
Education, years[§]	11.4 ± 4.9	10.2 ± 5.6	11.6 ± 4.8	12.1 ± 4.1	11.5 ± 4.8	.123	-
DM, %	18.5	27.6	23.2	9.6	11.3	.005	4 < 1, 3
Hyperlipidemia, %	40.8	47.4	43.2	36.5	35.7	.346	-
Other CVD, %	4.3	5.3	1.6	1.9	7.8	.090	-
Drinking, unit/week[§]	4.3 ± 9.6	4.9 ± 11.0	4.7 ± 9.4	1.5 ± 4.2	4.7 ± 10.4	.174	-
Smoking, pack/day[§]	0.2 ± 0.5	0.2 ± 0.4	0.2 ± 0.5	0.1 ± 0.3	0.3 ± 0.6	.056	-
SBP, mm Hg[§]	128.1 ± 14.8	129.8 ± 17.4	130.9 ± 13.6	124.7 ± 16.0	125.5 ± 13.2	.007	4 < 2
DBP, mm Hg[§]	76.7 ± 9.5	78.3 ± 10.0	76.7 ± 9.5	77.3 ± 9.8	75.2 ± 8.8	.146	-
WMH, cc[§]	10.2 ± 12.5	16.1 ± 15.0	8.0 ± 10.0	14.2 ± 10.2	6.8 ± 12.1	< .001	2, 4 < 1, 3
MCI, %	35.6	64.5	30.4	23.1	27.8	< .001	2, 3, 4 < 1

DM, diabetes mellitus; CVD, cardiovascular disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; WMH, volume of total white matter hyperintensity; MCI, mild cognitive impairment

[*]cHTO, cHTNY, nHTO and nHTNY indicate the participants with current controlled hypertension and estimated WMH age is older, the participants with current controlled hypertension and estimated WMH age is normal or younger, the participants without a history of hypertension and estimated WMH age is older and the participants without a history of hypertension and estimated WMH age is normal or younger, respectively

[†]Oneway analysis of variance for continuous variables and chi-square test for categorical variables with Bonferroni posthoc comparisons

[§]presented as mean ± standard deviation

Table 4. Demographic and clinical characteristics of the participants of different hypertension groups

	nHT[1]	cHT					Statistics		
	(n = 445)	All[2]	SBP		DBP		1 - 2[*]	1 – 3 - 4[†]	1 – 5 – 6 [†]
			NSBP[3]	LSBP[4]	NDBP[5]	LDBP[6]			
		(n = 445)	(n = 382)	(n = 63)	(n = 406)	(n = 39)			
Age, years[§]	73.3 ± 6.3	74.0 ± 5.3	74.0 ± 5.3	74.4 ± 5.3	74.0 ± 5.3	74.6 ± 4.9	.057	.138	.128
Women, %	58.2	62.7	64.1	54.0	63.5	53.8	.170	.121	.194
Education, years[§]	12.1 ± 4.7	11.2 ± 5.0	11.4 ± 5.1	10.4 ± 4.7	11.3 ± 5.0	10.2 ± 5.4	.006	.007 (4 < 1)	.008 (5, 6 < 1)
DM, %	15.3	27.3	25.8	36.5	26.5	35.9	< .001	< .001 (1 < 3, 4)	< .001 (1 < 5, 6)
Hyperlipidemia, %	37.7	52.5	53.5	46.0	53.4	42.1	< .001	< .001 (1 < 3)	< .001 (1 < 5)
Other CVD, %	5.2	3.6	16.4	20.6	16.4	23.1	.252	.005 (1 < 4)	.004 (1 < 6)
Drinking, unit/week[§]	4.0 ± 10.0	5.0 ± 12.3	4.9 ± 11.8	5.2 ± 15.0	5.0 ± 12.6	4.4 ± 8.7	.211	.446	.435
Smoking, pack/day[§]	0.3 ± 0.5	0.3 ± 0.5	0.3 ± 0.5	0.4 ± 0.6	0.3 ± 0.5	0.3 ± 0.6	.528	.254	.584
SBP, mm Hg[§]	121.6 ± 10.0	123.2 ± 9.9	126.1 ± 7.1	105.9 ± 6.1	124.5 ± 8.7	109.7 ± 11.5	.014	< .001 (4 < 1 < 3)	< .001 (6 < 1 < 5)
DBP, mm Hg[§]	73.1 ± 7.5	73.0 ± 7.6	74.5 ± 6.8	64.1 ± 6.3	74.5 ± 6.3	58.1 ± 2.8	.825	< .001 (4 < 1 < 3)	< .001 (6 < 1, 5)
WMH, cc[§]	8.2 ± 10.8	12.2 ± 13.9	11.2 ± 13.4	18.4 ± 15.0	11.9 ± 13.8	15.2 ± 14.6	< .001	< .001 (1 < 3 < 4)	< .001 (1 < 5, 6)
MCI, %	26.5	44.7	36.7	93.7	42.1	71.8	< .001	< .001 (1 < 3 < 4)	< .001 (1 < 5 < 6)

nHT, the participants without a history of hypertension whose ages were matched to cHT; cHT, participants with current controlled hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure; NSBP, normal SBP which SBP is greater than 110 mm Hg and less than 140 mm Hg; LSBP, low SBP which SBP is less than or equal to 110 mm Hg; NDBP, normal DBP which DBP is greater than 60 mm Hg and less than 90 mm Hg; LDBP, low DBP which DBP is less than or equal to 60 mm Hg; DM, diabetes mellitus; CVD, cardiovascular disease; WMH, volume of cerebral white matter hyperintensity; MCI, mild cognitive impairment

[*]Student t test for continuous variables and chi-square test for categorical variables

[†]Oneway analysis of variance for continuous variables and chi-square test for categorical variables with Bonferroni posthoc comparisons in parentheses

[§]Presented as mean ± standard deviation

Table 5. Association of different hypertension groups with cerebral white matter hyperintensity volume and cognitive performance

	nHT[1]	cHT					Statistics		
	(n = 445)	All[2]	SBP		DBP		1 – 2[*]	1 – 3 - 4[†]	1 – 5 – 6 [†]
		(n = 445)	NSBP[3] (n = 382)	LSBP[4] (n = 63)	NDBP[5] (n = 406)	LDBP[6] (n = 39)			
WMH, cc[§]	8.2 ± 10.8	12.2 ± 13.9	11.2 ± 13.4	18.4 ± 15.0	11.9 ± 13.8	15.2 ± 14.6	< .001	< .001 (1 < 3 < 4)	< .001 (1 < 6)
MMSE, point[§]	26.2 ± 3.5	25.6 ± 3.7	26.0 ± 3.5	24.2 ± 6.3	25.8 ± 3.5	23.7 ± 4.8	.044	.043 (4 < 1)	.001 (6 < 1, 5)
CERAD-TS, point[§]	69.0 ± 14.4	65.8 ± 15.7	66.8 ± 15.2	59.7 ± 17.6	66.5 ± 15.3	58.5 ± 18.0	.020	.001 (4 < 1, 3)	.003 (6 < 1, 5)
FAB, point[§]	14.4 ± 3.0	14.0 ± 3.4	14.2 ± 2.9	12.7 ± 3.8	14.1 ± 3.0	12.7 ± 4.0	.278	.011 (4 < 1, 3)	.082

nHT, the participants without a history of hypertension whose ages were matched to cHT; cHT, participants with current controlled hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure; NSBP, normal SBP which SBP is greater than 110 mm Hg and less than 140 mm Hg; LSBP, low SBP which SBP is less than or equal to 110 mm Hg; NDBP, normal DBP which DBP is greater than 60 mm Hg and less than 90 mm Hg; LDBP, low DBP which DBP is less than or equal to 60 mm Hg; MCI, mild cognitive impairment; WMH, white matter hyperintensity volume; MMSE, Mini mental status examination; CERAD-TS, Consortium to Establish a Registry for Alzheimer Disease neuropsychological battery total score; FAB, Frontal assessment battery

[*]Analysis of variance adjusting education, hyperlipidemia, and diabetes mellitus

[†]Analysis of variance adjusting education, hyperlipidemia, diabetes mellitus and other cardiovascular disease with Bonferroni posthoc comparisons in parenthesis

