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Association of brain microbleeds with risk factors, cognition and MRI markers in MESA

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Abstract

INTRODUCTION: Little is known about the epidemiology of brain microbleeds in race/ethnically diverse populations.

METHODS: In the Multi-Ethnic Study of Atherosclerosis, brain microbleeds were identified from 3T MRI susceptibility-weighted imaging sequences using deep learning models followed by radiologist review.

RESULTS: Among 1016 participants without prior stroke (25% Black, 15% Chinese, 19% Hispanic, 41% White, mean age 72), microbleed prevalence was 20% at age 60-64.9 and 45%

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CONFLICTS OF INTEREST

None.

CONSENT STATEMENT

All Multi-Ethnic Study of Atherosclerosis participants provided written informed consent.

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at ≥85 years. Deep microbleeds were associated with older age, hypertension, higher body mass index, and atrial fibrillation, and lobar microbleeds with male sex and atrial fibrillation. Overall, microbleeds were associated with greater white matter hyperintensity volume and lower total white matter fractional anisotropy.

DISCUSSION: Results suggest differing associations for lobar vs. deep locations. Sensitive microbleed quantification will facilitate future longitudinal studies of their potential role as an early indicator of vascular pathology.

Keywords

brain microbleeds; small vessel disease; hypertension; brain MRI; deep learning; cognition; race and ethnicity; atrial fibrillation; Multi-Ethnic Study of Atherosclerosis; white matter hyperintensity; white matter fractional anisotropy

1 | BACKGROUND

Brain microbleeds, small hemorrhages less than 10 mm in diameter seen on brain magnetic resonance imaging (MRI), are often manifestations of small vessel disease and amyloid pathology.[1,2] High microbleed number has been associated with impaired cognitive function and dementia.[3] However, limited information is available about the epidemiology of microbleeds in the general population of older individuals for race or ethnic groups other than White. Previous studies of the epidemiology of microbleeds have relied on manual identification of microbleeds,[2,4-6] but recently-developed deep learning models using the more sensitive susceptibility-weighted imaging (SWI) sequences at 3-Tesla, rather than gradient-echo imaging,[7] offer the possibility of automated, accurate, and more complete ascertainment of microbleeds.[8,9] To understand the epidemiology of brain microbleeds using these recently developed tools, we analyzed data from the Multi-Ethnic Study of Atherosclerosis (MESA) to examine cross-sectional associations of sociodemographic characteristics and cardiovascular risk factors with microbleed presence, number, and location. We further examined cross-sectional associations of microbleeds with cognitive test scores, physical function, and other aging-related markers on brain MRI.

2 | METHODS

2.1 | Multi-Ethnic Study of Atherosclerosis

MESA is a community-based cohort study of subclinical cardiovascular disease that enrolled 6,814 American men and women 45-84 years of age who self-identified with one of four groups: Black, Chinese, Hispanic, or White. Participants were free of clinically recognized cardiovascular disease at baseline in 2000-2002 and were recruited at six US field centers (Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; New York, New York; and St. Paul, Minnesota).[10] Five follow-up study visits have been conducted, including Exam 6 in 2016-2018. In 2018-2019, a median of 18 months after Exam 6, consenting participants in the MESA Atrial Fibrillation ancillary study[11] completed a brain MRI.[12] Each field center obtained Institutional Review Board approval, and all participants provided written informed consent.

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2.2 | Participant characteristics

Participant characteristics obtained at study baseline included self-reported sex, race and ethnicity, and educational attainment. Additional study measures were derived from the 2016-2018 (Exam 6) study visit, including age, weight, height, waist circumference, systolic and diastolic blood pressure, cigarette smoking status, medication use, and history of diabetes. Age was also ascertained at the brain MRI visit. Fasting blood specimens from Exam 6 were used to measure total and HDL cholesterol; LDL cholesterol was calculated using the Friedewald equation. At telephone contacts every 9 to 12 months throughout MESA follow-up, participants were asked to identify new hospitalizations and diagnoses, and medical records were obtained. During follow-up to the date of the brain MRI, clinically recognized myocardial infarction, heart failure,[13] and stroke[14] were adjudicated. Clinically recognized atrial fibrillation was identified from hospital discharge diagnoses and Medicare claims[15] and subclinical atrial fibrillation by 14-day ambulatory electrocardiographic monitoring at Exam 6.[11] *APOE* isoforms were estimated from single nucleotide polymorphisms rs429358 and rs7412.[16]

2.3 | Cognitive test scores and physical function

Four cognitive tests were administered at Exam 6: the Cognitive Abilities Screening Instrument (CASI, version 2), the Digit Symbol Coding Test, and the Digit Span Forward and Backward tests. The CASI was developed for cross-cultural use[17] and includes items representing nine cognitive domains: attention, concentration, orientation, short-term memory, long-term memory, language, visual construction, verbal fluency, and abstraction/judgment; the maximum score is 100. The Digit Symbol Coding Test is a subtest of the Wechsler Adult Intelligence Scale-III[18] that measures processing speed and working memory, with a maximum scores of 133. The Digit Span Forward and Backward tests, also subtests of the Wechsler Adult Intelligence Scale-III,[18] assess working memory, with maximum scores of 16 (Forward) and 14 (Backward). Physical function was assessed using the six-minute walk test.[19] The score is expressed in meters walked on a flat surface during six minutes.

