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Sex disparity of cerebral white matter hyperintensity in the hypertensive elderly: The Shanghai Changfeng study

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Abstract

White matter hyperintensity (WMH) is associated with vascular hemodynamic alterations and reflects white matter injury. To date, the sex difference of tract-specific WMH and the relationship between high blood pressure (BP) and tract-specific WMH remain unclear. We recruited 515 subjects from the Shanghai Changfeng study (range 53–89 years, mean age 67.33 years). Systolic and diastolic blood pressure (SBP and DBP) were collected and used to calculate pulse pressure (PP). Magnetic resonance T1 and T2 FLAIR images were acquired to measure WMH and calculate WMH index. The ANCOVA test was performed to test the difference between sexes, and the linear regression model was used to examine the associations between BP and WMH index. Men showed higher WMH index than women in all white matter tracts ($p < .001$, respectively) except for the bilateral superior longitudinal fasciculus (SLF) and its left temporal part (tSLF). High SBP and PP was associated with a lower WMH index on the left corticospinal tract (CST), SLF, tSLF and right cingulum in hippocampus ($p \leq .001$, respectively) in women, while high DBP was associated with a higher WMH index on the bilateral CST (left $p < .001$; right $p = .001$), left inferior longitudinal fasciculus ($p < .001$) and inferior fronto-occipital fasciculus ($p = .002$) in men. Men tend to have more WMH compared to women. A high SBP/PP relates to a lower WMH burden in women. This suggests that women could benefit from higher blood pressure in older age.

KEYWORDS

high blood pressure, MRI, sex difference, tract-specific white matter hyperintensity

Liangqi Wang and Huandong Lin have contributed equally to this work.

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1 | INTRODUCTION

White matter hyperintensities (WMHs), also referred to as leukoaraiosis, are generally patchy hyperintense lesions localized in deep white matter and/or peri-ventricle areas, which can be detected by FLAIR MR imaging (Sam et al., 2016). Histopathologically, WMH is a marker of cerebral small vessel disease (CSVD), and represents blood brain barrier disruption, small infarcts in the white matter, loss of oligodendrocytes as well as demyelination (Li et al., 2018). As a pathological signature of white matter injury, WMH is associated with vascular hemodynamic alterations (Blair et al., 2020; Furuta et al., 1991). A large proportion of dementia and stroke cases could be attributed to CSVD, with WMH being a predominant contributor to this relationship (Cannistraro et al., 2019). We have previously shown a very high detection rate of WMH in the community-dwelling elderly population (Wang et al., 2021).

Accumulating evidence suggests a central role for vascular risk factors in the pathogenesis of WMH (Dufouil et al., 2001; Fatemi et al., 2018; Gronewold et al., 2021; Guevarra et al., 2020; Sachdev et al., 2009; Sargurupremraj et al., 2020; Scott et al., 2015; van Dalen et al., 2016). As a leading cause of cerebral small vessel damage, hypertension was found to be associated with higher WMH volume (Gronewold et al., 2021). The hypertension persons were found to have a significant increase in WMH volume compared to normotensive persons due to impaired dynamic cerebrovascular autoregulation (Gronewold et al., 2021). A longitudinal study ranking WMH from none to severe also concluded that hypertension was a major risk factor for severe WMH (Dufouil et al., 2001). On the other hand, there could be sex disparity in brain biomarkers against aging and neurodegenerative diseases. The genetic study showed that more genes were expressed from the X chromosome than from autosomes in the brain (Nguyen & Disteche, 2006). KDM6A, an X-linked gene with increased expression if a second X chromosome is present, has been linked to reduced cognitive decline in aging and preclinical Alzheimer's disease in humans (Davis et al., 2020). A longitudinal study followed for 26 years demonstrated that men had approximately twice the morbidity and mortality of coronary heart disease than women (Lerner & Kannel, 1986). Other researcher also confirmed the health advantages of women (Dix, 2014). The study of sex disparity in hypertension status showed that women were less likely to be hypertensive compared to men (Everett & Zajacova, 2015). However, some pieces of evidence from the WMH sex difference studies are not in line with this point of view. The Mayo Clinic study of aging demonstrated that a significant higher WMH volume was found in women compared to men (Fatemi et al., 2018). Another aging study claimed that women had a greater burden of WMH lesions than men as well (Sachdev et al., 2009). The inconsistent phenomena of higher WMH load in the elderly women and lower burden of vascular disease throughout the lifespan in women might be due to the growth of female morbidity in older age, yet it needs to be further elucidated (Lerner & Kannel, 1986). Previous study showed that tract-specific changes in WMH could localize the abnormalities in a fiber specific manner (Kim et al., 2021). As such, the association between high blood pressure (BP) and tract-specific WMH in both sexes would highlight the role of vascular pathologic mechanisms in WMH in different sexes, as well as in different white matter fibers, and build a bridge between the vascular and white matter injuries. In addition, the relationship between tract-specific WMH and high BP in both sexes may help to explain the overlap effect of sex and vascular mechanisms on white matter injury in the elderly. To date, the sex difference of tract-specific WMH remains uncertain in the elderly. Additionally, the association of WMH in white matter tracts with high BP in both men and women has not previously been examined.