[§]presented as mean ± standard deviation

Table 6. Association of controlled hypertension, current systolic blood pressure, current diastolic blood pressure, and their interactions with the cerebral white matter hyperintensity volume and cognitive performance*

	cHT		LSBP		LDBP		cHT * LSBP		cHT * LDBP		LSBP * LDBP		cHT * LSBP * LDBP	
	F	*p*	F	*p*	F	*p*	F	*p*	F	*p*	F	*p*	F	*p*
WMH	21.674	< .001	5.646	.018	0.656	.618	11.005	.001	2.077	.169	1.752	.186	0.100	.752
MMSE	2.632	.043	7.042	.008	11.426	.001	5.662	.011	0.723	.395	2.411	.121	1.103	.294
CERAD-TS	5.338	.021	7.060	.008	8.981	.003	3.579	.059	0.375	.540	8.557	.004	0.791	.374
FAB	0.856	.355	5.219	.023	5.835	.016	5.556	.009	0.074	.785	0.212	.645	0.238	.636

cHT, controlled hypertension; LSBP, low systolic blood pressure group which systolic blood pressure is less than or equal to 110 mm Hg; LDBP, low diastolic blood pressure group which diastolic blood pressure is less than or equal to 60 mm Hg; WMH, white matter hyperintensity volume; MMSE, Mini mental status examination; CERAD-TS, Consortium to Establish a Registry for Alzheimer Disease neuropsychological battery total score; FAB, Frontal assessment battery

*Analysis of variance adjusting education, diabetes mellitus and hyperlipidemia as covariates

Table 7. Association of systolic blood pressure on the cerebral white matter hyperintensity volume and cognitive performance in the participants with controlled hypertension and those without hypertension

	nHT				cHT			
	NSBP (n = 359)	LSBP (n = 86)	Statistics*		NSBP (n = 382)	LSBP (n = 63)	Statistics	
			F	*p*			F	*p*
WMH, cc	8.3 ± 11.4	7.7 ± 8.0	0.458	.499	11.2 ± 13.4	18.4 ± 15.0	10.771	.001
MMSE, point	26.3 ± 3.2	25.4 ± 4.2	4.618	.032	26.0 ± 3.5	24.2 ± 4.3	4.875	.031
CERAD-TS, point	69.5 ± 14.0	66.9 ± 15.9	0.043	.836	66.8 ± 15.2	59.7 ± 17.6	7.807	.005
FAB, point	14.5 ± 2.9	14.1 ± 3.4	0.451	.502	14.2 ± 2.9	12.7 ± 3.8	8.113	.005

All values are presented as mean ± standard deviation

nHT, the participants without a history of hypertension whose ages were matched to cHT; cHT, participants with current controlled hypertension; NSBP, normal SBP which SBP is greater than 110 mm Hg and less than 140 mm Hg; LSBP, low SBP which SBP is less than or equal to 110 mm Hg; WMH, volume of cerebral white matter hyperintensity; MMSE, Mini mental status examination; CERAD-TS, Consortium to Establish a Registry for Alzheimer Disease neuropsychological battery total score; FAB, Frontal assessment battery

*Analysis of variance adjusting for education, diabetes mellitus, hyperlipidemia and diastolic blood pressure as covariates

Table 8. Distribution of white matter hyperintensity in the white matter hyperintensity probability map

	All	Age groups (years)					Statistics *	
		60–64[1]	65–69[2]	70–74[3]	75–79[4]	80+[5]	*p*	posthoc
Volume (cc)								
WMH								
Whole	8.4 ± 11.2	2.5 ± 2.7	4.3 ± 3.2	8.8 ± 11.4	9.8 ± 8.7	16.5 ± 17.1	< 0.001	1 < 3, 4, 5; 2 < 4, 5; 3, 4 < 5
Left	4.0 ± 5.4	1.1 ± 1.2	2.0 ± 1.5	4.3 ± 5.5	4.5 ± 4.1	8.0 ± 8.1	< 0.001	1 < 3, 4, 5; 2 < 4, 5; 3, 4 < 5
Right	4.4 ± 5.9	1.4 ± 1.6	2.2 ± 1.8	4.5 ± 5.9	5.3 ± 4.8	8.6 ± 9.1	< 0.001	1 < 3, 4, 5; 2 < 4, 5; 3, 4 < 5
Anterior	4.1 ± 5.4	1.2 ± 1.4	2.1 ± 1.7	4.1 ± 5.1	4.7 ± 4.2	8.2 ± 8.1	< 0.001	1 < 3, 4, 5; 2 < 4, 5; 3, 4 < 5
Posterior	4.3 ± 6.3	1.3 ± 1.5	2.2 ± 1.8	4.7 ± 6.6	5.1 ± 5.0	8.3 ± 9.7	< 0.001	1 < 3, 4, 5; 2, 3, 4 < 5
L/R ratio	0.9 ± 0.4	0.9 ± 0.5	1.0 ± 0.5	1.0 ± 0.3	0.9 ± 0.4	1.0 ± 0.3	0.691	-
A/P ratio	1.1 ± 0.6	1.1 ± 0.6	1.0 ± 0.5	1.1 ± 0.6	1.1± 0.6	1.2 ± 0.6	0.714	-
PVWMH								
Whole	7.4 ± 10.1 †	2.4 ± 2.5 †	3.8 ± 2.7 †	7.9 ± 10.6 †	8.6 ± 7.6 †	14.4 ± 15.6 †	< 0.001	1 < 3, 4, 5; 2 < 4, 5; 3, 4 < 5
Left	3.5 ± 4.8	1.0 ± 1.1	1.8 ± 1.3	3.8 ± 5.1	3.9 ± 3.5	6.9 ± 7.4	< 0.001	1 < 3, 4, 5; 2, 3, 4 < 5
Right	3.9 ± 5.4	1.3 ± 1.6	2.0 ± 1.5	4.4 ± 5.5	4.7 ± 4.2	7.5 ± 8.4	< 0.001	1 < 3, 4, 5; 2 < 4, 5; 3, 4 < 5
Anterior	3.6 ± 4.8	1.1 ± 1.3	1.9 ± 1.5	3.7 ± 4.7	4.2 ± 3.7	7.1 ± 7.4	< 0.001	1 < 3, 4, 5; 2 < 4, 5; 3, 4 < 5
Posterior	3.8 ± 5.7	1.2 ± 1.5	2.0 ± 1.6	4.2 ± 6.1	4.4 ± 4.3	7.3 ± 8.9	< 0.001	1 < 3, 4, 5; 2, 3, 4 < 5
L/R ratio	0.9 ± 0.4	0.9 ± 0.6	1.0 ± 0.5	1.0 ± 0.4	0.9 ± 0.4	1.0 ± 0.3	0.844	-
A/P ratio	1.0 ± 0.6	1.0 ± 0.7	1.0 ± 0.7	1.0± 0.7	1.1 ± 0.7	1.0± 0.7	0.871	-
DWMH								
Whole	1.0 ± 1.5	0.1 ± 0.3	0.4 ± 0.8	1.0 ± 1.1	1.2 ± 2.0	2.1 ± 1.9	< 0.001	1 < 3, 4, 5; 2 < 4, 5; 3, 4 < 5
Left	0.5 ± 0.8	0.0 ± 0.1	0.2 ± 0.4	0.5 ± 0.6	0.6 ± 1.1	1.0 ± 1.0	< 0.001	1 < 3, 4, 5; 2, 3, 4 < 5
Right	0.5 ± 0.8	0.0 ± 0.2	0.2 ± 0.4	0.5 ± 0.6	0.6 ± 0.9	1.1 ± 1.0	< 0.001	1 < 3, 4, 5; 2 < 4, 5; 3, 4 < 5
Anterior	0.5 ± 0.7	0.0 ± 0.1	0.2 ± 0.5	0.4 ± 0.5	0.5 ± 0.8	1.1 ± 1.1	< 0.001	1 < 3, 4, 5; 2, 3, 4 < 5
Posterior	0.5 ± 0.9	0.0 ± 0.2	0.2 ± 0.4	0.5 ± 0.7	0.6 ± 1.2	1.0 ± 1.1	< 0.001	1 < 3, 4, 5; 2 < 4, 5; 3, 4 < 5
L/R ratio	1.0 ± 0.4	1.0 ± 0.5	0.9 ± 0.4	1.0 ± 0.4	0.9 ± 0.3	1.0 ± 0.4	0.888	-
A/P ratio	1.1 ± 0.5	1.0 ± 0.6	1.1 ± 0.4	1.1 ± 0.6	1.0 ± 0.5	1.1 ± 0.6	0.739	-
Proportion (%)								
WMH								

