RESEARCH ARTICLE

Cerebral Microbleeds, Cerebral Amyloid Angiopathy, and Their Relationships to Quantitative Markers of Neurodegeneration

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Abstract

Background and Objectives

Age-related cognitive impairment is driven by the complex interplay of neurovascular and neurodegenerative disease. There is a strong relationship between cerebral microbleeds (CMBs), cerebral amyloid angiopathy (CAA), and the cognitive decline observed in conditions such as Alzheimer disease. However, in the early, preclinical phase of cognitive impairment, the extent to which CMBs and underlying CAA affect volumetric changes in the brain related to neurodegenerative disease remains unclear.

Methods

We performed cross-sectional analyses from 3 large cohorts: The Northern Manhattan Study (NOMAS), Alzheimer's Disease Neuroimaging Initiative (ADNI), and the Epidemiology of Dementia in Singapore study (EDIS). We conducted a confirmatory analysis of 82 autopsied cases from the Brain Arterial Remodeling Study (BARS). We implemented multivariate regression analyses to study the association between 2 related markers of cerebrovascular disease—MRI-based CMBs and autopsy-based CAA—as independent variables and volumetric markers of neurodegeneration as dependent variables. NOMAS included mostly dementia-free participants age 55 years or older from northern Manhattan. ADNI included participants living in the United States age 55–90 years with a range of cognitive status. EDIS included community-based participants living in Singapore age 60 years and older with a range of cognitive status. BARS included postmortem pathologic samples.

Results

We included 2,657 participants with available MRI data and 82 autopsy cases from BARS. In a meta-analysis of NOMAS, ADNI, and EDIS, superficial CMBs were associated with larger gray matter ($\beta = 4.49 \pm 1.13$, $p = 0.04$) and white matter ($\beta = 4.72 \pm 2.1$, $p = 0.03$) volumes. The association between superficial CMBs and larger white matter volume was more evident in participants with 1 CMB ($\beta = 5.17 \pm 2.47$, $p = 0.04$) than in those with ≥2 CMBs ($\beta = 1.97 \pm 3.41$, $p = 0.56$). In BARS, CAA was associated with increased cortical thickness ($\beta = 6.5 \pm 2.3$, $p = 0.016$) but not with increased brain weight ($\beta = 1.54 \pm 1.29$, $p = 0.26$).

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) 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 analysis or writing of this report. A complete listing of ADNI investigators can be found in the coinvestigators list at links.lww.com/WNL/B855.

Glossary

Aβ = β-amyloid; **AD** = Alzheimer disease; **ADNI** = Alzheimer's Disease Neuroimaging Initiative; **BARS** = Brain Arterial Remodeling Study; **CAA** = cerebral amyloid angiopathy; **CMB** = cerebral microbleed; **EDIS** = Epidemiology of Dementia in Singapore; **FLAIR** = fluid-attenuated inversion recovery; **GM** = gray matter; **GRE** = gradient echo; **MCI** = mild cognitive impairment; **NOMAS** = Northern Manhattan Study; **PVS** = dilated perivascular spaces; **WM** = white matter.

Discussion

Superficial CMBs are associated with larger morphometric brain measures, specifically white matter volume. This association is strongest in brains with fewer CMBs, suggesting that the CMB/CAA contribution to neurodegeneration may not relate to tissue loss, at least in early stages of disease.

Age-related cognitive decline is driven by the complex interactive effects of neurovascular and neurodegenerative disease.[1,2] This interplay is well illustrated by cerebral microbleeds (CMBs), which are small, round collections of hemosiderin-laden macrophages that represent foci of prior microhemorrhages in the brain.[3] CMBs located in deep brain regions (e.g., basal ganglia and infratentorial regions) represent radiologic biomarkers for small vessel vascular disease and are associated with risk factors such as hypertension, hyperlipidemia, and diabetes.[4,5] Conversely, CMBs in superficial (or lobar) regions of the brain are pathologically characterized by the gradual deposition of β-amyloid (Aβ) in vessel walls, known as cerebral amyloid angiopathy (CAA).[6,7] CAA is a clinical entity characterized by older age, disseminated superficial siderosis, macrobleeds, and multiple CMBs in the lobar regions of the brain.[8] The relationship between CMBs, CAA, and cognitive decline is complex but a strong association has emerged in recent years. CMBs are present in approximately 20% of older individuals with normal cognition but up to 40% of people with Alzheimer disease (AD).[9] There is a significant association between CMBs and increased cognitive impairment and mortality.[10-13] CAA and AD also overlap—both involve the aberrant deposition of Aβ, and an estimated 52%–98% of individuals with AD neuropathologic changes also have CAA.[14]

The structural hallmark of many neurodegenerative diseases such as AD is progressive cortical atrophy.[15] Previous work has indicated that brain atrophy may also be a key neuroimaging marker of neurovascular disease.[16] Small vessel disease, for example, is characterized on MRI by white matter (WM) hyperintensities, dilated perivascular spaces (PVS), lacunar infarcts, and CMBs, but these distinct markers are thought to ultimately coalesce into brain atrophy as the final common pathway.[17] In addition, a prior study demonstrated that people with both hereditary and sporadic CAA have decreased cortical thickness compared to age-matched healthy controls.[18] Although superficial CMBs are strongly linked to underlying CAA pathology, there are conflicting reports regarding the association of superficial CMBs and gray matter (GM) volume, with 2 recent studies finding no association[18,19] and 1 study finding superficial CMBs to be associated with smaller GM volumes.[20] Prior work has also shown similarly conflicting evidence regarding the relationship between superficial CMBs/CAA and WM volume.[19,21]

In light of these discrepancies, we attempted to elucidate how CMBs relate to morphologic changes in the brain (supratentorial brain volume, GM and WM volumes, and cortical thickness) while accounting for other markers of small vessel disease. Leveraging 3 population samples with available brain MRI and a collection of autopsied brains, we hypothesized that superficial CMBs and related CAA are associated with volumetric parameters of neurodegeneration.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

The institutional review boards and ethical standards committees at each participating institution approved of the study protocol, including participant data collection and subsequent publication of data related to each cohort. Written informed participant consent was obtained prior to participation in the study.

Cohort Participants

Northern Manhattan Study

The Northern Manhattan Study (NOMAS) is an observational, prospective, population-based cohort of stroke-free participants enrolled in Northern Manhattan that started in 1993. From 2003 to 2008, stroke-free participants 55 years or older were invited to undergo a brain MRI. Detailed descriptions of inclusion and exclusion criteria for the NOMAS cohort and MRI substudy were previously published.[22,23] Participants were not categorized by cognitive ability but were estimated to be dementia-free. In NOMAS, baseline demographic and clinical characteristics were self-reported, obtained from prescribed medications, or obtained from blood pressure/laboratory evidence, as previously described.[24] Smoking was defined as self-reported current smoking at the time of MRI.