2.4 | Brain MRI and microbleed quantification

Brain MRI was conducted on 3-Tesla scanners as previously described,[12] including 3D T1-weighted, T2-weighted, and fluid attenuated inversion recovery (FLAIR) structural imaging, axial 2D echo-planar diffusion-tensor imaging, and SWI. MRI scanner parameters are in the Supplemental Methods.[20] Microbleeds were initially identified by a deep learning-based method that used T2-weighted quantitative susceptibility mapping and SWI images to segment the lesions and differentiate microbleeds from iron deposits (Figure 1).[8] Identified lesions were then reviewed by a radiologist (JBW) who made the final classification, as previously described.[20] Microbleed location was classified by mapping the 146 MUlti-atlas region Segmentation utilizing Ensembles (MUSE) based regions of interest[21] to the Microbleed Anatomical Rating Scale (MARS) regions of interest[22] and grouping them into three categories: lobar (frontal, parietal, temporal, occipital, and insula), deep (basal ganglia, thalamus, internal capsule, corpus callosum, and deep and periventricular white matter [WM]), and infratentorial (brainstem and cerebellum). More details on mapping the regions

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of interest from MUSE to MARS definitions are in the Supplemental Methods and Table S1. Automated measurement of three aging-related MRI markers were made as previously described:[12] total gray matter volume as a measure of atrophy, and WM hyperintensity (WMH) volume and total WM fractional anisotropy as measures of WM injury. Fractional anisotropy, a scalar ranging from 0 to 1, reflects the degree to which water diffusion is limited to a single dimension; lower values are interpreted as indicating reduced WM microstructural integrity, a feature of small vessel disease.

2.5 | Statistical analysis

In our primary analyses, we compared participants with at least one microbleed to those without, both overall and in each of the lobar, deep, and infratentorial location categories. We used multivariable Poisson relative risk regression with robust standard errors to examine cross-sectional associations of participant characteristics and cardiovascular risk factors with the presence of microbleeds.[23] This analysis included age, sex, race and ethnicity, field center, educational attainment, body mass index, systolic blood pressure, diastolic blood pressure, use of antihypertensive medication, HDL and LDL cholesterol levels, *APOE* genotype, cigarette smoking status, diabetes mellitus, history of atrial fibrillation, and history of myocardial infarction or heart failure as covariates in a single model. Next, we used multivariable linear regression to examine cross-sectional associations of microbleed presence, both overall and by location, with the outcomes of cognitive test scores, six-minute walk, and three brain MRI measures: total gray matter volume, WMH volume, and total WM fractional anisotropy. Models for total gray matter volume and WMH volume included additional adjustment for total intracranial volume. WMH volume had a right-skewed distribution and was natural log transformed. Differences in test scores, six-minute walk distance, and brain MRI findings were expressed in standard deviation units.

In secondary analyses limited to participants with at least one microbleed, we analyzed participant characteristics and cardiovascular risk factors in relation to the number of microbleeds, both overall and by location, using linear regression with robust standard errors. Six participants had more than 12 microbleeds (81% of which were lobar); in analyses of microbleed counts these values were winsorized at 12 microbleeds. The number of microbleeds was log transformed, and results of multivariable analyses are presented as the geometric mean ratio, which provides the percentage difference in microbleed number per increment of the characteristic. For example, a geometric mean ratio of 1.07 for the association with age indicates a 7% higher number of microbleeds per 10-year increment of age. Next, we used linear regression to examine associations of log base 2-transformed microbleed number with cognitive test scores, six-minute walk, and aging-related findings on brain MRI, expressed in standard deviation units.

Multiple imputation with chained equations was used to impute missing values of education, systolic and diastolic blood pressure, treated hypertension, HDL and LDL cholesterol, smoking, prevalent diabetes, and *APOE* genotype (all <5% missing) using information on age, sex, race, body mass index, and history of myocardial infarction, heart failure, or atrial

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fibrillation. In sensitivity analyses, we examined associations with microbleeds for our main models after excluding participants who were using anticoagulant medications at Exam 6.

3 | RESULTS

Among the 3303 participants who attended Exam 6 (2016-2018), 1062 had a brain MRI (Figure 2). SWI sequence data were unavailable for 4, MRI images did not meet quality control criteria for 16, and we excluded 26 with a history of clinically recognized stroke before the MRI, leaving 1016 in the analysis. Participants self-reported Black (25%), Chinese (15%), Hispanic (19%), or White (41%) race and ethnicity; the average (SD) age at the time of MRI was 72 (8) years and 47% were men. Compared with Exam 6 participants not included in the analysis, those included were on average younger, a smaller proportion used antihypertensive medication, and a smaller proportion had experienced a myocardial infarction or heart failure before the brain MRI (Table S2).

On brain MRI, a total of 339 (33%) participants had at least one microbleed, of which 188 (55%) had a single microbleed, 68 (20%) had two, 76 (22%) had three to eleven, and one each had 12, 17, 20, 21, 25, 54, and 112 microbleeds (Figure 3, Panel A). Microbleeds were widely distributed in the brain (Figure 3, Panel B, Supporting Information video, and Table S1); of the total of 947 microbleeds detected, 67% were lobar, 22% deep, and 12% infratentorial. The prevalence of microbleeds increased with age (Figure 4) from 20% of participants aged 60-64.9 years to 45% of those over age 85. Compared with those with no microbleeds, participants with microbleeds were slightly older and had higher systolic blood pressure but lower LDL cholesterol, and a larger proportion were men, had treated hypertension, and had a history of atrial fibrillation (Table 1).