Whole	2.0 ± 2.7	0.6 ± 0.6	1.0 ± 0.8	2.1 ± 2.7	2.4 ± 2.1	4.0 ± 4.1	< 0.001	1 < 3, 4, 5; 2 < 4, 5; 3, 4 < 5
Left	1.9 ± 2.6	0.5 ± 0.6	1.0 ± 0.7	2.0 ± 2.6	2.1 ± 2.0	3.8 ± 3.9	< 0.001	1 < 3, 4, 5; 2, 3, 4 < 5
Right	2.1 ± 2.9	0.7 ± 0.8	1.1 ± 0.9	2.2 ± 2.9	2.6 ± 2.3	4.2 ± 4.4	< 0.001	1 < 3, 4, 5; 2 > 4, 5; 3, 4 < 5
Anterior	2.2 ± 2.9	0.6 ± 0.7	1.1 ± 0.9	2.2 ± 2.8	2.6 ± 2.3	4.5 ± 4.4	< 0.001	1 < 3, 4, 5; 2 > 4, 5; 3, 4 < 5
Posterior	1.9 ± 2.7	0.6 ± 0.7	0.9 ± 0.8	2.0 ± 2.9	2.2 ± 2.2	3.6 ± 4.2	< 0.001	1 < 3, 4, 5; 2, 3, 4 < 5
L/R ratio	0.9 ± 0.4	0.9 ± 0.5	1.0 ± 0.5	1.0 ± 0.3	0.9 ± 0.4	1.0 ± 0.3	0.691	-
A/P ratio	1.2 ± 0.6	1.2 ± 0.7	1.2 ± 0.6	1.2 ± 0.6	1.2 ± 0.6	1.2 ± 0.5	0.980	-
PVWMH								
Whole	1.8 ± 2.4 †	0.6 ± 0.6 †	0.9 ± 0.7 †	1.9 ± 2.5 †	2.1 ± 1.8 †	3.5 ± 3.8 †	< 0.001	1 < 3, 4, 5; 2 < 4, 5; 3, 4 < 5
Left	1.7 ± 2.3	0.5 ± 0.5	0.9 ± 0.6	1.8 ± 2.4	1.9 ± 1.7	3.2 ± 3.5	< 0.001	1 < 3, 4, 5; 2, 3, 4 < 5
Right	1.9 ± 2.6	0.6 ± 0.8	1.0 ± 0.8	2.0 ± 2.7	2.3 ± 2.1	3.6 ± 4.1	< 0.001	1 < 3, 4, 5; 2 < 4, 5; 3, 4 < 5
Anterior	2.0 ± 2.6	0.6 ± 0.7	1.0 ± 0.8	2.0 ± 2.6	2.3 ± 2.0	3.9 ± 4.0	< 0.001	1 < 3, 4, 5; 2 < 4, 5; 3, 4 < 5
Posterior	1.6 ± 2.5	0.5 ± 0.6	0.8 ± 0.7	1.8 ± 2.7	1.9 ± 1.9	3.1 ± 3.9	< 0.001	1 < 3, 4, 5; 2, 3, 4 < 5
L/R ratio	0.9 ± 0.4	0.9 ± 0.5	1.0 ± 0.5	1.0 ± 0.3	0.9 ± 0.4	0.9 ± 0.3	0.706	-
A/P ratio	1.2 ± 0.6	1.2 ± 0.7	1.2 ± 0.6	1.1 ± 0.5	1.2 ± 0.6	1.2 ± 0.5	0.992	-
DWMH								
Whole	0.4 ± 0.4	0.0 ± 0.1	0.1 ± 0.2	0.2 ± 0.3	0.3 ± 0.5	0.5 ± 0.5	< 0.001	1 < 3, 4, 5; 2 < 4, 5; 3, 4 < 5
Left	0.5 ± 0.7	0.0 ± 0.1	0.2 ± 0.4	0.5 ± 0.5	0.6 ± 0.9	1.0 ± 0.9	< 0.001	1 < 3, 4, 5; 2 < 4, 5; 3, 4 < 5
Right	0.5 ± 0.7	0.1 ± 0.2	0.2 ± 0.4	0.5 ± 0.6	0.6 ± 1.0	1.0 ± 0.9	< 0.001	1 < 3, 4, 5; 2 < 4, 5; 3, 4 < 5
Anterior	0.5 ± 0.8	0.1 ± 0.2	0.2 ± 0.4	0.5 ± 0.6	0.6 ± 1.1	1.1 ± 1.1	< 0.001	1 < 3, 4, 5; 2 < 4, 5; 3, 4 < 5
Posterior	0.4 ± 0.7	0.1 ± 0.1	0.2 ± 0.3	0.4 ± 0.5	0.5 ± 0.9	0.9 ± 0.8	< 0.001	1 < 3, 4, 5; 2 < 4, 5; 3, 4 < 5
L/R ratio	1.0 ± 0.0	1.0 ± 0.0	1.0 ± 0.0	1.0 ± 0.0	1.0 ± 0.0	1.0 ± 0.0	0.564	-
A/P ratio	1.2 ± 0.0	1.2 ± 0.0	1.2 ± 0.0	1.2 ± 0.0	1.2 ± 0.0	1.2 ± 0.0	0.405	-

All values are presented as mean ± standard deviation

WMH, white matter hyperintensity; PVWMH, periventricular white matter hyperintensity; DWMH, deep white matter hyperintensity; Left, left hemisphere; Right, right hemisphere; Anterior, anterior region; Posterior, posterior region; L/R ratio, ratio between left and right hemispheres; A/P ratio, ratio between anterior and posterior regions

* One-way analysis of variance with Bonferroni posthoc comparisons

† $p < 0.001$, compared to the volume or proportion of DWMH by Student t-tests

Table 9. Demographics and clinical characteristics of the participants included in the validation of the white matter hyperintensity probability map for older Koreans

	All (n = 890)	Estimated white matter hyperintensity age*			Statistics†	
		Normal (n = 249)[1]	Younger (n = 321)[2]	Older (n = 320)[3]	*p*	posthoc
Age, years§	73.6 ± 5.8	73.9 ± 6.9	75.2 ± 5.7	71.9 ± 4.4	< .001	3 < 1 < 2
Women, %	60.4	60.2	36.4	57.5	.292	-
Education, years§	11.7 ± 4.9	11.6 ± 4.7	12.1 ± 4.6	11.3 ± 5.2	.069	-
Hypertension, %	50.0	46.2	46.4	56.6	.013	1, 2 < 3
DM, %	21.3	21.8	14.7	27.6	< .001	2 < 3
Hyperlipidemia, %	45.1	38.6	47.5	47.8	.056	-
Other CVD, %	13.4	13.4	14.8	12.0	.595	-
Drinking, unit/week§	4.5 ± 11.2	4.7 ± 11.3	4.1 ± 10.1	4.7 ± 12.2	.736	-
Smoking, pack/day§	0.3 ± 0.5	0.3 ± 0.6	0.3 ± 0.5	0.3 ± 0.5	.770	-
SBP, mm Hg§	122.4 ± 10.0	122.0 ± 11.0	123.3 ± 8.6	120.7 ± 10.1	.152	-
DBP, mm Hg§	73.1 ± 7.6	72.9 ± 7.9	73.7 ± 7.2	72.6 ± 7.6	.213	-
WMH, cc§	10.2 ± 12.6	11.1 ± 13.9	3.4 ± 5.0	16.2 ± 13.5	< .001	2 < 1 < 3
MCI, %	35.6	36.5	22.7	47.8	< .001	2 < 1 < 3

DM, diabetes mellitus; CVD, cardiovascular disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; WMH, volume of cerebral white matter hyperintensity; MCI, mild cognitive impairment

*Estimated using the white matter hyperintensity probability map for older Koreans. Normal indicates the participants whose estimated white matter hyperintensity ages are equal to their chronological ages, younger indicates those whose estimated white matter hyperintensity ages are younger than their chronological ages, and older indicates those whose estimated white matter hyperintensity ages are older than their chronological ages

