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Distribution of cerebral microbleeds in the East and West

Individual participant meta-analysis

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Abstract

Objective

We investigated differences in the anatomical distribution of cerebral microbleeds (CMBs) on MRI, hypothesized to indicate the type of underlying cerebral small vessel disease (SVD), between Eastern and Western general populations.

Methods

We analyzed data from 11 studies identified by a PubMed search between 1996 and April 2014 according to the Preferred Reporting Items for a Systematic Review and Meta-analysis of Individual Participant Data. Study quality measures indicated low or medium risk of bias. We included stroke-free participants from populations aged between 55 and 75 years, categorized by geographic location (Eastern or Western). We categorized CMB distribution (strictly lobar, deep and/or infratentorial [D/I], or mixed [i.e., CMBs located in both lobar and D/I regions]). We tested the hypothesis that Eastern and Western populations have different anatomical distributions of CMBs using multivariable mixed effects logistic regression analyses adjusted for age, sex, and hypertension and clustering by institution.

Results

Among 8,595 stroke-free individuals (mean age [SD] 66.7 [5.6] years; 48% male; 42% from a Western population), 624 (7.3%) had CMBs (strictly lobar in 3.1%; D/I or mixed in 4.2%). In multivariable mixed effects models, Eastern populations had higher odds of D/I or mixed CMBs (adjusted odds ratio 2.78, 95% confidence interval [CI] 1.77–4.35) compared to Western populations. Eastern populations had a higher number of D/I or mixed CMBs (adjusted prevalence ratio 2.83, 95% CI 1.27–6.31).

Conclusions

Eastern and Western general populations have different anatomical distributions of CMBs, suggesting differences in the spectrum of predominant underlying SVDs, with potential implications for SVD diagnosis and treatment.

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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.

Glossary

CAA = cerebral amyloid angiopathy; CI = confidence interval; CMB = cerebral microbleed; D/I = deep and/or infratentorial; GE T2*-WI = gradient-echo T2*-weighted imaging; ICH = intracerebral hemorrhage; IPD = individual participant data; OR = odds ratio; PR = prevalence ratio; SVD = small vessel disease.

Sporadic cerebral small vessel disease (SVD) is one of the commonest age-related pathologic processes in the brain, and plays a crucial role in stroke and dementia.¹ Hypertensive arteriopathy and cerebral amyloid angiopathy (CAA) are the most common forms of SVD.^{1,2} Effective treatment and prevention for SVD and its associated clinical phenotypes (including spontaneous intracerebral hemorrhage [ICH] and dementia) requires a better understanding of the mechanisms and underlying spectrum of SVD.

Cerebral microbleeds (CMBs) detected using blood-sensitive MRI sequences are histologically characterized by the presence of hemosiderin around small vessels,³ and are a validated marker of SVD.^{4,5} CMBs are unique among SVD imaging biomarkers because of the well-established association between the topographic distribution of CMBs and pathology of SVD: CMBs in the deep and/or infratentorial (D/I) areas (with or without lobar areas) are associated with known markers of hypertensive arteriopathy, whereas CMBs in strictly lobar regions are associated with CAA.^{2,6–8}

There are major differences in the epidemiology of ICH, a key clinical phenotype of SVD, by geography or ethnicity; for example, there is a 2-fold higher incidence in Eastern compared to Western countries.^{9,10} Thus, there is major interest in whether the spectrum of SVD pathology differs between different geographic populations and ethnicities.² However, few large-scale in vivo comparisons of SVD pathologies across populations have been reported. In a large stroke-free individual participant data (IPD) meta-analysis, we tested the hypothesis^{11,12} that the anatomical distribution of CMBs differs between Eastern and Western populations.

Methods

Our study was performed and reported in line with the Preferred Reporting Items for a Systematic Review and Meta-analysis of Individual Participant Data (the PRISMA-IPD Statement) guidelines¹³ and the Meta-analysis of Observational Studies in Epidemiology.¹⁴

Search of eligible literatures and cohorts

We established an international collaborative network to increase the scale of data available and maximize scientific and statistical power.¹⁵ We undertook this study in accordance with a protocol finalized on May 20, 2014, and approved by the Distribution of the Cerebral Microbleeds in Multiple Eastern and Western populations (DICOM) study collaborators. As shown in the flow diagram of study selection (figure 1), to find

articles describing CMBs in general populations, 2 authors (Y.Y. and A.C.) searched PubMed between January 1, 1996, and April 30, 2014, using the predetermined search terms “cerebral microbleed(s)” or “micro(-)h(a)emorrhage(s)” in association with “general,” “community” or “healthy” or “population” or “asymptomatic.” We also searched reference lists from all included articles and the authors’ own files. Articles not published in English or Japanese and case reports were excluded. We found 39 potential articles. Final inclusion criteria were as follows: (1) inclusion of information on prevalence of CMBs on MRI sequences sensitive to magnetic susceptibility effects (i.e., blood-sensitive MRI); (2) inclusion of information on hypertension and/or blood pressure values; and (3) if 2 or more eligible articles were published from the same cohort, the article evaluating the larger number of participants was selected. After sending a copy of the protocol and invitation to collaborate to the corresponding authors of the selected 13 articles that were eligible for inclusion,^{11,16–27} followed by 1 or 2 reminders, we included 11 cohorts (table 1) with confirmation of provision of patient-level data.^{11,16–25} The authors of one study did not respond to the invitation to participate.²⁶ Another cohort (Rotterdam Scan Study) was not included in the primary analysis because the study had a policy of not sharing patient-level data,²⁷ but was included in group data analysis for prevalence of APOE4 carriers (described below). Detailed data of the 28 excluded articles are available from Dryad (supplemental material, including supplemental references and table, doi.org/10.5061/dryad.n459dm5).

