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RESEARCH ARTICLE

Association of enlarged perivascular spaces with cognitive function in dementia-free older adults: A population-based study

Mingqing Zhao[1,2] | **Yuanjing Li**[3] | **Xiaodong Han**[4] | **Chunyan Li**[1] | **Pin Wang**[4] | **Jiafeng Wang**[4] | **Tingting Hou**[1,4] | **Yongxiang Wang**[1,3,4,5] | **Lin Cong**[1,4] | **Joanna M. Wardlaw**[6] | **Lenore J. Launer**[7] | **Lin Song**[1,4] | **Yifeng Du**[1,4,5] | **Chengxuan Qiu**[1,3,4,5]

[1]Department of Neurology, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, Shandong, P. R. China

[2]Department of Neurology, Xuanwu Hospital Capital Medical University Jinan Branch, Jinan, Shandong, P. R. China

[3]Aging Research Center, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet-Stockholm University, Solna, Sweden

[4]Department of Neurology, Shandong Provincial Hospital, Shandong University, Jinan, Shandong, 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]Centre for Clinical Brain Sciences, UK Dementia Research Institute, University of Edinburgh, Edinburgh, UK

[7]Laboratory of Epidemiology and Population Sciences, Intramural Research Program, National Institute on Aging, National Institutes of Health, Baltimore, Maryland, USA

Correspondence
Yifeng Du and Lin Song, Department of Neurology, Shandong Provincial Hospital, Shandong University, No. 324 Jingwu Road, Jinan, Shandong 250021, P. R. China.
Email: duyifeng2013@163.com and zzusonglin@163.com

Yifeng Du, Chengxuan Qiu, and Lin Song share the senior authorship.

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Abstract

Introduction: We sought to characterize cognitive profiles associated with enlarged perivascular spaces (EPVS) among Chinese older adults.

Methods: This population-based study included 1191 dementia-free participants (age ≥60 years) in the MIND-China MRI Substudy (2018–2020). We visually evaluated EPVS in basal ganglia (BG) and centrum semiovale (CSO), white matter hyperintensities (WMHs), lacunes, cerebral microbleeds (CMBs), and cortical superficial siderosis. We used a neuropsychological test battery to assess cognitive function. Data were analyzed using general linear models.

Results: Greater BG-EPVS load was associated with lower *z*-scores in memory, verbal fluency, and global cognition ($p < 0.05$); these associations became non-significant when controlling for other cerebral small vessel disease (CSVD) markers (e.g., WMHs, lacunes, and mixed CMBs). Overall, CSO-EPVS load was not associated with cognitive *z*-scores ($p > 0.05$); among apolipoprotein E (*APOE*) -ε4 carriers, greater CSO-EPVS load was associated with lower verbal fluency *z*-score, even when controlling for other CSVD markers ($p < 0.05$).

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Discussion: The associations of BG-EPVS with poor cognitive function in older adults are largely attributable to other CSVD markers.

KEYWORDS

APOE genotype, cognitive function, enlarged perivascular spaces, magnetic resonance imaging, population-based study

HIGHLIGHTS

- The association of enlarged perivascular spaces (EPVS) with cognitive function in older people is poorly defined.
- The association of basal ganglia (BG)-EPVS with poor cognition is attributed to other cerebral small vessel disease (CSVD) markers.
- In apolipoprotein E (*APOE*) ε4 carriers, a higher centrum semiovale (CSO)-EPVS load is associated with poorer verbal fluency.

1 | BACKGROUND

Perivascular spaces (PVS) are fluid-filled cavities that surround small arterioles, capillaries, and venules in the brain traveling from the brain surface into the parenchyma.[1] Enlarged perivascular spaces (EPVS) visible on magnetic resonance imaging (MRI) scans, as an emerging marker of cerebral small vessel disease (CSVD),[2] are indicative of impaired clearance of cerebrospinal fluid (CSF) and metabolic products (i.e., glymphatic dysfunction) in the brain parenchyma.[3,4] The population-based Vanderbilt Memory and Aging Project Study of dementia-free older adults suggested that a higher EPVS burden was associated with poorer information-processing speed and executive function.[5] However, a meta-analysis of five population-based cohort studies and an additional community-based cohort study of older adults found no clear evidence supporting the associations of EPVS with cognitive impairment among dementia-free people.[6,7] Thus, the potential associations between EPVS load and the function of specific cognitive domains are still unclear in the general population settings. Moreover, EPVS are distributed predominantly in the basal ganglia (BG) and centrum semiovale (CSO), which are considered to reflect primarily hypertensive microangiopathy and cerebral amyloid angiopathy (CAA), respectively.[8,9] Therefore, investigating the potential differential associations of EPVS by brain regions with specific cognitive domains might shed light on the specific brain pathologies that underlie poor performance in different cognitive domains.

The burden of EPVS has been associated with older age, male sex, and apolipoprotein E (*APOE*) ε4 allele.[10–12] In addition, EPVS is correlated with white matter hyperintensities (WMHs), cerebral microbleeds (CMBs), and lacunes in older adults.[10,13,14] Given that other CSVD markers and demographic and genetic factors are closely related to cognitive function,[5,14–16] it is worth exploring whether the associations of EPVS load with domain-specific cognitive function are present independent of other CSVD markers or vary by demographic factors and *APOE* genotype.

Therefore, in this population-based study, we aimed to investigate the associations of EPVS with the function of multiple cognitive domains in dementia-free rural older adults in China while considering other CSVD markers and further exploring the potential effect modification of age, sex, and *APOE* genotype.

