Cerebral Microbleeds Correlated with White Matter and Hippocampal Volumes in Community-Dwelling Populations

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Abstract

Background: Few studies have investigated the correlation between cerebral microbleeds (CMBs), a hemorrhagic imaging marker of cerebral small vessel disease (CSVD), and brain volume.

Objective: We investigated the association between the burden and locations of CMBs and brain volume in community-dwelling populations.

Methods: Data were obtained from 1,029 participants who underwent brain magnetic resonance imaging (MRI) and APOE genotyping. Volumes of the whole brain, subcortical white matter (WM), cortical gray matter (GM), and hippocampus were extracted. Linear regression models were used to investigate the relationship between the CMB burden and their location with structural changes.

Results: Regarding burden, participants with ≥3 CMBs had significantly lower whole brain (β = −1.124, p = 0.0133), subcortical WM (β = −1.020, p = 0.0043), and hippocampus (β = −0.015, p = 0.0088) volumes than those without CMBs. Regarding location and burden, the presence of ≥3 strictly lobar CMBs was negatively associated with whole brain volume (β = −2.838, p = 0.0088). Additionally, higher CMB burdens in strictly lobar locations or deep/mixed locations were associated with lower subcortical WM volume (β = −1.689, p = 0.0042; β = −0.872, p = 0.0464, respectively). Finally, the presence of ≥3 deep/mixed CMBs was associated with lower hippocampus volume (β = −0.018, p = 0.0088), and these associations were independent of other ischemic markers of CSVD. However, the CMB burden and distributional pattern did not correlate with cortical GM volumes.

Conclusion: A higher CMB burden, in specific locations, is associated with decreased brain volumes in community-dwelling populations.

Keywords: brain volumes, cerebral microbleeds, cerebral small vessel disease, hippocampus, white matter
INTRODUCTION

Recent studies have associated functional loss with brain atrophy in patients with cerebral small vessel disease (CSVD). Chabriat et al. reported in patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leuкоencephalopathy (CADASIL), a model of CSVD, that brain atrophy independently predicts stroke incidence, dementia incidence, and progression toward moderate or severe disability [1]. This finding, armed with other evidence from elderly populations, highlights the importance of the association between CSVD and brain atrophy [2]. This raises an important question of how do CSVD lesions, which are commonly subcortical lesions, influence global, subcortical, and cortical brain atrophy?

As known, CSVD is characterized by the presence of ischemic and hemorrhagic imaging markers. Previous studies mainly investigated the association between brain atrophy and white matter hyperintensities (WMH) or lacunes [2–5], the ischemic imaging markers of CSVD, and found that the increased WMH volumes or number of lacunar lesions leads to greater cortical thinning or volume loss in community-dwelling populations and patients with mild cognitive impairment [6, 7]. It was speculated that disturbances of cortical-subcortical connectivity [7, 8] and cortical neuronal apoptosis might be potential mechanisms underlying brain volume loss in ischemic CSVD [9].

Notably, cerebral microbleeds (CMBs) are an important hemorrhagic marker of CSVD [2], and represent focal hemosiderin deposition on gradient-echo T2*-weighted MR images [10]. In addition, the distribution of CMBs, i.e., lobar or deep location, may relate to cerebral amyloid angiopathy (CAA) or hypertensive microangiopathy, respectively. It is potentially important to investigate the relationship between CMBs and brain volume, potentially furthering our understanding of how CSVD hemorrhagic lesions relate to secondary brain atrophy, and patterns of distributional CMBs might underlie different mechanisms involved in brain volume loss in CSVD.

However, few studies have investigated the relationship between brain volume and CMBs. A recent study reported vascular amyloid-mediated cortical thinning in patients with hereditary cerebral hemorrhage and amyloidosis as well as patients with sporadic CAA, which is recognized as typical advanced hemorrhagic CSVD [11]. Further research is necessary to determine the role of CMBs in brain atrophy, particularly subcortical white matter (WM) atrophy, which might aggravate functional loss in CSVD, and hippocampal atrophy, a pathology indicative of neurodegenerative processes.

