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RESEARCH ARTICLE

Synergistic associations of *CD33* variants and hypertension with brain and cognitive aging among dementia-free older adults: A population-based study

Min Zhu[1,2,3] | **Xunyao Tian**[2,3] | **Xiaodong Han**[4] | **Yixun Ma**[1,3] | **Wenxin Fa**[1,3] | **Nan Wang**[2,3] | **Rui Liu**[1,2,3] | **Yi Dong**[1,2,3] | **Yifei Ren**[2,3] | **Cuicui Liu**[1,2,3] | **Na Tian**[1,2,3] | **Heng Zhang**[1,2,3] | **Lin Song**[1,2,3] | **Shi Tang**[1,2,3] | **Lin Cong**[1,2,3] | **Yongxiang Wang**[1,2,3,5,6] | **Tingting Hou**[1,2,3] | **Chengxuan Qiu**[1,5,6] | **Yifeng Du**[1,2,3,5] | **Alzheimer's Disease Neuroimaging Initiative**

[1]Key Laboratory of Endocrine Glucose & Lipids Metabolism and Brain Aging, Ministry of Education, Department of Neurology, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, Shandong, P.R. China

[2]Key Laboratory of Endocrine Glucose & Lipids Metabolism and Brain Aging, Ministry of Education, Department of Neurology, Shandong Provincial Hospital, Shandong University, Jinan, Shandong, P.R. China

[3]Shandong Provincial Clinical Research Center for Neurological Diseases, Jinan, Shandong, P.R. China

[4]Innovation Center for Neurological Disorders and Department of Neurology, Xuanwu Hospital, National Clinical Research Center for Geriatric Diseases, Capital Medical University, Beijing, P.R. China

[5]Institute of Brain Science and Brain-Inspired Research, Shandong First Medical University & Shandong Academy of Medical Sciences, Jinan, Shandong, P.R. China

[6]Aging Research Center and Center for Alzheimer Research, Department of Neurobiology, Care Sciences and Society, Karolinska Institute-Stockholm University, Stockholm, Sweden

Correspondence
Yifeng Du, Chengxuan Qiu, and Tingting Hou, Key Laboratory of Endocrine Glucose & Lipids Metabolism and Brain Aging, Ministry of Education, Department of Neurology, Shandong Provincial Hospital Affiliated to Shandong First Medical University, No. 324 Jingwuweiqi Road, Jinan, Shandong 250021, P.R. China.
Email: duyifeng2013@163.com, chengxuan.qiu@ki.se and httl-001@163.com

Some of the data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI)

Abstract

INTRODUCTION: *CD33* rs3865444 and hypertension (HTN) are related to cognitive impairment, individually. However, little is known about their combined effects on cognitive function in older adults.

METHODS: This population-based study included 4368 dementia-free participants (age ≥65 years) in the Multimodal Interventions to Delay Dementia and Disability in Rural China (MIND-China), with data available in 1044 persons for gray matter volume and 85 persons for cerebral blood flow (CBF). We used general linear regression and mediation models to examine the associations of rs3865444 and HTN with cognition, brain atrophy, and CBF.

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database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in the analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

RESULTS: Among rs3865444 CC carriers, HTN and late-life HTN were significantly associated with impaired cognition. Midlife and late-life HTN were correlated with brain atrophy. *CD33* rs3865444 CC moderated the mediation effect of gray matter volume on the association between HTN and global cognition. HTN was correlated with low CBF in rs3865444 CC carriers.

DISCUSSION: There are synergistic associations of *CD33* rs3865444 and HTN with brain and cognitive aging in dementia-free older adults.

KEYWORDS
CD33 rs3865444, cerebral blood flow, cognitive impairment, gray matter, hypertension, population-based study

1 | BACKGROUND

Chronic hypertension (HTN) or elevated blood pressure (BP) is a well-established modifiable risk factor for cognitive impairment and dementia.[1] Numerous observational studies have shown that HTN, especially occurring in midlife, is associated with impaired cognitive function and dementia in old age.[2–4] Indeed, as people age, the strength of association between high BP and risk of cognitive impairment tends to decrease or even reverse, suggesting an age-varying association.[5,6]

The mechanisms linking HTN to cognitive impairment remain poorly understood. It is known that long-term high BP may lead to endothelial dysfunction and impaired cerebrovascular function, resulting in the reduction of cerebral blood flow (CBF).[7,8] Notably, endothelial cells are important components of the blood–brain barrier (BBB), which plays a role in the bidirectional exchange of nutrients and waste products between blood and brain. HTN has been associated with BBB disruption in several animal models.[8] Therefore, impairment of hemodynamic CBF regulation and BBB structure induced by chronic HTN may play a vital role in cognitive decline.[9] In addition, inflammation and immune dysfunction have been involved in the pathogenesis of cerebral atherosclerosis and microvascular lesions due to HTN.[10]

CD33 is a transmembrane glycoprotein that is expressed on the surface of myeloid progenitor cells, such as microglia, mature monocytes, and macrophages. As one of the key microglial receptors, *CD33* is involved in the innate immune pathway associated with anti-inflammatory signaling. Higher *CD33* expression levels in the brain have been associated with cognitive decline and Alzheimer's disease (AD).[11] A single nucleotide polymorphism (SNP), rs3865444, located upstream of the *CD33* gene, is a well-known risk locus for AD.[12] The rs3865444 C allele has been associated with greater cell surface expression of *CD33*, accumulation of amyloid protein in the brain, and increased numbers of activated human microglia.[11] Our previous study revealed an interactive effect of the *CD33* gene and lifestyle for brain health index on cognition, indicating the crucial role of gene–environment interaction in cognitive performance.[13] Further research that integrates genetic and environmental factors with structural brain imaging biomarkers may shed light on the potential mechanisms underlying the gene–environment interaction on cognitive function.