Multivariable associations of sociodemographic characteristics and cardiovascular risk factors with microbleeds

In a multivariable regression model, only older age and a history of atrial fibrillation were independently associated with microbleed presence overall (Figure 5 and Table S3). There was no association of use of anticoagulant (prevalence ratio= 0.95; 95% confidence interval (CI) 0.63-1.45) or antiplatelet agents (prevalence ratio = 0.99; 95% CI 0.82-1.18) with overall microbleed presence when added to this multivariable model. Lobar, deep, and infratentorial locations showed differing associations with risk factors. Older age was associated with both deep and infratentorial microbleeds, but not lobar microbleeds. Male sex was associated with lobar microbleeds but not with microbleeds at deep or infratentorial sites. Higher systolic blood pressure and treated hypertension were uniquely associated with deep microbleeds. A history of atrial fibrillation was associated with microbleeds in both lobar and deep locations. No associations were detected, either overall or by location, with diastolic blood pressure, diabetes, or the *APOE ε*4 allele.

Multivariable associations of microbleeds with cognitive test performance, six-minute walk, and brain MRI measures

In multivariable regression analyses, microbleed presence vs. absence was not associated with lower scores on any of the four cognitive tests or with lower six-minute walk distance

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(Figure 6 and Table S4). However, microbleed presence overall and in each of the 3 investigated location categories was associated with greater WMH volume, and total and deep microbleeds were associated with lower total WM fractional anisotropy (Figure 6 and Table S5). The associations with WM fractional anisotropy were little changed by additional adjustment for WMH volume. No association was detected between microbleed presence and total gray matter volume.

Among participants with at least one microbleed, multivariable associations with number of microbleeds

In multivariable analyses among those with at least one microbleed, associations of sociodemographic characteristics and cardiovascular risk factors with greater microbleed number were similar in direction to the associations for presence vs. absence of microbleeds (Table S6). Greater microbleed number both overall and in lobar locations was associated with greater WMH volume and lower total WM fractional anisotropy (Table S5). No association was detected between microbleed number and cognitive test scores, six-minute walk distance, or total gray matter volume.

In sensitivity analyses, exclusion of participants using anticoagulant medication did not materially change the results.

4 | DISCUSSION

In this analysis of a racially and ethnically diverse older community-based cohort with mean (SD) age of 72 (8) years and without prior clinically recognized stroke, brain microbleeds were present in 33% of participants overall and in 45% of participants aged 85 years or older. In cross-sectional multivariable analysis, advanced age, higher systolic blood pressure and body mass index, treated hypertension, and a history of atrial fibrillation were independently associated with deep microbleeds. Male sex and a history of atrial fibrillation were independently associated with lobar microbleeds. Both overall and in all three locations, microbleeds were strongly and independently associated with one or both brain MRI markers of WM injury: greater WMH volume and lower total WM fractional anisotropy.

Several strengths and limitations of our analysis should be noted. Strengths include the diverse sample of older participants and the assessment of both clinically recognized and subclinical atrial fibrillation. The brain MRI used high field strength (3-Tesla) and microbleeds were detected from SWI sequences using an automated and validated method followed by radiologist review,[8] and automated methods were used for WMH measurement.[12] We were able to examine associations with microbleeds by location within the brain. However, because our analyses were cross-sectional, we were unable to assess temporal relationships between study measures and microbleed development. Also, brain MRI readings of subclinical or covert infarcts, another important direct measure of cerebrovascular disease, were not available in this MESA dataset. Our analysis of associations with cognitive performance, physical function, and brain MRI markers of small vessel disease included several tests for significance, and type 1 error is possible as a result. However, correction for multiple testing would be overly conservative because the

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various measures are highly correlated with one another. We have presented point estimates and 95% confidence intervals without focusing exclusively on statistical significance. Participants able and willing to complete the brain MRI had fewer cardiovascular risk factors than those who did not; this bias would likely lead to underestimates for the prevalence of microbleeds at each age in the population at large.

Nonetheless, the measured prevalence of microbleeds was higher at comparable ages in MESA than in the UK Biobank, the only other large community-based study that used 3-Tesla field strength and SWI sequence data to identify microbleeds. Microbleed prevalence was 7% at a mean (SD) age of 62 (7) years in the UK Biobank[24] but 20% among those aged 60-64.9 years in MESA. The higher microbleed prevalence at comparable ages in MESA may be due to greater sensitivity of the deep learning method for microbleed detection as opposed to manual detection the UK Biobank. The higher prevalence may also be related to differences in cohort characteristics including the higher prevalence of diabetes and higher average body mass index in MESA participants. As expected, the use of 3-Tesla field strength and SWI sequence data[25] in MESA yielded higher age-specific microbleed prevalence than in community-based studies that did not use these techniques, including the Framingham Heart Study,[4] Rotterdam Scan Study,[2] Age, Gene/Environment Susceptibility Study,[5] and Atherosclerosis Risk in Communities (ARIC) Study.[6]

We found that a history of atrial fibrillation was strongly associated with microbleed prevalence both overall and in deep and lobar locations. This association has not been examined to date in most large community-based studies, but the Gothenburg H70 Birth Cohort study of 776 individuals examined at age 70 reported an association of atrial fibrillation with frontal microbleeds after adjustment for other cardiovascular risk factors.[26] A clinical study reported higher microbleed prevalence in patients with atrial fibrillation than in those without, but the analyses was not adjusted for other microbleed risk factors.[27] We previously showed that greater left atrial volume index was associated with microbleeds in MESA participants.[20] Taken together, these findings support the involvement of atrial fibrillation in the pathophysiology of microbleeds, but do not provide insight as to whether atrial fibrillation is causally related to microbleeds or is a manifestation of underlying vascular pathology or shared risk factors.