Grouping by geographical origin

All individuals in cohorts from Japan, South Korea, and China were defined by geographical origin as the Eastern population, in which all participants were East Asian. Individuals in cohorts from Iceland, Australia, and the United States were defined by geographical origin as the Western population (all participants from the Icelandic and Australian cohorts were Caucasian; participants in the cohort from the United States were predominantly Caucasian). Eastern population samples included 6 “medical check-up” cohorts (in which participants underwent health screening tests of the brain, including brain MRI, at their own expense) and 2 population-based cohorts, while all Western population samples were population-based cohorts.

Ethics

Protocols were approved by the institutional review board for 7 cohorts,^{11,16–18,21,23,25} while the other 4 cohorts^{19,20,22,24} had approved in advance the provision of patient-level data for secondary use in collaborative research. Because cohorts shared only anonymized data, no individual consent for this pooled analysis was required.

Table 1 Characteristics of included cohorts

	Eastern population								Western population		
	Ohta ¹⁶	Hakodate ¹⁷	Toon ¹⁸	Izumo ¹⁹	Sefuri ²⁰	Kashima ¹¹	Seoul ²¹	Shanghai ²²	Reykjavik ²³	Tasmania ²⁴	Framingham ²⁵
No. of participants											
At local study	450	209	443	2,012	368	1,575 ^a	1,452	278	4,368	368	1,965
Included in this study (%)^b	173 (38)	104 (50)	350 (79)	1,602 (76)	226 (61)	965 (61)	1,302 (90)	234 (84)	2,127 (49)	247 (67)	1,265 (64)
Nationality/population type	JPN/MC	JPN/MC	JPN/MC	JPN/MC	JPN/PB	JPN/MC	KOR/MC	CHN/PB	ISL/PB	AUS/PB	USA/PB
Age, y, median (SD)	59.6 (4.5)	61.9 (5.2)	66.7 (5.1)	63.9 (5.2)	64.0 (5.8)	62.9 (5.0)	68.6 (2.9)	66.9 (4.9)	71.6 (2.4)	67.8 (4.1)	64.5 (5.8)
Sex, male, %	65.3	52.9	35.7	51.9	48.2	45.3	57.6	45.7	40.6	55.1	47.2
HTN criteria											
BP ≥140/90 mm Hg	Used	Used	Used	Used	Used	Used	Used	Used	Used	Used	Used
Medication	Used	Used	Used	Used	Used	Used	Used	Used	Used	Used	Used
Self-report	Used	Not used	Not used	Not used	Not used	Not used	Not used	Not used	Not used	Used	Not used
HTN, n (%)	56 (32)	49 (47)	197 (56)	711 (44)	82 (36)	407 (42)	640 (49)	117 (50)	1,590 (75)	174 (70)	689 (55)
CMBS criteria											
Diameter, mm	<10	<10	2–10	2–10	≤10	≤10	<5	2–10	ND	2–10	≤10
Rating scale	MARS	MARS	MARS	MARS	MARS	MARS	MARS	MARS	MARS ^c	MARS	MARS
GE-MRI protocol											
Magnetic field strength, T	1.0	1.5	3.0	1.5	1.0	1.5	1.5	1.5	1.5	1.5	1.5
Echo time, ms	30	26	7	25	20	20	15	30	50	15	26
CMBS distribution, n (%)^d											
CMB presence (all)^e	7 (4)	11 (11)	15 (4)	77 (5)	9 (4)	102 (11)	122 (9)	18 (8)	176 (8)	11 (4)	76 (6)
Strictly lobar CMBS	0 (0)	3 (3)	5 (1)	16 (1)	1 (0.5)	38 (4)	30 (2)	7 (3)	116 (5)	2 (1)	49 (4)
D/I or mixed CMBS	7 (4)	8 (8)	10 (3)	61 (4)	8 (4)	64 (7)	92 (7)	11 (5)	60 (3)	9 (4)	27 (2)

Abbreviations: AUS = Australian; BP = blood pressure; CHN = Chinese; CMB = cerebral microbleed; D/I = deep and/or infratentorial; GE-MRI = gradient-echo MRI; HTN = hypertension; IQR = interquartile range; ISL = Icelandic; JPN = Japanese; KOR = Korean; MARS = Microbleed Anatomical Rating Scale; MC = medical checkup; PB = population-based; ND = not determined.

^a Additional data (n = 296) were provided by the corresponding author of the publication.