In this study, we examined whether the number and location of CMBs are independently associated with brain volume in community-dwelling populations to elucidate pre-symptomatic changes and provide new insights into mechanisms of brain volume loss in hemorrhagic CSVD. We hypothesize that 1) volumetric consequences due to hemorrhagic CSVD might depend on the burden of CMBs, and CMBs in different anatomic locations might be differently associated with brain volume; and 2) the hippocampus, a region known to be involved in neurodegeneration, might exhibit volumetric disturbance in amyloidal or hypertensive CMB pathologies.

METHODS

Study participants and clinical data collection

The Shunyi study is a population-based prospective cohort study designed to investigate the risk factors for and consequences of brain changes in community-dwelling adults in a Chinese population [12]. All inhabitants aged 35 years or older and living independently in five villages of Shunyi, a suburban district of Beijing, were invited to participate in this cohort study. The response rate of participation was 79.9%. From June 2013 to April 2016, 1,787 participants agreed to join the Shunyi study, and were enrolled for the standard baseline assessments comprising structured questionnaires, physical examination, and laboratory tests. All participants were initially proposed to undergo cerebral MRI; 464 refused or had contraindications for MRI. Subsequently, 1,323 MRI scans were obtained. Among those 1,323 participants, 136 without apolipoprotein E (APOE) genotype data, 75 with previous stroke incidence, and 99 without interpretable MRI scans were further excluded, finally resulting in 1,029 participants included in the present analysis (Fig. 1).

The baseline characteristics of participants analyzed and not analyzed in the current study were balanced, except that the analyzed participants had a lower proportion of men, current smokers, and participants with hypertension, and a higher proportion of participants with hyperlipidemia. All participants provided informed consent. The Medical Review Ethics Committee of Peking Union Medical College Hospital approved the study (reference number: B-160).

560 N. Su et al. / CMBs and Brain Volumes
MRI acquisition and definitions of imaging markers and severity

MRI was performed from July 2014 to April 2016 using a single 3-T Siemens Skyra scanner (Siemens; Erlangen, Germany). Three-dimensional T1-weighted images were acquired using magnetization-prepared rapid gradient-echo sequences in the sagittal plane. T2-weighted images, fluid-attenuated inversion recovery (FLAIR) images, and susceptibility-weighted imaging (SWI) scans were acquired in the axial plane. The details of the imaging standards of the Shunyi study have been published elsewhere [12].

CMBs were defined using standard published criteria [13] as round or ovoid hypointense lesions on SWI sequences. They were categorized by their presence, number (0 CMBs, 1–2 CMBs, ≥3 CMBs) [14], as well as location and number (0 CMBs, 1–2 strictly lobar CMBs, ≥3 strictly lobar CMBs, 1–2 deep or mixed CMBs, and ≥3 deep or mixed CMBs) [14–16]. Participants with CMBs confined to the lobar regions were considered as having strictly lobar CMBs and those with CMBs in a deep region, with or without coexisting lobar CMBs, were considered as having deep or mixed CMBs.

WMH on FLAIR scans were not or only faintly hypointense on T1-weighted images. Periventricular WM hyperintensities (PVWMH) and deep WM hyperintensities (DWMH) were scored based on axial FLAIR images using the Fazekas scale [17]. Individuals with severe WMH were defined as those with either PVWMH or DWMH rated at least 2 on the Fazekas scale. WMH were automatically segmented using the lesion growth algorithm as implemented in the lesion segmentation tool (LST) toolbox (http://www.statistical-modelling.de/lst.html) for Statistical Parametric Mapping at $\kappa = 0.15$ [18].

