Cerebral microbleeds (CMBs) are small, round, hypointense lesions detected on T2* gradient-recall echo (GRE) MRI sequences that have been associated with normal aging but also vascular risk factors,1–3 cerebrovascular disease,1,3,4 cognitive performance,5–7 and Alzheimer disease (AD)–related pathology.8 Cerebral microbleeds histologically correspond to foci of hemosiderin-laden macrophages from prior extravasation of red blood cells and have been associated with fibrohyalinosis of small penetrating vessels and amyloid angiopathy in patients with symptomatic intracerebral hemorrhage,9 but not in asymptomatic patients.10

The prevalence of CMBs in the general population has been reported to range from 3% to 27%.1,3,11,12 However, data are lacking on the prevalence of CMBs in samples free of stroke, as well as among racially and ethnically diverse community-based populations. Several studies have reported acute and chronic clinical manifestations based on CMB location,3 as well as differing etiologies based on location,1 with lobar CMBs having been associated with cerebral amyloid angiopathy (CAA) and hypertension, whereas deep CMBs are thought to be more specific to hypertensive vasculopathy.13 Location and distribution of CMBs also may relate to the apolipoprotein E (APOE) genotype, and racial and ethnic variations are poorly understood.1,14

The majority of studies of CMB prevalence and risk factors were done in samples that do not include blacks or Hispanics/Latinos, who may be at higher risk of stroke15 and dementia.16 We have previously found that blacks and Hispanics have a

Background—Cerebral microbleeds (CMBs) represent intracerebral hemorrhages due to amyloid angiopathy or exposure to modifiable risk factors. Few community-based stroke-free studies including blacks and Hispanics have been done.

Methods and Results—The Northern Manhattan Study (NOMAS) is a stroke-free, racially and ethnically diverse cohort study. Brain MRI was performed in 1290 participants, 925 of whom had available T2* gradient-recall echo data. We used multivariable logistic regression to examine the association of sociodemographics, vascular risk factors, apolipoprotein E (APOE) genotype, and brain MRI markers with CMB presence and location. The prevalence of CMBs in our cohort was 5%. Of the 46 participants with CMBs, 37% had only deep CMBs, 48% had only lobar CMBs, and 15% had CMBs in both locations. The difference in CMB distribution was not statistically significant across race/ethnic group or APOE genotype. In multivariable analyses, age (OR [95% CI]: 1.09 [1.04, 1.15]) and SBIs (2.58 [1.01, 6.59]) were positively associated with CMB presence, and diabetes medication use was negatively associated (0.25 [0.07, 0.86]).

Conclusions—CMBs may represent the severity of vascular disease in this racially and ethnically diverse cohort. Larger studies are needed to elucidate the association between diabetes medication use and CMB presence.

Key Words: cerebral microbleed • magnetic resonance imaging • risk factor
greater incidence of stroke than non-Hispanic whites and that the impact of stroke risk factors differs by race and ethnicity. Therefore, understanding how CMBs differentially relate to known risk factors of stroke and dementia in these understudied populations may provide insight into the prevention of these disabling neurological disorders.

We hypothesized that CMB prevalence and associations with particular risk factors would differ across race and ethnic groups and be associated with hypertension and APOE status in this diverse cohort.

Methods

Participant Recruitment

The Northern Manhattan Study (NOMAS) is an ongoing prospective cohort study designed to assess stroke risk factors and outcomes in racially and ethnically diverse, clinically stroke-free participants aged ≥40 years residing in the northern Manhattan area. The recruitment, design, and demographics of NOMAS have been previously described. In brief, eligible participants were stroke-free, at least 40 years of age, and residing in northern Manhattan for at least 3 months with a telephone in the household. Using random digit dialing, we recruited 3298 participants between 1993 and 2001. From 2003 to 2008, 199 unrelated household members were also recruited. Written informed consent was obtained from all participants. Institutional Review Boards of Columbia University Medical Center and the University of Miami approved the study.