Alzheimer's Disease Neuroimaging Initiative

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). 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, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early AD. ADNI included participants aged 55–90 years.[25] Full inclusion/exclusion criteria are described in detail at adni-info.org. Briefly, the cohort included participants classified as cognitively normal, MCI, or AD.[26] Clinical characteristics including hypertension, diabetes, hypercholesterolemia, and smoking status were obtained during a baseline visit using standardized measurements and medications.[25] We included a subset of ADNI who underwent 3T brain MRI from June 2010 until March 2012.

Epidemiology of Dementia in Singapore Study

The Epidemiology of Dementia in Singapore Study (EDIS) is a subsample of a population-based cohort of Chinese, Malay, and Indian participants aged 60 years and older. Participants were included if they screened positive with the Abbreviated Mental Test or a self-reported history of forgetfulness, as previously described.[27] In EDIS, vascular risk factors were obtained from standardized recordings, laboratory values, or use of medications for hypertension, diabetes, or hyperlipidemia. Smoking was categorized as never-smokers and any smoking history (past and current smokers).[27] We analyzed the subset of participants who underwent 3T MRI brain imaging and had available *APOE4* genotype.

Brain Arterial Remodeling Study

The Brain Arterial Remodeling Study (BARS) is a collection of more than 300 circle of Willis samples obtained at autopsy in various brain banks. Detailed descriptions of pathologic processing were provided previously.[28,29] More recently, we started adding brain samples corresponding to the circle of Willis of the New York Presbyterian Brain Bank as an extension of the investigation of the brain arterial remodeling role in neurodegeneration.

The study size for the cross-sectional analyses was based on the subject-level eligibility based on the inclusion and exclusion criteria for each respective cohort.

MRI Examination

NOMAS imaging was performed on a dedicated 1.5T research MRI system (Philips Medical Systems). CMBs were manually counted using T2* gradient echo (GRE) sequences in the coronal plane using the Brain Observer MicroBleed Scale, as previously described.[30] Using T1 axial sequences, we obtained total supratentorial brain volume (excluding ventricles), total GM volume, total WM volume, and cortical thickness. T1-weighted and fluid-attenuated inversion recovery (FLAIR) MRI sequences underwent motion correction, skull stripping, and transformation into Talairach space.[31] Images were segmented and GM and WM boundaries were identified and underwent automated topology correction and surface deformation. To obtain total supratentorial brain volume, nonbrain elements were removed manually by operator-guided tracing, as previously described.[32] Brain covert infarcts and dilated PVS were rated using a pathology-informed algorithm that aims at distinguishing infarcts from PVS using T1 and FLAIR sequences with good reliability.[23] Volumes were obtained by adding brain voxels from the segmentation of T1-weighted images. We used the Freesurfer image analysis suite version 5.1 (surfer.nmr.mgh.harvard.edu/) to measure cortical thickness.[32]

ADNI imaging was conducted on 3T MRI scanners at 54 different sites. A full description of MRI processing is available at adni.loni.usc.edu/methods/documents/mri-protocols/. Briefly, 2 radiologists used T2* GRE sequences to count CMBs as homogenous hypointense lesions up to 10 mm in diameter. The interrater agreement between the 2 radiologists on definite vs not definite CMBs was 85%, which corresponded to good agreement (κ = 68%).[33] Brain infarct information was downloaded from the ADNI website and used for analyses as present vs absent. Dilated PVS were rated by us using the same method as in NOMAS applied directly to downloaded T1 and FLAIR images.[23]

EDIS imaging was performed on a 3T MRI (Siemens Magnetom Trio Tim scanner), using a 32-channel head coil, at the Clinical Imaging Research Centre of the National University of Singapore.[27] CMBs (also imaged using T2* GRE sequences) were graded using the Brain Observer Microbleed Scale and were classified as lobar or deep microbleeds as dichotomous variables.[30] Brain infarcts were defined as hypointense lesions on T1-weighted images and hyperintense on T2-weighted images. Total intracranial volume was obtained using T1- and T2-weighted MRI. Regional volumes were quantified using automatic segmentation and a model-based automated procedure (FreeSurfer version 5.1.0) was used to measure cortical thickness, as previously described.[27] Dilated PVS were quantified in 4 brain regions and the sum of these regions was used for this analysis. Information on dilated PVS was available only in EDIS participants of Chinese and Malay ancestry.

Postmortem Brain Samples

Cerebral hemispheres were fixed with 10% buffered formalin and coronally sectioned at 0.3–0.5 cm interval thickness. Samples were processed systematically as described elsewhere.[34] At least 10 standardized anatomical sections were obtained and stained with Luxol/hematoxylin & eosin and submitted to Aβ (6E10; BioLegend; catalog number 803003) immunohistochemistry. The immunohistochemistry was performed by Ventana automated slide stainer without manual antigen retrieval and was detected using the Ventana ultraView universal DAB detection kit as recommended by the manufacturer. Each slide was digitized using a Leica

SCN400 microscope with constant light at 40× magnification. Aperio Image Scope (Leica Biosystem Pathology Imaging, version 12.4.3.5008) was used for visualization and processing of images. In the slides for Aβ, we quantified the presence and number of vessels with Aβ deposits by dividing each brain slide into 10 two-dimensional boxes (40 μm^2 in size). For each box, we manually counted the number of vessels with Aβ deposits to quantify the burden of CAA. We also classified the location of each vessel with Aβ deposits into subcortical, cortical, or leptomeningeal (or extracortical) areas (Figure 1, A–D). The maximum number of CAA vessels per 40 μm^2 box was capped at 100. Cortical thickness was measured in slices of the brain surface. To account for the natural variation in cortical thickness observed in pathology given sulci folding, we measured the cortical thickness in at least 5 areas that visually appeared homogenous in thickness to obtain the average cortical thickness in a given brain section.