†Oneway analysis of variance for continuous variables and chi-square test for categorical variables with Bonferroni posthoc comparisons

§presented as mean ± standard deviation

Table 10. Association of controlled hypertension, current systolic blood pressure, current diastolic blood pressure, and their interactions with the older white matter hyperintensity age

	F*	*p**
cHT	9.835	.002
LSBP	8.944	.003
LDBP	6.231	.013
cHT * LSBP	7.965	.005
cHT * LDBP	4.971	.026
LSBP * LDBP	0.218	.641
cHT * LSBP * LDBP	6.684	.010

cHT, participants with controlled hypertension; LSBP, low SBP which SBP is less than or equal to 110 mm Hg; LDBP, low DBP which DBP is less than or equal to 60 mm Hg

*Analysis of variance adjusting for education, diabetes mellitus and hyperlipidemia as covariates

Table 11. Association of estimated white matter hyperintensity age with cognitive performance

	Normal* (n = 249)[1]	Younger* (n = 321)[2]	Older* (n = 320)[3]	*p*†	posthoc†
MMSE, point	25.5 ± 3.5	26.5 ± 3.1	25.4 ± 3.9	< .001	1, 3 < 2
CERAD-TS, point	66.0 ± 15.5	70.9 ± 13.2	64.9 ± 16.3	< .001	1, 3 < 2
FAB, point	14.0 ± 3.1	14.7 ± 2.6	13.9 ± 3.4	< .001	1, 3 < 2

All values are presented as mean ± standard deviation

MMSE, Mini mental status examination; CERAD-TS, Consortium to Establish a Registry for Alzheimer Disease neuropsychological battery total score; FAB, Frontal assessment battery

*Estimated using the white matter hyperintensity probability map for older Koreans. Normal indicates the participants whose estimated white matter hyperintensity ages are equal to their chronological ages, younger indicates those whose estimated white matter hyperintensity ages are younger than their chronological ages, and older indicates those whose estimated white matter hyperintensity ages are older than their chronological ages

†Analysis of variance adjusted for chronological age, hypertension and diabetes mellitus with Bonferroni posthoc comparisons

Table 12. Impact of hypertension and estimated-white matter hyperintensity age groups on the cognitive performance from baseline over 2 years

	Hypertension and estimated WMH group*				Statistics†			
	cHTO (n = 76) [1]	cHTNY (n = 125) [2]	nHTO (n = 52) [3]	nHTNY (n = 115) [4]	Group	Time	Group*Time	posthoc
MMSE, point					.004	< .001	.024	2, 4 < 1
Baseline	25.6 ± 3.7	25.9 ± 2.9	26.7 ± 2.8	26.2 ± 3.2				
2-year follow-up	24.1 ± 4.2	25.0 ± 4.4	25.8 ± 4.4	25.4 ± 3.5				
CERAD-TS, point					.002	< .001	< .001	4 < 1
Baseline	66.3 ± 12.9	64.5 ± 14.7	67.5 ± 14.2	67.6 ± 14.3				
2-year follow-up	60.6 ± 14.2	61.8 ± 16.8	68.0 ± 18.1	67.1 ± 14.5				
FAB, point					.009	.115	.015	4 < 1
Baseline	13.9 ± 3.1	14.1 ± 2.6	14.4 ± 2.8	14.2 ± 2.8				
2-year follow-up	13.1 ± 3.3	13.7 ± 3.1	14.3 ± 3.3	14.3 ± 2.7				

All values are presented as mean ± standard deviation

MMSE, Mini mental status examination; CERAD-TS, Consortium to Establish a Registry for Alzheimer Disease neuropsychological battery total score; FAB, Frontal assessment battery

* cHTO, cHTNY, nHTO and nHTNY indicate the participants with current controlled hypertension and estimated WMH age is older, the participants with current controlled hypertension and estimated WMH age is normal or younger, the participants without a history of hypertension and estimated WMH age is older and the participants without a history of hypertension and estimated WMH age is normal or younger, respectively

†Repeated measure analysis of variance adjusted for chronological age and diabetes mellitus with Bonferroni posthoc comparisons

Table 13. Impact of hypertension and estimated-white matter hyperintensity age groups on the risk of incidence of mild cognitive impairment over 2 years

	OR (95% CI) [†]	*p*[†]
nHTNY [*]	1.00	-
nHTO[*]	0.71 (0.07 – 6.82)	0.763
cHTNY[*]	1.21 (0.32 – 4.66)	0.779
cHTO[*]	8.23 (2.41 – 28.09)	0.001

OR, odds ratio; CI, confidence interval

[*] nHTNY, nHTO, cHTNY and cHTO indicate the participants without a history of hypertension and estimated WMH age is normal or younger, the participants without a history of hypertension and estimated WMH age is older, the participants with current controlled hypertension and estimated WMH age is normal or younger and the participants with current controlled hypertension and estimated WMH age is older, respectively.

[†] Logistic regression model adjusting for chronological age and diabetes mellitus

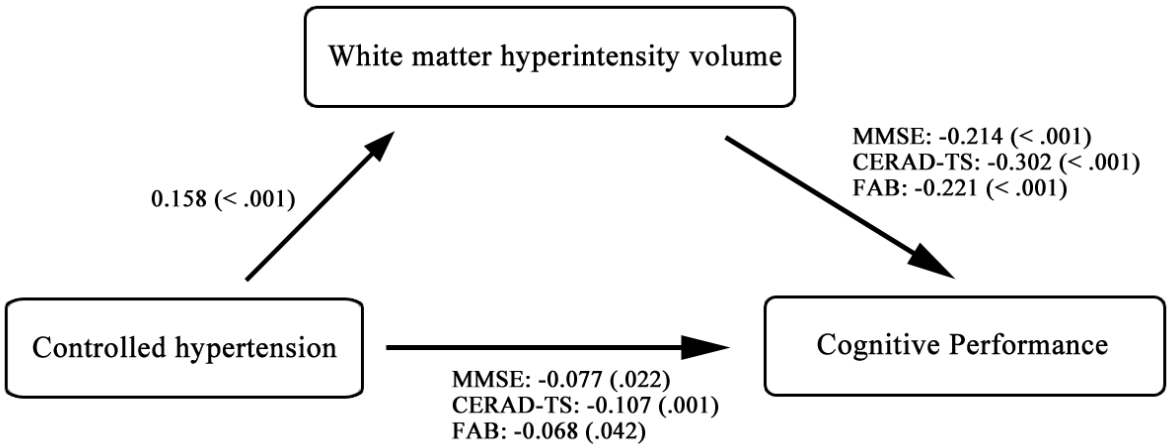


Figure 1. Mediation of cerebral white matter hyperintensity volume on the effect of controlled hypertension on the cognitive performance

MMSE, Mini Mental Status Examination; CERAD-TS, Consortium to Establish a Registry for Alzheimer Disease neuropsychological battery total score; FAB, Frontal Assessment Battery

All values are presented as standardized regression coefficients and *p*-values in parentheses