Hence, in a community-based population study of middle-aged and elderly adults, the Shanghai Changfeng study, we performed tract-specific WMH analysis to explore the difference in sex of WMH as well as the relationship between WMH and BP. The differences of tract-specific WMH burden between the sexes and the association of tract-specific WMH burden with BP were estimated. We hypothesized that WMH was greater in men than in women and WMH was associated with BP.

2 | MATERIALS AND METHODS

2.1 | Participants

This study was embedded in the Shanghai Changfeng Study, a community-based study initiated in 2009 that investigated age-related health changes in the middle-aged and elderly population. The design of the study has been carefully described elsewhere (Gao et al., 2010). Participants of the study had completed the baseline visit in 2012 and the second visit in 2017. At each visit, the participants underwent an interview and had medical examinations at the research center. From July 2017 to January 2020, 718 subjects aged over 50 years old were invited to undergo additional brain magnetic resonance imaging (MRI). The inclusion criteria were age over 50 years old, understanding and giving informed consent. The exclusion criteria

TABLE 1 The basic characteristics of participants of the Shanghai Changfeng study

	Total	Male	Female	*p*
N	515	211	304	
Sex, *n* (%, male)	211 (40.97)	/	/	/
BP status, *n* (%, High BP)	207 (40.19)	103 (48.82)	104 (34.21)	<.001
Age (years)	67.33 (7.46)	68.98 (7.51)	66.19 (7.22)	<.001
BMI (kg/m^2)	24.59 (2.95)	24.80 (2.62)	24.44 (3.15)	.149
Waist circumstance (cm)	82.17 (9.31)	86.03 (8.29)	79.49 (9.04)	<.001
Hip circumstance (cm)	92.16 (5.84)	92.95 (4.87)	91.61 (6.38)	.007
WHR	0.89 (0.09)	0.92 (0.07)	0.87 (0.09)	<.001
Education (years)	11.62 (3.17)	12.47 (3.41)	11.02 (2.85)	<.001
SBP (mmHg)	135.95 (19.90)	139.21 (20.03)	133.69 (19.53)	.002
DBP (mmHg)	75.28 (9.97)	77.69 (10.83)	73.60 (8.97)	<.001
PP (mmHg)	60.67 (14.84)	61.52 (14.83)	60.09 (14.83)	.283
ALT (U/L)	18.37 (11.96)	19.42 (11.16)	17.65 (12.46)	.092
AST (U/L)	21.23 (9.55)	21.15 (8.81)	21.28 (10.04)	.875
ALP (U/L)	71.27 (26.50)	69.71 (34.09)	72.36 (19.57)	.309
GGT (U/L)	31.31 (66.76)	40.46 (102.28)	24.96 (14.54)	.030
BUN (mmol/L)	5.25 (1.41)	5.31 (1.42)	5.22 (1.40)	.454
CR (μmol/L)	73.56 (17.28)	85.32 (15.03)	65.40 (13.67)	<.001
UA (μmol/L)	316.71 (77.20)	353.14 (80.62)	291.43 (63.55)	<.001
TC (mmol/L)	5.09 (0.94)	4.84 (0.96)	5.26 (0.90)	<.001
TG (mmol/L)	1.64 (1.18)	1.71 (1.54)	1.59 (0.83)	.284
HDL-c (mmol/L)	1.45 (0.40)	1.28 (0.32)	1.57 (0.41)	<.001
LDL-c (mmol/L)	2.92 (0.84)	2.82 (0.84)	2.98 (0.83)	.035
FBG (mmol/L)	5.84 (1.38)	6.10 (1.59)	5.65 (1.18)	.001
HbA1c (%)	5.93 (0.89)	6.01 (1.07)	5.87 (0.74)	.092

Note: Mean (SD).
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; BUN, blood urea nitrogen; CR, serum creatinine; DBP, diastolic blood pressure; FBG, fasting blood glucose; GGT, Gamma-Glutamyl Transferase; HbA1c, hemoglobin A1c.; HDL-c, high-density lipoprotein; LDL-c, low-density lipoprotein; PP, pulse pressure; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; UA, uric acid; WHR, waist to hip ratio.

included (1) brain tumors, (2) contraindications to MR imaging, (3) artifacts, or (4) incomplete imaging and clinical data (see Section 2.2 and Table 1). Eighty subjects refused to attend the MRI examination; 49 subjects did not complete the MRI due to contraindications, technical problems during the examination, and intolerance to the long acquisition time. Therefore, 589 subjects (82.0%) completed the acquisition of brain MRI in this population. Furthermore, we excluded 9 subjects due to missing clinical data and 65 subjects due to artifacts, or for other technical reasons. Finally, 515 subjects were included in this study. The study was performed in accordance with the Declaration of Helsinki of 1975 and approved by the ethics committee of the Zhongshan Hospital, Fudan University. Written informed consent was obtained from all participants.