Thus, in this population-based study, we sought to explore the associations of *CD33* rs3865444 and HTN with cognition using data from the Multimodal Interventions to Delay Dementia and Disability in Rural China (MIND-China).[14] Specifically, we aimed (1) to examine the combined association of rs3865444 and HTN with cognitive function and, further, (2) to explore the possible mechanisms underlying the associations. We hypothesized that *CD33* rs3865444 could modify the relationships of HTN, gray matter volume, and cognition, possibly by influencing CBF and BBB functions.

2 | METHODS

2.1 | Study design and study population

This population-based study used data from dementia-free participants recruited within the MIND-China project,[14,15] which is part of the World-Wide FINGERS Network.[16] Figure 1 shows the flowchart of the study participants. In brief, of the 5246 participants who were aged ≥65 years in the baseline assessments of MIND-China in March to September 2018, 302 were diagnosed with dementia. Of the remaining 4944 dementia-free participants, 576 were excluded due to missing information on cognitive tests (n = 403), *CD33* genotypes (n = 139), and BP measurements or use of antihypertensive drugs (n = 34), leaving 4368 participants for the analyses. Of these, data on gray matter volume were available in 1044 persons and CBF in 85 persons. In addition, for further exploration of the influence of *CD33* rs3865444 on the association between HTN and genes related to human brain vasculature,[8,17] 598 dementia-free participants in the Alzheimer's Disease Neuroimaging Initiative (ADNI) database were chosen for the current analysis.

The MIND-China protocol was approved by the ethics committee at Shandong Provincial Hospital affiliated with Shandong First Medical University in Jinan, Shandong. Written informed consent was obtained from all participants or, in the case of cognitively impaired persons, from a proxy (usually a guardian or a family member). MIND-China was registered in the Chinese Clinical Trial Registry (ChiCTR; Registration no.: ChiCTR1800017758). The ADNI protocol was approved by

the Institutional Review Boards of all the participating institutions.[18] Written informed consent was obtained from all participants before protocol-specific procedures were performed. All ADNI studies are conducted according to the Good Clinical Practice guidelines, the Declaration of Helsinki, and U.S. 21 CFR Part 50 (Protection of Human Subjects) and Part 56 (Institutional Review Boards).

2.2 | Data collection and assessments

In MIND-China, the trained medical staff collected data via face-to-face interviews, clinical examinations, cognitive testing, and laboratory tests, as previously described.[14] Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Diabetes was defined by medical history as ascertained by a physician or fasting blood glucose ≥7.0 mmol/L or use of blood glucose-lowering medication. Hyperlipidemia was defined as total serum cholesterol ≥6.2 mmol/L or triglycerides ≥2.3 mmol/L or low-density lipoprotein cholesterol ≥4.1 mmol/L or high-density lipoprotein cholesterol < 1.0 mmol/L or having received drug treatment for hyperlipidemia. After at least a 5-min rest, arterial BP was measured on the subjects' right upper arms. HTN was defined as systolic BP (SBP) ≥140 mmHg or diastolic BP (DBP) ≥90 mmHg, or current use of antihypertensive medicine according to our previous studies.[14] The age at onset of HTN was classified in midlife (onset age < 60 years) and late life (onset age ≥60 years).[19]

2.3 | *Apolipoprotein E* and *CD33* rs3865444 genotyping

Genomic DNA was extracted from venous blood leukocytes using the TIANamp blood DNA kit (Tiangen, Beijing, China) according to the manufacturer's instructions.[20] Sequencing libraries were generated using MultipSeqCustom Panel (iGeneTech, Beijing, China) and index codes were added to each sample. Qualified libraries were subjected to next-generation sequencing on a Novaseq system (Illumina). Raw reads were filtered to remove the low-quality reads by using FastQC. Genotypes of *CD33* rs3865444 and *apolipoprotein E* (*APOE*) SNPs were detected using a multiplex polymerase chain reaction assay.

2.4 | Cognitive assessments

Cognitive function was assessed at baseline in March to September 2018 by trained research staff via in-person interviews using a neuropsychological test battery that has been validated among Chinese rural adults.[21] In brief, we assessed the function of four specific cognitive domains: episodic memory (auditory verbal learning test [AVLT] – immediate recall, long-delayed free recall, and long-delayed recognition), verbal fluency (verbal fluency test [VFT] – categories of animals, fruits, and vegetables), attention (digit span test [DST] – forward and trail making test [TMT] A), and executive function (DST-backward and TMT B).[14,22] The raw test score for each cognitive test in a given cognitive domain was standardized into *z*-score, and then the composite *z*-score for the cognitive domain was calculated by averaging the *z*-scores of the tests for that domain. Then the global cognitive *z*-score was calculated by averaging the *z*-scores of at least two cognitive domains. In addition, we defined mild cognitive impairment (MCI) following the Petersen's criteria that were operationalized in the Mayo Clinic Study of Aging, as previously described.[22,23]

RESEARCH IN CONTEXT

1. **Systematic review**: The authors searched PubMed for relevant literature. Evidence has emerged that inflammatory and immune mechanisms are involved in the relationship between hypertension (HTN) and cognitive impairment. However, no research has examined the joint effect of HTN and *CD33*, an immune-related genetic susceptibility locus for cognitive impairment, on cognitive function in older adults.
2. **Interpretation**: HTN was associated with poor cognition and small cerebral blood flow in *CD33* rs3865444 CC carriers. rs3865444 also regulates the mediating effects of gray matter volume in the HTN–cognition association. These findings suggested the importance of the combined effects of genetic and HTN on cognitive function.
3. **Future directions**: Future studies should further elucidate the molecular mechanisms of *CD33* rs3865444-dependent effects of HTN and blood–brain barrier–related genes on cognitive and brain aging. Furthermore, the early identification of persons at risk could be a valuable preventive strategy to at least delay their evolution toward dementia.