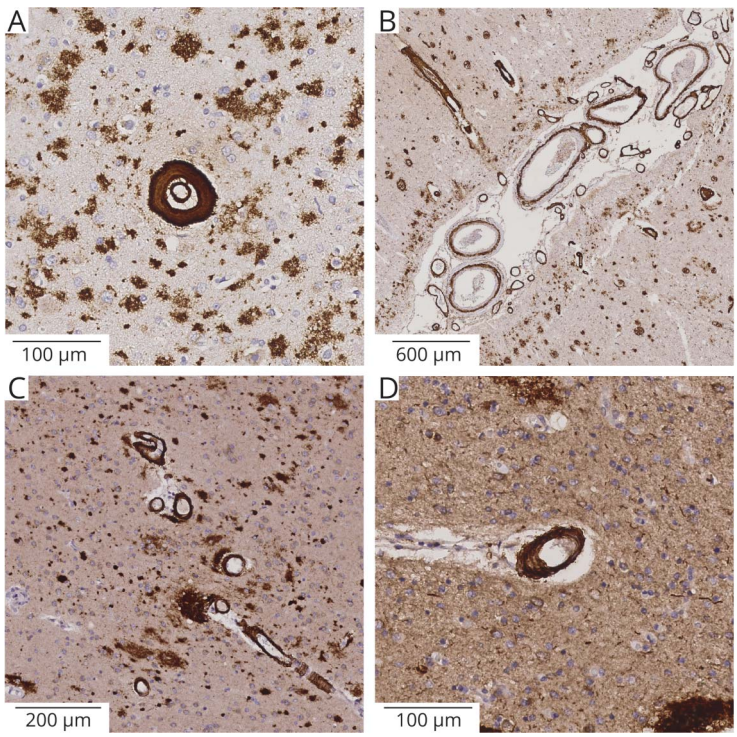
Statistical Analysis

Analyses were initially carried out separately in each sample and then combined in a meta-analysis. We assessed sample characteristics associated with any CMB in the 3 MRI cohorts and any CAA in BARS using Fisher exact and Student *t* tests, as indicated.

For the MRI samples, total brain and WM and GM volumes were transformed into their logarithmic expression to approximate normality. Cortical thickness (in mm) was normally distributed. CMBs were expressed as a binary variable, segregated into lobar and deep, and ordinally as 0 = no CMB, 1 = 1 CMB, and 2 = 2 or more CMBs. We built generalized linear models with an identity link to obtain type 1 errors and beta estimates. Models were adjusted for age, sex, race/ethnicity, hypertension, diabetes, dyslipidemia, smoking, *APOE4* status, prevalent chronic brain infarcts, head size, and WM hyperintensity volume. In a post hoc analysis, we ran the same models also adjusting for dilated PVS in the 3 population cohorts. Due to differences in population origin and methodology, we carried out a meta-analysis and not pooled cohort analyses. We meta-analyzed the results of the 3 cohorts, as well as ADNI and NOMAS separately, given their shared origin in the United States. RevMan 5.4 was used to perform all the meta-analyses (Review Manager, version 5.4, The Cochrane Collaboration, 2020). A random effects model was carried out to calculate mean differences for continuous outcome data. Heterogeneity was assessed by 2 methods: the Q statistic test and the I^2 statistic test. For the Q statistic test, a p value ≤ 0.05 was considered statistically significant. For the I^2 statistic test, heterogeneity increased with a rising I^2 value. A fixed statistical model (I^2 < 50%) or a random statistical model (I^2 > 50%) was used according to the I^2 value.

In BARS, we expressed CAA as present vs absent, and among those classified as present, the mean number of arteries with CAA per brain section. Due to limited availability of morphologic measures in sectioned postmortem specimens, we only assessed brain weight and cortical thickness. Because of the 2-level correlation in brain samples (number of arteries

Figure 1 Example Vessels With Cerebral Amyloid Angiopathy and Their Anatomic Distribution



(A) Double-barrel appearance of cerebral amyloid angiopathy (CAA) in the frontal cortex showing detachment and delamination of the outer part of the tunica media. Many neuritic plaques observed in surrounding tissue. (B) Copious vessels affected by CAA noted in the leptomeningeal space of the frontal cortex. (C) CAA vessels observed in the caudate nucleus. (D) CAA vessel observed in the globus pallidus.

with CAA within each brain slice and multiple brain slices per case), we built generalized linear mixed models adjusted for age, sex, race/ethnicity, hypertension, diabetes, dyslipidemia, smoking, and brain infarctions.

Statistical analyses were completed with SAS software (SAS version 9.4).

Data Availability

Anonymized data not provided in the article because of space limitations may be shared at the request of any qualified investigator for purposes of replicating procedures and results.

Results

Description of Cohorts

We included 2,657 participants with available data (918 from NOMAS, 1,017 from ADNI, and 722 from EDIS) and 82 autopsy cases from BARS. Baseline demographic characteristics of the samples are presented in Table 1.

The overall prevalence of CMBs was 6% in NOMAS, 22% in ADNI, and 31% in EDIS (Table 1). In the 3 cohorts, the prevalence of CMBs increased with age (Figure 2 and eTable1, links.lww.com/WNL/B854). Stratifying CMBs by anatomical location shows a consistently higher prevalence of cortical CMBs compared to deep CMBs across the 3 cohorts (Figure 2).

In BARS, the overall prevalence of CAA was 72% (23% purely cortical, 6% purely in the basal ganglia, and 43% mixed). CAA burden differed by anatomical region (Figure 3): the mean number of CAA vessels was highest in the lobar regions of the parietal (mean 7.4 ± 2.4) followed by occipital (mean 4.2 ± 1.5) and frontal (mean 4.2 ± 1.3) regions. Leptomeningeal (or extracortical) CAA was more prevalent in the occipital region (mean 3.8 ± 0.8) compared to the parietal (mean 3.6 ± 0.8) and frontal (mean 2.8 ± 0.6) regions. Subcortical/deep regions had the lowest amount of CAA, as observed in Figure 3.

Correlates of CMB/CAA

In a cross-sectional multivariate analysis, any CMB (collection of both superficial and deep CMBs) was associated with age across

Table 1 Baseline Demographic Characteristics

	NOMAS (n = 918)	ADNI (n = 1,017)	EDIS (n = 722)	BARS (n = 82)
Age, y	70 (9)	73 (7)	70 (7)	81 (11)
Women	573 (62)	500 (51)	359 (50)	38 (46)
Race/ethnicity				
Non-Hispanic White	161 (18)	908 (89)	—	61 (74)
Non-Hispanic Black	147 (16)	42 (4)	—	8 (10)
Hispanic	610 (66)	35 (3)	—	12 (16)
Chinese	—	—	223 (31)	—
Indian	—	—	259 (36)	—
Malay	—	—	240 (33)	—
***APOE4* carriers**	204 (23)	428 (42)	122 (17)	11 (41)[a]
Hypertension	707 (77)	537 (53)	576 (80)	42 (51)
Diabetes	221 (24)	124 (12)	258 (36)	10 (12)
Hypercholesterolemia	744 (81)	581 (57)	549 (76)	30 (37)
Current smoker	89 (10)	18 (2)	197 (27)	14 (17)
Any CMB (CAA for BARS)	61 (6)	228 (22)	223 (31)	64 (78)
Lobar	36 (4)	188 (19)	208 (27)	55 (67)
Deep (basal ganglia/brainstem)	25 (3)	77 (8)	124 (16)	39 (48)
Brain infarcts	137 (15)	36 (4)[b]	110 (17)	33 (40)
Cortical thickness, mm	2.29 (0.10)	2.46 (0.13)	2.37 (0.11)	2.57 (0.27)