2.2 | Clinical assessment

Demographic information was obtained at baseline. An analysis of BP was carried out using the mean of three resting measurements of both systolic and diastolic blood pressure (SBP and DBP). Pulse pressure (PP) was the difference between SBP and DBP. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Waist circumference was measured in standing position using a soft tape at the midpoint between the lowest rib and the iliac crest. We measured hip circumference at the widest level over the greater trochanters. Waist to hip ratio (WHR) was calculated as waist circumference divided by hip circumference. Serum total cholesterol (TC), HDL-cholesterol, LDL-cholesterol and triacylglycerol (TG) levels were measured by an oxidase method and the alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT) were measured by the ultraviolet lactate and malate dehydrogenase methods, respectively. Blood urea nitrogen (BUN), serum creatinine (CR), and uric acid (UA) were measured using an autoanalyzer (Hitachi 7600; Hitachi, Tokyo, Japan) and standard methods. Fasting blood glucose (FBG) was measured using the glucose oxidase method. Hemoglobin A1c (HbA1c) was also acquired using standard methods.

2.3 | Image acquisition

Magnetic resonance (MR) data were collected on a 3-Tesla scanner (GE Discovery 750 w, GE Healthcare) at Putuo Hospital, Shanghai. A16-channel head–neck coil with 12-channel for head was used. To minimize motion artifacts, cushions were filled inside the coil during image acquisition.

The high-resolution structural T1-weighted MR images (T1w) were collected using a 3D BRAVO sequence. Among the total participants, 71 subjects were scanned with a protocol in axial plane and others were scanned with another in sagittal plane. The T1-weighted imaging protocols for 71 participants were: TR/TE = 8.6/3.2 ms, flip angle 14°, FOV = 25.6, 148 slices, slice thickness 1 mm, matrix 256 × 256, voxel size = 1 × 1 × 1 mm^3; for 444 participants were: TR/TE = 8.5/3.2 ms, flip angle 12°, FOV = 25.6, 172 slices, slice thickness 1 mm, matrix 256 × 256, voxel size = 1 × 1 × 1 mm^3.

The fluid-attenuated inversion recovery (FLAIR) sequence was also acquired. Among the total participants, 71 subjects were scanned in the sagittal plane with a protocol, and others were scanned with another in the axial plane. The FLAIR imaging protocols for 71 participants were: TR/TE = 6000/90 ms, FOV = 25.6, 292 slices, slice thickness 1.2 mm, slice spacing 0 mm, matrix 256 × 224; for 444 participants were: TR/TE = 8944/118.9 ms, flip angle 111°, FOV = 25.6, 51 slices, slice thickness 3 mm, slice spacing 0 mm, matrix 256 × 192.

2.4 | Image processing

The Brain Extraction Tool in FSL (version: 5.0.11 https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FslInstallation) was used on the T1-weighted image and the FLAIR image to remove nonbrain tissues. Transformation matrices from the standard Montreal Neurological Institute (MNI) space to the native T1 space and the tissue volumes were created using voxel-based morphometry (VBM) procedures as follows. Briefly, unified tissue segmentation was used to segment the image into gray matter (GM), white matter (WM), and cerebral spinal fluid (CSF), which was then affinely registered to the standard Montreal Neurological Institute (MNI) space using SPM12. The refined inter-subject registration, then normalization and modulation were performed by diffeomorphic anatomical registration through exponentiated lie algebra (DARTEL). Modulation preserved the amount of tissue in each voxel, and areas that were expanded during warping were correspondingly reduced in intensity. Finally, the modulated images were smoothed with a Gaussian kernel of 6 mm to increase the signal-to-noise ratio. The total gray matter volume (GMV), white matter volume (WMV), and cerebral CSF volume were calculated by summing all voxels of a certain brain tissue. The sum of GMV, WMV, and CSF volume was calculated to obtain total intracranial volume (TIV). The preprocessing procedures above have been described previously and can be found in our published paper for more details (Wang et al., 2021).