2.5 | MRI acquisition and assessments of gray matter volume and CBF

In the MRI substudy of MIND-China, participants were scanned either on the Philips Ingenia 3.0T MR System (General Electric Company, Waukesha, WI, USA) in Southwestern Lu Hospital or the Philips Archiva 3.0T MR System (General Electric Company, Waukesha, WI, USA) in Liaocheng People's Hospital. The MRI protocols (acquisition, sequences, processing, and quantification) were previously described in detail.[14] We used AccuBrain (BrainNow Medical Technology Ltd., Shenzhen, Guangdong, China) to assess the volume of total gray matter and total intracranial volume (ICV) using the T1-weighted images. The ICV was estimated as the sum of gray matter, white matter, and cerebrospinal fluid volume. Resting-state CBF was evaluated using a

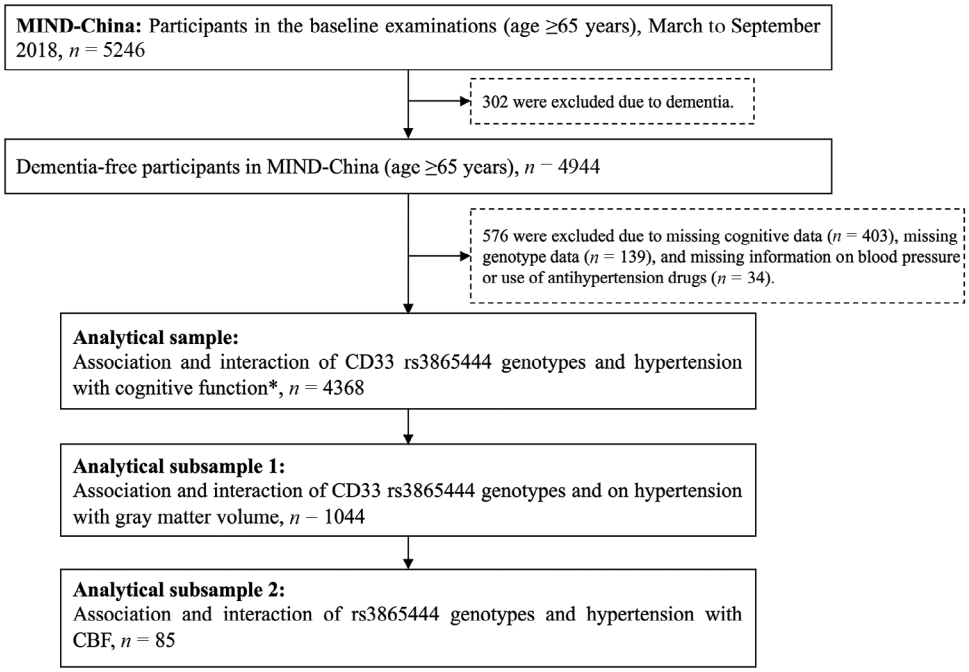

FIGURE 1 Flowchart of study participants in MIND-China, March to September 2018. *The sample sizes of cognition for analysis were 4368 for global cognition, 4312 for memory, 4362 for verbal fluency, 4349 for attention, and 4311 for executive function. CBF, cerebral blood flow; MIND-China, Multimodal Interventions to Delay Dementia and Disability in Rural China.

pseudo-continuous arterial spin labeling (pcASL) sequence with three-dimensional fast spin-echo acquisition performed in Liaocheng People's Hospital, following the protocols described in previous studies.[24] CBF was estimated in the whole brain, whole gray matter, frontal lobe (left and right), parietal lobe (left and right), temporal lobe (left and right), and occipital lobe (left and right).

2.6 | ADNI data acquisition and processing

Data on *CD33* rs3865444 genotypes, HTN, and gene expression microarray were obtained from the ADNI database (adni.loni.usc.edu). The genotypes of *CD33* rs3865444 were obtained from the ADNI genome-wide association study (GWAS) datasets using PLINK software (version 1.90).[25] HTN was defined by whether a participant had a SBP ≥140 mmHg or DBP ≥90 mmHg at baseline in ADNI VITALs or if a history of HTN was described in ADNI MODHACH.[26] Gene expression profiling from the blood samples of the participants was processed using R packages affy and limma. The processing procedures included probe ID conversion, deduplication, and batch normalization.[27] Then the mRNA expressions of genes related to human brain vasculature,[8,17] which participated in the regulation of CBF and BBB function, were extracted from the normalized expression files.

The ADNI was launched in 2003 as a public–private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial MRI, positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessments can be combined to measure the progression of MCI and early AD.

2.7 | Statistical analysis

We used student's *t* test to compare differences in continuous variables and χ^2 test for categorical variables. The χ^2 test was used to test Hardy–Weinberg equilibrium. In the total samples, we analyzed the associations of HTN with cognition, gray matter volume, and CBF using multivariable linear regression models. To determine the interactive effects of HTN and *CD33* on cognition, multivariable linear regression analyses separately modeled cognitive *z*-scores (global cognition, memory, verbal, attention, and executive function) as a function of HTN, *CD33* variant, and their interaction. Multivariable linear regression analyses were also used to examine the interaction of HTN and *CD33* rs3865444 on gray matter volume and CBF. If a statistical interaction was detected (p for interaction < 0.05), further stratified analyses by *CD33* rs3865444 genotypes were performed to determine the magnitude and direction of the associations of HTN with cognition and CBF, respectively. We reported the results from two models: Model 1 was adjusted for age, sex, education, and *APOE* genotypes; and in Model 2, we further controlled for BMI, smoking, alcohol consumption, and clinical conditions (history of stroke, diabetes, hyperlipoidemia, and coronary heart disease). The use of HTN medication was additionally adjusted in the analyses involving BP measurements and onset age of HTN. Total ICV and MRI scan centers were also

adjusted for when MRI-related indicators were analyzed. In the mediation analysis, we adjusted for age, sex, education, *APOE* genotypes, BMI, smoking, alcohol consumption, clinical conditions, ICV, and MRI scan centers.