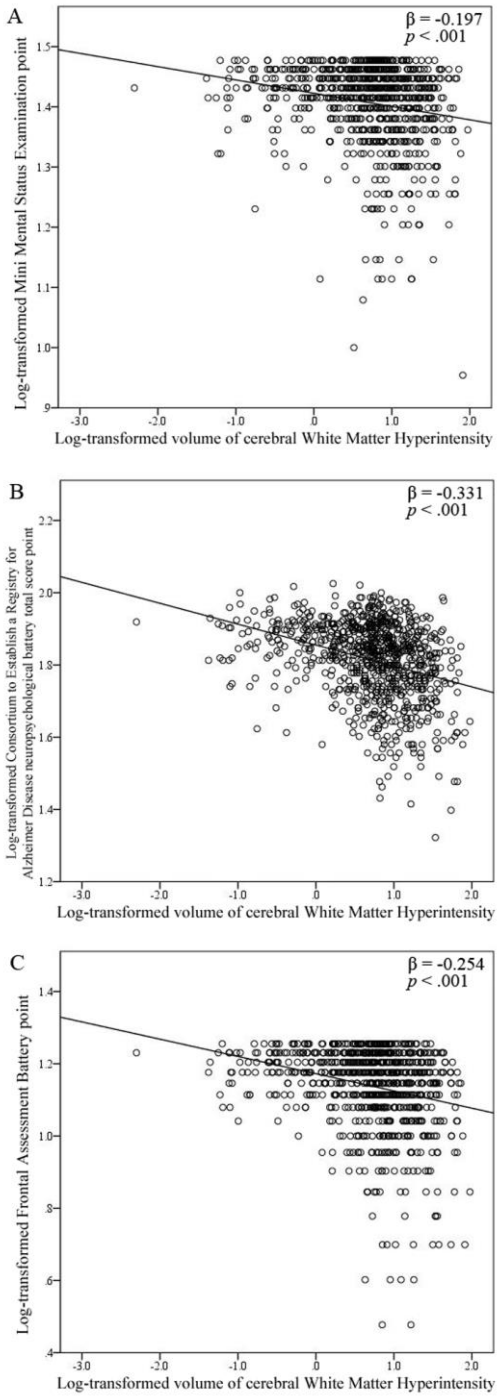


Figure 2. Association of log-transformed volume of cerebral white matter hyperintensity with log-transformed cognitive test points in participants with controlled hypertension using linear regression analysis adjusting education, diabetes mellitus and hyperlipidemia as covariates. A, Mini Mental Status Examination; B, Consortium to Establish a Registry for Alzheimer Disease neuropsychological battery total score; C, Frontal Assessment Battery

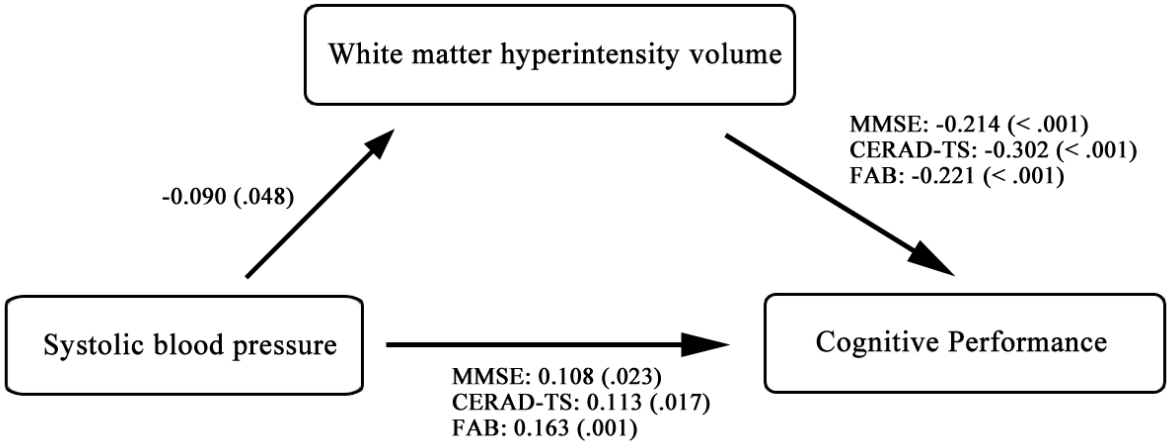


Figure 3. Mediation of cerebral white matter hyperintensity volume on the effect of systolic blood pressure on the cognitive performance in the participants with controlled hypertension

MMSE, Mini Mental Status Examination; CERAD-TS, Consortium to Establish a Registry for Alzheimer Disease neuropsychological battery total score; FAB, Frontal Assessment Battery

All values are presented as standardized regression coefficients and *p*-values in parentheses.

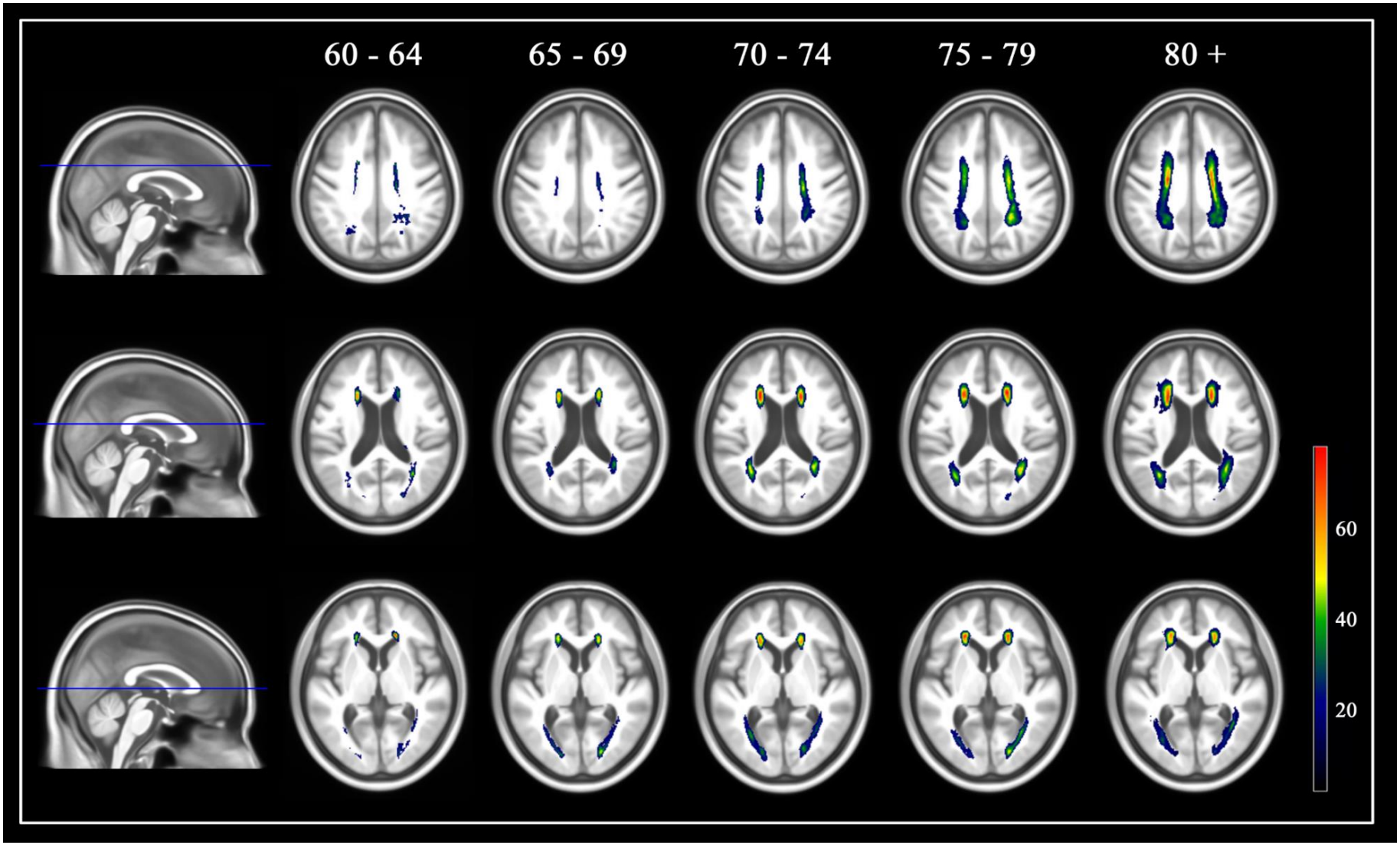


Figure 4. White matter hyperintensity probability maps of the levels of centrum semiovale, corona radiata, and striatocapsular region

