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Association of estimated white matter hyperintensity age with cognition in elderly with controlled hypertension

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ABSTRACT

Introduction: Hypertension is associated with white matter hyperintensity (WMH) and cognitive impairment. Further, WMH is associated with cognitive impairment including executive, attention and visuospatial functions. The aim of this study was to investigate the effects of controlled hypertension (cHT) and previously developed concept, 'WMH age' on cognitive function and the mediating role of WMH in the effect of cHT on cognitive impairment.

Methods: We enrolled 855 Koreans without dementia aged 60 years or older, 326 of whom completed 2-year follow-up assessment. We measured their blood pressure thrice in a sitting position using an automated blood pressure monitoring device. We estimated 'WMH age' of every participant using previously developed WMH probability map of healthy older Koreans. We analyzed the mediating effect of WMH age in the association of cHT and cognitive function using the PROCESS Macro model.

Results: Old WMH age was associated with a faster decline in the Mini-Mental Status Examination (MMSE; p =.003), Consortium to Establish a Registry for Alzheimer's Disease total score (CERAD-TS; p =.003), and Frontal Assessment Battery (FAB; p =.007). Old WMH age showed an approximately-six times higher risk of incident mild cognitive impairment (OR = 6.47, 95 % CI = 1.37 – 9.50, p =.024) compared to young or normal WMH age over the 2-year follow-up period in the cHT group. WMH age mediated the effects of cHT on the MMSE, CERAD-TS, and FAB scores at baseline and two-year follow-up period.

Conclusions: WMH mediates the adverse effect of hypertension on cognitive function. Elders with cHT who have older WMH age may be at a higher risk of cognitive decline.

1. Introduction

Hypertension, a major contributor to premature morbidity and mortality, affects approximately-one billion individuals worldwide. (Chobanian, 2003) However, only about one-third of patients with hypertension are well controlled. (Vedanthan et al., 2019) Hypertension also increases the risks of cognitive decline, mild cognitive impairment (MCI), and dementia. (Rodrigue, 2013; Waldstein et al., 20052005) In addition, hypertension is a well-established risk factor for cerebral white matter hyperintensity (WMH) on T2-weighted or fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI). In the Epidemiology of Vascular Aging study (Dufouil et al., 2001) and Rotterdam Scan Study, (de Leeuw et al., 20022002) hypertension increased the future risk of WMH, and controlling it reduced the future risk of WMH. However, we found that poorly controlled hypertension, such as low systolic blood pressure (SBP), may significantly increase cerebral WMH (Kim et al., 2020) similar to untreated cases.

Since WMH has been consistently found to increase the risks of

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current and future cognitive impairments, (Gunning-Dixon et al., 2009; Smith et al., 2008) the detrimental effect of controlled hypertension (cHT) on cognitive function may be fully or partially mediated by its effect on the risk of WMH. Although previous studies investigated the mediational role of WMH in the effect of hypertension or blood pressure on cognition (Chesebro et al., 2020; Gronewold et al., 2022), the mediational role of WMH in the effect of cHT on cognitive function has not been directly investigated. Furthermore, in previous studies on the relationship among hypertension, WMH, and cognition, age-associated WMH was not controlled despite that WMH is also common in healthy older adults without known risk factors including hypertension and hypotension (Zhuang et al., 2018) and can be attributable to the risk factors other than hypertension and hypotension. (Kim et al., 2008).

In the current study, we investigated the effect of cHT on the risks of prevalent and incident cognitive impairment after adjusting the effect of 'WMH age'. We developed a new concept, i.e., 'WMH age', to measure the burden of WMH after excluding age-associated burden of WMH. We estimated 'WMH age' using a WMH probability map (WMHPM) of healthy older Koreans that we had reported in our previous work. (Kim, 2021) In addition, we also investigated the mediation role of WMH age on the effect of cHT on cognitive performance.

2. Materials and methods

2.1. Participants

We enrolled 430 participants without a history of hypertension and 425 age- and sex-matched individuals aged 60 years or older with controlled hypertension and no dementia in the current study, including 366 visitors from the Dementia Clinic of the Seoul National University Bundang Hospital (SNUBH) from 2011 to 2020 and 489 participants of the Korean Longitudinal Study on Cognitive Aging and Dementia (KLOSCAD). (Han et al., 2018) Exclusion criteria were as follows: uncontrolled hypertension with an office-measured SBP $\geq$ 140 mmHg or a diastolic blood pressure (DBP) $\geq$ 90 mmHg; major neurologic or psychiatric disorders; dementia; time gap between the clinical assessment and the brain MRI acquisition $>$ 1 year; and history of cardiovascular comorbidities such as arterial diseases and stroke.