For the WMH segmentation on the FLAIR image, we used the lesion segmentation toolbox (LST) under the SPM12 (version: 7484 https://www.fil.ion.ucl.ac.uk/spm/) in the MATLAB (R2018a) environment with the lesion prediction algorithm (LPA) to obtain the WMH probability map. The John Hopkins University (JHU) white-matter tract probability map was used to evaluate the WMH of 20 tracts, including bilateral anterior thalamic radiation (ATR), corticospinal tract (CST), inferior longitudinal fasciculus (ILF), inferior fronto-occipital fasciculus (IFO), uncinated fasciculus (UNC), superior longitudinal fasciculus (SLF) and its temporal part (tSLF), cingulum in cingulate gyrus (CgC), cingulum in hippocampus (CgH), forceps minor (Fmi) and forceps major (Fma) (Hua et al., 2008). Unlike VBM, the intensity of the WMH probability may be reduced if mapped into the MNI space; due to the nonlinear transformation, the WMH probability map was not considered as absolute volumes, and therefore, we conducted the computation in the individual native T1 space. Transformation matrices were applied to the JHU white-matter tract probability map to bring them into the individual native T1 space. The FLAIR image and the WMH probability map were transformed to the native T1 space using the co-registration tool in SPM 12. The WMH index was calculated by the probability of tractography, WMH, and the voxel size, according to the formula below:

$$\mathrm{WMH}_{\mathrm{index}} = \frac{\sum (P_{\mathrm{tract}} \times P_{\mathrm{WMH}} \times \mathrm{Voxelsize})}{\sum P_{\mathrm{tract}}} \times 1000$$

P_{tract} was the probability of each voxel lying on the specific tracts of the JHU tract probability map; P_{WMH} was the probability of each voxel on the WMH probability map in native T1 space.

2.5 | Statistical analysis

Student *t* test and Chi-square test were used for continuous and categorical variables. The ANCOVA test was performed to analyze the group difference of total WMH index and WMH index of each tract between men and women with age, BP measurements (SBP, DBP or PP), TIV and education time as covariates. Two-way (i.e., sex × age, age × BP measurements, sex × BP measurements) and three-way interactions (i.e., sex × age × BP measurements) were also implemented in the model. Linear regression was used to investigate the relationship between BP measurements (SBP, DBP or PP) and WMH index in male and female subgroups with age, TIV and education time as covariates. Two-way (i.e., age × BP measurements) interaction was also implemented in the linear regression model. For visualization of results, BP were dichotomized by the median value of SBP, DBP and PP. We used restricted cubic spline regression with three knots at the 25th, 50th, 75th percentiles of BP parameters to further examine the nonlinear relationships between SBP, DBP, PP and WMH index. The sensitivity analysis was performed to assess the robustness of the results in subjects with data from the same MRI protocol. We explored the effect among those participants who received the same MRI protocol for WMH measures. $p < .05$ was considered statistically significant. The Bonferroni corrected alpha level of 0.05/20 = 0.0025 was used to adjust for multiple comparisons. All statistical analyses were performed on the MATLAB (version 2018a) and RStudio (version 1.2.5019) platform.

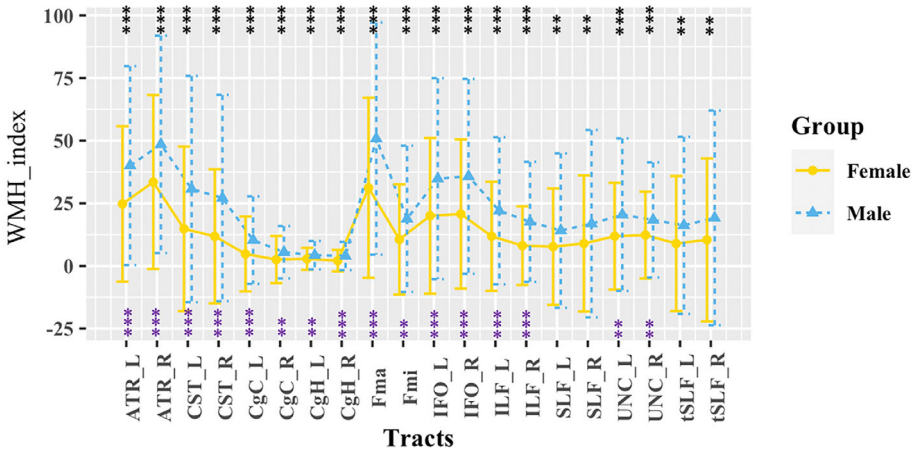

FIGURE 1 Difference of WMH index between male and female subjects. WMH index (mean ± SD) between male and female subjects. Men displayed significantly higher WMH index in most of the JHU white matter tracts than women. *p-value < .05, **p-value < .01, ***p-value <.001. Black asterisk denotes significant difference without multiple comparison correction, violet asterisk denotes significant difference with Bonferroni correction