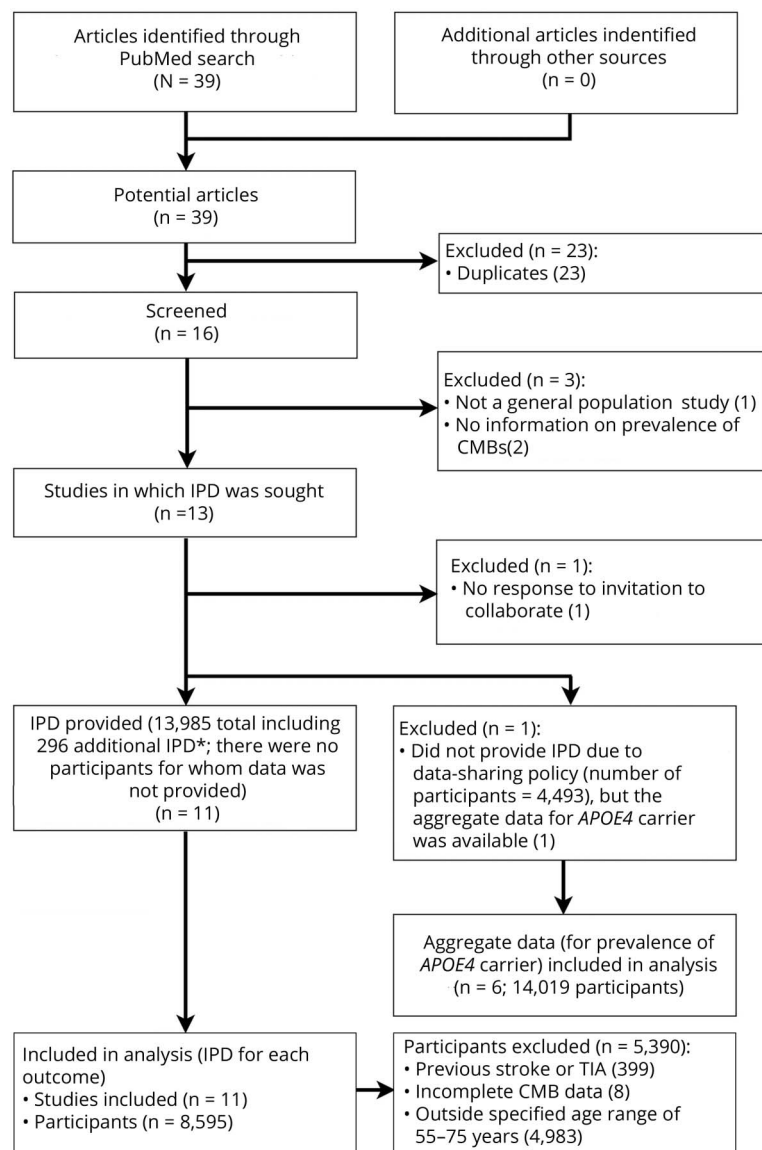
^b Proportion (%) of participants included in this study among participants at local study.

^c Similar to MARS.

^d Proportion (%) of participants with each CMBS distribution among participants at local study.

^e Totals may not be exact due to rounding.

Figure 1 Preferred Reporting Items for a Systematic Review and Meta-analysis of Individual Participant Data (PRISMA-IPD) flow diagram



The search of electronic databases (PubMed between January 1, 1996, and April 30, 2014; no articles identified through other sources), using English and Japanese language limit, performed by 2 authors (Y.Y. and A.C.), yielded 39 publications. After 23 duplicates were removed, we identified 16 potential articles. Of those that were reviewed in full-text, we invited 13 independent studies for collaboration with providing individual data. Finally, we included 11 studies that could provide individual data. CMB = cerebral microbleed; IPD = individual participant data. *Additional data (n = 296) were provided by the corresponding author of the publication.¹¹

Data collection

On January 2, 2016, following necessary regulatory approvals, we proceeded to collect IPD of age at MRI, sex, presence of hypertension (as defined by local protocol), CMBs number, and used anatomical rating scale for CMBs.^{28,29} Information on magnetic field strength and echo time for blood-sensitive MRI, both of which could affect CMBs rating,⁵ were obtained from published articles. Some eligible studies for inclusion in our study had data available for *APOE4* allele, a known marker for CAA, especially if present concurrently with CMBs located in strictly lobar regions.^{7,30} We therefore obtained the prevalence of *APOE4* carrier from published or unpublished meta-data of included cohorts,^{24,25,31–33} and published meta-data from the Rotterdam Scan Study.³⁴

Criteria and MRI protocol

Criteria for hypertension, CMB definition, and information on blood-sensitive MRI sequences in each cohort are summarized in table 1. All cohorts defined hypertension as stage 1 or higher hypertension status according to the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7) criteria: systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg.³⁵ In addition, medication (i.e., use of antihypertensive drugs: in 10 cohorts)^{11,16–24} or self-report of history of hypertension (in 2 cohorts)^{16,24} were also used to define hypertension in several cohorts. In all included cohorts, CMB was detected on gradient-echo T2*-weighted imaging (GE T2*-WI) MRI as a rounded area of signal loss according to recent consensus.^{5,28,29} Maximum and

minimum diameters of CMBs ranged within 5–10 and 0–2 mm (the Age, Gene/Environment Susceptibility [AGES]–Reykjavik cohort²³ did not use size criteria for CMBs). CMBs were evaluated by local laboratory review. If required, collaborators re-rated according to validated rating scales.^{28,29} Magnetic field strength and echo time for GE T2*-WI MRI ranged from 1.0 to 3.0 T and 7 to 50 ms, respectively.