At the baseline assessment, 552 out of 855 participants were cognitively normal. We invited the cognitively normal participants at the baseline assessment to the 2-year follow-up assessment. Among the 552 cognitively normal participants, 226 have not completed follow-up studies or have not accepted follow-up invitations. Thus, 326 were included in the prospective analysis.

All participants and/or their legal guardians provided written informed consent for participation in this study. Both SNUBH (B-2005–615-001) and KLOSCAD (B-0912–089-010) were approved by the Institutional Review Board of the Seoul National University Bundang Hospital.

2.2. Assessments

A trained research nurse measured the blood pressure of participants thrice with a 5-min interval, when they visited the hospital, over their right brachial artery, in a sitting position, using an automated blood pressure monitoring device (OMRON HBP-9020, Omron healthcare Co., ltd., Kyoto, Japan). We used the mean value of the three measurements in determining cHT. We defined cHT as the diagnosis of hypertension but current SBP and DBP under control at $<$ 140 and 90 mmHg, respectively. We defined controls with no hypertension (nHT) as no history of hypertension, current SBP $\geq$ 90 mmHg but $<$ 140 mmHg, and current DBP $\geq$ 60 mmHg but $<$ 90 mmHg.

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, apolipoprotein E (APOE) genotyping, and serological tests for syphilis; echocardiography; and chest radiography. 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), Mini-Mental Status Examination (MMSE), word list memory test (WLMT), Constructional Praxis Test (CPT), word list recall test (WLRT), word-list recognition test (WLRcT), Constructional Recall Test, Trail-Making Test A/B, Digit Span Test, and Frontal Assessment Battery (FAB). (Lee, 2002) We calculated the CERAD total score (CERAD-TS) by adding the points of VFT, BNT, WLMT, WLRT, WLRcT, and CPT.

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, (American Psychiatric Association, 2000) and MCI according to the consensus criteria proposed by the International Working Group on MCI. (Winblad et al., 2004).

2.3. Acquisition of brain MRI and processing

We performed brain MRI using a 3.0 Tesla Achieva Scanner (Philips Medical Systems; Eindhoven, NL) with a uniform protocol (acquired voxel size = 1.0 × 0.5 × 0.5 mm; echo time = 4.6 ms; repetition time = 8.1 ms; axial-plane acquisition matrix size = 240 × 240 mm; number of excitations = 1; flip angle = 8°; inversion time = not applied for T1-weighted images; and acquired voxel size = 0.47 × 0.47 × 3.0 mm; slice thickness = 3 mm; spacing between slices = 3 mm; echo time = 125 ms; repetition time = 9,900 ms; axial-plane acquisition matrix size = 256 × 256 mm; number of excitations = 1; flip angle = 90°; and inversion time = 2,800 ms for FLAIR images).

We conducted 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 the Korean normal elderly (KNE). (Lee et al., 2016) By normalizing to a common stereotaxic space (voxel size: 1 × 1 × 1 mm; slice thickness = 1 mm), we aimed to correct inter-individual differences in brain size and shape. Meanwhile, we applied a bias correction on FLAIR images to correct non-uniformities caused by the bias field owing to different tissue properties and physics of MRI, using the "Segment" tool from SPM8. Next, we co-registered bias-corrected FLAIR images to native T1 images. We then applied transformation parameters produced from the normalization step of T1 images to bias-corrected, T1-coregistered FLAIR images to produce spatially KNE-normalized FLAIR images.

We segmented WMH from spatial 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). (Yoo et al., 2014) This code was developed to compute an optimal threshold for segmenting WMH and found to work well on different protocols from different scanners without any parameter adjustment. We calculated the overall cerebral WMH volume using an in-house code run on MATLAB 2014a.

2.4. Estimation of the WMH age

We overlaid the segmented WMH mask of each participant to the WMHPM of healthy older Koreans. (Kim, 2021) Subsequently, we subtracted the voxel value of the segmented WMH mask (0 and 1, reflecting absence and presence, respectively) from the voxel value of WMHPMs (0 to 1). We summed the absolute values of the subtracted values from all voxels and obtained the deviance value by dividing that sum by the total number of voxels. We defined the estimated WMH age of each participant as the age range in WMHPM, which showed the lowest deviance value from the participant's segmented WMH mask. Subsequently, we classified participants into two groups using the estimated WMH age group: the older WMH age group, whose estimated WMH age range was

above the chronological age (hereinafter referred to as the "OLDWMH group"), and the normal or younger WMH age group, whose estimated WMH age range was below or equal to the chronological age (hereinafter referred to as the "NOYWMH group") (Fig. 1).

2.5. Statistical analyses

We compared continuous variables using Student's *t*-test and categorical variables using the chi-square test between groups.