For independent and dependent variables, participants with missing values were excluded from the analyses. For covariates, missing values were imputed with mean for continuous variables and were recoded as dummy variables for categorical variables. We used R version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria) for the main analyses. The moderated mediation analysis was conducted using the bruceR package. Two-tailed $p < 0.05$ was considered statistically significant. For the analysis of ADNI data, multiple unpaired *t* tests were used to compare the differences among different groups by Graphpad Prism (version 9.1.1). *P* values were adjusted by false discovery rate (FDR). The statistical significance was defined as the FDR-adjusted *p* value < 0.05.

3 | RESULTS

3.1 | Characteristics of study population

The mean age of the 4368 participants was 70.99 (standard deviation = 4.70) years, 56.27% were women, 16.02% were *APOE* ε4 allele carriers, and 36.95% were illiterate (Table S1). Compared to participants carrying *CD33* rs3865444 CC genotype, those with AA+AC genotypes were more likely to carry the *APOE* ε4 allele ($p < 0.001$) and have reduced CBF in the right frontal lobe ($p = 0.040$) and right temporal lobe ($p = 0.030$). The two groups did not differ significantly in the distribution of age, sex, BMI, educational levels, smoking, alcohol consumption, history of HTN, diabetes, hyperlipidemia, coronary heart disease, and stroke and in mean BP, cognitive *z*-scores, gray matter volume, ICV, and CBF of eight other brain regions ($p > 0.05$).

3.2 | Association and interaction of *CD33* rs3865444 and HTN with cognitive performance (*n* = 4368)

The multivariable-adjusted β coefficients (95% confidential intervals) associated with HTN were −0.038 (−0.073, −0.004) for global cognition, −0.022 (−0.076, 0.032) for memory, −0.049 (−0.097, −0.001) for verbal fluency, −0.025 (−0.072, 0.021) for attention, and −0.058 (−0.106, −0.010) for executive function in the total sample (Table 1 and Tables S2 and S3). We detected a statistically significant interaction of HTN and *CD33* rs3865444 with global cognition (*p* for interaction = 0.028; Table 1 and Figure S1) and attention (*p* for interaction = 0.010 and Table S3), but not for memory, verbal fluency, or executive function in multivariable linear regression analyses. In the stratified analyses, HTN was significantly associated with lower *z*-scores of global cognition and attention, even in the multivariable-adjusted model (β = −0.064 [−0.107, −0.022]) for global cognition;

TABLE 1 Associations of HTN with global cognition in total sample and by *CD33* rs3865444 genotypes (*n* = 4368).

	Total sample (*n* = 4368)		*CD33* rs3865444 CC carriers (*n* = 2840)		*CD33* rs3865444 AA + AC carriers (*n* = 1528)	
HTN status	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
HTN						
No (*n* = 1441)	0.000 (reference)	0.000 (reference)	0.000 (reference)	0.000 (reference)	0.000 (reference)	0.000 (reference)
Yes (*n* = 2927)	−0.036 (−0.070, −0.002)*	−0.038 (−0.073, −0.004)*	−0.064 (−0.107, −0.022)*	−0.064 (−0.107, −0.022)*	0.019 (−0.039, 0.077)	0.012 (−0.047, 0.071)
HTN by onset age						
No (*n* = 1441)	0.000 (reference)	0.000 (reference)	0.000 (reference)	0.000 (reference)	0.000 (reference)	0.000 (reference)
Midlife (*n* = 514)	−0.036 (−0.095, 0.023)	−0.035 (−0.095, 0.025)	−0.043 (−0.116, 0.029)	−0.038 (−0.111, 0.036)	−0.026 (−0.128, 0.077)	−0.035 (−0.139, 0.069)
Late life (*n* = 2413)	−0.033 (−0.07, 0.005)	−0.039 (−0.076, −0.002)*	−0.050 (−0.096, −0.004)*	−0.056 (−0.102, −0.010)*	0.002 (−0.061, 0.065)	−0.007 (−0.070, 0.056)

Note: P for HTN×rs3865444 interaction on global cognition = 0.028. β coefficients (95% confidential intervals) were adjusted for age, sex, education, and *APOE* genotypes in Model 1 and additionally adjusted for BMI, smoking, alcohol consumption, and clinical conditions in Model 2.

Abbreviations: BMI, body mass index; HTN, hypertension.

*$p < 0.05$.

TABLE 2 Association between HTN and gray matter volume in total MRI sample ($n = 1044$).

	Model 1		Model 2	
HTN status	**β coefficient (95% CI)**	***p* value**	**β coefficient (95% CI)**	***p* value**
HTN				
No ($n = 331$)	0.000 (reference)		0.000 (reference)	
Yes ($n = 713$)	−2.589 (−5.02, −0.157)	0.037	−3.698 (−6.162, −1.234)	0.003
HTN by onset age				
No ($n = 331$)	0.000 (reference)		0.000 (reference)	
Midlife ($n = 121$)	−6.134 (−10.459, −1.809)	0.005	−7.752 (−12.133, −3.371)	0.001
Late life ($n = 592$)	−1.930 (−4.590, 0.730)	0.155	−2.707 (−5.356, −0.058)	0.045

Note: β coefficients (95% confidence intervals) were adjusted for age, sex, education, *APOE* genotype, total ICV, and magnetic resonance imaging center in Model 1, and additionally adjusted for BMI, smoking, alcohol consumption, and clinical conditions in Model 2.
Abbreviations: BMI, body mass index; CI, confidential interval; HTN, hypertension; ICV, intracranial volume; MRI, magnetic resonance imaging.

$\beta = -0.073$ [−0.130, −0.015] for attention) among *CD33* rs3865444 CC-homozygote carriers, but not among *CD33* rs3865444 A carriers (Table 1 and Table S3).

When HTN was analyzed by onset age, we found that late-life onset HTN ($\beta = -0.056$ [−0.102, −0.010]), but not midlife onset HTN, was significantly associated with lower global cognitive *z*-score among *CD33* rs3865444 CC carriers (Table 1). Similar results for attention were observed (Table S3). In contrast, regardless of the HTN onset age, HTN was not significantly associated with cognitive function among *CD33* A carriers.