Lacunes were defined as focal lesions ranging from 3 to 15 mm in size with the same signal characteristics as cerebrospinal fluid on all sequences situated in the basal ganglia or WM. Lacunar infarcts were rated on three-dimensional T1-weighted images; T2 and FLAIR images were used to confirm lesions.

Well-trained readers blinded to all clinical data independently rated WMH, lacunes, and CMBs. Intrarater agreement was assessed in a random sample of 50 individuals with an interval of more than 1 month between the first and second readings. Kappa values for the intrarater agreements were 0.84 for PVWMH, 0.89 for DWMH, 0.73 for lacunes, and 0.90 for CMBs.

Using T1-weighted images, automated issue segmentation was applied within the CIVET pipeline, yielding volumetric measures of the intracranial volume (ICV), total parenchymal volume [19], and WM and cortical gray matter (GM) volume. The brain parenchymal fraction (BPF) was defined as the ratio of brain tissue volume (WM and GM volume) to ICV. The WM and cortical GM fraction were defined as the ratio of WM and cortical GM volume to ICV, respectively. Hippocampi were accurately extracted using the FIRST algorithm [20] embedded in FSL (FMRIB Software Library, v5.0). Bilateral volumes were summed for the hippocampi. The hippocampal fraction was defined as the ratio of hippocampal volumes to ICV.

APOE genotyping

Using a standard protocol, genomic DNA was extracted from whole blood samples. APOE e2, e3, and e4 alleles were identified by manually combining the alleles from the single nucleotide polymorphisms rs429358 and rs7412 as follows: at nucleotides 388 and 526 (amino acids 130 and 176), e2 = TT (CysCys), e3 = TC (CysArg), and e4 = CC (ArgArg). Any APOE e4+ was identified as e2/e4, e3/e4, and e4/e4, and APOE e4- as e2/e2, e2/e3, and e3/e3 [21].
Assessment of cognitive function

Participants received a face-to-face neuropsychological examination performed by trained interviewers. The global cognitive performance was examined using the Mini-Mental State Examination (MMSE) test.

Cardiovascular risk factors

Cardiovascular risk factors were defined as follows: hypertension was defined by blood pressure $\geq 140/90$ mmHg, a history of hypertension as reported by the participant, or use of antihypertensive therapy; diabetes mellitus was defined as a fasting plasma glucose level $\geq 7.0$ mmol/L, 2-h plasma glucose level $\geq 11.1$ mmol/L during an oral glucose tolerance test, a self-reported history, or use of antidiabetic treatment; hyperlipidemia was defined as total cholesterol $> 5.2$ mmol/L, low-density lipoprotein $> 2.58$ mmol/L, use of lipid-lowering drugs, or a reported history of hyperlipidemia; and current smoker was defined as an individual smoking at least 1 cigarette per day for more than 6 months before enrollment. Neurological examination was performed at all sites.

Statistical analyses

Continuous variables are expressed as mean and standard deviation (SD), and categorical variables are expressed as frequencies and proportions. Demographic characteristics, vascular risk factors, CSVD burden, APOE genotype, and brain measures were compared between CMB number groups (0 CMB, 1–2 CMBs, $\geq$ 3 CMBs) using the chi-squared test or analysis of variance. We first estimated the association between the CMB groups and brain measures (BPF, subcortical WM fraction, cortical GM fraction, and hippocampal fraction) using general linear model analyses, with CMB groups as a determinant and brain measures as outcome variables. Since CMBs, lacunes, and WMHs all serve as the imaging markers of CSVD, to minimize the effects of ischemic lesions on brain volumes, WMH volume and presence of lacunes were adjusted for in the statistical models. WMH volume was natural log transformed to normalize skewness. The models used to assess the brain measures were adjusted as follows: Model 1 was adjusted for age and sex. Model 2 was the same as Model 1, with further adjustments for hypertension, WMH volume, presence of lacunes, and $APOE \epsilon 4$ status. For supplemental analysis, further adjustment of cognitive status (MMSE scores) and educational levels (high school and above versus below) in the multivariable models were performed (data not shown). Two-sided $p < 0.05$ indicated statistical significance. The fulfillment of different assumptions for the regression analyses (e.g., multicollinearity [tolerance], autocorrelation [Durbin–Watson test], and adjusted $R^2$ [explanation of variance]) were checked. All analyses were repeated according to the CMB count and location categories. All statistical analyses were performed using SAS Version 9.4 (SAS Institute, Inc, Cary, NC, USA).