We examined the effects of cHT, OLDWMH, and their interaction on the cognitive performance at baseline using the analysis of variance (ANOVA), and on the changes of cognitive performance over the two-year follow-up period using repeated-measures ANOVA (rmANOVA). We also analyzed the effects of cHT, OLDWMH, and their interaction on the risks of prevalent MCI at the baseline assessment and incident MCI at the two-year follow-up assessment using logistic regression analyses.

Within the cHT group and the nHT group, we analyzed the effect of OLDWMH on the cognitive performance at baseline using ANCOVA and on the changes of cognitive performance over the two-year follow-up period using rmANOVA. We also analyzed the effect of OLDWMH on the risks of prevalent and incident MCI using logistic regression analyses.

We performed mediation analyses to investigate the mediating role of the cerebral WMH age in the effect of cHT on cognitive performance using Model 4 in the PROCESS Macro (Hayes et al., 2022). For the best test of mediation effect, the bootstrapping procedure to measure indirect effect was carried out and 95 % confidence intervals were estimated, where they are considered significant if there is no zero between lower and upper confidence interval (CI). The number of bootstrap samples was 5000.

We used SPSS for Windows (version 20.0; IBM Co., Armonk, NY, USA), and considered a two-sided *p*-value below 0.05 to be statistically significant.

3. Results

Among the 855 participants without dementia, the cHT group was more likely to have DM (p <.001), hyperlipidemia (p <.001), other cardiovascular disease (CVD) (p =.003), and MCI (p <.001); showed higher SBP (p =.011) and cerebral WMH volume (p <.001); and performed MMSE (p =.031), CERAD-TS (p =.002), and FAB (p =.031) worse compared to the nHT group. The OLDWMH group was more likely to have cHT (p <.001), DM (p <.001), and MCI (p <.001); showed higher cerebral WMH volume (p <.001); and performed MMSE (p =.012), CERAD-TS (p =.003), and FAB (p =.012) worse compared to the NOYWMH group (Table 1).

When we analyzed the 326 participants with normal cognition who completed the 2-year follow-up, the cHT group was more likely to have DM (p =.001) and showed higher SBP (p =.001) compared to the nHT group but comparable WMH volume, MMSE score, CERAD-TS, and FAB score to the nHT group at baseline (p > 0.05). The OLDWMH group showed comparable education level and frequencies of cHT and DM to the NOYWMH group (p > 0.1) and was younger than the NOYWMH group (p <.001). However, the OLDWMH group performed MMSE (p =.018), CERAD-TS (p =.031), and FAB (p =.021) worse than the NOYWMH group at baseline (Table 2).

Among 855 participants, only 326 participants completed the follow up assessment, whereas 529 participants did not complete. The participants who did not complete the follow up assessment were more likely to have DM (p <.001) and CVD (p <.001) and showed lower SBP (p =.002), DBP (p =.037), MMSE (p =.017), CERAD-TS (p =.024) and FAB (p =.031) than the participants who completed the follow up assessment. However, the participants who did not complete the follow up assessment showed higher WMH (p =.009) than the participants who completed the follow up assessment (Supplementary table 1).

Among the 855 participants without dementia, the OLDWMH group was associated with a lower MMSE score ($F_{1,\ 845}$ = 9.869, p =.003), CERAD-TS ($F_{1,\ 845}$ = 4.869, p =.003), FAB score ($F_{1,\ 845}$ = 4.153, p =.007, Table 3), and risk of prevalent MCI (odds ratio [OR] = 2.87, 95 % confidence interval [CI] = 1.96–3.35, p <.001, Table 4) at baseline. Compared to nHT in the NOYWMH group, cHT in the OLDWMH group showed an approximately-five times higher risk of prevalent MCI (OR = 4.89, 95 % CI = 2.31–9.14, p <.001, Table 4).

Among the 326 participants with normal cognition, the OLDWMH group was associated with faster declines in the MMSE score ($F_{1,\ 316}$ = 6.201, p =.001), CERAD-TS ($F_{1,\ 316}$ = 9.112, p =.001), FAB score ($F_{1,\ 316}$ = 5.003, p =.020, Table 3), and risk of incident MCI (OR = 3.37, 95 % CI = 1.31–6.10, p =.012, Table 4) during the follow-up period. Compared to nHT in the NOYWMH group, cHT in the OLDWMH group showed an approximately-six times higher risk of incident MCI during the follow-up period (OR = 6.47, 95 % CI = 1.37–9.50, p =.024, Table 4).