Definition of CMBs category

CMBs were categorized into different anatomical regions including lobar (cortical and subcortical regions); deep (basal ganglia, thalamus, internal capsule, external capsule, corpus callosum, and deep and periventricular white matter); and infratentorial areas (brainstem and cerebellum).^{8,28} Participants were divided into no CMBs and CMBs present (1 or more CMBs) groups. The CMBs present group was divided into a “strictly lobar CMBs group” and a “D/I or mixed CMBs group (i.e., participants had CMBs located in strictly deep and/or infratentorial regions or in both lobar and D/I regions).” Regarding CMB burden, we counted the number of CMBs in each anatomical region (all, lobar, deep, and infratentorial region).

Assessment of risk of bias.

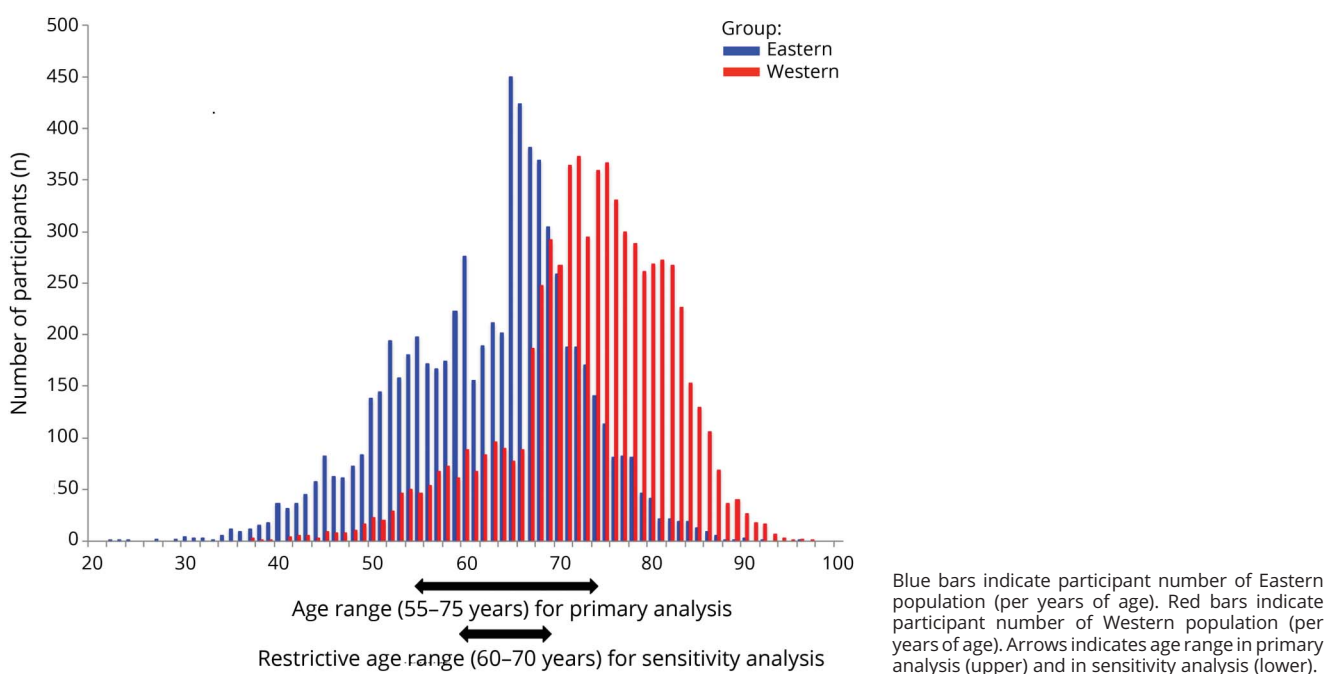
As our primary target data (i.e., distribution of CMBs) were evaluated in cross-sectional observational study of each cohort, the assessments for exposure (i.e., interventions) and outcome (i.e., assessments for quality of follow-up outcomes) were considered as not applicable in this study. For this study design, the most important bias would be representativeness of

cohort (i.e., how the participants of the cohort represent the average of CMB prevalence in the community). Thus, each cohort was assessed by population type (medical checkup cohort or population cohort). According to the Newcastle–Ottawa Scale,³⁶ a medical check-up cohort was classified as “somewhat representative” of the CMB prevalence in the community, while a population-based cohort was evaluated as truly representative of the whole population.

Statistical analysis

To increase comparability between the Eastern and Western cohorts, we first defined an age inclusion criterion of 55–75 years (figure 1), because the Western cohorts tended to have much older participants (figure 2). Statistical analysis was performed using STATA version 15.0 (StataCorp LP, College Station, TX). Mixed effects linear regression was used to compare age, whereas mixed effect logistic regression was used for hypertension and sex. We adjusted for clustering by individual institute using random effects. As MRI measures and population type were cluster-level covariates, we compared them between Eastern centers (n = 8) and Western centers (n = 3) using the Mann-Whitney *U* test or χ^2 test without center clustering, as appropriate. Selection of potential confounders for the following analyses was based on a priori consideration of factors known to be associated with CMBs detection on MRI, including age, sex, and hypertension on the individual level; radiologic factors (magnetic field strength [1.0, 1.5, or 3.0T] and echo time from GE T2*-WI MRI); and population type (medical check-up or population-based), measured on the cohort level.