In multiply adjusted analyses in the multi-ethnic MESA population, race and ethnicity were not associated with microbleed presence, either overall or by location. However, our finding of a prevalence ratio of 1.62 for deep microbleeds in Chinese vs. White participants is intriguing given previous findings of a higher prevalence of deep and/or infratentorial or mixed microbleeds in Eastern (Japanese and Chinese) than in White Western participants.[28] Additional investigation will be needed to elucidate a possible relation to the two-fold higher observed incidence of intracerebral hemorrhage in East and Southeast Asian compared with White populations.[29]

Our findings that older age, higher systolic blood pressure, and treated hypertension were associated with deep microbleeds are in accord with findings from other community-based studies,[2,24] as is the lack of association with diabetes or hemoglobin A1c. The strong association of deep microbleeds with high blood pressure and with MRI markers of small

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vessel disease support the hypothesis that deep microbleeds are mainly of vascular origin in distinction to lobar microbleeds, which may reflect amyloid-related pathologies.[30]

We did not detect an association of lobar microbleeds with *APOE ε*4 genotype, the strongest genetic marker of Alzheimer's disease; such an association has been reported in studies of largely White populations.[2,24,31] The multi-ethnic character of MESA may explain this discrepancy, in that the contribution of *APOE ε*4 allele to alterations in cognition and brain health may vary by race and ethnicity.[32,33] Despite the higher proportion reporting use of anticoagulants among participants with more microbleeds, after adjustment for sociodemographic characteristics and cardiovascular risk factors, we found no association of anticoagulant use with microbleeds, in agreement with the Rotterdam and ARIC studies.[34,35] In addition, we report that use of antiplatelet agents was not associated with microbleeds in adjusted analyses. Associations of microbleeds with other risk factors were not affected by exclusion of participants who used anticoagulant medication.

Previous studies of clinical and community-based samples have described associations of microbleeds with cognitive impairment,[36,37] cognitive decline,[3] and dementia[3,5,38] and with elevation in cerebrospinal fluid amyloid-beta and phosphorylated tau 181 protein levels.[36] In cross-sectional analyses in MESA, we did not detect an association of microbleeds with cognitive test scores. However, the cognitive tests administered in MESA were limited and did not provide a comprehensive assessment of all cognitive domains. Thus, based on findings in previous studies, microbleeds should not be considered benign with respect to cognition. Future analysis in MESA of change in cognitive test scores over time and adjudicated cognitive status will provide a more sensitive assessment of associations of microbleeds with cognition.

In cross-sectional but not in longitudinal analyses in the ARIC study, greater microbleed number was associated with slower gait speed.[39] In our cross-sectional analysis, we did not detect an association with distance walked. Both the present study and the UK Biobank found strong associations of microbleed presence with greater WMH volume and total WM fractional anisotropy but not with gray matter volume.[24] Longitudinal analysis of repeated brain MRIs will be needed to elucidate the temporal sequence of development of microbleeds, reduction in WM fractional anisotropy, and increase in WMH volume.

5 | CONCLUSION

The results of our analysis of brain microbleeds in a diverse community-based cohort of older individuals without prior stroke suggests that microbleeds are common and are associated with older age, atrial fibrillation, and MRI measures of WM injury. Our findings are consistent with the existing view that deep microbleeds reflect vascular brain injury. Sensitive quantification of microbleeds will facilitate future longitudinal studies of the potential role of microbleeds as an early indicator of vascular pathology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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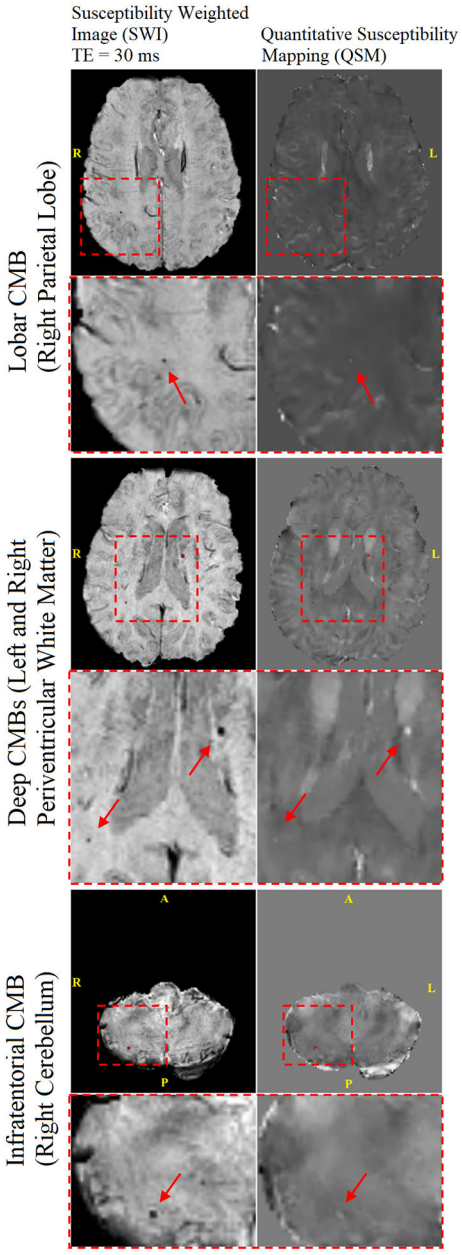

FIGURE 1.

Examples of microbleeds detected in lobar, deep and infratentorial regions segmented by our inhouse developed deep learning model trained with susceptibility weighted, T2-weighted, and quantitative susceptibility mapping images. The unmagnified views show the microbleed segmentation masks (in red, 2-10 voxels in volume). The magnified views show the same microbleeds indicated by red arrows and without the segmentation mask.