An interaction between the OLDWMH and cHT groups was observed for the MMSE score, CERAD-TS, FAB score, and risk of MCI at both baseline and 2-year follow-up (Tables 3 and 4). When we analyzed the cHT and nHT groups separately, the OLDWMH group was associated with a lower MMSE score ($F_{1,\ 419}$ = 7.421, p =.007), CERAD-TS ($F_{1,\ 419}$ = 8.195, p =.003), and FAB score ($F_{1,\ 419}$ = 7.883, p =.004) at baseline and faster declines in the MMSE score ($F_{1,\ 168}$ = 11.774, p <.001), CERAD-TS ($F_{1,\ 168}$ = 7.186, p =.005), and FAB score ($F_{1,\ 168}$ = 5.896, p

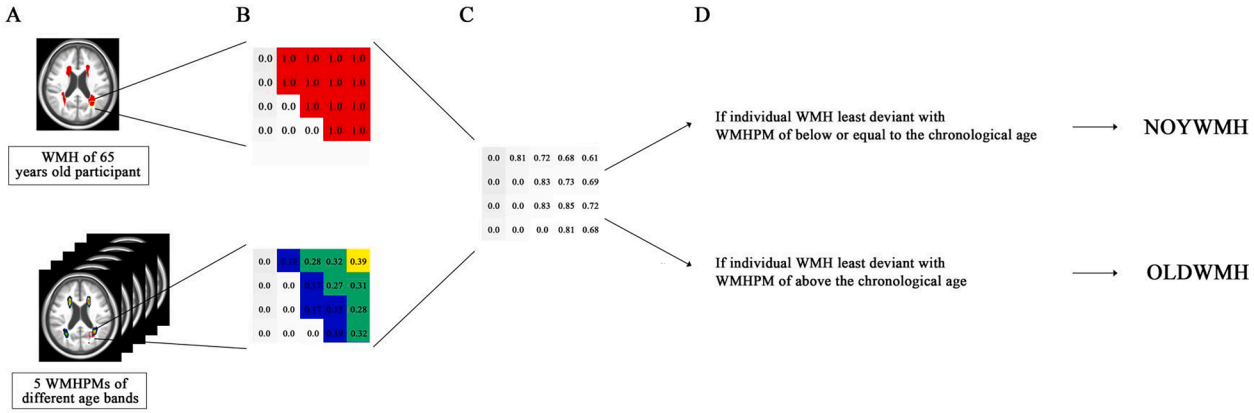

Fig. 1. Example of determining the estimated white matter hyperintensity age of 65-year-old participant. A) Prepare 65 years old individual WMH mask and 5 WMHPMs of different age band (60–64, 65–69, 70–74, 75–79 and 80 +); B) Calculate each voxel value of the segmented WMH mask (0 and 1, reflecting absence and presence, respectively) and each of WMHPMs (0 to 1); C) Subtract values of the segmented WMH mask from the voxel value of 5 WMHPM one-by-one, and record the mean value of absolute values of the subtracted values; D) if individual WMH least deviant with WMHPM of below or equal to the chronological age (in this case, WMHPM of 60–64 or 65–69), then referred to as NOYWMH, else is (in this case, WMHPM of 70–74, 75–79 or 80 +) OLDWMH.

Table 1
Characteristics of participants who completed the baseline assessment.

	All (n = 855)	Hypertension[†] nHT (n = 430)	cHT (n = 425)	$p^{‡}$	Estimated WMH age NOYWMH (n = 539)	OLDWMH (n = 316)	$p^{‡}$
Age, years[§]	73.6 ± 5.8	73.6 ± 6.0	73.7 ± 5.5	0.753	73.7 ± 6.0	73.5 ± 5.4	0.716
Women, %	60.4	60.6	60.1	0.899	59.4	62.0	0.443
Education, years[§]	11.7 ± 4.9	11.6 ± 5.0	11.8 ± 4.8	0.551	11.6 ± 5.0	12.0 ± 4.6	0.246
Hypertension, %	50.2	–	–	–	45.3	58.5	< 0.001
DM, %	21.3	15.3	27.3	< 0.001	17.3	28.2	< 0.001
Hyperlipidemia, %	45.0	37.8	52.2	< 0.001	43.6	47.5	0.272
CVD, %	13.7	10.2	17.2	0.003	14.4	12.5	0.434
Alcohol intake, unit/week[§]	4.5 ± 11.3	4.8 ± 12.2	4.2 ± 10.3	0.456	4.7 ± 12.4	4.0 ± 9.0	0.365
Smoking, pack/day[§]	0.3 ± 0.5	0.3 ± 0.5	0.3 ± 0.5	0.639	0.3 ± 0.5	0.3 ± 0.5	0.446
APOE ε4, %	26.0	26.3	25.6	0.828	25.8	26.3	0.878
SBP, mm Hg[§]	122.2 ± 10.0	121.4 ± 10.0	123.1 ± 10.0	0.011	121.4 ± 9.6	120.2 ± 10.4	0.171
DBP, mm Hg[§]	73.0 ± 7.6	73.1 ± 7.5	73.0 ± 7.7	0.857	73.5 ± 7.5	72.2 ± 7.7	0.066
WMH, cc[§]	10.3 ± 12.5	8.3 ± 10.8	12.2 ± 13.7	< 0.001	6.2 ± 9.1	17.2 ± 14.4	< 0.001
MMSE, point[§]	25.9 ± 3.5	26.2 ± 3.4	25.7 ± 3.7	0.031	26.2 ± 3.2	25.5 ± 3.9	0.012
CERAD-TS, point[§]	67.5 ± 15.2	69.1 ± 14.4	66.0 ± 15.8	0.002	68.7 ± 14.7	65.5 ± 15.8	0.003
FAB, point[§]	14.2 ± 3.0	14.6 ± 3.0	13.8 ± 3.1	0.031	14.4 ± 2.8	13.9 ± 3.4	0.012
MCI, %	35.4	26.8	44.1	< 0.001	26.7	50.3	< 0.001
Followed, %[‖]	36.6	34.7	41.5	0.647	39.5	35.8	0.485