2 | METHODS

2.1 | Study design and participants

This population-based cross-sectional study used data from the Multimodal Intervention to delay Dementia and disability in rural China (MIND-China, registration no.: ChiCTR1800017758),[17] which targeted people who were ≥60 years of age and living in the 52 villages of Yanlou Town, Yanggu County, western Shandong Province. In March–September 2018, a total of 5765 (74.9% of all eligible) participants were examined for MIND-China. Of these, using the cluster (village)–based sampling approach, 1844 participants from 26 villages that were randomly selected from all the 52 villages were invited for the MRI substudy. Of these, 1304 (70.7%) signed informed consent and underwent the structural brain MRI scans at either Southwestern Lu Hospital (n = 1178) or Liaocheng People's Hospital (n = 126) from September 2018 to November 2020. Of these, we excluded 113 persons due to incomplete MRI scans (n = 39), suboptimal image quality (n = 28), missing *APOE* genotype data (n = 27), or missing data on all cognitive domains (n = 19), leaving 1191 participants who were free of dementia for the current analysis. Figure 1 shows the flowchart of the study participants.

2.2 | Data collection and assessments

Following administration of a structured questionnaire, data were collected by trained staff through face-to-face interviews, clinical

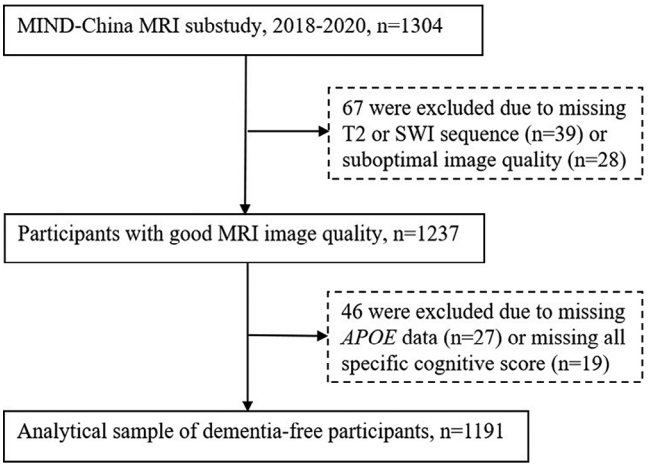

FIGURE 1 Flowchart of the study participants in the MIND-China MRI substudy. *APOE*, apolipoprotein E gene; MIND-China, the Multimodal INterventions to delay Dementia and disability in rural China; MRI, magnetic resonance imaging; SWI, susceptibility-weighted image.

examinations, neuropsychological testing, or laboratory tests. These data included demographic characteristics (e.g., age, sex, and education), lifestyle factors (e.g., smoking and alcohol drinking), health conditions (e.g., hypertension, diabetes, heart disease, and stroke), use of medication, history of head injury/trauma, and genetic factors (e.g., *APOE* genotype).[17] Education was categorized as no formal school education, primary school, and middle school or above. Smoking and alcohol consumption were categorized as never versus ever smoking or alcohol consumption, respectively. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared, and obesity was defined as a BMI $\geq$ 28 kg/m^2 according to the national guidelines for Chinese adults.[18] All medications were classified and coded following the Anatomical Therapeutic Chemical (ATC) Classification System, as described previously.[19] Hypertension was defined as self-reported physician diagnosis of hypertension, blood pressure $\geq$140/90 mmHg, or current use of antihypertensive drugs (ATC codes C02, C03, and C07–C09); diabetes as self-reported physician diagnosis of diabetes, fasting blood glucose $\geq$7 mmol/L, or current use of oral hypoglycemic medication or insulin injection (ATC code A10); and hyperlipidemia as total cholesterol $\geq$6.2 mmol/L, triglycerides $\geq$2.3 mmol/L, low density lipoprotein cholesterol (LDL-C) $\geq$4.1 mmol/L, high density lipoprotein cholesterol (HDL-C) $\leq$1.0 mmol/L, or current use of hypolipidemic agents (ATC code C10).[20] Coronary heart disease and clinical stroke were ascertained according to self-reported history, clinical and neurological examinations, and electronic annual health check-up records.[19] *APOE* genotype was determined using multiple-polymerase chain reaction amplification, as described previously,[21] and was dichotomized into carriers versus non-carriers of the *APOE* ε4 allele.

2.3 | Neuropsychological assessments

The Chinese version of a neuropsychological test battery was used to assess the function of four cognitive domains, as described previously.[17,21] Briefly, memory function was assessed using the Auditory Verbal Learning Test, immediate recall, long-delayed free recall, and long-delayed recognition; verbal fluency was assessed using the Verbal Fluency Test categories of animals, fruits, and vegetables; attention function was assessed using the Digit Span Test and the Trail Making Test (Part A); and executive function was assessed using the Digit Span Test (backward test) and Trail Making Test (Part B). For the Trail Making Test, we used the score divided by the time taken to complete the test. We carefully chose those tests (e.g., carton and picture) that were suitable for persons with no or limited education. The raw test scores were standardized according to the means and SDs among all participants who were free from dementia. The composite *z*-score for each cognitive domain was calculated by averaging the standard *z*-scores of all tests for that domain. A composite *z*-score for global cognitive function was computed as the mean of all cognitive *z*-scores for individuals with data available in at least two of the four cognitive domains.