Figure 2 Frequency distribution of participants by age between the Eastern population and Western population (all collected data of 13,985 participants)



Univariable mixed effects logistic regression was used separately to compare binary (yes/no) imaging characteristics (all CMBs group, strictly lobar CMB group, and D/I or mixed CMBs group) between the Eastern and Western population (each result was presented as an odds ratio [OR]). To compare number of CMBs, we used a mixed-effects negative binomial regression model, again adjusting for institute level clustering. This model was used in preference to a Poisson model as CMB number was heavily skewed to the right. The results are presented as prevalence ratios (PR), which quantify the relative number of CMBs for the Eastern population compared to the Western population. For example, a PR of 1.17 for “CMBs (all)” suggests that there are 17% more CMBs in the Eastern population compared to the Western population.

Multivariable mixed effects logistic regression was undertaken in a similar manner with the addition of age, sex, and hypertension as fixed effects. MRI measures and population types were not included in the regression analyses as they are cluster level variables. To further decrease the bias of age range difference between the Eastern population and the Western population, we performed sensitivity analyses using an even more restrictive age range (60–70 years). As a further sensitivity analysis, due to the lower interrater reliability for a single CMB,^{28,29} we compared prevalence (but not number) of multiple CMBs (i.e., multiple CMBs [all], multiple strictly lobar CMBs, and multiple D/I or mixed CMBs) in Eastern and Western populations, using the same age range of 55–75 years as for the primary analyses.

We used meta-analysis to estimate the prevalence of *APOE4* carriers and displayed the results using a forest plot. Heterogeneity was quantified using the I^2 statistic. Values of $p < 0.05$ were considered statistically significant.

Data availability

Studies participating in this IPD meta-analysis have separate and specific data request and approval policies, depending on local, national, and international laws and regulations. Because of restrictions based on such privacy laws and regulations and informed consent of the participants, data cannot be made freely available in a public repository for the participating studies. Requests for information on procedures and formal data requests can be submitted to investigators from the respective studies.^{11,16–25}

Results

We completed IPD collection from 13,985 participants of 11 cohort studies. Regarding assessments for risk of bias, 6 cohorts were medical check-up cohorts (i.e., somewhat representative of the average of CMBs prevalence in the community) and 5 cohorts were population-based cohorts (i.e., truly representative of the average of CMB prevalence in the community), indicating low or medium risk of bias. Among those participants, 407 were excluded because of previous symptomatic stroke or TIA ($n = 399$), or because of incomplete data of CMBs prevalence and number ($n = 8$). Thus, we collected complete data from 13,578 stroke-free individuals (mean age [SD] 67.8 [10.6] years; age range 22–97 years; male 48%, Western population 49%). Of these, 1,108 participants (8.2%)

Table 2 Univariable differences in Eastern population vs Western population with regard to demographics, risk factors, and blood-sensitive MRI measures ($n = 8,595$)

	Western population ($n = 3,639$)	Eastern population ($n = 4,956$)	Difference for Eastern population (95% CI) ^a	<i>p</i> Value ^a
Age, y, mean (SD)	68.9 (5.2) ^b	65.1 (5.3) ^b	Coef. -3.65 years (-7.38 to 0.07)	0.055 ^c
Sex, male, n (%)	1,597 (44) ^b	2,528 (51) ^b	OR 1.13 (0.75–1.69)	0.564
Hypertension, n (%)	2,453 (67) ^b	2,259 (46) ^b	OR 0.40 (0.26–0.61)	<0.001 ^d
	Western centers ($n = 3$)	Eastern centers ($n = 8$)	Cluster level covariates	<i>p</i> Value ^e
MRI field strength, T, median (IQR)	1.5 (1.5–1.5)	1.5 (1.3–1.5)	NA	0.697
MRI echo time, ms, median (IQR)	26 (21–38)	23 (18–28)	NA	0.537
Population type, population-based, n (%)	3 (100)	2 (25.0)	NA	0.026

Abbreviations: CI = confidence interval; Coef = coefficient; IQR = interquartile range; NA = not applicable; OR = odds ratio.

^a Evaluated with adjusting for center clustering.

^b Values are not adjusted for clustering.

^c The Eastern population likely to be younger (but not significant) by average of 3.65 years after adjusting for center clustering.

^d Meaning the odds of hypertension are 2.5 times larger in Western population compared to Eastern population.

^e As MRI measures and population type were cluster-level covariates, we compared them between Eastern centers ($n = 8$) and Western centers ($n = 3$) using Mann-Whitney *U* test or χ^2 test without center clustering, as appropriate.

had one or more CMBs: these were strictly lobar in 3.8% and D/I or mixed in 4.4%. After excluding participants ($n = 4,983$) outside of our specified age range (55–75 years), we included 8,595 (mean age [SD], 66.7 [5.6] years; male 48%), including 4,956 Eastern individuals (58%; i.e., the Eastern population) and 3,639 Western individuals (42%; i.e., the Western population), in the primary analysis. Characteristics of the included cohorts are summarized in table 1.

Univariate differences between the Eastern and Western population with regard to age, sex, and hypertension, after adjusting for center clustering, are shown in table 2. The Eastern population was younger than the Western population (65.1 vs 68.9 years), but this did not reach significance level after adjusting for center clustering (coefficient -3.65 years, 95% confidence interval [CI] -7.38 to 0.07 , cluster level adjusted $p = 0.055$). There were proportionately more men in the Eastern (51%) compared to the Western population (44%), but no differences were seen (cluster level adjusted $p = 0.564$). Hypertension was more common in the Western population than the Eastern population (46% in the Eastern vs 67% in the Western, cluster level adjusted $p < 0.001$). There were no differences in blood-sensitive MRI measures between the Eastern centers ($n = 8$) and the Western centers ($n = 3$). Regarding source population type, population-based study was higher in the Western centers ($p = 0.026$) compared to the Eastern centers.