DM, diabetes mellitus; CVD, other cardiovascular disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; WMH, white matter hyperintensity; MMSE, Mini-Mental Status Examination; CERAD-TS, Consortium to Establish a Registry for Alzheimer's Disease total score; FAB, Frontal Assessment Battery; MCI, mild cognitive impairment; nHT, without history of hypertension; cHT, controlled hypertension; NOYWMH, participants whose estimated white matter hyperintensity ages are equal to or below their chronological ages; OLDWMH, participants whose estimated white matter hyperintensity ages are older than their chronological ages.

[†] History of hypertension.

[‡] Student's *t*-test for continuous variables and chi-square test for categorical variables.

[§] Expressed as mean ± standard deviation.

[‖] Participants who completed the 2-year follow-up assessment.

Table 2
Baseline characteristics of participants who completed the 2-year follow-up assessment.

	All (n = 326)	Hypertension[†] nHT (n = 148)	cHT (n = 178)	$p^{‡}$	Estimated WMH age NOYWMH (n = 213)	OLDWMH (n = 113)	$p^{‡}$
Age, years[§]	72.7 ± 6.9	71.9 ± 7.3	73.5 ± 6.5	0.082	74.2 ± 7.0	68.8 ± 4.9	< 0.001
Women, %	61.6	60.2	63.2	0.589	59.4	67.2	0.269
Education, years[§]	11.9 ± 4.7	12.1 ± 4.4	11.8 ± 5.1	0.560	12.0 ± 4.6	11.8 ± 5.0	0.783
Hypertension, %	48.1	–	–	–	51.2	40.3	0.131
DM, %	16.5	10.6	22.8	0.001	18.2	11.9	0.239
Hyperlipidemia, %	42.6	39.8	45.6	0.085	41.2	46.3	0.475
CVD, %	4.6	7.3	1.8	0.160	5.9	1.5	0.148
Alcohol intake, unit/week[§]	4.8 ± 9.9	4.0 ± 9.1	5.7 ± 10.8	0.184	5.0 ± 10.0	4.5 ± 9.8	0.772
Smoking, pack/day[§]	0.2 ± 0.5	0.3 ± 0.5	0.2 ± 0.4	0.228	0.3 ± 0.5	0.2 ± 0.3	0.105
SBP, mm Hg[§]	128.7 ± 14.3	125.6 ± 14.1	132.0 ± 13.9	0.001	128.8 ± 13.5	128.5 ± 16.1	0.895
DBP, mm Hg[§]	77.7 ± 9.0	76.6 ± 8.5	79.0 ± 9.4	0.038	77.0 ± 8.6	79.6 ± 9.7	0.063
WMH, cc[§]	8.3 ± 10.1	7.9 ± 10.5	8.7 ± 9.6	0.131	6.8 ± 10.1	12.0 ± 9.1	< 0.001
MMSE, point[§]	26.8 ± 2.8	27.0 ± 2.8	26.3 ± 3.1	0.550	27.7 ± 2.8	25.0 ± 3.4	0.018
CERAD-TS, point[§]	70.9 ± 14.0	71.5 ± 14.0	68.9 ± 12.5	0.497	72.5 ± 14.1	66.8 ± 11.4	0.031
FAB, point[§]	14.7 ± 2.6	14.7 ± 2.7	14.6 ± 2.5	0.798	15.2 ± 2.6	13.6 ± 3.0	0.021

DM, diabetes mellitus; CVD, other cardiovascular disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; WMH, white matter hyperintensity; MMSE, Mini-Mental Status Examination; CERAD-TS, Consortium to Establish a Registry for Alzheimer's Disease total score; FAB, Frontal Assessment Battery; MCI, mild cognitive impairment; nHT, without history of hypertension; cHT, controlled hypertension; NOYWMH, participants whose estimated white matter hyperintensity ages are equal to or below their chronological ages; OLDWMH, participants whose estimated white matter hyperintensity ages are older than their chronological ages.