RESEARCH IN CONTEXT

1. **Systematic review**: Several clinical-based studies have linked enlarged perivascular spaces (EPVS) with poor cognition. The potential associations between EPVS load and the function of specific cognitive domains in the general population setting remain unclear.
2. **Interpretation**: In this population-based cross-sectional 3T magnetic resonance imaging (MRI) study (n = 1191) of rural-dwelling Chinese older adults who were free of dementia, we revealed that overall, a greater basal ganglia (BG)-EPVS load was associated with poorer performance in global cognition, memory, and verbal fluency. We further revealed that the observed associations could be explained largely by other cerebral small vessel disease (CSVD) markers. In addition, a greater centrum semiovale (CSO)-EPVS load was associated with lower verbal fluency *z*-score in apolipoprotein E (*APOE*) ε4 carriers independent of other CSVD markers (i.e., deep white matter hyperintensity [DWMH], strict lobar lacunes, and strict lobar cerebral microbleeds [CMBs]).
3. **Future directions**: Future longitudinal studies are warranted to further elucidate the cognitive consequences of EPVS, which will contribute to the development of clinical guidelines for the optimal management of visible perivascular spaces in older adults.

2.4 | MRI acquisition and assessment protocols

All eligible participants were scanned on either the Philips Ingenia 3.0T MR System (Philips Healthcare, Best, The Netherlands) in

Southwestern Lu Hospital or the Philips Archiva 3.0T MR System (Philips Healthcare, Best, The Netherlands) in Liaocheng People's Hospital, as described previously.[17] A 16-channel head-neck coil was used at both hospitals. The core MRI sequences included the sagittal three-dimensional (3D) T1-weighted, axial T2-weighted, and sagittal 3D fluid-attenuated inversion recovery (FLAIR) images. The parameters of these core MRI sequences were provided elsewhere.[17] Briefly, in the Southwestern Lu Hospital, the parameters for the T1-weighted sequence were: repetition time (TR) = 8.30 ms, echo time (TE) = 3.80 ms, field of view (FOV) = 240 × 219 mm^2, matrix = 240 × 219, flip angle (FA) = 8°, and slice thickness = 1.00 mm; the parameters for T2-weighted sequence were: TR = 4000.00 ms, TE = 106.00 ms, FOV = 230 × 210 mm^2, matrix = 384 × 330, FA = 90°, and thickness = 5.00 mm; the parameters for T2-FLAIR sequence were: TR = 4800.00 ms, TE = 296.00 ms, FOV = 250 × 250 mm^2, matrix = 224 × 224, and thickness = 1.12 mm; and the parameters for susceptibility-weighted image (SWI) sequence were: TR = 18.00 ms, TE = 25.00 ms, FOV = 221 × 182 mm^2, matrix = 220 × 183, FA = 10°, and thickness = 1.2 mm. In the Liaocheng People's Hospital, the parameters for T1-weighted sequence were: TR = 7.00 ms, TE = 3.30 ms, FOV = 240 × 240 mm^2, matrix = 220 × 218, FA = 8°, and thickness = 1.10 mm; the parameters for T2-weighted sequence were: TR = 7583.00 ms, TE = 107.00 ms, FOV = 230 × 230, matrix = 232 × 228, FA = 90°, and thickness = 5.00 mm; the parameters for T2-FLAIR sequence were: TR = 4800.00 ms, TE = 259.00 ms, FOV = 250 × 250 mm^2, matrix = 224 × 224, and thickness = 1.12 mm; and the parameters for SWI sequence were: TR = 16.00 ms, TE = 22.00 ms, FOV = 221 × 182 mm^2, matrix = 220 × 182, FA = 15°, and thickness = 1.0 mm.

EPVS were manually assessed on the axial T2-weighted sequence following a validated protocol.[22] Briefly, EPVS appeared linear when imaged parallel to the course of the vessel, and round or ovoid with a diameter <3 mm when imaged perpendicular to the course of the vessel.[1] The trained rater (M.Z., a junior neurologist), blinded to the clinical information, visually counted EPVS in BG and CSO bilaterally under the supervision of an experienced clinical neurologist (L.S.). The rater first reviewed all MRI slices for EPVS in the areas of BG and CSO and then counted bilateral BG-EPVS and CSO-EPVS on all slices. We categorized EPVS in BG and CSO according to the highest number of EPVS on the slice and hemisphere with the most EPVS, by following the scale as described previously[23]: 0 = no EPVS, 1 = 1–10 EPVS, 2 = 11–20 EPVS, 3 = 21–40 EPVS, and 4 = >40 EPVS. Figure 2 shows EPVS in example images. For EPVS in CSO and BG, the scale collapsed categories 0 and 1 into "none/mild" severity, scale category 2 was called "moderate" severity, and scale categories 3 and 4 were collapsed to "severe" EPVS in line with a previous study.[24] Three months after the initial assessment, EPVS were re-assessed on MR images of 30 randomly selected subjects, which yielded the Cohen's kappa value of 0.75 for BG-EPVS and 0.74 for CSO-EPVS.

We used FLAIR images to evaluate periventricular white matter hyperintensity (PWMH) and deep white matter hyperintensity (DWMH) following the Fazekas scale,[25] with a grade ≥2 indicating severe degree. Lacunes were defined as focal lesions of 3–15 mm with the same signal intensities as CSF and a hyperintense rim on the FLAIR images, according to the STandards for ReportIng Vascular changes on nEuroimaging (STRIVE) criteria.[1] CMBs were defined as small (<10 mm in diameter), homogeneous, and round foci of low signal on SWIs.[26] Lacunes and CMBs were categorized as strict lobar and mixed areas, respectively. Strict lobar lacunes or CMBs refer to those only in the frontal, parietal, temporal, and occipital lobes. Lacunes or CMBs in mixed areas referred to those in the deep brain regions (BG, thalamus, internal capsule, and external capsule) or infratentorial regions (brainstem and cerebellum) with or without concomitant lobar lacunes or lobar CMBs.[27,28] We defined cortical superficial siderosis (cSS) as a linear gyriform pattern of hypointense signals on SWIs.[29] The trained rater (J.W.) who was blinded to clinical data assessed lacunes, PWMH, and DWMH under the supervision of a senior neurologist (L.S.) and an experienced neuroradiologist (T.G.). Six months later, MR images of 200 randomly selected subjects were re-evaluated for lacunes, PWMH, and DWMH, which yielded Cohen's kappa value of 0.84 for lacunes, 0.89 for PWMH, and 0.86 for DWMH. The trained rater (M.Z.) who was blinded to clinical data assessed CMBs and cSS under the supervision of an experienced neuroradiologist (T.G.). Two weeks after the initial assessment, CMBs and cSS were re-assessed on MR images of all subjects, which yielded Cohen's kappa value of 0.84 for CMBs and 0.91 for cSS.