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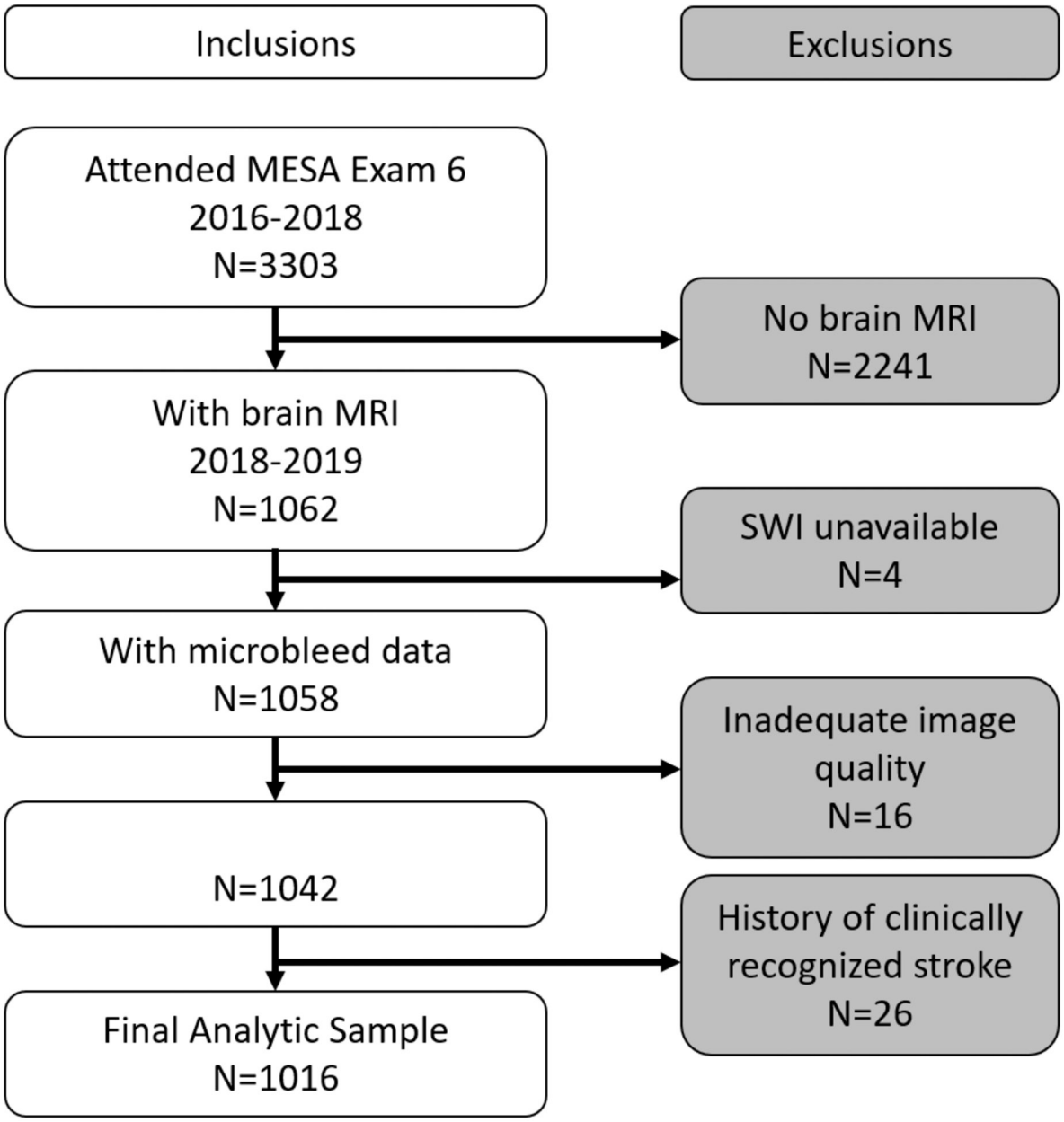

FIGURE 2.
Study inclusion diagram
MESA=Multi-Ethnic Study of Atherosclerosis, MRI=magnetic resonance imaging, SWI=susceptibility-weighted imaging sequence

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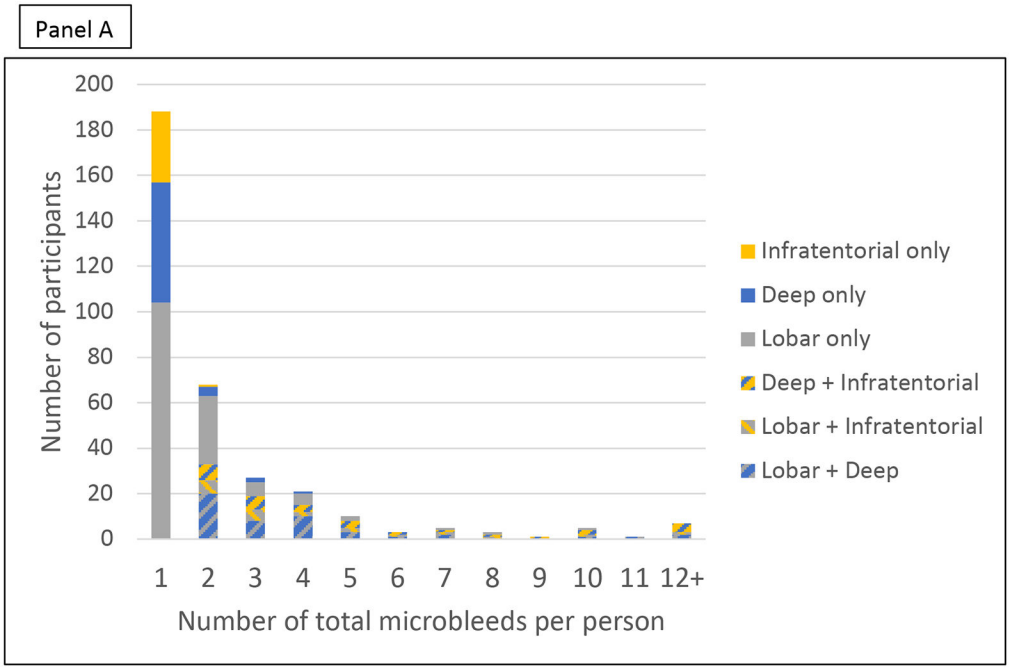