TABLE 2 The sex difference of the total WMH index

	Total (N = 515)		Male (N = 211)		Female (N = 304)	
	F value	*p*	*β*	*p*	*β*	*p*
SBP	0.69	.405	26.71	.076	−26.88	.007**
Sex	29.14	<.001***	/	/	/	/
Age	184.06	<.001***	88.13	.004**	−27.93	.172
Age × SBP	0.03	.869	−0.38	.079	0.42	.005**
Sex × Age	1.31	.254	/	/	/	/
Sex × SBP	0.27	.602	/	/	/	/
Sex × Age × SBP	10.00	.002**	/	/	/	/
DBP	0.04	.850	81.96	.004**	−0.21	.992
Sex	29.21	<.001***	/	/	/	/
Age	184.47	<.001***	127.16	<.001***	0.29	.224
Age × DBP	6.41	.012*	−1.20	.003**	0.02	.954
Sex × Age	1.17	.281	/	/	/	/
Sex × DBP	0.09	.763	/	/	/	/
Sex × Age × DBP	5.75	.017*	/	/	/	/
PP	1.07	.303	9.26	.670	−44.23	<.001***
Sex	29.09	<.001***	/	/	/	/
Age	183.73	<.001***	42.59	.026*	−12.20	.311
Age × PP	3.11	.078	−0.11	.696	0.68	<.001***
Sex × Age	1.29	.256	/	/	/	/
Sex × PP	0.63	.427	/	/	/	/
Sex × Age*PP	5.26	.022*	/	/	/	/

Note: The ANCOVA was used to test the sex difference of the total WMH index, with an interaction of main effects, adjusted for confounding variables. Linear regression analysis was used to examine the relationship between SBP, DBP, PP, and total WMH index in males and females, with an interaction of main effects, adjusted for confounding variables. Confounders: age, total intracranial volume and education time.

Abbreviations: DBP, diastolic blood pressure; PP, pulse pressure; SBP, systolic blood pressure.

*p-Value < .05; **p-Value < .01; ***p-Value < .001.

3 | RESULTS

3.1 | Participant characteristics

Characteristics of the 515 participants were presented in Table 1. Participants consisted of 211 males were aged from 53 to 89 (mean = 67.33, SD = 7.46) years old. Compared to women, men were elder (p < .001), well-educated (p < .001) and had higher waist circumstance (p < .001), hip circumstance (p = .007), waist to hip ratio (WHR, p < .001), systolic blood pressure (SBP, p = .002), diastolic blood pressure (DBP, p < .001), gamma-glutamyl Transferase (GGT, p = .030), serum creatinine (CR, p < .001), uric acid (UA, p < .001),

FIGURE 2 The interaction of age and blood pressure in prediction of total WMH index. Relationship between age and total WMH index in high SBP and low SBP female subjects (A). Relationship between age and total WMH index in high DBP and low DBP male subjects (B). Relationship between age and total WMH index in high PP and low PP female subjects (C). Blood pressure was dichotomized by the median value of SBP, DBP and PP. DBP, diastolic blood pressure; PP, pulse pressure; SBP, systolic blood pressure; WMH_index, white matter hyperintensity index

fasting blood glucose (FBG, $p = .001$), as well as lower total cholesterol (TC, $p < .001$), HDL-cholesterol (HDL-c, $p < .001$) and LDL-cholesterol (LDL-c, $p = .035$). See Table 1 and Table S1 for detailed information.

3.2 | Comparisons of WMH index between sexes

Group differences of WMH index between men and women were shown in Figure 1 and Table 2, Table S2. The WMH index had shown significant differences between sexes in total WMH ($p < .001$) and in bilateral ATR, CST, CgC, CgH, IFO, ILF, UNC, Fma and Fmi ($p < .001$, respectively) after Bonferroni correction. DBP and age interaction effect was found in total WMH and in the bilateral CST (left CST, $p = .001$; right CST, $p = .002$), ILF (left ILF, $p < .001$; right ILF, $p = .002$), and left IFO ($p = .002$) after Bonferroni correction. Sex, age, and SBP interaction effect was found in total WMH and in bilateral CST (left CST, $p < .001$; right CST, $p = .001$), ILF (left ILF, $p = .001$; right ILF, $p = .001$) right CgH ($p < .001$), left SLF ($p = .001$) and tSLF ($p = .001$) under Bonferroni correction. Sex, age, and DBP interaction effect was found in total WMH ($p = .017$). Sex, age, and PP interaction effect was found in total WMH ($p = .022$).

3.3 | Relationships between BP and WMH index

Relationship between BP measurements and total WMH index were shown in Figure 2 and Table 2. Higher SBP was found to be correlated with lower total WMH index in females ($p = .007$). PP was also found to be negatively correlated with total WMH index in females ($p < .001$). However, DBP was found to be positively correlated with total WMH index in males ($p = .004$). The interaction effect of age × SBP ($p = .005$) and age × PP ($p < .001$) were significant for females. The increase in total WMH index over age was greater in high SBP/PP than low SBP/PP. The interaction effect of age × DBP ($p = .003$) was significant for males. The increase in total WMH index over age was greater in low DBP than high DBP.