2.5 | Statistical analysis

EPVS in both BG and CSO regions were considered as categorical variables, categorized by severity of EPVS, as described above. Clinical and neuroimaging characteristics of the study participants by the severity of EPVS were compared using one-way analysis of variance (ANOVA) for continuous variables and the chi-square test or Fisher's exact test for categorical variables. We used the general linear regression models to examine the associations of EPVS load with cognitive *z*-scores. The assumptions of the models were verified to be satisfied. We tested the statistical interaction of EPVS burden with age (<75 vs ≥75 years), sex, and *APOE* genotypes on cognitive *z*-scores. When a statistical interaction was detected, further stratifying analysis was performed to verify the direction and magnitude of the interaction. We reported the main results from two models: Model 1 was adjusted for sociodemographic variables (age, sex, and education), *APOE* genotype, and vascular risk factors that showed a relevant association with EPVS at $p < 0.20$ in Table 1; and Model 2 was additionally adjusted for other relevant CSVD markers that were associated with EPVS at $p < 0.20$ in Table 1. Stata Statistical Software: Release 15 for Windows (Stata Corp LLC., College Station, TX, USA) was used for all analyses.

3 | RESULTS

3.1 | Characteristics of the study participants

Of the 1191 participants, the mean age was 69.4 years (SD, 4.3; age range, 60–82 years), 694 (58.3%) were female, 410 (34.4%) were