An elevated SBP (per 10-mmHg increase) was significantly correlated with reduced *z*-scores of global cognition (multivariable-adjusted $\beta = -0.015$; 95% CI: −0.022, and −0.007) and attention (−0.018; −0.029, and −0.007), while DBP was only significantly associated with a reduced global cognitive *z*-score (−0.018; −0.033, −0.003; and Table S4). No statistically significant interaction was detected between BP measurements and *CD33* rs3865444 genotypes on cognition.

3.3 | Association between HTN and total gray matter volume in total sample ($n = 1044$)

The multivariable-adjusted β coefficient (95% CI) of gray matter volume associated with HTN was −3.698 (−6.162, −1.234) (Table 2). In addition, when HTN was analyzed by onset age, we found that midlife and late-life onset HTN were both associated with reduced total gray matter volume (−7.752; −12.133, −3.371 for midlife HTN; −2.707; −5.356, −0.058 for late-life HTN; Table 2). Notably, per 10-mmHg increase in SBP and DBP was correlated with multivariable-adjusted β coefficient of −0.947 (−1.521, −0.374) and −1.756 (−2.793, −0.719), respectively, for total brain tissue volume (Table S4). No statistically significant interaction between HTN or BP measurements and *CD33* rs3865444 on total gray matter volume was detected.

3.4 | *CD33* rs3865444-dependent mediation of gray matter in association of HTN with global cognition ($n = 1044$)

In the total MRI subsample ($n = 1044$), gray matter volume could partially mediate the association of HTN with global cognition ($\beta = -0.012$; 95% CI: −0.024, −0.003; mediation effect: 11.01%; Figure 2A). Notably, among carriers of the *CD33* rs3865444 CC homozygotes, total gray matter volume significantly mediated the association of HTN with global cognition ($\beta = -0.013$; 95% CI: −0.028, −0.002), with the proportion of mediation being 8.18% of the total effects (Figure 2B). By contrast, among the *CD33* rs3865444 A carriers, there was no significant mediation of gray matter volume in the association of HTN with global cognition ($\beta = -0.010$; 95% CI: −0.033, 0.002; and Figure 2B).

When BP measurements were analyzed as continuous variables, each 10-mmHg increase in SBP was associated with a multivariable-adjusted β coefficient of −0.003 (−0.006, −0.001) for global cognitive function, with the proportion of mediation by gray matter volume being 15%. In addition, each 10-mmHg increase in DBP was significantly associated with a multivariable-adjusted β coefficient of −0.006 (−0.011, −0.002) for global cognition, with the proportion of mediation by gray matter volume being 31.58%. We further conducted mediation analysis by *CD33* rs3865444 genotypes. The analysis showed that the observed mediation was significant among the *CD33* rs3865444 CC carriers (SBP: $\beta = -0.004$ [−0.007, −0.001]; mediation effect: 16%; DBP: $\beta = -0.006$ [−0.013, −0.001]; mediation effect: 30%; Figure S2). No significant mediation effect was found in the rs3865444 AA+AC carriers (Figure S2).

3.5 | Association and interaction of *CD33* rs3865444 and HTN with CBF ($n = 85$)

The multivariable-adjusted β coefficients (95% CI) of CBF associated with HTN were −2.313 (−5.687, 1.060) for the whole brain, −2.757

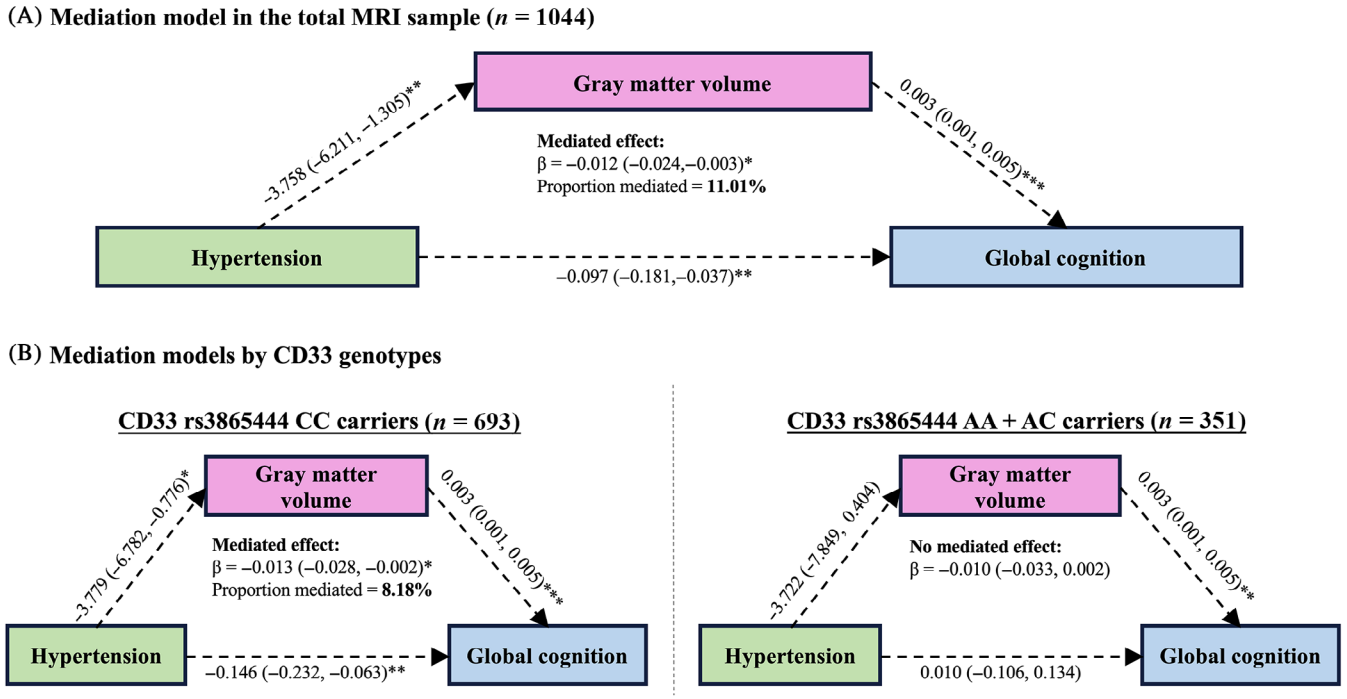

FIGURE 2 Gray matter volume partially mediates association of HTN with global cognition in total MRI sample and among *CD33* rs3865444 CC carriers ($n = 1044$). $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$. HTN, hypertension; MRI, magnetic resonance imaging.