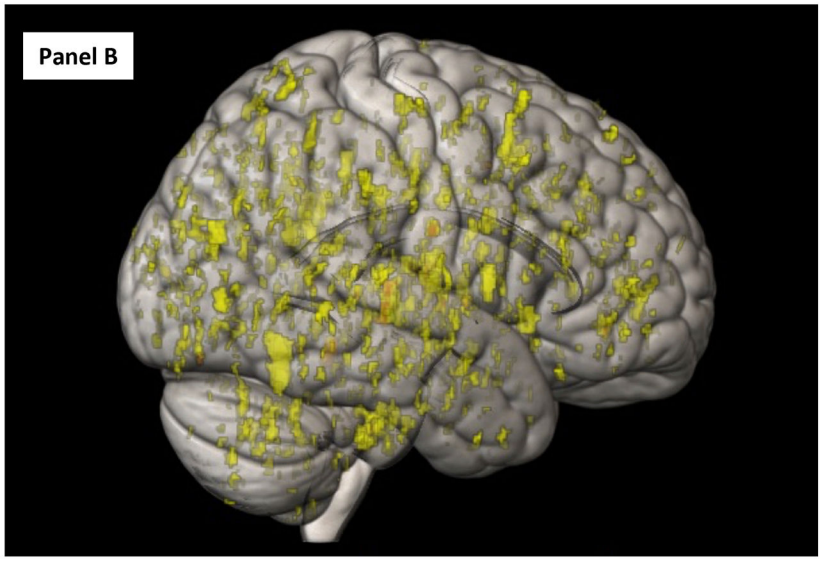

FIGURE 3.

A. By location, number of microbleeds per person among 339 participants with at least one microbleed

B. 3-dimensional rendering of all microbleeds observed in the MESA sample; orange color indicates anatomical locations where 2 microbleeds were observed; brighter yellow areas are more superficial while indistinct areas are deeper. See Supporting Information video, ‘MBvideo_SuppInfo.MP4’.

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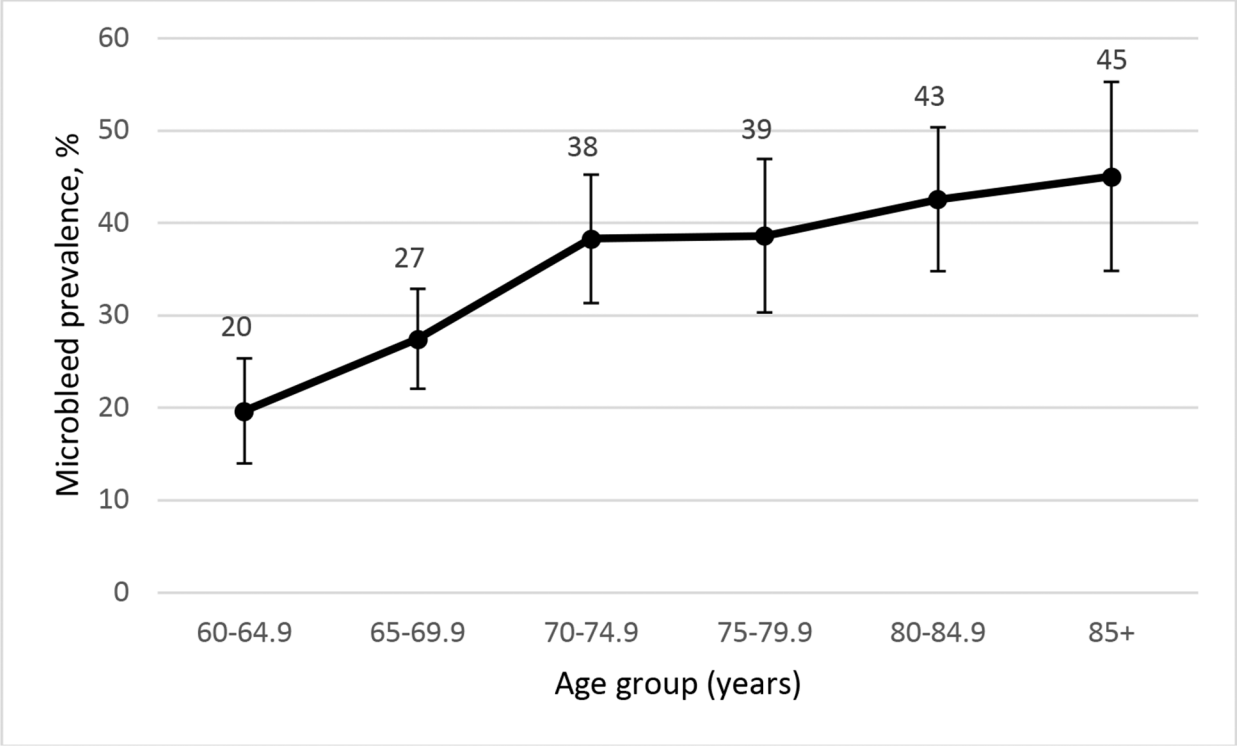

FIGURE 4.
Microbleed prevalence by age group among 1016 MESA participants, 2018-2019. Bars indicate 95% confidence intervals.