Relationship between BP measurements and tract-specific WMH index were shown in Figure 3 and Table S2. Higher SBP was found to be correlated with lower WMH index in left CST ($p = .001$), SLF ($p < .001$), tSLF ($p < .001$) and right CgH ($p = .001$) under Bonferroni correction in females. PP was also found to be negatively correlated with WMH index in bilateral CST (left CST, $p < .001$; right CST, $p = .002$), IFO (left IFO, $p = .001$; right IFO, $p = .002$), ILF (left ILF, $p < .001$; right ILF, $p < .001$), left SLF ($p < .001$), tSLF ($p < .001$), right CgH ($p < .001$), and Fma ($p = .002$) under Bonferroni correction in females. However, DBP was found to be positively correlated with WMH index in bilateral CST (left CST, $p < .001$; right CST, $p = .001$), left IFO ($p = .002$) and ILF ($p < .001$) under Bonferroni correction in males. The interaction effect of age × SBP was significant in left CST ($p = .001$), SLF ($p < .001$), tSLF ($p < .001$) and right CgH ($p = .001$) for females. The increase in WMH index over age was greater in high SBP than low SBP. The interaction effect of age*PP was significant in bilateral CST (left CST, $p < .001$; right CST, $p = .001$), IFO (left IFO, $p < .001$; right IFO, $p = .001$), ILF (left ILF, $p < .001$; right ILF, $p < .001$), left SLF ($p < .001$), tSLF ($p < .001$), right CgH ($p < .001$), and Fma ($p = .001$) for females. The increase in WMH index over age was greater in high PP than low PP. The interaction effect of age × DBP was significant in bilateral CST (left CST, $p < .001$; right CST, $p = .001$), left IFO ($p = .002$), ILF ($p < .001$) and right CgH ($p = .002$) for males. The increase in WMH index over age was greater in low DBP than high DBP. We did not find any significant nonlinear relationship between SBP, DBP, PP and WMH index. See Supplementary Materials for more details.