Among the 8,595 participants, 624 participants (7.3%) had CMBs. Of these, 267 (3.1%) participants had strictly lobar CMBs and 357 (4.2%) had D/I or mixed CMBs (table 3).

Table 4 shows the primary results of analyses for the multivariable OR and PR (i.e., a rate of CMBs presence) for the Eastern population (vs the Western population) for each outcome. There were no differences in the prevalence of all CMBs between the populations. However, in multivariable analysis, the Eastern population had a higher prevalence of D/I or mixed CMBs (multivariable model, OR 2.78, 95% CI 1.77–4.35, $p < 0.001$) compared to the Western population. Similar findings were also seen in the multivariable model of sensitivity analyses using more a restrictive age range (multivariable model, OR for Eastern group [vs Western group]: all CMBs, OR 1.69, 95% CI 0.96–3.00, $p = 0.070$; strictly lobar CMBs, OR 0.67, 95% CI 0.28–1.61, $p = 0.369$; D/I or mixed CMBs, OR 3.40, 95% CI 1.96–5.89, $p < 0.001$). A sensitivity analysis comparing the prevalence of multiple CMBs (i.e., ≥ 2 CMBs)—using the same age range as the primary analyses—showed similar findings (multivariable model, OR for Eastern group [vs Western group]: all multiple CMBs, OR 1.75, 95% CI 0.89–3.45, $p = 0.105$; multiple D/I or mixed CMBs, OR 3.25, 95% CI 1.61–6.68, $p = 0.001$), but a slightly higher prevalence of multiple strictly lobar CMBs in the Western population (multivariable model, OR for Eastern 0.43, 95% CI 0.17–1.04, $p = 0.062$). Regarding CMB number, the Eastern population had a higher number of D/I or mixed CMBs (multivariable model: 2.83, 95% CI 1.27–6.31, $p = 0.011$) in the primary analysis (table 4) and sensitivity

Table 3 Prevalence of cerebral microbleeds (CMBs) in all included participants ($n = 8,595$) according to Eastern or Western population

	All ($n = 8,595$)	Western population ($n = 4,956$)	Eastern population ($n = 3,639$)
CMBs prevalence, n (%)^a			
CMBs (all)			
1	422 (4.9)	181 (5.0)	241 (4.9)
≥ 2	202 (2.4)	82 (2.3)	120 (2.4)
Any (≥ 1)	624 (7.3)	263 (7.2)	361 (7.3)
Strictly lobar CMBs			
1	203 (2.4)	120 (3.3)	83 (1.7)
≥ 2	64 (0.7)	47 (1.3)	17 (0.3)
Any (≥ 1)	267 (3.1)	167 (4.6)	100 (2.0)
D/I or mixed CMBs			
1	219 (2.6)	61 (1.7)	158 (3.2)
≥ 2	138 (1.6)	35 (1.0)	103 (2.1)
Any (≥ 1)	357 (4.2)	96 (2.6)	161 (5.3)
CMB number, median (IQR) for participants with any CMBs			
CMBs group ($n = 624$)	1 (1–2)	1 (1–2)	1 (1–2)
Strictly lobar CMBs group ($n = 267$)	1 (1–1)	1 (1–2)	1 (1–1)
D/I or mixed CMBs group ($n = 357$)	1 (1–2)	1 (1–2)	1 (1–2)

Abbreviations: D/I = deep and/or infratentorial; IQR = interquartile range. Values indicate raw data (not adjusted for center clustering).
^a Totals may not be exact due to rounding.

analysis using a more restrictive age range (multivariable model, PR 3.00, 95% CI 1.21–7.47, $p = 0.018$). There was no difference in the number of all CMBs, as well as strictly lobar CMBs, between the Eastern and Western population in the primary analyses (multivariable model, PR for Eastern group [vs Western group]: all CMBs, PR 1.66, 95% CI 0.80–3.43, $p = 0.171$; strictly lobar CMBs, PR 0.61, 95% CI 0.26–1.43, $p = 0.254$), and the sensitivity analyses using a more restrictive age range (multivariable model, PR for Eastern group [vs Western group]: all CMBs, PR 1.65, 95% CI 0.71–3.85, $p = 0.249$; strictly lobar CMBs, PR 0.51, 95% CI 0.19–1.36, $p = 0.179$).