Abbreviations: ADNI = Alzheimer's Disease Neuroimaging Initiative; BARS = Brain Arterial Remodeling Study; CAA = cerebral amyloid angiopathy; CMB = cerebral microbleed; EDIS = Epidemiology of Dementia in Singapore; NOMAS = Northern Manhattan Study.
Values are mean (SD) or n (%).
[a] Only available in 27 cases.
[b] Data on brain infarcts from ADNI are missing; self-reported history of stroke was used as a surrogate.

all 3 cohorts. The strength of association and statistical significance varied across cohorts for sex, ethnicity, vascular risk factors, *APOE4* genotype, and MRI markers of covert cerebrovascular disease (eTable 1, links.lww.com/WNL/B854).

Association of CMBs/CAA With Cortical Thickness and Brain Volumes

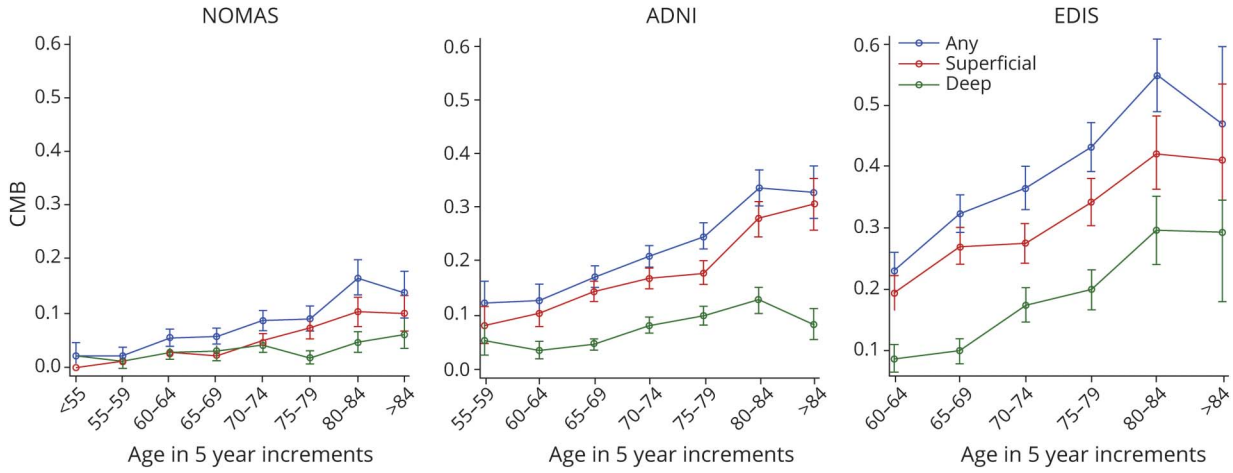
In each cohort, we assessed the relationship between CMBs and morphologic brain metrics including total brain, WM, and GM volumes, in addition to cortical thickness (Table 2). In a meta-analysis of NOMAS, ADNI, and EDIS, superficial CMBs were associated with larger GM ($\beta = 4.49 \pm 1.13$, $p = 0.04$) and WM ($\beta = 4.72 \pm 2.1$, $p = 0.03$) volumes (Table 3). Stratifying by CMB severity, the association between superficial CMBs and larger WM volume was more evident in participants with 1 CMB ($\beta = 5.17 \pm 2.47$, $p = 0.04$) than in those with ≥2 CMBs ($\beta = 1.97 \pm 3.41$, $p = 0.56$). The direction of associations was more consistent between ADNI and NOMAS than with EDIS (Table 2 and eFigures 1–4, links.lww.com/WNL/B854). We also found a positive correlation between superficial/deep CMBs and GM volumes ($\beta = 5.63 \pm 1.27$ and $\beta = 9.27 \pm 3.52$, $p < 0.05$). CMBs were nominally associated with greater thickness ($\beta = 12.21 \pm 7.72$, $p = 0.10$) only in NOMAS and ADNI meta-analyses. In post hoc analyses, adding on dilated PVS scores in the 3 populations did not change the significance of the association between CMB and higher WM volumes. Dilated PVS were independently associated with higher WM volume in NOMAS ($\beta = 1.25 \pm 0.59$, $p = 0.04$) and EDIS ($\beta = 0.35 \pm 0.16$, $p = 0.03$) and nominally in the ADNI cohort ($\beta = 0.37 \pm 0.47$, $p = 0.43$, eTable 2).

In BARS, the 2 main outcomes were brain weight at autopsy and cortical thickness, and the main exposure was CAA, expressed continuously as the mean number of vessels with CAA in each brain section of each case. In a model adjusted for age, sex, demographics, vascular risk factors, and presence of brain infarcts, CAA was associated with increased cortical thickness ($\beta = 6.5 \pm 2.3$ μm, $p = 0.016$) but not with increased brain weight ($\beta = 1.54 \pm 1.29$, $p = 0.26$). We did not adjust for *APOE*4 genotype because it was available on only a small subsample.