Supplementary table 1. Association of controlled hypertension with cognitive performance

	nHT[1]	cHT					Statistics		
	(n = 445)	All[2]	SBP		DBP		1 – 2[*]	1 – 3 - 4[†]	1 – 5 – 6 [†]
			NSBP[3]	LSBP[4]	NDBP[5]	LDBP[6]			
		(n = 445)	(n = 382)	(n = 63)	(n = 406)	(n = 39)			
MCI, %	26.5	44.7	36.6	93.7	42.1	61.8	< .001	< .001 (1 < 3 < 4)	.007 (1 < 5 < 6)
VFT, point[§]	15.7 ± 5.4	14.6 ± 5.5	14.9 ± 5.4	13.1 ± 5.7	14.8 ± 5.5	13.1 ± 5.5	.034	.023 (4 < 1)	.060
BNT, point[§]	13.4 ± 1.9	13.0 ± 2.3	13.2 ± 2.2	12.1 ± 2.9	13.1 ± 2.2	11.7 ± 2.9	.008	< .001 (4 < 1, 3)	< .001 (6 < 1, 5)
MMSE, point[§]	26.2 ± 3.5	25.6 ± 3.7	25.8 ± 3.5	24.6 ± 6.3	25.8 ± 3.5	23.7 ± 4.8	.044	.043 (4 < 1)	.001 (6 < 1, 5)
WLMT, point[§]	16.8 ± 4.9	16.0 ± 5.2	16.3 ± 5.0	14.1 ± 5.8	16.3 ± 5.0	13.5 ± 5.8	.108	.011 (4 < 1, 3)	.005 (6 < 1, 5)
WLRT, point[§]	5.0 ± 2.5	4.5 ± 2.8	4.5 ± 2.8	4.0 ± 2.5	4.5 ± 2.7	3.9 ± 2.9	.011	.033 (4 < 1)	.053
WLRcT, point[§]	8.2 ± 2.2	7.9 ± 2.4	8.1 ± 2.3	7.1 ± 2.6	8.0 ± 2.3	7.1 ± 2.7	.093	.009 (4 < 1, 3)	.081
CPT, point[§]	10.0 ± 1.4	9.8 ± 1.5	9.9 ± 1.5	9.2 ± 1.9	9.8 ± 1.5	9.2 ± 2.0	.094	.012 (4 < 1, 3)	.020 (6 < 1)
CRT, point[§]	5.8 ± 3.2	5.6 ± 3.4	5.6 ± 3.5	5.3 ± 3.4	5.7 ± 3.4	4.2 ± 3.2	.725	.945	.116
TMT-A, second[§]	62.6 ± 51.9	71.1 ± 54.9	70.3 ± 55.7	76.3 ± 50.0	68.7 ± 50.4	76.0 ± 86.2	.230	.492	.115
TMT-B, second[§]	186.6 ± 106.0	208.4 ± 104.7	201.8 ± 103.6	248.4 ± 103.6	204.2 ± 103.6	252.6 ± 108.1	.068	.016 (1 < 4)	.025 (1 < 6)
DST, point[§]	11.7 ± 4.3	10.6 ± 4.0	10.8 ± 4.0	9.5 ± 3.8	10.7 ± 3.9	9.9 ± 4.4	.005	.010 (4 < 1)	.073
FAB, point[§]	14.4 ± 3.0	14.0 ± 3.4	14.2 ± 2.9	12.7 ± 3.8	14.1 ± 3.0	12.7 ± 4.0	.278	.011 (4 < 1, 3)	.082
VM, point[§]	18.8 ± 5.5	17.7 ± 6.2	18.0 ± 6.1	15.9 ± 6.6	17.9 ± 6.1	15.5 ± 7.0	.032	.011 (4 < 1)	.019 (6 < 1)

nHT, the participants without a history of hypertension whose ages were matched to cHT; cHT, participants with current controlled hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure; NSBP, normal SBP which SBP is greater than 110 mm Hg and less than 140 mm Hg; LSBP, low SBP which SBP is less than or equal to 110 mm Hg; NDBP, normal DBP which DBP is greater than 60 mm Hg and less than 90 mm Hg; LDBP, low DBP which DBP is less than or equal to 60 mm Hg; MCI, mild cognitive impairment; VFT, Verbal fluency test; BNT, Boston naming test; MMSE, Mini mental status examination; WLMT, Word list memory test; WLRT, Word list recall test; WLRcT, Word list recognition test; CPT, Constructional praxis test; CRT, Constructional recall test; TMT-A, Trail making test A; TMT-B, Trail making test B; DST, Digit span test; FAB, Frontal assessment battery; VM, Verbal Memory

[*]Analysis of variance adjusting education, hyperlipidemia, diabetes mellitus, other cardiac diseases and systolic blood pressure

[†]Analysis of variance adjusting education, hyperlipidemia, diabetes mellitus and other cardiac diseases with Bonferroni posthoc comparisons in parenthesis

[§]presented as mean ± standard deviation

Supplementary table 2. Association of estimated white matter hyperintensity age with cognitive performance

	Normal [1*] (n = 249)	Younger [2*] (n = 321)	Older [3*] (n = 320)	$p^{\dagger}$	posthoc[†]
MCI, %	36.5	22.7	47.8	< .001	2 < 1 < 3
VFT, point[§]	14.6 ± 5.6	16.2 ± 5.3	14.4 ± 5.5	< .001	1, 3 < 2
BNT, point[§]	12.9 ± 2.2	13.7 ± 1.8	12.9 ± 2.4	< .001	1, 3 < 2
MMSE, point[§]	25.5 ± 3.5	26.7 ± 3.1	25.3 ± 3.9	< .001	1, 3 < 2
WLMT, point[§]	15.8 ± 5.3	17.9 ± 4.6	15.3 ± 5.0	< .001	1, 3 < 2
WLRT, point[§]	4.2 ± 2.8	5.6 ± 2.4	4.2 ± 2.6	< .001	1, 3 < 2
WLRcT, point[§]	7.6 ± 2.7	8.6 ± 2.4	7.8 ± 2.6	< .001	1, 3 < 2
CPT, point[§]	9.9 ± 1.4	10.2 ± 1.3	9.7 ± 1.6	< .001	3 < 2
CRT, point[§]	5.5 ± 3.4	6.5 ± 3.1	5.0 ± 3.4	< .001	1, 3 < 2
TMT-A, point[§]	70.0 ± 55.5	57.4 ± 44.3	74.1 ± 59.7	< .001	2 < 1, 3
TMT-B, point[§]	208.9 ± 110.6	176.0 ± 101.2	210.6 ± 105.2	< .001	2 < 1, 3
DST, point[§]	10.7 ± 4.3	11.8 ± 3.6	10.8 ± 4.6	.002	1, 3 < 2
FAB, point[§]	14.0 ± 3.1	14.8 ± 2.6	13.7 ± 3.4	< .001	1, 3 < 2
VM, point[§]	17.1 ± 6.6	19.7 ± 5.0	17.7 ± 5.7	< .001	1, 3 < 2

MCI, Mild cognitive impairment; VFT, Verbal fluency test; BNT, Boston naming test; MMSE, Mini mental status examination; WLMT, Word list memory test; WLRT, Word list recall test; WLRcT, Word list recognition test; CPT, Constructional praxis test; CRT, Constructional recall test; TMT-A, Trail making test A; TMT-B, Trail making test B; DST, Digit span test; FAB, Frontal assessment battery; VM, Verbal Memory

[*]Estimated using the white matter hyperintensity probability map for older Koreans. Normal indicates the participants whose estimated white matter hyperintensity ages are equal to their chronological ages, younger indicates those whose estimated white matter hyperintensity ages are younger than their chronological ages, and older indicates those whose estimated white matter hyperintensity ages are older than their chronological ages.