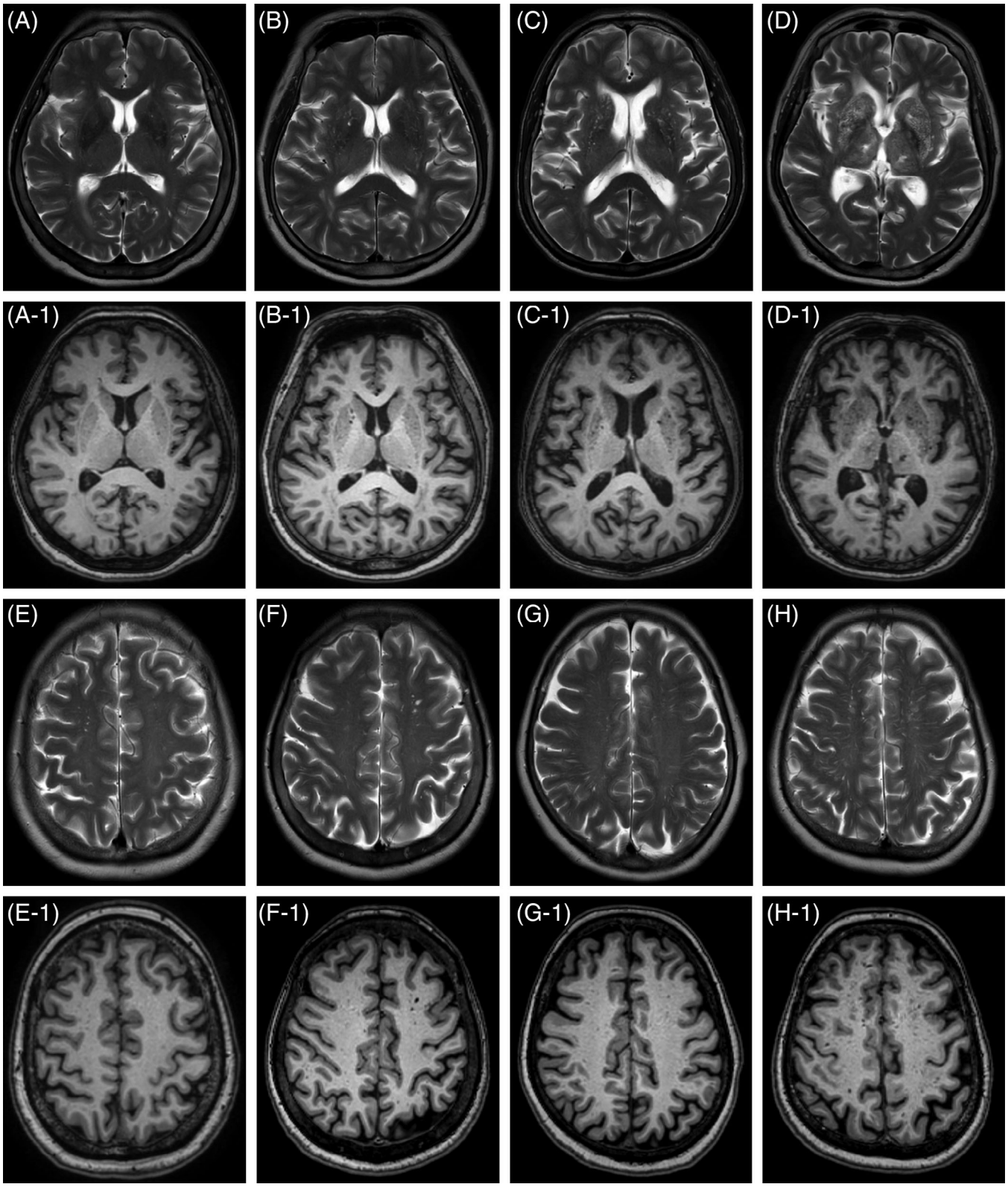

FIGURE 2 Example images of various grades of enlarged perivascular spaces by brain topography. (A–D) are images of basal ganglia: (A) Grade I (1–10 EPVS counts), (B) Grade II (11–20 EPVS counts), (C). Grade III (21–40 EPVS counts), (D) Grade IV (>40 EPVS counts). E–H are images of centrum semiovale. (E) Grade I (1–10 EPVS counts), (F) Grade II (11–20 EPVS counts), (G) Grade III (21–40 EPVS counts), (H) Grade IV (>40 EPVS counts). EPVS were assessed on the axial T2-weighted sequence. A-1-H-1, axial T1-weighted sequence; A-H, axial T2-weighted sequence; EPVS, enlarged perivascular space.

TABLE 1 Characteristics of study participants by severity of enlarged perivascular spaces.

Characteristics	Total sample, $n = 1191$	BG-EPVS				CSO-EPVS			
		None/mild (grade 0–1) ($n = 476$)	Moderate (grade 2) ($n = 437$)	Severe (grade 3–4) ($n = 278$)	p	None/mild (grade 0–1) ($n = 280$)	Moderate (grade 2) ($n = 474$)	Severe (grade 3–4) ($n = 437$)	p
Age, years	69.39 (4.27)	68.30 (3.98)	69.58 (4.36)	70.97 (4.08)	**<0.001**	69.46 (4.47)	69.12 (4.33)	69.64 (4.07)	0.176
Female, *n* (%)	694 (58.27)	291 (61.13)	245 (56.06)	158 (56.83)	0.257	180 (64.29)	275 (58.02)	239 (54.69)	**0.039**
Education, *n* (%)					**0.022**				**0.005**
Illiterate	410 (34.42)	181 (38.03)	143 (32.72)	86 (30.94)		116 (41.43)	161 (33.97)	133 (30.43)	
Primary school	541 (45.42)	196 (41.18)	198 (45.31)	147 (52.88)		120 (42.86)	225 (47.47)	196 (44.85)	
Middle school or above	240 (20.15)	99 (20.80)	96 (21.97)	45 (16.19)		44 (15.71)	88 (18.57)	108 (24.71)	
APOE ε4 carrier, *n* (%)	177 (14.86)	71 (14.92)	67 (15.33)	39 (14.03)	0.891	47 (16.79)	66 (13.92)	64 (14.65)	0.559
Ever smoking, *n* (%)	421 (35.35)	155 (32.56)	172 (39.36)	94 (33.81)	0.083	90 (32.14)	161 (33.97)	170 (38.90)	0.131
Ever alcohol intake, *n* (%)	430 (36.10)	159 (33.40)	175 (40.05)	96 (34.53)	0.093	93 (33.21)	167 (35.23)	170 (38.90)	0.265
Obesity, *n* (%)	230 (19.31)	86 (18.07)	89 (20.37)	55 (19.78)	0.662	52 (18.57)	85 (17.93)	93 (21.28)	0.414
Diabetes, *n* (%)	178 (14.95)	77 (16.18)	65 (14.87)	36 (12.95)	0.487	44 (15.71)	73 (15.40)	61 (13.96)	0.763
Hyperlipoidemia, *n* (%)	284 (23.85)	112 (24.49)	107 (24.49)	65 (23.38)	0.924	72 (25.71)	110 (23.21)	102 (23.34)	0.702
Hypertension, *n* (%)	805 (67.59)	277 (58.19)	310 (70.94)	218 (78.42)	**<0.001**	177(63.21)	325(68.57)	303 (69.34)	0.196
Coronary heart disease, *n* (%)	215 (18.05)	79 (16.60)	76 (17.39)	60 (21.58)	0.207	48 (17.14)	78 (16.46)	89 (20.37)	0.279
Stroke, *n* (%)	143 (12.01)	39 (8.19)	59 (13.50)	45 (16.19)	**0.002**	35 (12.50)	59 (12.45)	49 (11.21)	0.814
Severe PWMH, *n* (%)	654 (54.91)	139 (29.20)	261 (59.73)	254 (91.37)	**<0.001**	149 (53.21)	253 (53.38)	252 (57.67)	0.347
Severe DWMH, *n* (%)	584 (48.67)	156 (32.43)	219 (49.89)	209 (74.64)	**<0.001**	114 (40.71)	208 (43.88)	259 (59.27)	**<0.001**
Strict lobar lacunes, *n* (%)	97 (8.14)	23 (4.83)	39 (8.92)	35 (12.59)	**0.001**	13 (4.64)	36 (7.59)	48 (10.98)	**0.009**
Mixed lacunes, *n* (%)	247 (20.74)	46 (9.66)	92 (21.05)	109 (39.21)	**<0.001**	54 (19.29)	107 (22.57)	86 (19.68)	0.443
Strict lobar CMBs, *n* (%)	160 (13.43)	55 (11.55)	61 (13.96)	44 (15.83)	0.232	25 (8.93)	59 (12.45)	76 (17.39)	**0.004**
Mixed CMBs, *n* (%)	209 (17.55)	40 (8.04)	76 (17.39)	93 (33.45)	**<0.001**	51 (18.21)	81 (17.09)	77 (17.62)	0.925
Presence of cSS, *n* (%)	19 (1.60)	6 (1.26)	10 (2.29)	3 (1.08)	0.342	3 (1.07)	6 (1.27)	10 (2.29)	0.341

Note: Data were mean (SD), unless otherwise specified.