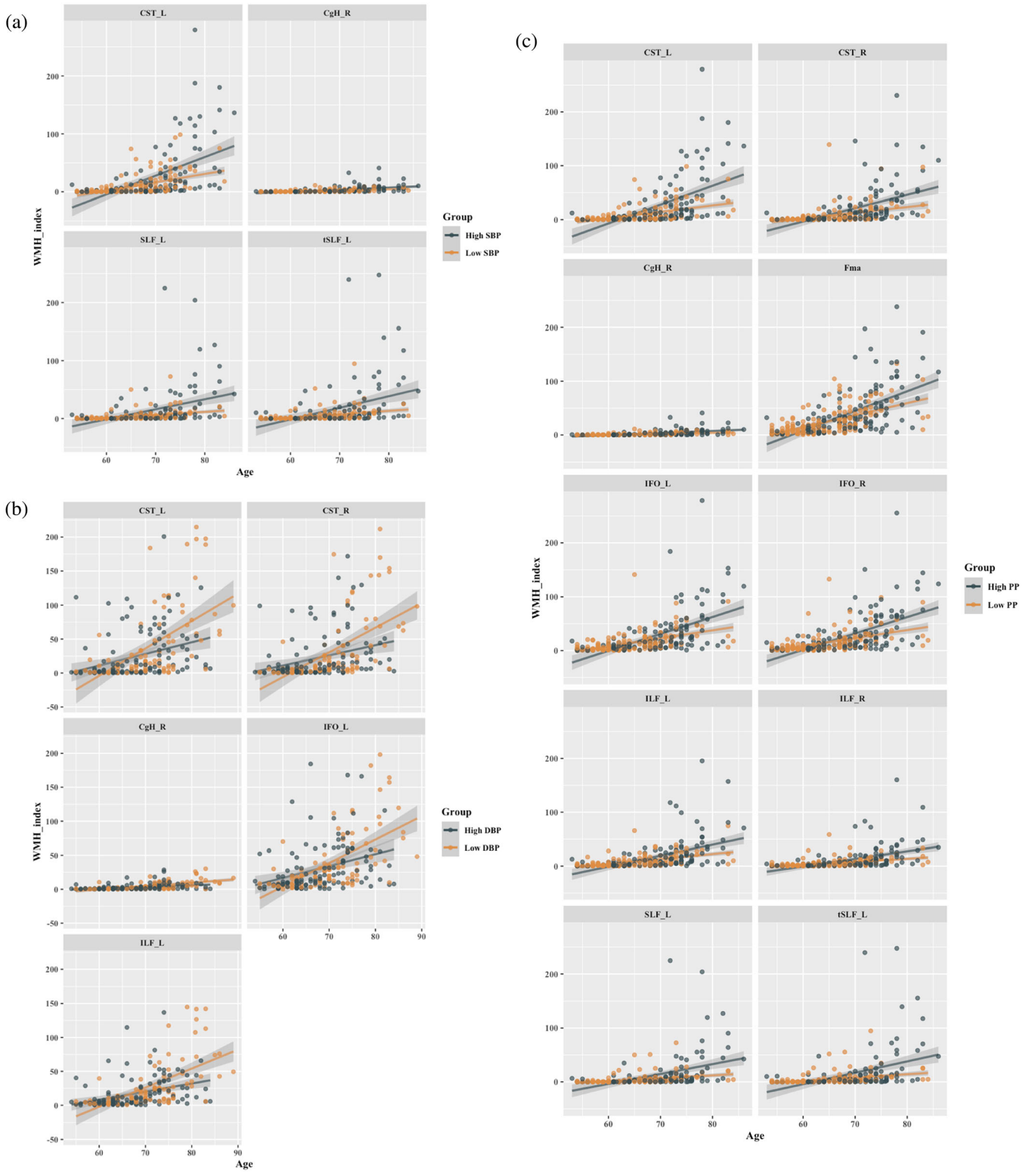

FIGURE 3 Relationship between age and tract-specific WMH index in high-blood pressure and low-blood pressure subjects. Relationship between age and tract-specific WMH index in high SBP and low SBP female subjects (A). Relationship between age and tract-specific WMH index in high DBP and low DBP male subjects (B). Relationship between age and tract-specific WMH index in high PP and low PP female subjects (C). Blood pressure was dichotomized by the median value of SBP, DBP and PP. DBP: diastolic blood pressure; PP: pulse pressure; SBP: systolic blood pressure; WMH_index: white matter hyperintensity index

3.4 | Sensitivity analysis

To minimize the differences between protocols in their WMH measures, we performed a sensitivity analysis. In total, 444 out of 515 (86.21%) participants with data from the same protocol were included in the sensitivity analysis. Basic demographic and clinical characteristics did not differ except for a higher ALP in the female group (Table S6). The positive correlations between DBP and WMH index were attenuated in men. None of the tracts survived the Bonferroni correction. However, the correlations between SBP and WMH index were found in the bilateral CST (left CST, $p < .001$; right CST, $p = .002$), IFO (left IFO, $p = .001$; right IFO, $p = .001$), ILF (left ILF, $p = .001$; right ILF, $p < .001$), left ATR ($p = .001$), CgC ($p = .002$), SLF ($p < .001$), UNC ($p = .001$), tSLF ($p < .001$), and right CgH ($p < .001$) under Bonferroni correction in females. PP was also found to be negatively correlated with WMH index in bilateral CST (left CST, $p < .001$; right CST, $p < .001$), IFO (left IFO, $p < .001$; right IFO, $p < .001$), ILF (left ILF, $p < .001$; right ILF, $p < .001$), left ATR ($p = .001$), SLF ($p < .001$), UNC ($p = .002$), tSLF ($p < .001$), right CgH ($p < .001$), and Fma ($p < .001$) under Bonferroni correction in females. Exclusion of participants from different MRI protocols strengthened the outcomes in women, but attenuated the results in men. See Supplementary Materials for more details.

4 | DISCUSSION

In this community-based sample of middle-aged and elderly adults, we found that men displayed significantly higher WMH index in all white matter tracts than women except for bilateral SLF and tSLF, reflecting an extensive higher WMH load. Our finding showed that high DBP was associated with a higher WMH index on the bilateral CST, left IFO and ILF in men, while high SBP and PP was associated with a lower WMH index on the left CST, SLF, tSLF and right CgH in women. The interaction effect showed that the increase in WMH index over age was greater in high SBP/PP than low SBP/PP in women. In contrast, the increase in WMH index over age was smaller in high DBP than low DBP in men. The findings suggested that vascular pathology contributed differently to white matter injury in men and women.

The majority of previous studies stated that WMHs, whether measured by visual rating scales or volumetric method, were more common in women than in men (De Leeuw et al., 2001; Fatemi et al., 2018; Sachdev et al., 2009). Another study claimed that there was no significant difference of WMH volume between men and women among a broad age ranges (Zhuang et al., 2018). However, in our population-based study, the volume of WMH differed between sexes in all white matter tracts except for bilateral SLF and tSLF, and men showed greater WMH burden than women. One possibility is that an increasing susceptibility for men to develop cerebral vascular diseases than women plays a part. Epidemiological studies demonstrated that men showed twice of the morbidity and mortality rate of coronary heart disease than women, and the mortality rate of stroke was approximately twice as high in men as compared with women up until late in life (Bots et al., 2017; Lerner & Kannel, 1986). Diffusion tensor study has also shown that MD increased more accelerated with age in men than in women, demonstrating that white matter degeneration was more pronounced in men (Abe et al., 2010). In the animal study, remyelination was relatively delayed in males compared to females, which meant that males would be more susceptible to chronically demyelination and might suffer from a greater WMH load (Li et al., 2006). Therefore, the male brain may be more vulnerable to develop WMH. It should be noted that the inconsistent result could also be due to differences in populations in which the studies were conducted, or different analytical methods, i.e., the tract-specific WMH index used in this study instead of the whole-brain WMH volume.