[†] History of hypertension: nHT indicates participants without a history of hypertension, and cHT indicates participants with current controlled hypertension.

[‡] Student's *t*-test for continuous variables and chi-square test for categorical variables.

[§] Expressed as mean ± standard deviation.

=.010) during the follow-up in the cHT group only (Table 5). The OLDWMH group was associated with a risk of prevalent MCI at baseline (OR = 5.07, 95 % CI = 3.22–8.01, p <.001) and that of incident MCI at the 2-year follow-up (OR = 5.14, 95 % CI = 1.62–15.82, p =.005) in the cHT group but not in the nHT group (Table 6).

Among the 855 participants without dementia, the significance of the direct and indirect effects in the mediation model was identified after controlling DM, hyperlipidemia and other cardiovascular diseases as covariates, which were significantly different between nHT and cHT. The direct effects of cHT on the MMSE (Effect = 0.655; Standard error (SE) = 0.245, 95 % CI = [0.175, 1.135]), CERAD-TS (Effect = 3.732; SE = 1.038, 95 % CI = [1.696, 5.769]) and FAB (Effect = 0.488; SE = 0.209, 95 % CI = [0.078, 0.898]) were observed. Moreover, the indirect effect of cHT on the MMSE (Effect = 0.662; SE = 0.244, 95 % CI = [0.184, 1.141]), CERAD-TS (Effect = 1.704; SE = 0.035, 95 % CI = [0.673, 3.735]) and FAB (Effect = 0.503; SE = 0.208, 95 % CI = [0.094, 0.912]) through WMH age were observed (Table 7).

Among the 326 participants with normal cognition, the significance of the direct and indirect effects in the mediation model was identified after controlling DM as covariate, which was significantly different between nHT and cHT. The direct effects of cHT on the MMSE (Effect = 1.036; SE = 0.435, 95 % CI = [0.180, 1.891]), CERAD-TS (Effect = 5.440; SE = 1.186, 95 % CI = [2.124, 8.756]) and FAB (Effect = 0.978; SE = 0.325, 95 % CI = [0.339, 1.617]) were observed. Moreover, the

Table 3
Effects of controlled hypertension and the white matter hyperintensity age as well as their interactions on the cognitive performance.

	Baseline†			Follow-up†		
	F	d.f.	p	F	d.f.	p
MMSE						
cHT	0.103	1, 845	0.773	5.088	1, 316	0.011
OLDWMH	9.869	1, 845	0.003	6.201	1, 316	0.001
cHT*OLDWMH	0.255	1, 843	0.600	3.356	1, 314	0.031
CETAD-TS						
cHT	4.589	1, 845	0.046	7.402	1, 316	0.002
OLDWMH	4.869	1, 845	0.003	9.112	1, 316	0.001
cHT*OLDWMH	5.148	1, 843	0.001	5.121	1, 314	0.009
FAB						
cHT	0.357	1, 845	0.587	0.521	1, 316	0.713
OLDWMH	4.153	1, 845	0.007	5.003	1, 316	0.020
cHT*OLDWMH	0.633	1, 843	0.481	4.018	1, 314	0.010

cHT, controlled hypertension; OLDWMH, older estimated white matter hyperintensity age; MMSE, Mini-Mental Status Examination; FAB, Frontal Assessment Battery; CERAD-TS, Consortium to Establish a Registry for Alzheimer's Disease total score.

† Two-way analysis of variance after adjusting for chronological age, sex, education, diabetes mellitus, hyperlipidemia, smoking, alcohol intake and apolipoprotein E ε4 as covariates.

‡ Repeated-measures analysis of variance after adjusting for chronological age, sex, education, diabetes mellitus, hyperlipidemia, smoking, alcohol intake and apolipoprotein E ε4 as covariates.

Table 4
Effects of controlled hypertension and the white matter hyperintensity age as well as their interactions on the risks of prevalent and incident mild cognitive impairments.

	Baseline†		Follow-up†	
	OR (95 % CI)	p	OR (95 % CI)	p
cHT‡	2.17 (1.60 – 3.01)	< 0.001	2.40 (1.12 – 6.34)	0.036
OLDWMH§	2.87 (1.96 – 3.35)	< 0.001	3.37 (1.31 – 6.10)	0.012
cHT*OLDWMH‖	4.89 (2.31 – 9.14)	< 0.001	6.47 (1.37 – 9.50)	0.024

OR, odds ratio; CI, confidence interval; cHT, controlled hypertension; OLDWMH, older estimated white matter hyperintensity age.