Abbreviations: *APOE*, apolipoprotein E gene; BG, basal ganglia; CMBs, cerebral microbleeds; CSO, centrum semiovale; cSS, cortical superficial siderosis.; DWMH, deep white matter hyperintensity; EPVS, enlarged perivascular space; PWMH, periventricular white matter hyperintensity.

illiterate, and 177 (14.9%) carried the *APOE* ε4 allele. Participants with a higher BG-EPVS burden were older and less educated, and more likely to have hypertension, a history of stroke, severe PWMH and DWMH, strict lobar and mixed lacunes, and mixed CMBs, whereas those with a higher CSO-EPVS burden were more likely to be male and to have high education, severe DWMH, strict lobar lacunes, and strict lobar CMBs ($p < 0.05$) (Table 1).

3.2 | Associations of EPVS burden with cognitive *z*-scores

With controlling for sociodemographic variables, *APOE* ε4 allele, and relevant vascular risk factors, severe BG-EPVS, compared with none or mild BG-EPVS, was significantly associated with lower *z*-scores of memory, verbal fluency, and global cognition ($p < 0.05$), but not with *z*-scores of attention and executive function ($p > 0.05$) (Table 2, Model 1). However, the associations were substantially diluted and became non-significant after further adjusting for other relevant CSVD markers (PWMH, DWMH, strict lobar and mixed lacunes, and mixed CMBs) (Table 2, Model 2). The burden of CSO-EPVS was not significantly associated with any of the examined cognitive *z*-scores ($p > 0.05$, Table 2).

3.3 | Interactions of EPVS burden with age, sex, and *APOE* genotype on cognitive *z*-scores

We detected statistical interactions of greater burdens of BG-EPVS with sex on the *z*-scores of attention (multivariable-adjusted *p* for interaction < 0.05) (Figure 3). Stratified analyses by sex revealed that the linear association between a higher burden of BG-EPVS and lower attention *z*-scores was statistically significant in male but not in female participants; however, the linear associations in male participants were substantially attenuated and became non-significant when entering PWMH, DWMH, strict lobar and mixed lacunes, and mixed CMBs variables into the model (Figure 3A). In addition, we detected statistical interactions of CSO-EPVS with *APOE* genotype on verbal fluency *z*-score (*p* for interaction < 0.05). Further analysis stratified by *APOE* ε4 allele suggested that severe CSO-EPVS were significantly associated with a lower *z*-score of verbal fluency among *APOE* ε4 carriers, even in Model 2 when DWMH, strict lobar lacunes, and strict lobar CMBs were controlled for, whereas there was no significant association between EPVS load and verbal fluency *z*-score among *APOE* ε4 non-carriers in either model (Figure 3B). We detected no statistical interaction of EPVS load with age on cognitive *z*-scores.

4 | DISCUSSION

The main findings from this population-based study of rural-dwelling dementia-free older adults in China can be summarized as follows: (1) the higher burden of BG-EPVS was associated with poorer performance in global cognition, memory, and verbal fluency, but the observed associations were largely attributable to other CSVD markers (e.g., WMHs, lacunes, and mixed CMBs); and (2) the associations of a greater EPVS load with worse cognitive function varied with sex and *APOE* genotype, such that the associations were evident mainly in male participants and the *APOE* ε4 allele carriers. Notably, a greater CSO-EPVS load was associated with poorer verbal fluency in *APOE* ε4 allele carriers independent of a range of potential confounders as well as other CSVD markers.

We found that the associations between a greater burden of BG-EPVS with poorer cognitive performance in dementia-free older people were largely attributable to other CSVD markers (e.g., WMHs, lacunes, and mixed CMBs), which was in line with the results from the meta-analysis of five population-based studies from the community-based clinical-neuropathological studies in United States, and the memory clinic-based study in Korea.[6,7,14] In contrast, the community-based Vanderbilt Memory and Aging Project suggested that a higher BG-EPVS burden was associated with worse perceptual speed and executive function among older adults independent of other CSVD markers.[5] The differences in the findings across studies could be due in part to the wide variety of definitions and rating scales used to quantify EPVS, and MRI sequences for assessing EPVS (e.g., T2-weighted vs T1-weighted and FLAIR images). BG-EPVS are closely correlated to WMHs, lacunes, and mixed CMBs, and these CSVD markers may share similar pathophysiological mechanisms of arteriolosclerosis, which predominantly affect deep perforating arterioles.[8,30] Moreover, previous studies have suggested that other CSVD markers were associated with worse performance in cognitive domains such as memory and language.[5,31,32] Taken together, these studies support the notion that the association between a higher BG-EPVS burden and poorer performances in memory, verbal fluency, and global function could be explained, at least in part, by other CSVD markers.

Overall, we found no association between CSO-EPVS load and cognitive performance, which was again in accordance with results from the meta-analysis of five population-based studies and the Lothian Birth Cohort 1936 study.[6,33] However, the community-based Sydney Memory and Ageing Study did show that having more CSO-EPVS, but not BG-EPVS, was associated with a faster decline in global cognition, whereas having more EPVS in either region was not associated with any of the examined cognitive domains (i.e., memory, language, attention, visuospatial function, and executive function).[34] Differences in the study design (cross-sectional vs longitudinal study), demographic features of the study sample (rural residents with no or very limited education vs highly educated urban residents), and different quantitative approaches of EPVS might partly contribute to the discrepant findings across studies. The potential cognitive consequences of EPVS in older people should be further characterized in large-scale population-based prospective cohort studies.