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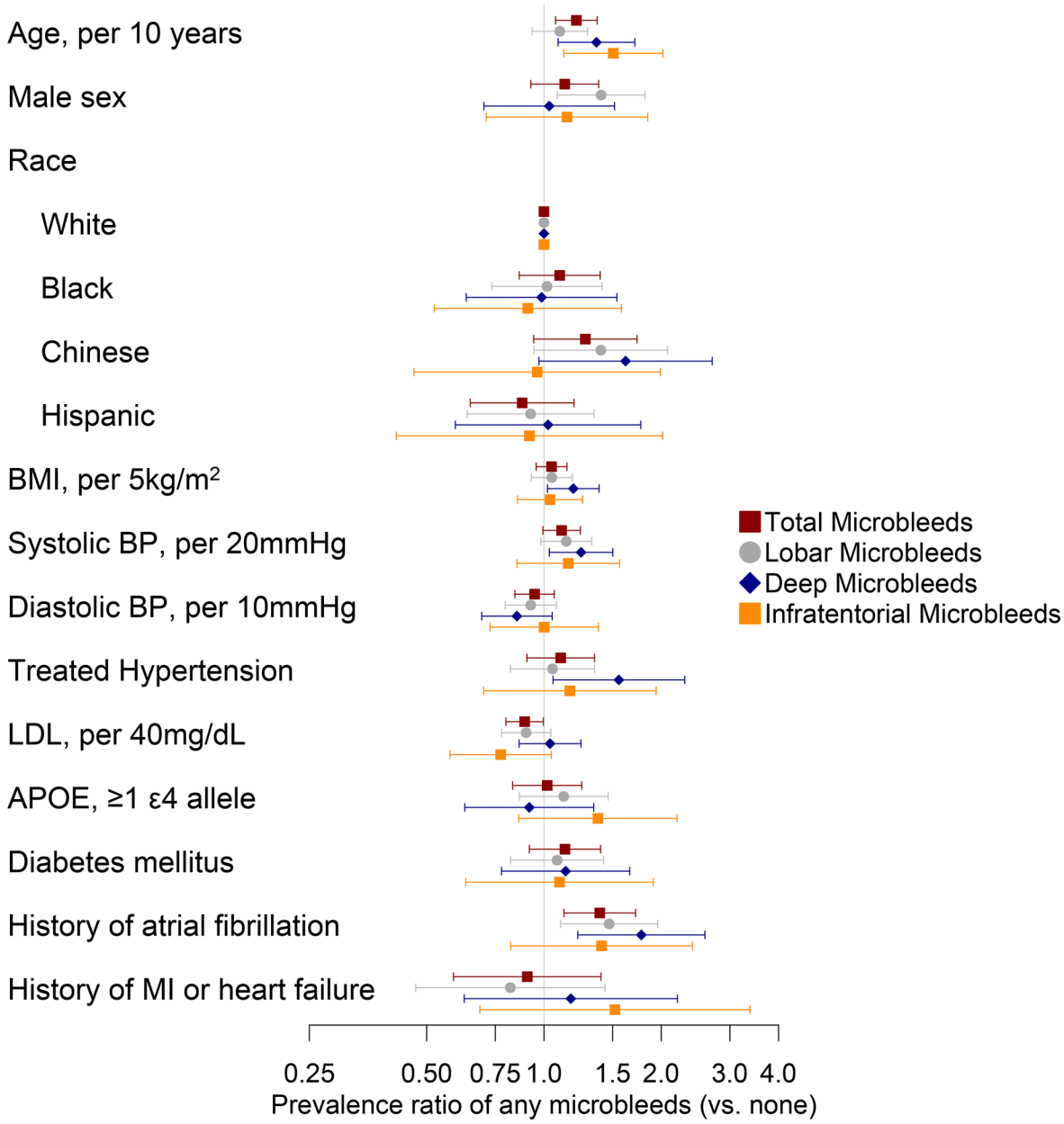

FIGURE 5.

Multivariable* association of sociodemographic characteristics and cardiovascular risk factors with the presence of brain microbleeds, overall and by microbleed location

BMI = body mass index, BP = blood pressure, LDL = low density lipoprotein cholesterol, APOE = apolipoprotein E, MI = myocardial infarction

* Also adjusted for field center, educational attainment, smoking (never, former, current), and HDL cholesterol