Discussion

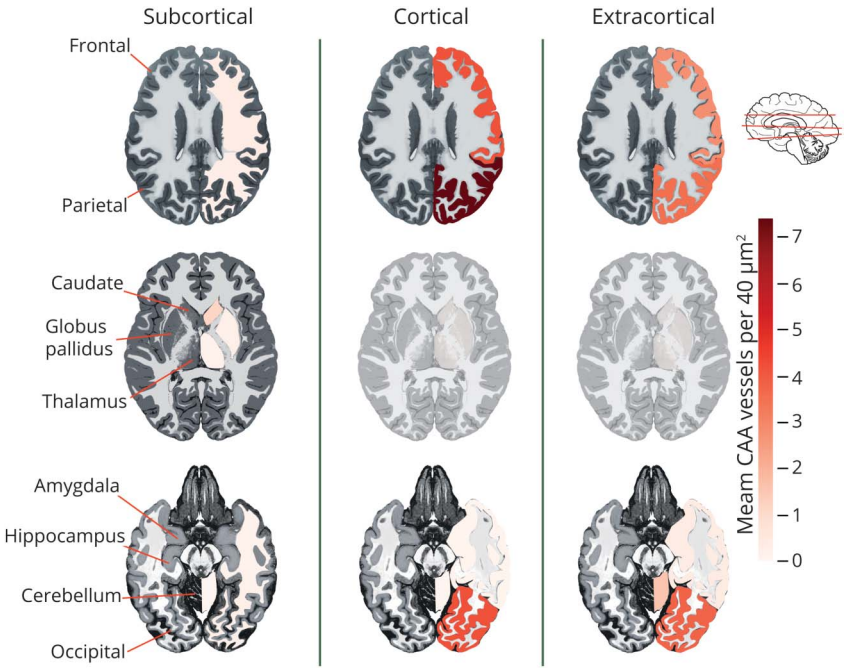
Growing evidence suggests that cognitive decline in the aging brain is driven by overlapping neurovascular and neurodegenerative disease. CAA and AD pathologic changes share a particularly close connection. Aβ underlies the pathogenesis of both conditions, and clinically, they frequently coexist and correlate in severity.[1,14] CMBs are also more prevalent in AD compared to other forms of dementia.[10] To further investigate this interrelationship, we tested whether CMBs (and underlying CAA) correlate with key morphologic markers of neurodegeneration. Contrary to our initial hypothesis, we found that lobar CMBs were independently associated with increased MRI-based total supratentorial brain volume and WM volume. We also found an unexpected significant association between autopsy-based CAA burden and increased cortical thickness. Prior work has demonstrated conflicting results regarding the relationship of CMBs and WM volume. One recent study of memory clinic patients indicated that lobar CMBs, as opposed to deep microbleeds, were associated with reduced WM volume.[35] However, in agreement with our findings, Wang and colleagues[19] studied a population without stroke or dementia and found increased WM volume in patients with lobar CMBs. One prior study examining cohorts of patients with hereditary cerebral hemorrhage with amyloidosis–Dutch type (HCHWA-D) and sporadic CAA

Figure 2 Mean Prevalence of Cerebral Microbleeds by Age and Anatomical Location for the 3 Cohorts



Age is discretized into 5-year increments. (1) Blue indicates any cerebral microbleed (CMB). (2) Red indicates superficial (or lobar) CMBs (i.e., cortical or adjacent subcortical white matter). (3) Green indicates deep (basal ganglia, brainstem, or cerebellar nuclei) CMBs. The prevalence of CMBs was significantly associated with age in Northern Manhattan Study (NOMAS) (odds ratio [OR] 1.035 [1.008–1.063]), Alzheimer's Disease Neuroimaging Initiative (ADNI) (OR 1.040 [1.021–1.059]), and Epidemiology of Dementia in Singapore (EDIS) (OR 1.036 [1.008–1.064]) cohorts.

Figure 3 Mean Cerebral Amyloid Angiopathy Number of Vessels per 40 μm^2 in BARS Cohort



The gray matter areas seen in the caudate, internal capsule, globus pallidus, and thalamus were excluded from the cortical and extracortical columns and represented instead under the subcortical column. BARS = Brain Arterial Remodeling Study; CAA = cerebral amyloid angiopathy.

provided evidence that CAA is associated with cortical atrophy, independent of AD.[18] We found consistent trends in the opposite association in our study. This relationship was particularly notable in the American cohorts and the full study meta-analysis, but not in the Singaporean cohort. One reason for the discrepancy may be due to differences in baseline disease. That is, we observed significantly more CMBs in the Singaporean cohort compared to the American cohorts, which could suggest more advanced disease in the Singaporean cohort.[36] There may also be social or genetic differences between the cohorts that were not accounted for in our study. We noted no difference in the proportion of *APOE*4 mutations between the study groups.

In all 3 imaging cohorts, we found that CMBs were associated with older age, consistent with prior studies.[4,5] Presumably, this relationship is due to weakened vessel walls and blood leakage into surrounding tissues seen with aging.[37] We found no association between CMBs and *APOE*4 carrier status, despite previous work showing that individuals with the *APOE*4 allele are more likely to have lobar microbleeds.[4] Our MRI populations did have a predominance of lobar compared to deep microbleeds, which was unanticipated given the high proportion of vascular risk factors, hypertension, and hyperlipidemia in each cohort. Research has indicated that a population with predominately lobar CMBs is likely to be associated with underlying amyloid angiopathy.[38] In agreement with prior work,[39,40] we found a high proportion of CMBs in the frontal and parietal regions, and in pathologic samples, we found more CAA in cortical regions compared to subcortical or deep regions of the brain. We also found a high proportion of CAA in leptomeningeal vessels and in the occipitoparietal lobar regions. CAA is thought to develop from the posterior lobar regions to the anterior regions,[41] a progression that is associated with worsening executive function.[42]

The glymphatic system of the brain may help explain our unexpected results. The glymphatic system refers to paravascular flow of CSF to remove important interstitial waste solutes, such as Aβ.[43] This flux is driven by arterial pulsation and vasomotion and can be adversely affected by small vessel disease and stroke.[44-47] Pathologically, AD is characterized by the accumulation of neuritic plaques that result, at least in part, from dysfunctional clearance of Aβ in the glymphatic system. In CAA, Aβ accumulation in vessel walls is also likely the result of failure of intramural perivascular drainage.[48] These 2 overlapping pathologies are thought to create a feed-forward cycle, whereby increased vascular Aβ leads to decreased clearance of Aβ, worsening both CAA and AD.[2] The combined interaction may represent a unifying therapeutic target to treat both conditions. It is clear from a large body of work that clinical dementia is associated with brain atrophy, but in the preclinical stages of disease, failure of the glymphatic system may lead to relative increase in interstitial fluid, which is reflected by increased brain morphometric measures, particularly WM volume. Our finding of a significant relationship between dilated PVS and WM volume may support this hypothesis. Future mechanistic studies are needed to assess whether larger brain volumes may be seen as a preclinical stage of Aβ deposition–related brain pathology.