RESULTS

Sample characteristics

The prevalence of CMBs was 10.4% ($n = 107$), of 1–2 CMBs was 7.9%, and of $\geq$ 3 CMBs was 2.5% (Table 1). Compared to participants without CMBs, those with 1–2 or $\geq$ 3 CMBs were older, more likely to be male and have hypertension with higher levels of systolic blood pressure, and more likely to have higher burdens of severe WMH and higher prevalence of lacunes, whereas the percentage of $APOE \epsilon 4$ carriers did not differ between the CMB count groups. The global cognitive functions assessed by MMSE scores did not have significant differences among the CMB burden groups. In addition, participants with higher CMB burdens tended to have lower whole brain (total parenchymal volume), WM, cortical GM, and hippocampus volumes (Table 1).

Among participants with CMBs ($n = 107$), 46.7% ($n = 50$) had CMBs in a strictly lobar location, and 53.3% ($n = 57$) had them in deep or mixed locations (including those with mixed CMBs in both deep and lobar locations, $n = 16$). Univariate analysis on the associations between high burden of CMBs in different regions and brain volume was shown in Supplementary Table 1.

Association between CMBs and whole brain volumes

In the fully adjusted models, presence of CMBs was not associated with BPF (Table 2). Compared to participants with no CMBs, those with $\geq$ 3 CMBs had smaller total parenchymal volume ($\beta = -1.124$, $p = 0.0133$). Participants with $\geq$ 3 CMBs in a strictly lobar location had significantly smaller whole brain volume ($\beta = -2.838$, $p = 0.0088$). No association was
Table 1
Baseline characteristics by CMB number groups

<table>
<thead>
<tr>
<th></th>
<th>Total (n = 1,029)</th>
<th>No CMBs (n = 922)</th>
<th>1–2 CMBs (n = 81)</th>
<th>≥3 CMBs (n = 26)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic characteristics</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Age, y, mean (SD)</td>
<td>56.9 (9.6)</td>
<td>56.2 (9.5)</td>
<td>61.3 (8.4)</td>
<td>66.5 (7.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>369 (35.9%)</td>
<td>318 (34.5%)</td>
<td>32 (39.5%)</td>
<td>19 (73.1%)</td>
<td>0.0002</td>
</tr>
<tr>
<td>High school and above, n (%)</td>
<td>154 (15.1%)</td>
<td>140 (15.4%)</td>
<td>10 (12.3%)</td>
<td>4 (15.4%)</td>
<td>0.7670</td>
</tr>
<tr>
<td><strong>BMI, kg/m²</strong></td>
<td>26.4 (3.8)</td>
<td>26.4 (3.8)</td>
<td>26.4 (3.8)</td>
<td>26.2 (3.5)</td>
<td>0.9713</td>
</tr>
<tr>
<td><strong>Current smoker, n (%)</strong></td>
<td>228 (22.5%)</td>
<td>202 (22.3%)</td>
<td>17 (21.0%)</td>
<td>9 (34.6%)</td>
<td>0.3141</td>
</tr>
<tr>
<td><strong>DM, n (%)</strong></td>
<td>160 (15.5%)</td>
<td>139 (15.1%)</td>
<td>15 (18.5%)</td>
<td>6 (23.1%)</td>
<td>0.4019</td>
</tr>
<tr>
<td><strong>Hyperlipidemia, n (%)</strong></td>
<td>481 (46.7%)</td>
<td>430 (46.6%)</td>
<td>38 (46.9%)</td>
<td>13 (50.0%)</td>
<td>0.9437</td>
</tr>
<tr>
<td><strong>Hypertension, n (%)</strong></td>
<td>504 (49.0%)</td>
<td>434 (47.1%)</td>
<td>48 (59.3%)</td>
<td>22 (84.6%)</td>
<td>0.0001</td>
</tr>
<tr>
<td><strong>SBP, mm Hg, mean (SD)</strong></td>
<td>133 (19.0)</td>
<td>132.0 (18.9)</td>
<td>133.2 (18.2)</td>
<td>147.4 (19.0)</td>
<td>0.0003</td>
</tr>
<tr>
<td><strong>DBP, mm Hg, mean (SD)</strong></td>
<td>78.3 (10.7)</td>
<td>78.2 (10.6)</td>
<td>77.3 (10.5)</td>
<td>82.4 (13.5)</td>
<td>0.1097</td>
</tr>
<tr>
<td>Any APOE e4+, n (%)</td>
<td>162 (15.7%)</td>
<td>147 (15.9%)</td>
<td>11 (13.6%)</td>
<td>4 (15.4%)</td>
<td>0.8538</td>
</tr>
</tbody>
</table>