Metadata on the prevalence of APOE4 carriers was available from 6 studies (figure 3: no restriction on age range). The overall pooled estimate (%) was 24.14 (95% CI 20.13–28.14); the I^2 value of 96.3% suggests considerable heterogeneity between the studies. The prevalence of APOE4 was higher in the Western cohorts of Reykjavik (28.10%, 95% CI 26.85–29.35) and Rotterdam (27.10%, 95% CI 25.67–28.53),

Table 4 Primary results of univariable and multivariable odds ratio (OR) and prevalence ratios for Eastern population (vs Western population) for each outcome

CMBs prevalence ^a	Univariable analyses ^c		Multivariable analyses ^d	
	OR (95% CI)	p Value	OR (95% CI)	p Value
CMBs (all)	1.05 (0.64–1.72)	0.853	1.52 (0.90–2.59)	0.119
Strictly lobar CMBs	0.51 (0.21–1.24)	0.139	0.70 (0.29–1.72)	0.439
D/I or mixed CMBs	1.92 (1.25–2.94)	0.003	2.78 (1.77–4.35)	<0.001

CMB number ^b	Univariable analyses ^c		Multivariable analyses ^d	
	PR (95% CI)	p Value	PR (95% CI)	p Value
CMBs (all)	1.17 (0.61–2.21)	0.546	1.66 (0.80–3.43)	0.171
Strictly lobar CMBs	0.47 (0.20–1.07)	0.930	0.61 (0.26–1.43)	0.254
D/I or mixed CMBs	1.70 (0.89–3.24)	0.105	2.83 (1.27–6.31)	0.011

Abbreviations: CI = confidence interval; CMB = cerebral microbleed; D/I = deep and/or infratentorial; PR = prevalence ratio (indicating the relative number of CMBs: for example, the multivariable analysis suggests that there are 2.83 times more D/I or mixed CMBs in the Eastern population compared to the Western population).

^a In this analysis (n = 8,595), each category is compared to the reference category of participants having no CMBs.

^b In each analysis (n = 8,595), the reference category is participants with no CMBs, no strictly lobar CMBs, or no D/I or mixed CMBs, as appropriate.

^c Variables were analyzed with adjustment for clustering by institution.

^d Variables were analyzed with adjustment for age, sex, hypertension, and clustering by institution.

and lower in the Eastern Shanghai cohort (17.80%, 95% CI 16.40–19.20).

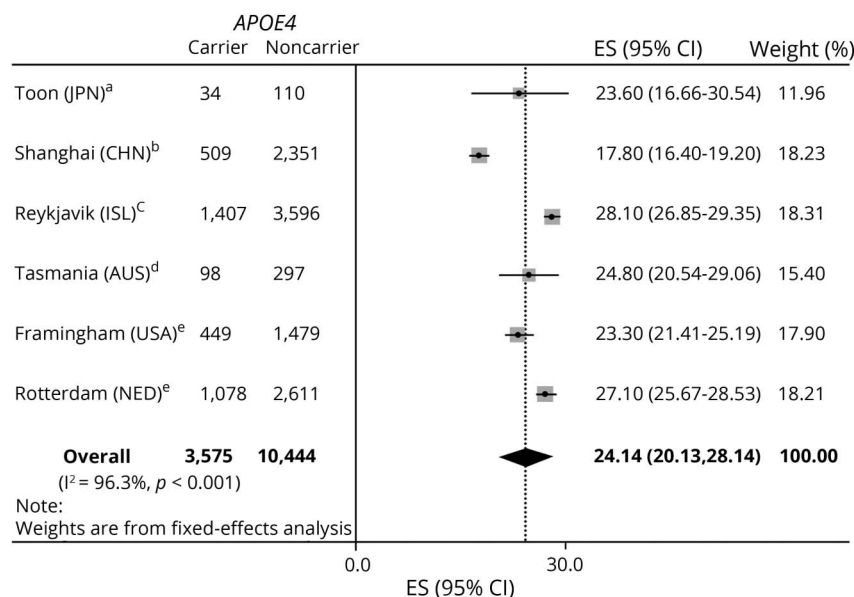
Discussion

Our large pooled IPD analyses of MRI scans from stroke-free participants provide new large-scale in vivo evidence on the anatomical distribution of CMBs between Eastern and

Western populations, suggesting different underlying patterns of SVD. Our primary results show that the prevalence and the number of D/I or mixed CMBs is higher in Eastern compared to Western populations.

Only a few previous small cohort studies have investigated differences in CMB prevalence or anatomical pattern between different ethnicities.^{37–39} In a small cohort study,³⁷ the

Figure 3 Forest plots of prevalence of APOE4 carriers made with metadata obtained from published or unpublished metadata



^a Published data of participants with ambulatory blood pressure monitoring in the related cohort study.³³ ^b Unpublished data provided from coauthor (D.D.).³¹ ^c Unpublished data provided from coauthor (L.J.L.).³² ^d Unpublished data (including participants with previous stroke/TIA) provided from coauthor (V.S.).²⁴ ^e Published data.^{25,34} CI = confidence interval; ES = effect size.

prevalence of CMBs was higher in black patients than in white patients, which was interpreted as being most likely due to the increased rate of hypertension in the black population. Conversely, other individual population-based studies found no association between overall CMBs prevalence and ethnicity,^{38,39} consistent with our result. Only one small single-center multiethnic cohort study investigated associations between CMB distribution and ethnicity, but found no relationship.³⁹ However, our global sample of over 8,000 participants provides much greater statistical power and more reliable estimates of CMB anatomical patterns across populations.