The methodologic strengths of this study include the large, ethnically diverse sample of participants, the clinical and

Table 2 Associations Between Cerebral Microbleeds by Anatomical Location and Severity With Brain Volumetric Measures and Cortical Thickness

	Total brain volume	Gray matter volume	White matter volume	Cortical thickness, μm
NOMAS				
Model 1				
Any CMB	10.06 ± 5.07	7.54 ± 5.64	19.31 ± 8.33	8.43 ± 11.99
Model 2				
Superficial CMB	11.99 ± 6.63[a]	7.10 ± 1.38	31.92 ± 10.87[b]	11.28 ± 15.66
Deep CMB	−1.81 ± 7.67	12.70 ± 5.58	1.85 ± 12.64	15.40 ± 18.21
Model 3				
Superficial				
No CMB	Reference			
1 CMB	11.96 ± 7.95	4.82 ± 8.73	20.40 ± 12.80	16.8 ± 18.57
≥2 CMB	6.31 ± 11.78	2.87 ± 14.24	54.47 ± 20.91[b]	−17.38 ± 30.27
Deep				
No CMB	Reference			
1 CMB	8.17 ± 6.93	10.73 ± 7.68	4.32 ± 11.28	13.43 ± 16.34
≥2 CMB	17.27 ± 11.49	7.94 ± 24.35	19.88 ± 35.76	−57.52 ± 51.76
ADNI				
Model 1				
Any CMB	2.75 ± 2.32	0.59 ± 2.92	6.15 ± 4.78	14.9 ± 10.1
Model 2				
Superficial CMB	1.57 ± 2.58	−2.52 ± 3.25	7.12 ± 5.32	8.3 ± 11.2
Deep CMB	4.55 ± 3.59	7.0 ± 4.552	3.03 ± 7.38	13.5 ± 16.4
Model 3				
Superficial				
No CMB	Reference			
1 CMB	2.67 ± 3.01	−3.56 ± 3.79	9.28 ± 6.19	17.31 ± 12.8
≥2 CMB	−2.25 ± 1.46	−0.77 ± 5.25	−0.37 ± 8.56	−12.7 ± 18.40
Deep				
No CMB	Reference			
1 CMB	1.64 ± 3.92	5.87 ± 4.94	−2.64 ± 8.07	14.34 ± 17.35
≥2 CMB	20.30 ± 1.91[b]	10.10 ± 9.97	33.77 ± 16.27[b]	28.84 ± 39.30
EDIS (Singapore)				
Model 1				
Any CMB	−0.06 ± 1.16	−1.14 ± 2.29	3.02 ± 2.18	−11.13 ± 8.17
Model 2				
Superficial CMB	0.11 ± 1.25	0.20 ± 2.47	2.96 ± 2.36	−1.86 ± 8.82
Deep CMB	−1.39 ± 1.58	−3.99 ± 3.12	−0.38 ± 2.96	−13.87 ± 11.15

Continued

Table 2 Associations Between Cerebral Microbleeds by Anatomical Location and Severity With Brain Volumetric Measures and Cortical Thickness *(continued)*

	Total brain volume	Gray matter volume	White matter volume	Cortical thickness, μm
Model 3				
Superficial				
No CMB	Reference			
1 CMB	1.50 ± 1.46	1.41 ± 2.90	3.65 ± 2.76	7.01 ± 14.01
≥2 CMBs	−2.83 ± 2.00	−1.98 ± 3.96	0.71 ± 3.78	−4.73 ± 10.38
Deep				
No CMB	Reference			
1 CMB	−1.16 ± 1.79	−3.31 ± 3.56	−1.26 ± 3.36	−7.8 ± 12.69
≥2 CMB	0.49 ± 2.86	−3.19 ± 5.67	2.40 ± 5.38	−34.63 ± 20.22

Abbreviations: ADNI = Alzheimer's Disease Neuroimaging Initiative; CMB = cerebral microbleed; EDIS = Epidemiology of Dementia in Singapore; NOMAS = Northern Manhattan Study.
Models adjusted for age, sex, race/ethnicity, *APOE4*, head size, prevalence of hypertension, diabetes, hypercholesterolemia, smoking, MRI evidence of infarction, and total white matter hyperintensity volume. Values are log-transformed β estimates ± SE.
[a] $p = 0.10–0.05$.
[b] $p < 0.05$.

imaging data, and the cross-validation of the analyses using autopsies, the gold standard to diagnose CAA, in BARS. The results of this study should be contextualized within certain limitations. First, in the 3 imaging cohorts, we assessed for CMBs, while in BARS, we pathologically diagnosed CAA. The most likely cause of cortical CMBs is CAA, but prior work has indicated that CMBs and CAA do not overlap perfectly in the brain.[40] In addition, radiologic–histopathologic correlation studies indicate that the true-positive detection rate of CMBs ranges between 48% and 89%, and false-positive mimics (including microdissections, microaneurysms, and microcalcifications) occur at a rate between 11% and 24%.[3] Furthermore, up to 50% of CMBs are missed on MRI compared to postmortem analysis.[49] We also did not assess other radiologic markers of CAA such as superficial siderosis. A higher Tesla magnet would increase the sensitivity to detect CMBs and potentially yield closer results in the MRI and pathology cohorts. Failing to identify CMBs increases type 2 error. Therefore, we paid attention to the direction of associations in other morphometric brain measures to assess whether more precise diagnosis of CMBs could result in greater statistical power. The precision of CAA diagnosis provided by pathology in BARS may be the reason why in a smaller sample we were able to detect an association between CAA and cortical thickness.

Our study has inherent limitations regarding its cross-sectional nature. In addition, the 3 cohorts differed in various respects that may have introduced selection biases. For instance, the NOMAS cohort was composed of mostly dementia-free participants, while both ADNI and EDIS obtained patients with a range of cognitive ability. In NOMAS, participants were scanned with 1.5T machines, while ADNI and EDIS implemented 3T machines. The higher Tesla magnet may have identified a larger number of CMBs in a cognitively worse population, skewing the associations. In addition, each study implemented T2* GRE sequences, which is less sensitive than susceptibility-weighted imaging for the detection of CMBs.[50] Our models did adjust for a large range of clinical factors including age, sex, race/ethnicity, *APOE4*, head size, prevalence of hypertension, diabetes, hypercholesterolemia, smoking, MRI evidence of infarction, and total WM hyperintensity volume, but there may have been other unmeasured clinical factors for which we did not account. We also did not conduct morphologic analyses on each specific cortical area and thus there may be regional variations that were not fully assessed in this study. One may propose that brain regions particularly important to aging (e.g., hippocampus, occipital, and parietal) may demonstrate differential morphologic changes compared to other regions. Our study should be interpreted with these limitations in mind and future work should be conducted to assess the generalizability of our results.

We found that CMBs—and the underlying pathologic entity, CAA—do not correlate with traditional markers of neurodegenerative disease such as atrophy or cortical thinning. Instead, our results indicate an association between CMBs and CAA and larger morphologic brain measures.