CMBs, cerebral microbleeds; BMI, body mass index; DM, diabetes mellitus; SBP, systolic blood pressure; DBP, diastolic blood pressure; APOE, apolipoprotein E; MMSE, Mini-Mental State Examination; WMH, white matter hyperintensity; ICV, total intracranial volume; GM, gray matter; WM, white matter.

observed for deep/mixed CMBs with respect to the CMB burden (Table 2).

**Association between CMBs and subcortical WM volumes**

We subsequently assessed whether CMBs were associated with subcortical WM volume (Table 2). The presence of CMBs was independently associated with WM volume ($\beta=-0.378$, $p=0.0374$). Compared with participants without CMBs, those with $\geq 3$ CMBs had significantly lower WM volume ($\beta=-1.020$, $p=0.0043$). Similarly, in the fully adjusted model, $\geq 3$ strictly lobar CMBs and $\geq 3$ deep/mixed CMBs were significantly associated with decreased WM volumes ($\beta=-1.689$, $p=0.0482$; $\beta=-0.872$, $p=0.0464$, respectively).

**Association between CMBs and cortical GM volumes**

We further evaluated the association between CMBs and cortical GM volumes. No significant association was observed between CMBs and cortical GM volumes, irrespective of CMB burden or anatomical distribution (Table 2).

**Association between CMBs and hippocampal volumes**

Compared with no CMBs, higher CMB burdens ($\geq 3$ CMBs) were associated with lower hippocampal volume ($\beta=-0.015$, $p=0.0088$) (Table 2). A similar pattern of association was observed for those with $\geq 3$ deep/mixed CMBs ($\beta=-0.018$, $p=0.0088$).

**DISCUSSION**

In this community-dwelling population study, we demonstrated that the number and location of CMBs were related to reduced brain volume. The presence of $\geq 3$ CMBs was associated with smaller whole brain, subcortical WM, and hippocampal volume, and these associations were independent of other ischemic imaging markers of CSVD. Further evaluation of the location and burden of CMBs suggested that the presence of $\geq 3$ CMBs in strictly lobar or deep/mixed locations contributed to lower subcortical WM volumes, while the association with $\geq 3$ CMBs in deep/mixed locations was stronger for the hippocampus. Our findings might help elucidate the pathogenesis of secondary brain volume loss related to the hemorrhagic imaging markers of CSVD.
Table 2
Association between CMBs and brain volume