We found a higher prevalence of D/I or mixed CMBs (i.e., a marker of hypertensive arteriopathy) in the Eastern population, despite a lower prevalence of hypertension (including participants taking antihypertensive drugs). One explanation could be that Western populations are more likely to be diagnosed with hypertension and treated early, so that achieving better blood pressure control during midlife might result in a lower prevalence of severe hypertensive arteriopathy compared to Eastern populations. However, hypertension awareness, treatment, and control rates in the 1990s in a Japanese population were similar to those in Western countries.⁴⁰ Since most participants of the Eastern population were Japanese (75%), this hypothesis might therefore not fully explain our results. Another possible contributory factor might be differences in genetic factors: different ethnicities may have different susceptibilities of small vessels to hypertension (e.g., in the sensitivity of endothelial cells). Furthermore, hypertensive arteriopathy may be driven by factors other than hypertension: for example, some recent evidence suggests that inflammation and endothelial activation may play a larger role than previously considered, and inflammation-mediated endothelial damage appears to differ among ethnicities.^{41–43} One human study demonstrated that despite preserved kidney function and controlled blood pressure, circulating inflammatory endothelial cells, as a marker of endothelial damage, were elevated in black hypertensive patients compared to white hypertensive patients, implying differences in the tolerance of endothelial cells for hypertension across ethnicities.⁴² Among eligible plasma biomarkers, soluble E-selectin, reported as a promising inflammatory biomarker of CMBs,⁴⁴ was also elevated in black hypertensive patients compared to white hypertensive patients.⁴²

Although a previous systematic review of autopsy series showed a possible higher prevalence of CAA in the Western population compared to the Eastern population,⁴⁵ our primary analyses did not show a difference in the prevalence and number of strictly lobar CMBs (a putative marker of CAA) between Eastern and Western populations. Indeed, we found a higher prevalence of *APOE4* carriers in Western populations, and a sensitivity analysis showed a slightly higher prevalence of multiple strictly lobar CMBs in Western populations ($p = 0.062$); these findings are consistent with a possible higher prevalence of CAA in Western compared to Eastern populations.⁴⁵ However, the diagnostic accuracy of

the Boston criteria might be lower in general populations than in hospital cohorts.⁴⁶ Furthermore, the possible lower prevalence of CAA-related ICH in Eastern countries probably reflects a higher incidence of hypertensive brain hemorrhage rather than a decreased incidence of CAA.⁴⁵ Thus, to confirm population differences in CAA, further investigations including neuropathologic data (ideally from population-based autopsy studies) are needed.

The major strengths of our study were as follows: first, our international collaborative analysis pooled IPD from over 8,000 participants, giving us greater power than any single study to investigate differences in number and location of CMBs; second, CMBs were rated on similar MRI sequences using a validated rating scale,²⁸ improving reliability (although one Western study [Reykjavik]²³ used a similar but not identical scale); third, each population comprised purely East Asian individuals or purely Caucasian individuals, suggesting that our primary results are due to not only geographical variation, but from true between-population ethnic differences, which include genetic, dietary, culture, medical care, and unknown or unmeasured confounders; finally, we were also able to describe and account for individual subject data on age, sex, hypertension, magnetic field strength, and echo time, which are well-established confounders for CMBs prevalence.^{4,5,47}

Some limitations of our study must also be considered. First, there was a difference in prevalence of hypertension among the included cohorts. However, our results adjusted for hypertension as well as for clustering by institution using mixed effect models, to decrease the effect of such bias. Second, the proportion of medical check-up populations selected for self-funded health screening, evaluated as somewhat representative of the true CMBs prevalence in the community, was more common in Eastern cohorts; since health screening tests of the brain were performed partially at the expense of the patient, this might introduce a bias toward more affluent individuals with strong motivation to maintain their own health, and different socioeconomic, educational, diet, and cardiovascular disease profiles.⁴⁸ We minimized this potential confounding influence by adjustment for clustering by institution; however, this will not reduce confounding on an individual level. Third, we did not have information on all potential confounding factors potentially associated with CMBs (e.g., diabetes mellitus, antithrombotic pharmacotherapy, or white matter changes^{4,7,49}). Fourth, compared to patient cohort, the frequency of CMBs in this general population cohort was low, and if present, most were single. However, our data reflect the distribution of CMBs in the population. Fifth, CMBs were evaluated by local laboratory review, but not by central core laboratory review; however, our protocol specified the use of validated anatomical rating scales, and previous publications from the included studies indicate good reliability for CMB rating. Sixth, it should be noted that the characteristics of the Eastern population in this study reflected only East Asian populations. Finally, although our study supports a possible

higher prevalence of hypertensive arteriopathy in Eastern compared to the Western populations, we could not definitively prove this pathologically.

Our large global collaborative individual participant data study adds novel evidence of different patterns of CMBs between Eastern (East Asian) and Western populations, apparently independent of differences in the prevalence of hypertension. Our results suggest that an important determinant of underlying SVD type might be attributable to population ethnic (genetic) susceptibility factors yet to be elucidated, and that optimal SVD treatment and prevention strategies might differ between Eastern and Western populations.

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Andreas Charidimou, MD, PhD	UCL, London, UK	Author	Study concept and design, literature search, data interpretation, revising of the manuscript
Alexa Beiser, PhD	Boston University and the NHLBI's Framingham Heart Study, MA	Author	Data collection, data interpretation, revising of the manuscript

Continued

Appendix (continued)

Name	Location	Role	Contribution
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David J Werring, FRCP, PhD	UCL, London, UK	Author, director of the study, corresponding author	Study concept and design, literature search, data collection, statistical analysis, interpretation of data, drafting/ revising of the manuscript, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis

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