Prior studies have almost invariably shown that there were higher WMH volume among hypertension subjects in cross-sectional studies (Gronewold et al., 2021; Zhao et al., 2019); and hypertension was regarded as a major risk factor for severe WMH in a longitudinal study (Dufouil et al., 2001). Our findings showed that there was a different relationship between BP and WMH index in men and women. In women, high SBP/PP was associated with lower WMH index, suggesting that high SBP/PP may be a protective factor for white matter injury. Compared with the low SBP/PP group, the high SBP/PP group had a greater effect of aging on increasing WMH index. Possibly, as the low SBP/PP group already had a high WMH index, the age effect was limited for them. The thickening of the medial wall of cerebral small vessels, coupled with proliferating intima, increased cerebral vascular resistance in patients with CSVD (Birns et al., 2005). Organ perfusion decreases if perfusion pressure decreases with an increased vascular resistance (Meng, 2021). Previous study found that cerebral perfusion was reduced in areas of WMH compared with areas with normal white matter (Marstrand et al., 2002). It is possible that lower SBP/PP might lead to WMH via altered cerebral perfusion. Additionally, vasomotor reactivity was also impaired by CSVD (Terborg et al., 2000). In subjects with chronic hypertension, the limits of cerebral autoregulation shift upward due to structural vascular adaptation, and a higher BP is needed to maintain adequate cerebral blood flow (Barry, 1985). Hence, patients with established CSVD may require a high SBP/PP to maintain adequate perfusion of deep subcortical structures to prevent further damage to white matter (Birns et al., 2005). The findings of our study extended this viewpoint to the spatial distribution in left CSTs, SLFs, tSLFs, and right CgHs in women. The SLF is thought to act as a conduit for the neural system that maintains attention and engages in visual perception, while the cingulum is thought to promote the valence of somatic sensations, attention, motivation, and memory (Schmahmann et al., 2008). The association with cognition, which we did not attempt to investigate in this study, suggested a potential role of white matter damage that might lead to cognitive dysfunction in the women brain. In men, high DBP was found to be related to higher WMH index, indicating that high DBP was a potential risk factor for white matter injury. The effect of aging on increasing WMH index was higher in the low DBP group as compared with the high DBP group. It is possible that the high DBP group already had a high WMH index, so the age effect was limited for this group. PP widened with lower DBP, causing a

significant degree of resistance in large arteries, while attenuating increases in cerebral microvascular pressure, partly allowing cerebral autoregulation to keep cerebral blood flow (Faraci & Heistad, 1990; Safar et al., 2012). In line with our findings, previous study demonstrated that low DBP levels were related to lower WMH load (Caunca et al., 2020). Our result showed that it seems reasonable to maintain a higher SBP/PP in women in middle-aged and elderly adults, and emphasized the importance of sex stratification when considering the vascular risk on WMH with increasing age.

Strengths of this study are its population-based design and multimodal imaging acquisition protocol with high sensitivity and accuracy for WMH detection and processing. In addition, we assessed a broad range of white matter tracts, providing the possibility to investigate the distinction between different locations of WMH in the brain. Several limitations of the present study should be noted. First, this cross-sectional study restricted the causality interpretation, although it is biologically less possible that white matter injury leads to hypertension instead of vice versa. Second, although the JHU white matter probability map covered a fairly large amount of WMH, some lesions might still be excluded in the white matter tissue. As it is unlikely that this misclassification would be different for the sexes, the resulting bias will be nondifferential. Third, due to partial volume effects, different MRI protocols may result in incorrect localization of WMH. Advanced 3D T2 FLAIR sequences could improve WMH discovery in the future. Lastly, even though the present study employed a relatively large sample size and demographic measures such as education time as covariates, a selection bias might still exist.

In conclusion, men tend to have more WMHs compared to women in our middle-aged and elderly population, highlighting the health advantage for women in older age. According to this study, a higher SBP/PP was associated with a lower WMH burden in women. This suggests that women may benefit from a higher blood pressure in older age. BP related white matter injuries may occur predominantly in association tracts in women. We postulate that such white matter damage consequently contributes to cognitive dysfunction.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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