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Presence of CMBs</th>
<th>1–2 CMBs</th>
<th>≥3 CMBs</th>
<th>1–2 Strictly lobar CMBs</th>
<th>≥3 Strictly lobar CMBs</th>
<th>1–2 Deep or mixed CMBs</th>
<th>≥3 Deep or mixed CMBs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β (SE)</td>
<td>β (SE)</td>
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<td>p</td>
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<td>BPF</td>
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<td></td>
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</tr>
<tr>
<td>Model 1</td>
<td>-0.556 (0.238)</td>
<td>-0.135 (0.266)</td>
<td>-1.944 (0.461)</td>
<td>-0.589 (0.344)</td>
<td>-3.191 (1.141)</td>
<td>0.334 (0.369)</td>
<td>-2.044 (0.561)</td>
</tr>
<tr>
<td>Model 2</td>
<td>-0.160 (0.231)</td>
<td>0.107 (0.254)</td>
<td>-1.124 (0.453)</td>
<td>-0.315 (0.326)</td>
<td>-2.838 (1.081)</td>
<td>0.582 (0.356)</td>
<td>-0.964 (0.553)</td>
</tr>
<tr>
<td>Subcortical WM fraction</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>-0.598 (0.180)</td>
<td>-0.335 (0.201)</td>
<td>-1.463 (0.349)</td>
<td>-0.486 (0.261)</td>
<td>-1.914 (0.866)</td>
<td>-1.689 (0.854)</td>
<td>-1.451 (0.426)</td>
</tr>
<tr>
<td>Model 2</td>
<td>-0.378 (0.182)</td>
<td>-0.201 (0.200)</td>
<td>-1.020 (0.357)</td>
<td>-0.846 (0.261)</td>
<td>-1.048 (0.386)</td>
<td>-1.325 (0.281)</td>
<td>-0.872 (0.437)</td>
</tr>
<tr>
<td>Cortical GM fraction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>0.0959</td>
<td>0.3169</td>
<td>-0.004 (0.319)</td>
<td>0.207 (0.238)</td>
<td>0.361 (0.255)</td>
<td>0.376 (0.261)</td>
<td>-0.398 (0.389)</td>
</tr>
<tr>
<td>Model 2</td>
<td>0.169 (0.169)</td>
<td>0.287 (0.186)</td>
<td>0.2106</td>
<td>0.3850</td>
<td>0.1581</td>
<td>0.1507</td>
<td>-0.024 (0.007)</td>
</tr>
<tr>
<td>Hippocampal fraction</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>0.121 (0.164)</td>
<td>0.279 (0.184)</td>
<td>-0.399 (0.319)</td>
<td>0.207 (0.238)</td>
<td>0.361 (0.255)</td>
<td>0.376 (0.261)</td>
<td>-0.398 (0.389)</td>
</tr>
<tr>
<td>Model 2</td>
<td>0.4599</td>
<td>0.1286</td>
<td>0.2106</td>
<td>0.3850</td>
<td>0.1581</td>
<td>0.1507</td>
<td>-0.024 (0.007)</td>
</tr>
</tbody>
</table>

CMBs, cerebral microbleeds; BPF, brain parenchymal fraction; WM, white matter; GM, gray matter. Model 1: adjusted for age and sex. Model 2: adjusted for age, sex, hypertension, WMH volumes, presence of lacunes, and APOE e4 status. *p < 0.05.

Previous studies have investigated the relationship between CMBs and WM volumes. Considering the findings from previous studies that the presence of multiple CMBs is associated with disruptions of the cerebral network in patients with early Alzheimer’s disease [22], it could be speculated that higher CMB burdens, reflecting the severity of individual or combined effects of hypertensive vasculopathy and CAA pathologies, might play a role in subcortical WM atrophy by interrupting brain network connectivity. The present results are inconsistent with previous findings that suggest that CMBs were not associated with WM atrophy [7]; however, methodological differences might explain these discrepancies. SWI, as opposed to the gradient echo T2*-weighted MRI performed in previous studies, in addition to higher field strengths used in this study, assured better accuracy for CMB detection. Further investigation is needed to evaluate this correlation between CMB burden and WM atrophy.