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Table 3 Associations Between Cerebral Microbleeds by Anatomical Location and Severity With Brain Volumetric Measures and Cortical Thickness

	Total brain volume	Gray matter volume	White matter volume	Cortical thickness, μm
Meta-analysis (United States)				
Model 1				
Any CMB	4.02 ± 2.11	2.06 ± 2.59	9.41 ± 4.14[b]	12.21 ± 7.72
Model 2				
Superficial CMB	2.94 ± 2.41	5.63 ± 1.27[b]	11.91 ± 4.77[b]	9.31 ± 9.11
Deep CMB	3.41 ± 3.25	9.27 ± 3.52[b]	2.73 ± 6.37	14.35 ± 12.19
Model 3				
Superficial				
No CMB	Reference			
1 CMB	10.19 ± 6.59	−2.23 ± 3.47	11.38 ± 5.57[b]	17.14 ± 10.54[a]
≥2 CMB	−2.12 ± 1.45	−0.33 ± 4.92	7.50 ± 7.92	−13.96 ± 15.72
Deep				
No CMB	Reference			
1 CMB	3.22 ± 3.41	7.29 ± 4.15[a]	−0.28 ± 6.56	13.86 ± 11.89
≥2 CMB	20.21 ± 1.88[b]	9.79 ± 9.23	31.38 ± 14.8[b]	−2.74 ± 31.3
Meta-analysis (all 3 cohorts)				
Model 1				
Any CMB	0.89 ± 1.02	0.26 ± 1.72	4.4 ± 1.93[b]	1.2 ± 5.61
Model 2				
Superficial CMB	0.71 ± 1.11	4.49 ± 1.13[b]	4.72 ± 2.11[b]	3.54 ± 6.34
Deep CMB	−0.47 ± 1.42	1.84 ± 2.34	0.17 ± 2.68	−1.01 ± 8.22
Model 3				
Superficial				
No CMB	Reference			
1 CMB	1.99 ± 1.3	−0.08 ± 2.22	5.17 ± 2.47[b]	13.48 ± 8.42
≥2 CMBs	−2.36 ± 1.17[b]	−1.33 ± 3.09	1.97 ± 3.41	−7.53 ± 8.66
Deep				
No CMB	Reference			
1 CMB	−0.21 ± 1.58	1.18 ± 2.7	−1.06 ± 2.99	3.73 ± 8.68
≥2 CMB	14.25 ± 1.57[b]	0.37 ± 4.83	5.78 ± 5.06	−25.24 ± 16.98

Analytic notes: Models adjusted for age, sex, race/ethnicity, apoe4, head size, prevalence of hypertension, diabetes, hypercholesterolemia, smoking, MRI evidence of infarction, and total white matter hyperintensity volume. Values are log-transformed β estimates ± SE.
[a] $p = 0.10–0.05$.
[b] $p < 0.05$.

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Continued

Appendix 1 *(continued)*

Name	Location	Contribution
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Appendix 2 Coinvestigators

Coinvestigators are listed at links.lww.com/WNL/B855.