Furthermore, we detected the independent association of the greater BG-EPVS load with poorer cognition only in men, although the linear trend of the association was attenuated substantially after further adjustment for other CSVD markers. Indeed, previous studies showed that compared to women, men were more vulnerable to car-

TABLE 2 Associations of enlarged perivascular spaces with cognitive function ($n = 1191$).

EPVS severity by regions	β-coefficient (95% confidence interval), cognitive z-scores									
	Memory ($n = 1184$)		Verbal fluency ($n = 1185$)		Attention ($n = 1190$)		Executive function ($n = 1182$)		Global cognition ($n = 1190$)	
	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
BG-EPVS										
None/mild	0 (reference)	0 (reference)	0 (reference)	0 (reference)	0 (reference)	0 (reference)	0 (reference)	0 (reference)	0 (reference)	0 (reference)
Moderate	−0.01 (−0.11–0.10)	0.02 (−0.09–0.13)	0.04 (−0.06–0.13)	0.05 (−0.05–0.15)	−0.02 (−0.11–0.08)	−0.01 (−0.11–0.09)	−0.03 (−0.13–0.07)	−0.01 (−0.11–0.09)	−0.01 (−0.08–0.07)	0.01 (−0.06–0.08)
Severe	−0.17 (−0.30–−0.05)**	−0.10 (−0.24–0.04)	−0.16 (−0.27–−0.04)**	−0.12 (−0.25–0.01)	−0.04 (−0.16–0.07)	0.02 (−0.15–0.11)	−0.07 (−0.19–0.05)	−0.03 (−0.17–0.10)	−0.12 (−0.20–−0.03)**	−0.08 (−0.17–0.02)
CSO-EPVS										
None/mild	0 (reference)	0 (reference)	0 (reference)	0 (reference)	0 (reference)	0 (reference)	0 (reference)	0 (reference)	0 (reference)	0 (reference)
Moderate	0.01 (−0.11–0.13)	0.01 (−0.11–0.14)	0.03 (−0.07–0.14)	0.04 (−0.07–0.15)	0.06 (−0.05–0.16)	0.06 (−0.05–0.17)	0.07 (−0.04–0.18)	0.07 (−0.04–0.18)	0.04 (−0.04–0.12)	0.05 (−0.03–0.13)
Severe	−0.01 (−0.13–0.12)	0.01 (−0.12–0.13)	0.02 (−0.09–0.13)	0.03 (−0.08–0.15)	0.08 (−0.04–0.18)	0.08 (−0.03–0.19)	0.05 (−0.07–0.16)	0.05 (−0.07–0.16)	0.04 (−0.05–0.12)	0.04 (−0.04–0.13)

Note: Data were missing for seven participants for memory z-score, six for verbal fluency z-score, one for attention z-score, nine for executive function z-score, and one for global cognitive z-score. **$p < 0.01$. Model 1 was adjusted for age, sex, education, *APOE* genotype, and vascular risk factors that were associated with EPVS at $p < 0.20$ in Table 1; Model 2 was additionally adjusted for other CSVD markers that were associated with EPVS at $p < 0.20$ in Table 1.

Abbreviations: *APOE*, apolipoprotein E gene; BG, basal ganglia; CSO, centrum semiovale; CSVD, cerebral small vessel disease; EPVS, enlarged perivascular space.