Notably, higher CMB burden in strictly lobar regions was found to be negatively associated with subcortical WM volume in this community cohort, which was in line with findings in previous studies [23–25]. A recent diffusion tensor imaging study revealed that reduced structural brain network efficiency was related to cortical amyloid load in patients with CAA [23]. In addition, another study reported that cortical microbleeds correlated with subcortical WM lesions in healthy elderly subjects [24] and in patients with CSVD-related intracerebral hemorrhage [25]. In general, cerebral hypoperfusion caused by amyloid deposition in the cerebral vasculature [26], along with the disruption of brain network connectivity, might lead to the progression of WM lesions [27], which subsequently induce subcortical WM volume loss.

In contrast, a negative association was found between CMBs and cortical GM volumes, which might suggest relatively preserved cortical structures with hemorrhagic lesions in these presymptomatic individuals [11, 28]. However, the current study was performed with a large number of Asian participants, with relatively low prevalence of CMBs (age-standardized prevalence of CMBs in the Shunyi Study was 12.7%) compared with Caucasians (15.3% in the Rotterdam Scan study) [29, 30]. The differences in race and prevalence of CMBs might explain the discrepancies.

Interestingly, in the present study, higher CMB burden, in particular higher CMB burden in deep/mixed locations, was found to be associated with smaller hippocampal volumes, which is consistent with previous studies showing CMBs are associated with hippocampal atrophy in healthy subjects [24]. A number of potential mechanisms may explain the
findings in the current study [31, 32]. Hypertension was reported to be associated with worse hippocampal glucose hypometabolism [31]. Furthermore, hypertension was found to have an early and sustained effect on the upregulation of receptors for advanced glycation end products in the brain vessels of the cortex and hippocampus, which favors parenchymal amyloid deposition, finally leading to chronic hypoperfusion [32, 33]. These may lead to a higher risk of neuronal injury and degeneration in hypertensive hemorrhagic CSVD. Indeed, CSVD frequently coexists with neurodegenerative disease, and can exacerbate symptoms of neurodegeneration [2]. Although the relationship between CSVD and neurodegeneration is not yet fully elucidated, the involvement of the hippocampus with hemorrhagic lesions in CSVD could play a critical role in linking these relationships.

The strengths of our study include the large number of participants from a community-based setting outside of Europe and the US, application of high-resolution MRI, automated volumetric computational methods, and systematic evaluation of other CSVD imaging markers that enabled us to control for potential confounders. Our study is limited by its cross-sectional design and lack of Pittsburgh compound B evaluation for amyloid deposition. Therefore, we could not examine whether the observed correlations between strictly lobar CMBs and brain volumes are specific to CAA. Emerging evidence showed that there might be a discrepancy between CMBs of MRI and pathological findings, indicating CMBs on imaging could also be hemorrhagic microinfarcts in pathology [34]. In general, future diffusion tensor imaging, functional MRI, and pathological studies would also be important to provide a functional and pathological basis to support the current findings. Furthermore, although hypertension has been adjusted for in the multivariable models, the sample might be biased to those with less cardiovascular risk, leading to underestimates of the current findings. Finally, the patients with mild cognitive impairment or subjects with cognitive complaints were not excluded from the study. However, adjustment of cognitive status and educational levels in the multivariable models did not change the initial results.

Conclusion

This study demonstrates that CMB burdens contribute to reduced WM and hippocampal volume in community-dwelling populations and also highlights the association between region-specific CMBs and loss of WM and hippocampal volume. The findings may provide new insights into the etiology of brain atrophy with hemorrhagic CSVD, and management of CMBs might help to decelerate the neurodegenerative process. Further investigations are needed to establish the additional etiological and prognostic significance of CMBs, leading to brain atrophy.

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SUPPLEMENTARY MATERIAL

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