(−6.458, 0.945) for gray matter, −1.574 (−4.632, 1.484) for left frontal lobe, −3.084 (−6.203, 0.035) for right frontal lobe, −2.006 (−5.983, 1.971) for left parietal lobe, −3.243 (−7.621, 1.135) for right parietal lobe, −3.318 (−6.828, 0.192) for right temporal lobe, −1.695 (−5.187, 1.797) for left temporal lobe, −1.650 (−6.185, 2.886) for left occipital lobe, and −2.711 (−7.210, 1.788) for right occipital lobe (Tables 3 and Table S5). Multivariable linear regression analyses revealed a significant interaction of HTN with *CD33* rs3865444 on CBF at different brain regions, including the whole brain (p for interaction = 0.031), gray matter (p for interaction = 0.019), left frontal lobe (p for interaction = 0.010), right frontal lobe (p for interaction = 0.009), left parietal lobe (p for interaction = 0.021), and right temporal lobe (p for interaction = 0.023; Table 3 and Figure S3). The analyses stratified by *CD33* rs3865444 genotypes suggested that HTN was significantly associated with reduced CBF in the aforementioned brain regions among *CD33* rs3865444 CC-homozygote carriers, but not among *CD33* rs3865444 A carriers (Table 3).

3.6 | Combined effects of *CD33* rs3865444 CC genotype and HTN on expression of genes related to human brain vasculature in ADNI ($n = 598$)

To elucidate the mechanisms underlying the regulation of *CD33* rs3865444 on the association of HTN and CBF, we used ADNI data to further examine whether *CD33* rs3865444 could modify the association of HTN with mRNA expressions of genes related to human brain vasculature, which were involved in the regulation of CBF and BBB function ($n = 598$; Table S6). Among carriers of the *CD33* rs3865444 CC genotype ($n = 300$), participants with HTN ($n = 209$) showed higher expression in seven genes (ie, *LGALS3*, *PDGFRB*, *SLC38A5*, *MT1A*, *CNN1*, *RGS16*, and *AGT*) than those without HTN (FDR < 0.05; Figure 3 and Table S6). However, HTN was not significantly associated with the expression of any of the seven genes among *CD33* rs3865444 A carriers ($n = 298$; HTN: $n = 196$; FDR > 0.05; Figure 3 and Table S6).

3.7 | Sensitivity analysis

To assess the impact of MCI on the main results, we repeated the analyses among participants who were free of MCI ($n = 3198$), which yielded results that were overall similar to those from the aforementioned main analyses (Tables S7 to S10, Figure S4).

4 | DISCUSSION

The current study revealed the synergistic association of *CD33* rs3865444 and HTN with poor cognition, brain atrophy, and impaired CBF in dementia-free older individuals. Specifically, among *CD33* rs3865444 CC homozygotes, HTN was associated with poorer attention and global cognition, smaller gray matter volume, and lower CBF, whereas among carriers of the *CD33* rs3865444 A allele, HTN was not related to cognition, brain volume, or CBF. Notably, the *CD33* rs3865444 CC genotype appeared to moderate the mediation effect of gray matter volume in the association between HTN and poor global cognition. Moreover, data from the ADNI cohort showed that mRNA expressions of genes related to human brain vasculature were higher

TABLE 3 Association of HTN with CBF in MRI sample with ASL images and by *CD33* rs3865444 genotypes ($n = 85$).

	Total MRI sample with ASL images ($n = 85$)		*CD33* rs3865444 CC carriers ($n = 57$)		*CD33* rs3865444 AA + AC carriers ($n = 28$)	
CBF by brain region	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
Whole brain	−3.038 (−6.214, 0.137)	−2.313 (−5.687, 1.060)	−5.813 (−10.407, −1.219)*	−5.047 (−10.015, −0.079)*	1.005 (−2.924, 4.933)	1.707 (−3.684, 7.098)
Gray matter	−3.603 (−7.089, −0.118)*	−2.757 (−6.458, 0.945)	−6.910 (−11.916, −1.903)*	−6.150 (−11.567, −0.734)*	1.177 (−3.211, 5.565)	2.124 (−3.889, 8.136)
Frontal lobe (left)	−2.269 (−5.103, 0.565)	−1.574 (−4.632, 1.484)	−5.215 (−9.274, −1.156)*	−4.766 (−9.342, −0.189)*	2.024 (−1.383, 5.431)	2.553 (−1.929, 7.035)
Frontal lobe (right)	−3.8 (−6.715, −0.886)*	−3.084 (−6.203, 0.035)	−6.940 (−11.022, −2.857)*	−6.670 (−11.068, −2.272)*	0.957 (−2.746, 4.659)	1.286 (−3.595, 6.167)
Parietal lobe (left)	−2.718 (−6.43, 0.994)	−2.006 (−5.983, 1.971)	−6.370 (−11.592, −1.149)*	−5.263 (−11.070, 0.543)	2.814 (−2.189, 7.818)	3.466 (−3.283, 10.215)
Temporal lobe (right)	−4.084 (−7.391, −0.777)*	−3.318 (−6.828, 0.192)	−7.194 (−11.980, −.409)*	−6.433 (−11.569, −1.297)*	0.289 (−3.677, 4.255)	0.849 (−4.702, 6.400)