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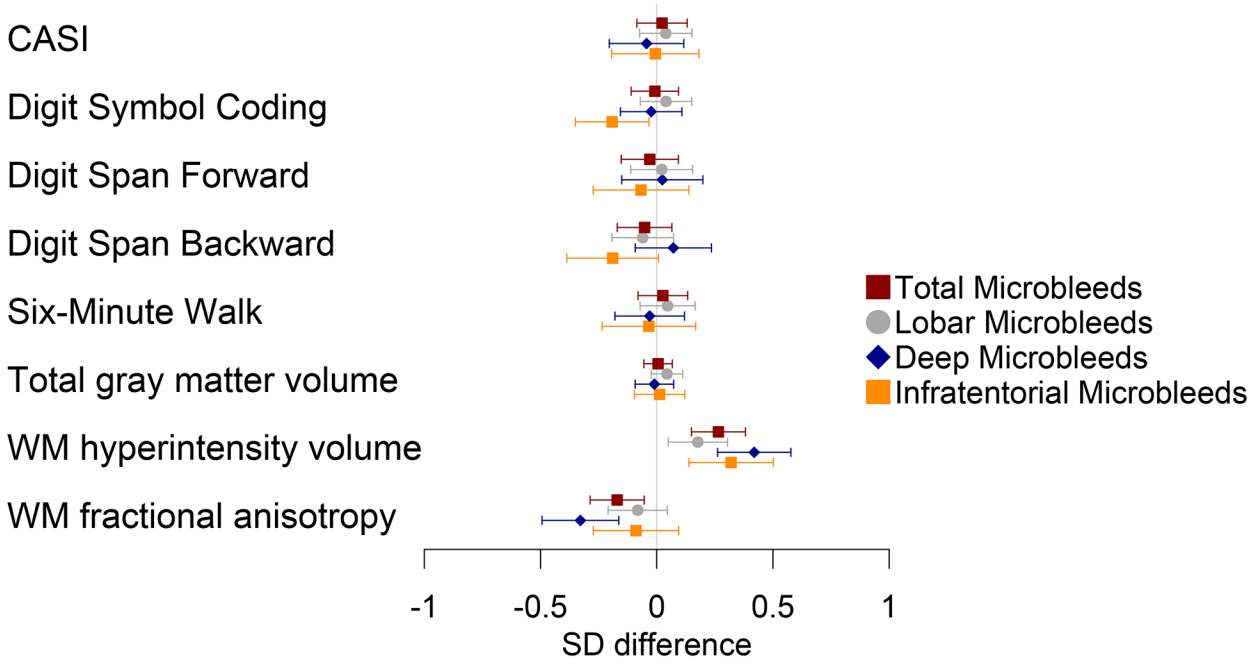

FIGURE 6.

Adjusted associations* of microbleed presence with cognitive test performance, six-minute walk distance, and brain MRI measures, overall and by microbleed location

CASI = Cognitive Abilities Screening Instrument

*All models adjusted for age, sex, race and ethnicity, field center, educational attainment, body mass index, systolic blood pressure, diastolic blood pressure, use of antihypertensive medication, HDL and LDL cholesterol, cigarette smoking status, diabetes mellitus, history of atrial fibrillation, and history of myocardial infarction or heart failure. Total gray matter volume and WM hyperintensity volume models are also adjusted for total intracranial volume.

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TABLE 1.

Characteristics of 1016 MESA participants in 2016-2018 (Exam 6) by presence and number of microbleeds on brain MRI

	No microbleeds (N=677)		1+ microbleed (N=339)		1 microbleed (N=188)		2 microbleeds (N=68)		≥3 microbleeds (N=83)	
	Mean or %	SD	Mean or %	SD	Mean or %	SD	Mean or %	SD	Mean or %	SD
Age, years	71	8	74	8	74	8	74	8	76	9
Sex, % male	45%		50%		47%		47%		60%	
Race, %										
Black	23%		27%		28%		29%		25%	
Chinese	14%		17%		16%		18%		18%	
Hispanic	22%		15%		12%		21%		19%	
White	41%		40%		44%		32%		37%	
Education, %										
< High school	11%		13%		14%		12%		12%	
High school graduate	17%		13%		11%		16%		14%	
Some college	32%		25%		26%		21%		27%	
College graduate	41%		49%		49%		51%		47%	
Body mass index, kg/m^2	28	6	28	5	27	5	29	4	29	5
Height, cm	165	10	165	10	165	10	165	10	165	9
Weight, kg	77	17	77	15	75	16	78	14	79	15
Waist circumference, cm	98	13	99	12	97	13	100	12	102	10
Systolic BP, mmHg	125	19	129	22	128	22	127	20	134	22
Diastolic BP, mmHg	69	10	69	10	69	11	68	10	70	9
Treated hypertension, %	54%		66%		62%		64%		77%	
Smoking history, %										
Current	6%		5%		4%		6%		7%	
Past	45%		49%		49%		49%		49%	
HDL cholesterol, mg/dL	60	19	61	18	63	20	58	16	57	13
LDL cholesterol, mg/dL	111	35	102	34	103	35	99	34	101	31
Anticoagulation use, %	3%		5%		4%		4%		8%	
Antiplatelet * use, %	43%		48%		46%		51%		51%	
APOE, ≥1 *ε4* allele, %	28%		27%		24%		24%		35%	
Diabetes mellitus, %	20%		25%		24%		28%		26%	
History of AF, %	10%		19%		15%		22%		28%	
History of MI or heart failure, %	3%		4%		3%		3%		7%	
CASI Score	90	7	90	7	90	7	90	6	89	8
Digit Symbol Coding score	53	18	50	18	52	19	48	16	48	16
Digit Span Forward score	10	3	10	3	10	3	10	3	10	3
Digit Span Backward score	6	2	6	2	6	2	6	2	5	2
Six-minute walk, m	426	95	419	93	427	88	420	109	397	89

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	No microbleeds (N=677)		1+ microbleed (N=339)		1 microbleed (N=188)		2 microbleeds (N=68)		≥3 microbleeds (N=83)	
	Mean or %	SD	Mean or %	SD	Mean or %	SD	Mean or %	SD	Mean or %	SD
Total brain volume, mL	1094	111	1089	118	1083	118	1095	125	1095	112
Total grey matter vol, mL	600	63	591	67	589	66	596	75	593	64
WMH volume, mL	5.6	9.0	9.2	12.5	7.6	11.1	7.4	8.3	14.3	16.4
Fractional anisotropy	0.40	0.02	0.40	0.03	0.39	0.03	0.39	0.03	0.38	0.03

BP = blood pressure, HDL = high density lipoprotein cholesterol, LDL = low density lipoprotein cholesterol, *APOE* = apolipoprotein E, AF = atrial fibrillation, MI = myocardial infarction, CASI = Cognitive Abilities Screening Instrument, WMH = white matter hyperintensity

*Antiplatelet agents included regular aspirin (at least 3 days per week) or ADP receptor inhibitors