[†]Analysis of variance adjusted for chronological age, hypertension and diabetes mellitus with Bonferroni posthoc comparisons

[§]presented as mean ± standard deviation

Supplementary table 3. Impact of hypertension and estimated-white matter hyperintensity age groups on the cognitive performance from baseline over 2 years

	Hypertension and estimated WMH group*				Statistics†			
	cHTO (n = 76) [1]	cHTNY (n = 125) [2]	nHTO (n = 52) [3]	nHTNY (n = 115) [4]	Group	Time	Group*Time	posthoc
VFT, point					< .001	.023	.027	4 < 1
Baseline	14.2 ± 4.7	14.2 ± 5.1	14.6 ± 5.2	15.3 ± 5.5				
2-year follow-up	12.2 ± 5.1	13.1 ± 5.6	14.3 ± 6.1	14.8 ± 5.3				
BNT, point					.021	.145	.050	4 < 1
Baseline	13.1 ± 2.0	13.0 ± 1.7	13.2 ± 1.9	13.3 ± 1.9				
2-year follow-up	12.7 ± 2.2	13.0 ± 2.0	13.2 ± 2.3	13.3 ± 1.8				
MMSE, point					.004	< .001	.024	2, 4 < 1
Baseline	25.6 ± 3.7	25.9 ± 2.9	26.7 ± 2.8	26.2 ± 3.2				
2-year follow-up	24.1 ± 4.2	25.0 ± 4.4	25.8 ± 4.4	25.4 ± 3.5				
WLMT, point					.111	< .001	< .001	-
Baseline	16.5 ± 4.4	15.5 ± 5.0	16.5 ± 4.8	16.2 ± 5.1				
2-year follow-up	14.9 ± 4.3	15.0 ± 5.3	17.1 ± 5.9	16.4 ± 4.8				
WLRT, point					.015	< .001	.002	4 < 1
Baseline	4.6 ± 2.5	4.0 ± 2.7	4.6 ± 2.6	4.8 ± 2.5				
2-year follow-up	3.9 ± 2.6	3.8 ± 2.9	5.1 ± 3.1	4.8 ± 2.6				
WLRcT, point					.701	< .001	.033	-
Baseline	8.2 ± 1.9	7.7 ± 2.7	7.9 ± 2.4	7.9 ± 2.4				
2-year follow-up	7.8 ± 2.4	7.1 ± 3.0	8.0 ± 2.6	7.8 ± 2.5				
CPT, point					.005	.291	.044	2, 4 < 1
Baseline	9.7 ± 1.6	10.0 ± 1.5	10.3 ± 0.9	10.0 ± 1.3				
2-year follow-up	9.1 ± 2.1	9.8 ± 1.7	9.9 ± 1.3	9.8 ± 1.5				

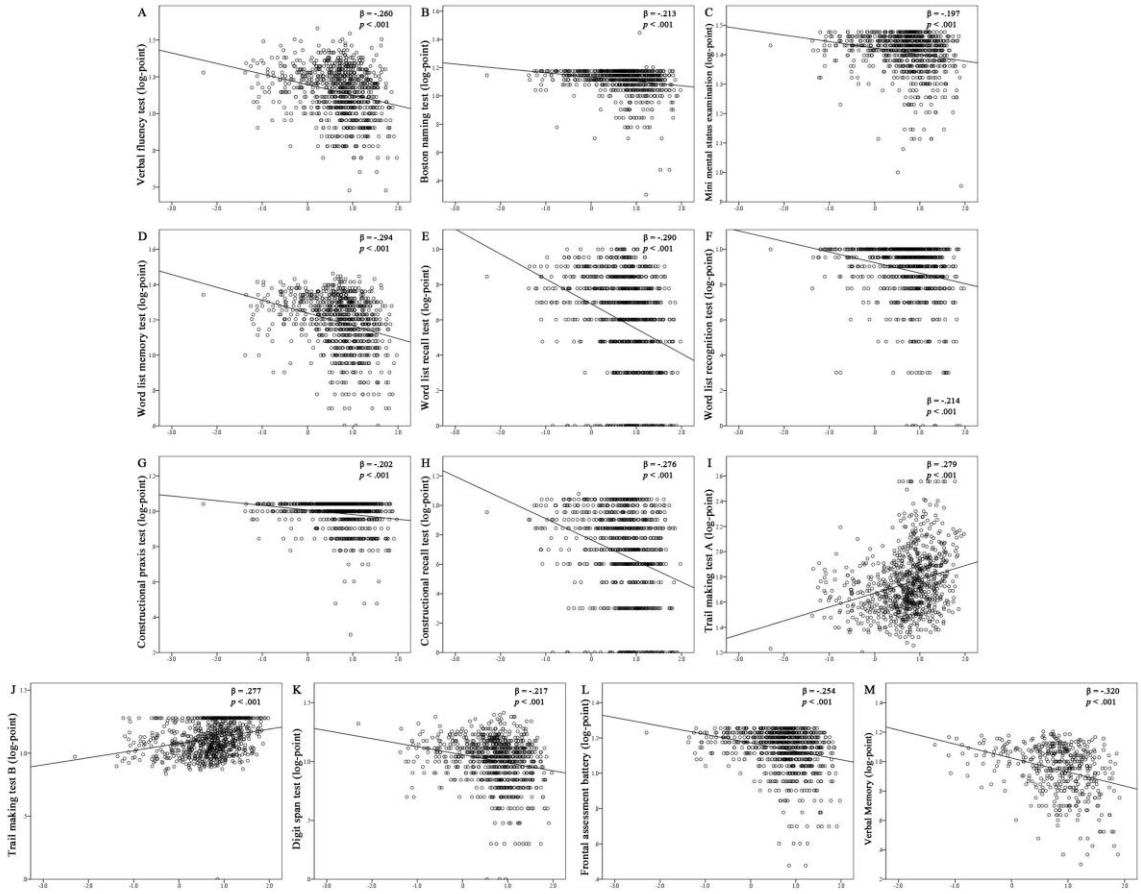
CRT, point					.047	.889	.166	-
Baseline	5.4 ± 3.5	5.2 ± 3.3	5.6 ± 3.6	5.6 ± 3.3				
2-year follow-up	4.8 ± 3.2	4.7 ± 3.7	5.7 ± 3.5	5.6 ± 3.1				
TMT-A, second					.377	.198	.400	-
Baseline	63.2 ± 42.3	73.3 ± 56.8	52.3 ± 24.6	66.2 ± 48.8				
2-year follow-up	74.5 ± 58.4	78.3 ± 67.0	52.5 ± 23.1	69.1 ± 56.9				
TMT-B, second					.046	.971	.487	-
Baseline	195.8 ± 105.4	202.3 ± 103.9	186.9 ± 104.4	187.9 ± 104.4				
2-year follow-up	210.7 ± 105.3	213.8 ± 107.9	187.4 ± 101.0	192.0 ± 103.5				
DST, point					.013	.341	.019	4 < 1
Baseline	10.9 ± 1.2	10.6 ± 3.8	12.2 ± 4.7	11.5 ± 3.5				
2-year follow-up	9.6 ± 3.7	10.0 ± 3.8	11.5 ± 4.2	11.2 ± 3.4				
FAB, point					.009	.115	.015	4 < 1
Baseline	13.9 ± 3.1	14.1 ± 2.6	14.4 ± 2.8	14.2 ± 2.8				
2-year follow-up	13.1 ± 3.3	13.7 ± 3.1	14.3 ± 3.3	14.3 ± 2.7				
VM, point					.092	< .001	< .001	-
Baseline	18.2 ± 5.4	16.8 ± 6.4	18.3 ± 5.8	18.1 ± 5.7				
2-year follow-up	16.7 ± 5.6	15.8 ± 7.0	19.1 ± 7.0	18.1 ± 5.8				