† Logistic regression model after adjusting for chronological age, sex, education, diabetes mellitus, hyperlipidemia, smoking, alcohol intake and apolipoprotein E ε4 as covariates.

‡ Reference group without a history of hypertension.

§ Reference group equal to or below the estimated white matter hyperintensity group.

‖ Reference group without a history of hypertension but equal to or below the estimated white matter hyperintensity group.

indirect effect of cHT on the MMSE (Effect = 1.047; SE = 0.434, 95 % CI = [0.194, 1.900]), CERAD-TS (Effect = 3.416; SE = 0.681, 95 % CI = [1.111, 6.722]) and FAB (Effect = 0.955; SE = 0.324, 95 % CI = [0.358, 1.633]) through WMH age were observed (Table 7).

4. Discussion

In this study, cHT increased the risks of current and future cognitive impairments partially by increasing WMH. In many previous studies, patients with hypertension with a greater WMH grade showed higher risks of current and future cognitive impairments. (Chesebro et al., 2020; Hajjar et al., 2011) However, the mediating role of WMH age on the effect of cHT on current or future cognitive performance has rarely been demonstrated. This study directly demonstrated the mediating role of WMH age in the effect of cHT on current and future cognitive performances and controlled effect of age-associated WMH by employing the WMH age estimated from a WMHPM of healthy older adults.

Table 5
Effect of the old white matter hyperintensity age on cognitive performance.

	cHT			nHT		
	F	d.f.	p	F	d.f.	p
Baseline†						
MMSE	7.421	1, 419	0.007	5.498	1, 416	0.019
CETAD-TS	8.195	1, 419	0.003	10.513	1, 416	< 0.001
FAB	7.883	1, 419	0.004	7.224	1, 416	0.006
Follow-up‡						
MMSE	11.774	1, 168	< 0.001	1.079	1, 138	0.289
CETAD-TS	7.186	1, 168	0.005	0.139	1, 138	0.730
FAB	5.896	1, 168	0.010	0.251	1, 138	0.705

cHT, controlled hypertension; nHT, no history of hypertension; MMSE, Mini-Mental Status Examination; CERAD-TS, Consortium to Establish a Registry for Alzheimer's Disease total score; FAB, Frontal Assessment Battery.

† Analysis of covariance after adjusting for the chronological age, sex, education, diabetes mellitus, hyperlipidemia, smoking, alcohol intake and apolipoprotein E ε4 as covariates.

‡ Repeated-measures analysis of variance after adjusting for chronological age, sex, education, diabetes mellitus, hyperlipidemia, smoking, alcohol intake and apolipoprotein E ε4 as covariates.

Table 6
Effect of the old white matter hyperintensity age on the risk of mild cognitive impairment.

	cHT		nHT	
	OR (95 % CI)	p	OR (95 % CI)	p
Baseline†	5.07 (3.22 – 8.01)	< 0.001	1.28 (0.70 – 1.85)	0.597
Follow-up†	5.14 (1.62 – 15.82)	0.005	1.11 (0.11 – 12.51)	0.875

OR, odds ratio; CI, confidence interval; cHT, controlled hypertension.

† Logistic regression after adjusting for the chronological age, sex, education, diabetes mellitus, hyperlipidemia, smoking, alcohol intake and apolipoprotein E ε4 as covariates.

We only invited the cognitively normal participants at the baseline assessment to the 2-year follow-up assessment. We found out the demographical difference between participants who completed the follow up assessment and participants who did not complete the follow up assessment, which were lower WMH volume and higher cognitive assessment score in those who completed follow up assessment. However, these were expected since the participants were composed of normal cognition and these differences were not enough to determine the results of the study.

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. (Chesebro et al., 2020) The Cardiovascular Health Study also revealed that cerebral WMH mediated the adverse effect of hypertension on mobility, cognition, and mood. (Hajjar et al., 2011) Hypertension results in various structural and functional changes in cerebral vessels and hemodynamics. (de Montgolfier, 2019; Mulvany, 2012) These changes associated with hypertension may increase WMH, which is a well-established risk factor for cognitive impairment or accelerated cognitive decline. (Dufouil et al., 2001; de Leeuw et al., 20022002; Gunning-Dixon et al., 2009) Among patients with treated hypertension, hypotension is prevalent up to 20 % at age 60 years or older (Barochiner et al., 2019; Divisón-Garrote et al., 2020) and 30 % at age 80 years or older. (Divison-Garrote, 2017) Since the limits of cerebral autoregulation shift toward higher levels of blood pressure, (Strandgaard et al., 1973) patients with hypertension and masked hypotension may be vulnerable to cerebral hypoperfusion (Liu et al., 2016) and show a larger WMH volume, (Kim et al., 2020) which may increase the risk of cognitive impairment.