Note: *P* for HTNxrs3865444 interaction on CBF of whole brain, gray matter, left frontal lobe, right frontal lobe, left parietal lobe, and right temporal lobe = 0.031, 0.019, 0.010, 0.009, 0.021, and 0.023, respectively. β coefficients (95% confidential intervals) were adjusted for age, sex, education, and *APOE* genotypes in Model 1 and additionally adjusted for BMI, smoking, alcohol consumption, and clinical conditions in Model 2.
Abbreviations: ASL, arterial spin labeling; BMI, body mass index; CBF, cerebral blood flow; HTN, hypertension; MRI, magnetic resonance imaging.
*$p < 0.05$.

in HTN individuals than those without HTN among *CD33* rs3865444 CC homozygotes, suggesting a role of HTN in vascular injury mechanisms. Importantly, findings from the sensitivity analysis among older individuals free of MCI were robust.

As a transmembrane receptor protein involved in the innate immune pathway, *CD33* is correlated with beta amyloid (Aβ) clearance and cognition in AD mouse models.[28] The mendelian randomization study showed evidence of the causal relationship of elevated peripheral expression of *CD33* to the development of AD.[29] GWAS studies have also linked *CD33* rs3865444 A allele with reduced risk of AD.[12] The *CD33* rs3865444 A allele is a protective allele, whereas the C allele is a relatively risky allele for AD.[30] Our study revealed for the first time the synergistic association of *CD33* variants and HTN with poor cognitive function. We observed that HTN was associated with poor cognition among CC homozygous carriers, but not among A allele carriers. Previous studies also indicated that the *CD33* rs3865444 CC genotype was associated with accelerated cognitive decline.[31,32] Of note, we found that late-life HTN, but not midlife HTN, was associated with poor cognitive performance in the CC homozygous group, which needs further exploration. Taken together, our results suggest a potential link between HTN and poor cognitive function that might vary by *CD33* rs3865444 genotype.

To explore the mechanisms underlying the association of HTN with poor cognitive function, we further investigated the relationship between HTN and brain atrophy by *CD33* rs3865444 genotype. We found that individuals with *CD33* rs3865444 CC homozygotes with HTN had more severe gray matter atrophy than those without HTN. Interestingly, among CC homozygous carriers, midlife HTN showed a stronger association with brain atrophy than late-life HTN. This may reflect the long-term cumulative effect of HTN on brain health and cognitive function that is of particularly concern among *CD33* CC carriers. However, we found that the association with poor cognitive function was evident for late-life HTN but not for midlife HTN; the impact of selective survival associated with midlife HTN deserves further investigation. Furthermore, we found that the mediation effect of gray matter volume on the association between HTN and poor global cognition was evident mainly among *CD33* rs3865444 CC carriers. The current literature[33,34] suggested that HTN could cause cognitive impairment via oxidative stress, vascular injury, white matter hyperintensities, and so on. In our study, the results indicated that, besides these pathways, HTN may impair global cognitive function in part by decreasing gray matter volume, particularly in *CD33* rs3865444 CC carriers. This suggests the important role of the *CD33* rs3865444 genotype in the relationships among HTN, brain atrophy, and cognition. Previous studies showed that the genetic variations in *CD33* were associated with brain atrophy.[35] Some studies also demonstrated an association of elevated BP with low gray matter volume and poor cognitive function.[36,37] Our study further highlights the importance of the combined effects of genetic susceptibility and HTN on cognitive phenotypes in old age. Overall, there is potential that among *CD33* rs3865444 carriers, chronic HTN may contribute to accelerated cognitive decline through gray matter atrophy.