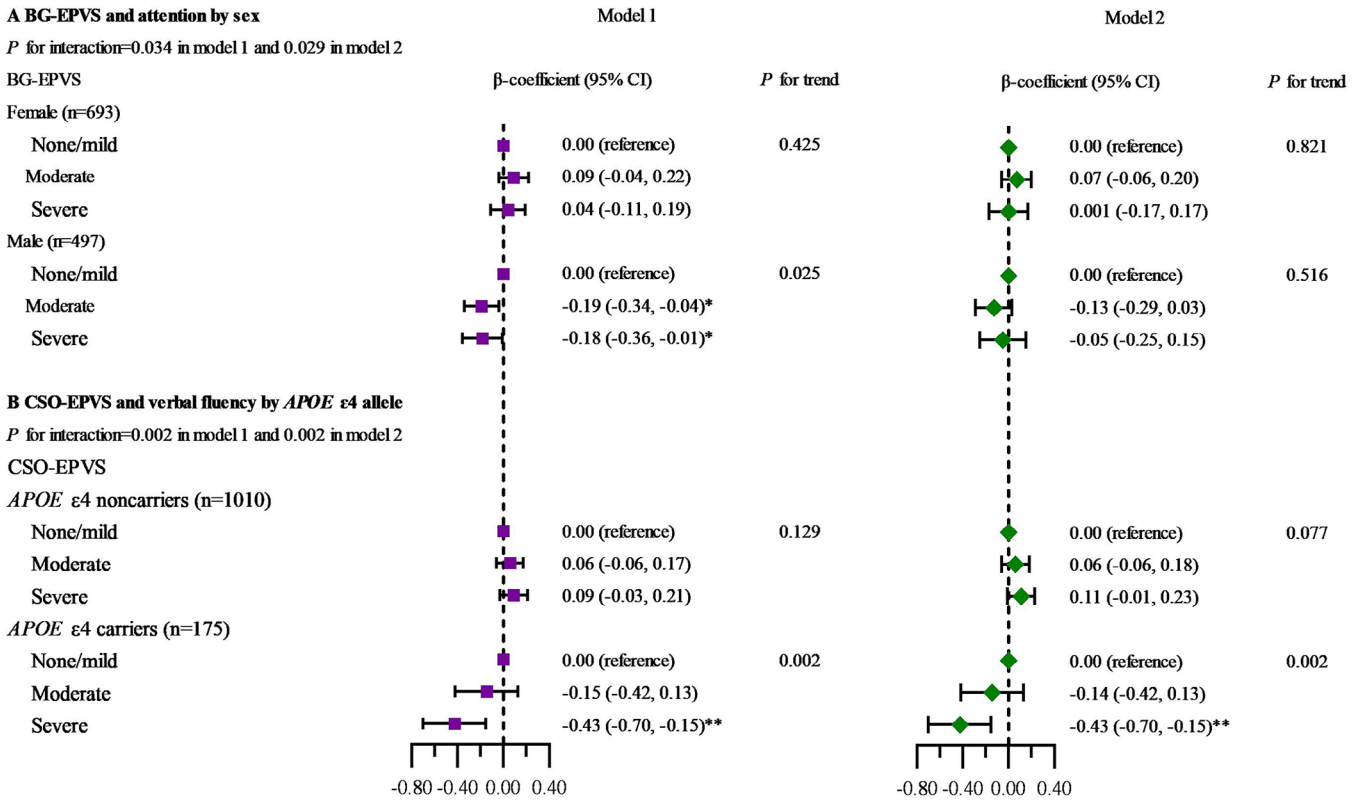

FIGURE 3 Associations of enlarged perivascular spaces with cognitive *z*-scores by sex and *APOE* genotype. (A) Associations of BG-EPVS with attention *z*-score by sex. (B). Association of CSO-EPVS with verbal fluency *z*-score by *APOE* ε4 allele. Model 1 was adjusted for age, education, and vascular risk factors that were associated with EPVS at $p < 0.20$ in Table 1, and wherever applicable, for *APOE* genotype and sex; Model 2 was additionally adjusted for other CSVD markers that were associated with EPVS at $p < 0.20$ in Table 1. *APOE*, apolipoprotein E gene; BG, basal ganglia; CSO, centrum semiovale; CSVD, cerebral small vessel disease; DWMH, deep white matter hyperintensity; EPVS, enlarged perivascular space; PWMH, periventricular white matter hyperintensity. Note: Data were missing in one participant for attention *z*-score and six for verbal fluency *z*-score. $^{*}p < 0.05$, $^{**}p < 0.01$. EPVS, enlarged perivascular space.

diovascular risk factors (e.g., hypertension and smoking),[35,] and had more cerebral microvascular lesions.[10,36] These cerebral microvascular lesions might disrupt the fronto-subcortical circuits and then lead to impaired attention.[37] This may partly account for the sex-varying associations of a higher BG-EPVS burden with worse cognitive function. We also found that the association of a higher CSO-EPVS burden with poorer verbal fluency was evident only among *APOE* ε4 carriers. This was consistent with the reports from a population-based study from Sweden and the clinic-based Sunnybrook Dementia Study from Canada.[38,39] The load of CSO-EPVS was correlated with strict lobar lacunes and strict lobar CMBs, which are indicative of CAA.[26,27,40] CAA, which results from amyloid beta (Aβ) deposition within small cortical and leptomeningeal arteries, is associated with increased blood–brain barrier permeability, lobar CMBs, cortical microinfarcts, and alterations of structural connectivity. All these neuropathological features have been linked with cognitive impairment.[41,42] Meanwhile, the *APOE* ε4 allele is associated with CAA and disruption of soluble Aβ clearance in the brain,[43,44] which might partly explain the finding that carrying the *APOE* ε4 allele could strengthen the association of severe CSO-EPVS with poor cognitive performance.

The major strengths of our study include the population-based design with a relatively large sample, and the integration of high-quality brain 3.0T MRI data with comprehensive clinical and neurocognitive data. In addition, our study engaged older adults who were living in rural communities in China and who had received no or very limited formal education, a sociodemographic group that has been substantially underrepresented in research on brain aging, cognition, and dementia.[45] However, our study has some limitations. First, the cross-sectional nature of the study cannot determine a temporal relationship for the observed associations. Furthermore, we assessed the EPVS burden by counting the total number of typical EPVS (<3 mm), which might be less precise than EPVS volume, computational count, or other computational parameters. Indeed, automatic segmentation techniques for identifying and quantifying EPVS have been developed in recent years, but the visual rating scores were correlated well with the automatically segmented EPVS count and volume.[46] Finally, participants in the brain MRI substudy were relatively younger, healthier, and more likely to be male than in the MIND-China total sample,[21] which should be kept in mind when generalizing our findings to other rural populations in China.

In summary, our population-based study of rural-dwelling older adults in China supports the association of a greater BG-EPVS burden with poorer performance in global cognition and multiple cognitive domains (memory and verbal fluency), but the observed associations

are largely attributable to other CSVD markers (e.g., WMHs, lacunes, and mixed CMBs). Notably, a greater CSO-EPVS load is associated with worse cognition among *APOE* ε4 allele carriers independent of other CSVD markers. This result suggests that patients with severe CSO-EPVS who are *APOE* ε4 carriers may have cognitive decline due to cerebral amyloid angiopathy or Alzheimer's disease pathology. Therefore, in the clinical setting, if severe CSO-EPVS is incidentally observed, it may be worthwhile to consider cognitive function testing. Future longitudinal studies are warranted to further characterize cognitive consequences associated with EPVS, which will contribute to the development of clinical guidelines for the optimal management of visible PVSs in older adults.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest. Author disclosures are available in the Supporting information.

CONSENT STATEMENT

The MIND-CHINA protocol was approved by the ethics committee at Shandong Provincial Hospital affiliated with Shandong University in Jinan, Shandong, China. 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).

ORCID

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

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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