References

1. Boyle PA, Yu L, Wilson RS, Leurgans SE, Schneider JA, Bennett DA. Person-specific contribution of neuropathologies to cognitive loss in old age. *Ann Neurol.* 2018;83(1):74-83.
2. Greenberg SM, Bacskai BJ, Hernandez-Guillamon M, Pruzin J, Sperling R, van Veluw SJ. Cerebral amyloid angiopathy and Alzheimer disease: one peptide, two pathways. *Nat Rev Neurol.* 2020;16(1):30-42.
3. Haller S, Vernooij MW, Kuijer JPA, Larsson EM, Jager HR, Barkhof F. Cerebral microbleeds: imaging and clinical significance. *Radiology.* 2018;287(1):11-28.
4. Poels MM, Vernooij MW, Ikram MA, et al. Prevalence and risk factors of cerebral microbleeds: an update of the Rotterdam scan study. *Stroke.* 2010;41(10 suppl):S103-S106.
5. Romero JR, Preis SR, Beiser A, et al. Risk factors, stroke prevention treatments, and prevalence of cerebral microbleeds in the Framingham Heart Study. *Stroke.* 2014;45(5):1492-1494.
6. Viswanathan A, Greenberg SM. Cerebral amyloid angiopathy in the elderly. *Ann Neurol.* 2011;70(6):871-880.
7. Greenberg SM, Charidimou A. Diagnosis of cerebral amyloid angiopathy: evolution of the Boston criteria. *Stroke.* 2018;49(2):491-497.
8. Greenberg SM. Cerebral amyloid angiopathy: prospects for clinical diagnosis and treatment. *Neurology.* 1998;51(3):690-694.
9. Yates PA, Desmond PM, Phal PM, et al. Incidence of cerebral microbleeds in preclinical Alzheimer disease. *Neurology.* 2014;82(14):1266-1273.
10. Cordonnier C, van der Flier WM, Sluimer JD, Leys D, Barkhof F, Scheltens P. Prevalence and severity of microbleeds in a memory clinic setting. *Neurology.* 2006;66(9):1356-1360.
11. Goos JD, Kester MI, Barkhof F, et al. Patients with Alzheimer disease with multiple microbleeds: relation with cerebrospinal fluid biomarkers and cognition. *Stroke.* 2009;40(11):3455-3460.
12. Henneman WJ, Sluimer JD, Cordonnier C, et al. MRI biomarkers of vascular damage and atrophy predicting mortality in a memory clinic population. *Stroke.* 2009;40(2):492-498.
13. Sepehry AA, Lang D, Hsiung GY, Rauscher A. Prevalence of brain microbleeds in Alzheimer disease: a systematic review and meta-analysis on the influence of neuroimaging techniques. *AJNR Am J Neuroradiol.* 2016;37(2):215-222.
14. Brenowitz WD, Nelson PT, Besser LM, Heller KB, Kukull WA. Cerebral amyloid angiopathy and its co-occurrence with Alzheimer's disease and other cerebrovascular neuropathologic changes. *Neurobiol Aging.* 2015;36(10):2702-2708.
15. Karas GB, Burton EJ, Rombouts SA, et al. A comprehensive study of gray matter loss in patients with Alzheimer's disease using optimized voxel-based morphometry. *Neuroimage.* 2003;18(4):895-907.
16. Nitkunan A, Lanfranconi S, Charlton RA, Barrick TR, Markus HS. Brain atrophy and cerebral small vessel disease: a prospective follow-up study. *Stroke.* 2011;42(1):133-138.
17. De Guio F, Duering M, Fazekas F, et al. Brain atrophy in cerebral small vessel diseases: extent, consequences, technical limitations and perspectives: the HARNESS initiative. *J Cereb Blood Flow Metab.* 2020;40(2):231-245.
18. Fotiadis P, van Rooden S, van der Grond J, et al. Cortical atrophy in patients with cerebral amyloid angiopathy: a case-control study. *Lancet Neurol.* 2016;15(8):811-819.
19. Wang PN, Chou KH, Peng LN, et al. Strictly lobar cerebral microbleeds are associated with increased white matter volume. *Transl Stroke Res.* 2020;11(1):29-38.
20. Graff-Radford J, Simino J, Kantarci K, et al. Neuroimaging correlates of cerebral microbleeds: the ARIC study (Atherosclerosis Risk In Communities). *Stroke.* 2017;48(11):2964-2972.
21. Fotiadis P, Reijmer YD, Van Veluw SJ, et al. White matter atrophy in cerebral amyloid angiopathy. *Neurology.* 2020;95(5):e554–e562.
22. Boden-Albala B, Cammack S, Chong J, et al. Diabetes, fasting glucose levels, and risk of ischemic stroke and vascular events: findings from the Northern Manhattan Study (NOMAS). *Diabetes Care.* 2008;31(6):1132-1137.
23. Gutierrez J, Elkind MS, Cheung K, Rundek T, Sacco RL, Wright CB. Pulsatile and steady components of blood pressure and subclinical cerebrovascular disease: the Northern Manhattan Study. *J Hypertens.* 2015;33(10):2115-2122.
24. Gutierrez J, Elkind MSV, Dong C, et al. Brain perivascular spaces as biomarkers of vascular risk: results from the Northern Manhattan Study. *AJNR Am J Neuroradiol.* 2017;38(5):862-867.
25. Weiner MW, Veitch DP, Aisen PS, et al. The Alzheimer's Disease Neuroimaging Initiative: a review of papers published since its inception. *Alzheimers Dement.* 2013;9(5):e111-94.
26. Landau SM, Mintun MA, Joshi AD, et al. Amyloid deposition, hypometabolism, and longitudinal cognitive decline. *Ann Neurol.* 2012;72(4):578-586.
27. Tan B, Venketasubramanian N, Vrooman H, et al. Haemoglobin, magnetic resonance imaging markers and cognition: a subsample of population-based study. *Alzheimers Res Ther.* 2018;10(1):114.
28. Gutierrez J, Menshawy K, Gonzalez M, et al. Brain large artery inflammation associated with HIV and large artery remodeling. *AIDS.* 2016;30(3):415-423.
29. Gutierrez J, Rosoklija G, Murray J, et al. A quantitative perspective to the study of brain arterial remodeling of donors with and without HIV in the Brain Arterial Remodeling Study (BARS). *Front Physiol.* 2014;5:56.
30. Cordonnier C, Potter GM, Jackson CA, et al. Improving interrater agreement about brain microbleeds: development of the Brain Observer MicroBleed Scale (BOMBS). *Stroke.* 2009;40(1):94-99.
31. Dale AM, Fischl B, Sereno MI. Cortical surface-based analysis: I: segmentation and surface reconstruction. *Neuroimage.* 1999;9(2):179-194.
32. Dong C, Nabizadeh N, Caunca M, et al. Cognitive correlates of white matter lesion load and brain atrophy: the Northern Manhattan Study. *Neurology.* 2015;85(5):441-449.
33. Kantarci K, Gunter JL, Tosakulwong N, et al. Focal hemosiderin deposits and beta-amyloid load in the ADNI cohort. *Alzheimers Dement.* 2013;9(5 suppl):S116-S123.
34. Vonsattel JP, Del Amaya MP, Keller CE. Twenty-first century brain banking: processing brains for research: the Columbia University methods. *Acta Neuropathol.* 2008;115(5):509-532.
35. Gyanwali B, Shaik MA, Tan CS, et al. Mixed-location cerebral microbleeds as a biomarker of neurodegeneration in a memory clinic population. *Aging.* 2019;11(22):10581-10596.
36. Hilal S, Mok V, Youn YC, Wong A, Ikram MK, Chen CL. Prevalence, risk factors and consequences of cerebral small vessel diseases: data from three Asian countries. *J Neurol Neurosurg Psychiatry.* 2017;88(8):669-674.
37. Farrall AJ, Wardlaw JM. Blood-brain barrier: ageing and microvascular disease: systematic review and meta-analysis. *Neurobiol Aging.* 2009;30(3):337-352.
38. Tsai HH, Tsai LK, Chen YF, et al. Correlation of cerebral microbleed distribution to amyloid burden in patients with primary intracerebral hemorrhage. *Sci Rep.* 2017;177:44715.
39. Sveinbjornsdottir S, Sigurdsson S, Aspelund T, et al. Cerebral microbleeds in the population based AGES-Reykjavik study: prevalence and location. *J Neurol Neurosurg Psychiatry.* 2008;79(9):1002-1006.
40. Kovari E, Charidimou A, Herrmann FR, Giannakopoulos P, Bouras C, Gold G. No neuropathological evidence for a direct topographical relation between microbleeds and cerebral amyloid angiopathy. *Acta Neuropathol Commun.* 2015;3:49.
41. Kovari E, Herrmann FR, Hof PR, Bouras C. The relationship between cerebral amyloid angiopathy and cortical microinfarcts in brain ageing and Alzheimer's disease. *Neuropathol Appl Neurobiol.* 2013;39(5):498-509.
42. Reijmer YD, Fotiadis P, Riley GA, et al. Progression of brain network alterations in cerebral amyloid angiopathy. *Stroke.* 2016;47(10):2470-2475.
43. Iliff JJ, Wang M, Liao Y, et al. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid beta. *Sci Transl Med.* 2012;4(147):147ra111.
44. Hadaczek P, Yamashita Y, Mirek H, et al. The "perivascular pump" driven by arterial pulsation is a powerful mechanism for the distribution of therapeutic molecules within the brain. *Mol Ther.* 2006;14(1):69-78.
45. Mestre H, Tithof J, Du T, et al. Flow of cerebrospinal fluid is driven by arterial pulsations and is reduced in hypertension. *Nat Commun.* 2018;9(1):4878.
46. Mestre H, Du T, Sweeney AM, et al. Cerebrospinal fluid influx drives acute ischemic tissue swelling. *Science.* 2020;367(6483):eaax7171.
47. van Veluw SJ, Hou SS, Calvo-Rodriguez M, et al. Vasomotion as a driving force for paravascular clearance in the awake mouse brain. *Neuron.* 2020;105(3):549-561 e5.
48. Weller RO, Subash M, Preston SD, Mazanti I, Carare RO. Perivascular drainage of amyloid-beta peptides from the brain and its failure in cerebral amyloid angiopathy and Alzheimer's disease. *Brain Pathol.* 2008;18(2):253-266.
49. Haller S, Montandon ML, Lazeyras F, et al. Radiologic-histopathologic correlation of cerebral microbleeds using pre-mortem and post-mortem MRI. *PLoS One.* 2016;11(12):e0167743.
50. Shams S, Martola J, Cavallin L, et al. SWI or T2*: which MRI sequence to use in the detection of cerebral microbleeds? The Karolinska Imaging Dementia Study. *AJNR Am J Neuroradiol.* 2015;36(6):1089-1095.