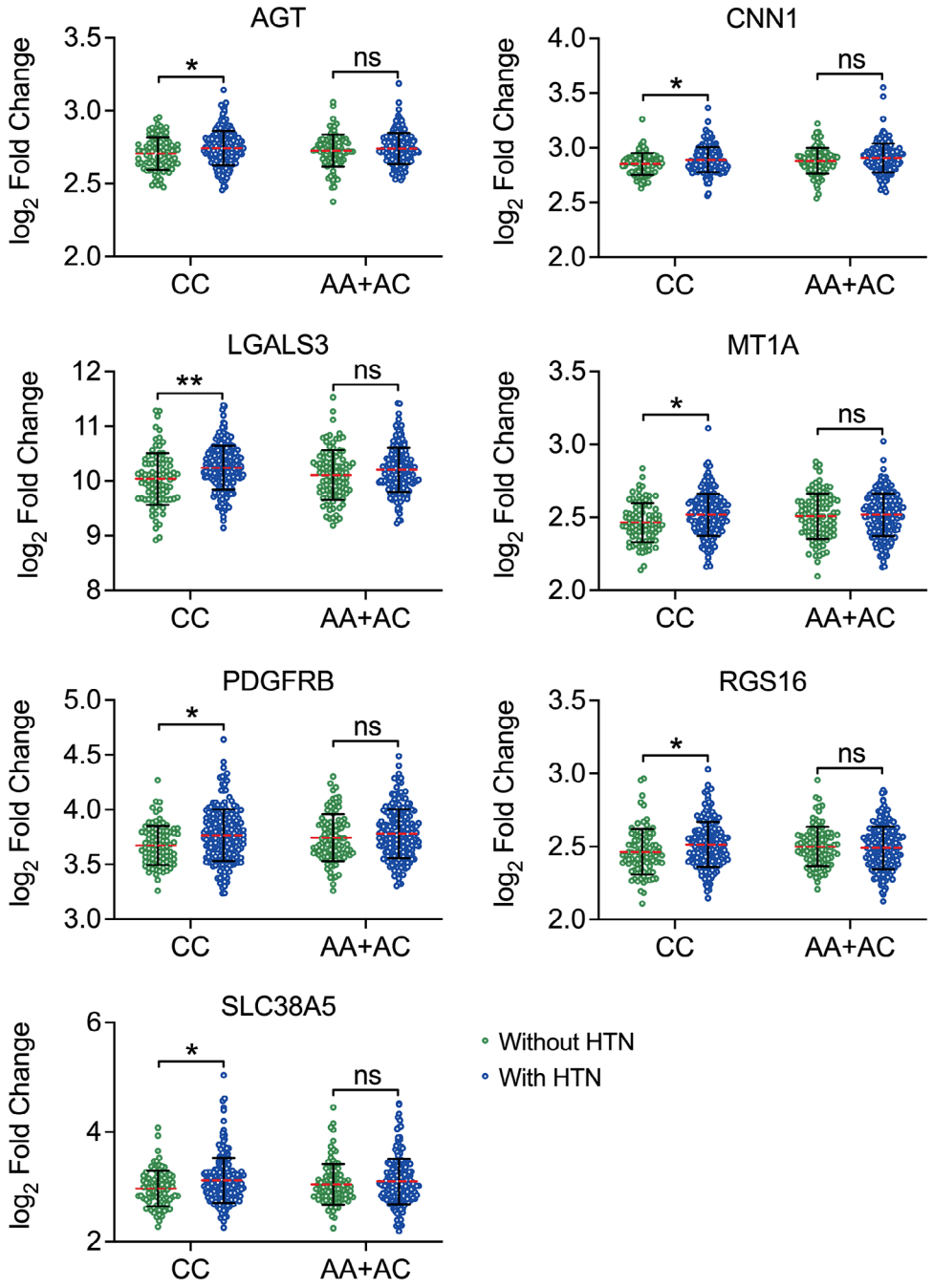

FIGURE 3 Differences in expression of genes associated with brain vasculature between individuals with and without HTN among *CD33* rs3865444 CC carriers ($n = 300$) and rs3865444 AA+AC carriers ($n = 298$) from ADNI dataset. Data were presented as mean (standard deviation). ADNI, Alzheimer's Disease Neuroimaging Initiative; AGT, angiotensinogen; CNN1, calponin 1; FDR, false discovery rate; HTN, hypertension; LGALS3, Galectin 3; MT1A, Metallothionein 1A; ns, no significance; PDGFRB, platelet-derived growth factor receptor beta; RGS16, regulator of G protein signaling 16; SLC38A5, solute carrier family 38 member 5. *FDR < 0.05; **FDR < 0.01.

We found that HTN was associated with reduced CBF in *CD33* rs3865444 CC carriers, suggesting that CBF was dysregulated in people with HTN and the rs3865444 CC genotype. Additional analysis of ADNI data indicated that genes related to human brain vasculature, which play important roles in CBF modulation and BBB function, did show higher mRNA expressions in individuals with HTN than those without HTN among rs3865444 CC carriers. These genes are *LGALS3*, *PDGFRB*, *SLC38A5*, *MT1A*, *CNN1*, *RGS16*, and *AGT*. *LGALS3*, which encodes a member of the galectin family of carbohydrate-binding proteins, was found to be related to neurogenesis, inflammation, and endothelial functions.[38] *PDGFRB* was supposed to restore the pericyte and BBB function.[39] *SLC38A5*, expressed in endothelial cells, can act as a serine and glutamine transporter at the BBB, which is essential for brain development.[40] *MT1A*, a member of the metallothionein family,

and *RGS16*, known as a regulator of G protein signaling 16, were found to modulate smooth muscle cell proliferation and migration.[17] *CNN1*, which is involved in the negative regulation of vascular smooth muscle cell proliferation, could induce the senescence of cerebral endothelial cells and astrocytes.[17] *AGT*, known as angiotensinogen, can eventually generate the physiologically active enzyme angiotensin II, which could initiate BBB disruption and cause neurovascular coupling impairment.[9] The differential expression of these genes may indicate the dysfunction of BBB and its influence on CBF. Therefore, it revealed that the *CD33* rs3865444 CC genotype and HTN may interact to affect CBF and BBB function.

Our study is the first population-based study to identify the potential modifying roles of *CD33* rs3865444 in the association of HTN with poor cognition and the possible underlying mechanisms among dementia-free Chinese older adults. However, the study has several limitations. First, it is a cross-sectional observational study, and information on onset age of HTN was collected retrospectively, so we cannot rule out the possible impacts of reverse causality and information bias for the observed associations. Future prospective cohort studies are needed to further reveal their cause-and-effect relationships. Second, our study sample was derived only from one rural area, and the analytical sample was relatively healthy. Thus, caution is needed when generalizing our research findings to other rural populations. Third, other mechanisms related to HTN, such as vessel wall thickening, atherosclerosis, and decreased perivascular drainage, may also affect brain structure and deposition of beta-amyloid and, thus, influence cognition, which deserves further exploration.

In summary, our study reveals a synergistic association of HTN and *CD33* variants with poor global cognition in cognitively unimpaired older adults, suggesting the importance of genetic variations in the HTN–cognition relationship. Moreover, HTN was related to gray matter atrophy and reduced CBF mainly among *CD33* rs3865444 CC carriers. Finally, using the ADNI dataset, we found that BBB dysfunction may also be a potential factor affecting the modulation of the *CD33* rs3865444 CC genotype in the association between HTN and cognition. Further investigations are needed to elucidate the molecular mechanisms of *CD33* rs3865444-dependent effects of HTN and BBB-related genes on cognition and brain aging. Furthermore, early identification of persons at risk could lead to the development of effective interventions to at least delay their progression toward clinical dementia.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Author disclosures are available in the Supporting Information.

DATA AVAILABILITY STATEMENT

The MIND-China data that support the findings of this study are available from the corresponding authors upon reasonable request.

CONSENT STATEMENT

Written informed consent was obtained from all participants or, in the case of cognitively impaired persons, from an informant (usually a guardian or a family member).

ORCID

Yifeng Du https://orcid.org/0000-0002-4672-6654

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