All values are presented as mean ± standard deviation

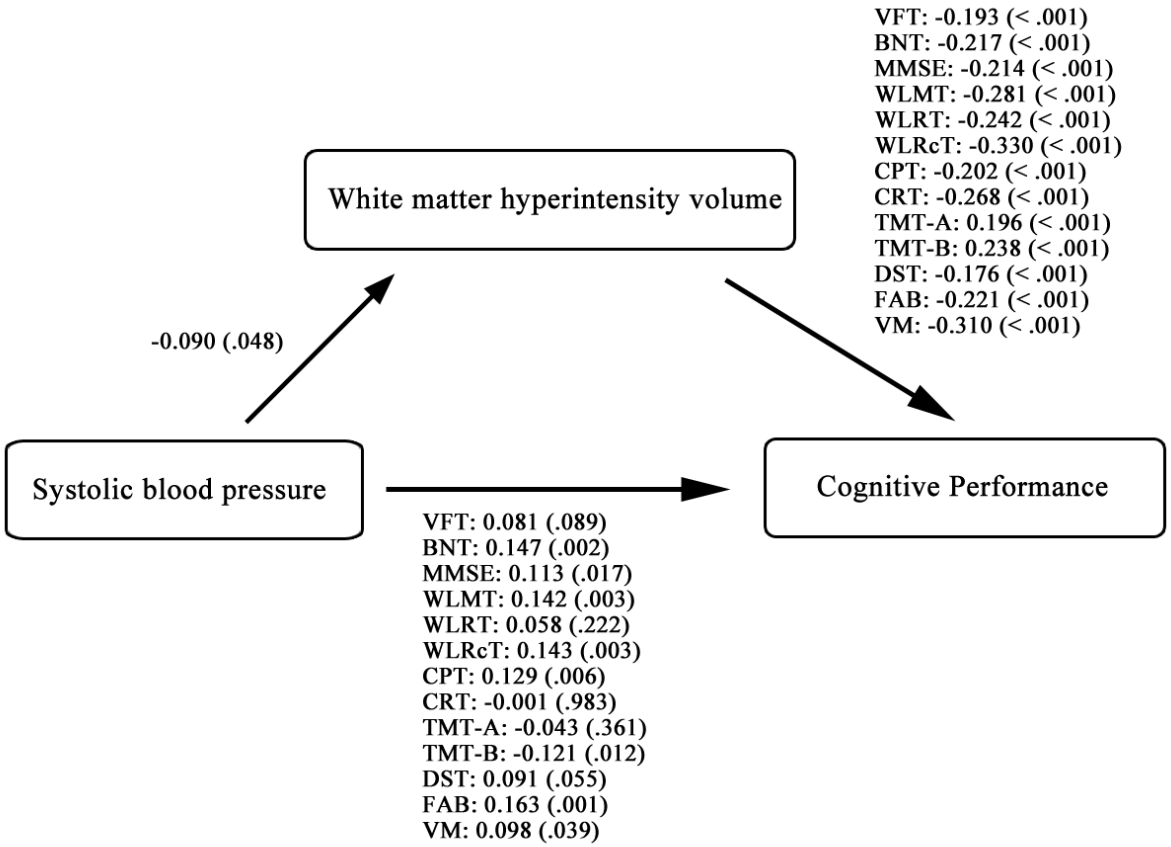
VFT, Verbal Fluency Test; BNT, Boston Naming Test; MMSE, Mini Mental Status Examination; WLMT, Word List Memory Test; WLRT, Word List Recall Test; WLRcT, Word List Recognition Test; CPT, Constructional Praxis Test; CRT, Constructional Recall Test; TMT-A, Trail Making Test A; TMT-B, Trail Making Test B; DST, Digit Span Test; FAB, Frontal Assessment Battery; VM, Verbal Memory

* cHTO, cHTNY, nHTO and nHTNY indicate the participants with current controlled hypertension and estimated WMH age is older, the participants with current controlled hypertension and estimated WMH age is normal or younger, the participants without a history of hypertension and estimated WMH age is older and the participants without a history of hypertension and estimated WMH age is normal or younger, respectively.

†Repeated measure analysis of variance adjusted for chronological age and diabetes mellitus with Bonferroni posthoc comparisons



Supplementary figure 1. Association of log-transformed volume of cerebral white matter hyperintensity with log-transformed cognitive test points in participants with controlled hypertension using linear regression analysis adjusting education, diabetes mellitus and hyperlipidemia as covariates. A, Verbal fluency test; B, Boston naming test; C, Mini mental status examination; D, Word list memory test; E, Word list recall test; F, Word list recognition test; G, Constructional praxis test; H, Constructional recall test; I, Trail making test A; J, Trail making test B; K, Digit span test; L, Frontal assessment battery; M, Verbal Memory



Supplementary figure 2. Mediation of cerebral white matter hyperintensity volume on the effect of systolic blood pressure on the cognitive performance in the participants with controlled hypertension.
VFT, Verbal Fluency Test; BNT, 15-item Boston Naming Test; MMSE, Mini Mental Status Examination; WLMT, Word List Memory Test; WLRT, Word List Recall Test; WLRcT, Word List Recognition Test; CPT, Constructional Praxis Test; CRT, Constructional Recall Test; TMT-A, Trail Making Test A; TMT-B, Trail Making Test B; DST, Digit Span Test; FAB, Frontal Assessment Battery; VM, Verbal Memory
All values are presented as standardized regression coefficients and *p*-values in parentheses.

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국문 초록

노인에서 조절 중인 고혈압이 대뇌백질고강도신호와 인지기능에 미치는 영향

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연구배경 및 목적: 고혈압은 인지장애의 위험인자이다. 또한, 고혈압은 대뇌백질고강도신호 (WMH)의 위험인자이고 WMH는 인지장애의 위험인자이지만, WMH의 고혈압과 인지기능간의 매개효과는 아직 충분히 검증된 적이 없다. 고혈압환자에서 WMH가 인지장애를 매개한다면, WMH의 존재나 크기는 인지장애를 판단할 수 있는 중요한 지표가 될 것이다. 하지만 건강한 노인의 WMH 확률지도 (WMHPM)나 WMHPM을 활용한 인지장애에 대한 연구는 아직까지 진행된바 없다. 본 연구에서는 두 개의 가설을 검증하고자 한다. 1) 비치매 노인에서의 WMH가 조절된 고혈압이 인지기능에 미치는 영향을 조정하는가? 2) WMHPM를 사용하여 추정된 WMH 나이가 조절된 고혈압 노인의 현재의 인지장애와 미래의 인지저하를 예측할 수 있는가?

연구방법: 본 연구는 주요 정신학적 또는 신경학적 질환이 없는 890명의 지역사회 거주 60세 이상의 비치매 노인을 대상으로 진행하였다. 그 중 368명이 2년후 추적검사를 하였다. WMHPM은 300명의 주요 정신학적 또는 신경학적 질환이 없고 인지기능이 정상인 건강한 60세 이상 지역사회 거주노인으로 구성하였다. 대상자의 혈압은 좌위 자세에서 자동혈압측정기를 이용하여 세 번 측정값의 평균값을 이용하였다. 조절된 고혈압 (cHT)은 고혈압병력이 있고 측정된 수축기 혈압이 140 mm Hg 미만이면서 이완기 혈압은 90 mm Hg 미만인 자로 정의하였다. 낮은 수축기 혈압 (LSBP)는 측정된 수축기

혈압이 110 mm Hg 이하인 자로 정의하였고, 낮은 이완기 혈압 (LDBP)는 측정된 이완기 혈압이 60 mm Hg 이하인 자로 정의하였다. 인지기능은 CERAD-K 신경심리검사, 전두엽기능평가, 숫자외우기 검사를 시행하였다. CERAD-TS 점수를 계산하였다. WMH 추출은 3.0T 액체감쇠역전회복 자기공명영상을 이용하였다. 개인의 WMH 영상과 5개의 연령대의 WMHPM 사이의 최저 편차 값을 계산하여 개인의 WMH 연령을 계산하였다. WMH연령이 실제연령과 같을 시 normal WMH 나이, 높을 시 older WMH 나이, 낮을 시 younger WMH 나이로 분류하였다. WMH가 고혈압이 인지기능에 미치는 영향을 조정하는지 Baron과 Kenny 방법으로 매개효과를 검증하였다. 로지스틱회귀분석을 이용하여 고혈압과 WMH나이가 인지장애에 미치는 영향을 분석하였다.

연구결과: cHT (p < .001), LSBP (p = .018)와 상호작용 (p < .001)은 WMH용적의 커짐과 관련이 있다. WMH용적은 인지기능의 낮은 수행점수와 관련이 있었다 (모든 인지검사: p < .001). WMH는 수축기 혈압이 1 mm Hg 감소할 때 인지기능점수가 0.016 ~ 0.030 포인트 감소하는 관계에 매개하였다. Younger 혹은 normal WMH 나이에 비해 older WMH 나이 군이 모든 인지기능 검사에서 낮은 수행능력을 보였다. (모든 인지검사: p < .001; DST: p = .002 for DST). cHT (p = .002), LSBP (p = .003), LDBP (p = .013), 상호작용 (p = .010)이 older WMH와 관련이 있었다. cHT군 중 older WMH 나이인 사람들은 정상혈압을 가진 normal 혹은 younger WMH 나이인 사람들에 비해 2년후 인지기능저하가 빠르고 경도인지장애가 발병할 확률이 8배 높았다.

결론: cHT 환자에서 LSBP는 WMH 용적을 증가시킴으로써 인지기능저하와 관련이 있었다. 건강한 노인의 WMHPM을 사용하면 임상환경에서 WMH 연령을 추정하여 인지저하 위험이 있는 고혈압환자를 구별해낼 수 있다.

주요어: 대뇌백질고강도신호, 고혈압, 인지기능, 자기공명영상, 노인

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