Hemodynamic abnormalities and reduced cerebral blood flow are observed even in normal-appearing white matter from the early stage of hypertension (Wang et al., 2016). However, cerebral blood flow

Table 7
Mediation of white matter hyperintensity age on the effect of controlled hypertension on cognitive performances at baseline and 2-years follow-up period.

	MMSE				CERAD-TS				FAB			
	Effect	SE	LL 95 % CI	UL 95 % CI	Effect	SE	LL 95 % CI	UL 95 % CI	Effect	SE	LL 95 % CI	UL 95 % CI
Baseline												
Direct effect	0.655	0.245	0.175	1.135	3.732	1.038	1.696	5.769	0.488	0.209	0.078	0.898
Indirect effect	0.662	0.244	0.184	1.141	1.704	0.035	0.673	3.735	0.503	0.208	0.094	0.912
2-year follow-up												
Direct effect	1.036	0.435	0.180	1.891	5.440	1.186	2.124	8.756	0.978	0.325	0.339	1.617
Indirect effect	1.047	0.434	0.194	1.900	3.416	0.681	1.111	6.722	0.995	0.324	0.358	1.633

MMSE, Mini-Mental Status Examination; CERAD-TS, Consortium to Establish a Registry for Alzheimer's Disease total score; FAB, Frontal Assessment Battery; SE, Standard error; LL 95 % CI, Lower limit 95 % confidence interval; UL 95 % CI, upper limit 95 % confidence interval.
Model 4 of PROCESS Macro of SPSS with the number of bootstrap sample of 5,000.

decreases by 4.8 mL/min every year (Buijs et al., 1998), and the cerebral metabolic rate decreases approximately 6 % every decade (Petit-Taboué et al., 1998) with advancing age in people with normal blood pressure. The cerebral metabolic rate is coupled with cerebral blood flow. (Leenders et al., 1990) Previous studies reported that WMH can develop with an advancing age across the adult lifespan without clinically identifiable diseases associated with the risk of WMH. (Zhuang et al., 2018; Kim, 2021) In our WMHPM of healthy older adults without hypertension, people aged 80 years or older showed an approximately-six times higher WMH volume compared to those aged 60 ~ 64 years.

This study revealed that older adults with cHT and WMH were at an approximately-five times higher risk of current MCI and approximately-eight times higher risk of future MCI. The OLDWMH group was associated with faster cognitive decline over 2 years in older adults with cHT but not in those with nHT. Although many studies reported the association of WMH and cognitive impairment in patients with hypertension, it has not been established how patients with hypertension could be determined to be at a risk of cognitive impairment in clinical settings. The current study clearly demonstrated that the WMH age estimated from the WMHPM of healthy older adults could be a useful biomarker of current and/or future cognitive impairment(s) in older adults with hypertension. In addition, the WMH age could be a good candidate marker for the risk of cognitive impairment in patients with other diseases that may increase the risk of WMH. (Sudre et al., 2018).

The current study has several limitations. First, our multivariable analyses might not have fully adjusted for all potential factors that may confound the association between blood pressure, WMH, and cognition, such as use of antihypertensive drugs, (Stuhec et al., 2017) duration of hypertension, (Li, 2014) blood pressure fluctuations, (Sabayan et al., 2013) and duration of follow-up, which may be subject to recall biases in a retrospective case-control study. Second, all participants were Koreans. Since the brain shape, (Zilles et al., 2001) risk of cerebrovascular disease, (Feldmann et al., 1990) and prevalence of WMH (Liao et al., 1997) differ between Asians and Caucasians, the results of the current study may not be generalizable to other ethnic groups. Lastly, the chronological age of the OLDWMH group was comparable to that of the NOYWMH group at the baseline assessment but lower than that of the NOYWMH group at the two-year follow-up assessment. These results indicate that the OLDWMH group might have had different survival from the NOYWMH group.

5. Conclusions

Older adults with cHT are at a higher risk of cognitive impairment. Since WMH mediates the adverse effect of hypertension on cognitive function, the WMH age could be useful in identifying patients with hypertension at a risk of cognitive impairment in clinical settings.

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CRediT authorship contribution statement

Jun Sung Kim: Conceptualization, Methodology, Formal analysis, Investigation, Resources, Writing – original draft, Writing – review & editing. **Jong Bin Bae:** Investigation, Resources. **Ji Won Han:** Investigation, Resources. **Dae Jong Oh:** Investigation, Resources. **Seung Wan Suh:** Investigation, Resources. **Jae Hyoung Kim:** Investigation, Resources. **Ki Woong Kim:** Conceptualization, Methodology, Formal analysis, Writing – original draft, Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

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