Sociodemographics and Vascular Risk Factors

All participants underwent an evaluation conducted by study physicians and bilingual research assistants, which included a physical and neurological exam, comprehensive medical history, medical record review, and measurements of blood pressure, fasting blood glucose, and lipids at the time of MRI. Standardized questions were adapted from the Centers for Disease Control and Prevention Behavioral Risk Factor Surveillance System. A questionnaire based on the National Health Interview survey was used to measure leisure-time physical activity, cardiovascular risk factors were collected through interviews with trained bilingual research assistants in English or Spanish. Race and ethnicity were based on self-identification. Body mass index (BMI, kg/m²) was calculated. Measurement of blood pressure (BP) and fasting glucose and lipids as well as the definitions of smoking status, physical activity, and alcohol use have been described previously. Smoking status was self-reported and categorized as current (within the past year), former, or never (includes use of cigarettes, cigars, or pipes). Moderate alcohol use was defined as drinking >1 alcoholic drink/month and ≤2 drinks/day. Moderate to heavy physical activity was defined as involvement in 1 or more selected rigorous physical activities in a typical 14-day period, as described previously. BP was measured twice (before and after the physical examination) from the right brachial artery after a 10-minute rest in a seated position (Dinamap Pro100, Critikon Inc); the 2 BP measures were averaged to obtain systolic (SBP) and diastolic blood pressures (DBP). Use of all medications was self-reported. Antiplatelet medication use also included the use of aspirin. We used self-reported antiplatelet and warfarin use from any time in NOMAS for each participant. Cholesterol-lowering, antihypertensive, and diabetes medication use was reported at follow-up.

MRI Protocol

The MRI substudy (2003–2008) enrolled NOMAS participants aged ≥50 years with no contraindications for MRI who signed the informed consent. The imaging protocol has been published. All exams were performed on a 1.5T MRI system (Philips Medical Systems, Best, the Netherlands) at the Columbia University Hatch Research Center. White matter hyperintensity volume (WMHV) and total cerebral volume were expressed as a fraction of the total intracranial volume. Total cerebral volume is labeled as the cerebral parenchymal fraction (CPF). We used a T2* gradient echo sequence with a 5-mm slice thickness and no gap (20 slices) to quantify CMB (TR 300 ms, TE 45 ms, and flip angle of 10°). Images were acquired in the coronal orientation. Extreme anterior and posterior brain slices were excluded to limit susceptibility artifacts and reduce scan time. A single rater (V.J.D.) blinded to participant characteristics read all gradient echo images using the validated semiquantitative Brain Observer Micro-Bleed Scale (BOMBS). A second rater (N.D.) read all scans with CMB blinded to the other’s ratings, and disagreements were resolved by consensus. Only CMB rated as “certain” by both readers were used in this analysis.

APOE Genotyping

The number of APOE alleles (APOE e2, e3, or e4) carried by each participant was determined by HhaI digestion of PCR products amplified from genomic DNA as described previously.

Statistical Analysis

Descriptive statistics were presented as frequencies and proportions (percentage prevalence of those with CMBs in each group) for categorical variables as well as means and standard deviations for continuous variables. Student t tests
or chi-squared tests were performed to determine participant characteristics that differed by CMB status. Sample characteristics associated with CMB presence at an unadjusted level of significance of $P<0.20$ were included in a multivariable logistic regression model. A $P$ value of <0.05 was considered statistically significant. Based on results of the multivariable model, we examined interactions between APOE 4 carrier status and systolic blood pressure as well as between SBP and hypertension medication use. We excluded those with both deep and lobar CMBs from the multivariable logistic regression analysis. Results remained consistent after adding these participants to both the “only deep” and “only lobar” groups (data not shown). All data analyses were carried out using SAS version 9.3 (SAS Institute Inc, Cary, NC).

**Results**

Of 1290 participants who had brain MRI, 935 (mean age 70±9 years, 61% women, 15% black, 70% Hispanic/Latino, and 14% white) had T2* GRE data available. Demographic, cardiovascular, and brain MRI variables are described for the entire sample in Table 1.

CMBs were identified in 46 participants (prevalence=5% [95% CI 4% to 7%]). Of the 46 people with CMB, 9 participants had 2 CMBs, 19 participants had 3 CMBs, 1 participant had 4 CMBs, 8 participants had 5 CMBs, 4 participants had 6 CMBs, 2 participants had 9 CMBs, 1 participant had 12 CMBs, 1 participant had 15 CMBs, and 1 participant had 30 CMBs. CMBs were located only in lobar regions in 22 participants (48%), only in deep regions in 17 participants (37%), and in mixed locations in 7 (15%) participants (Table 1).

In unadjusted analyses, participants with CMBs were older (mean [SD]=76 [9] years, $P<0.0001$) and had greater WMHV (mean percentage [SD]=1.2 [1.4] of TIV, $P=0.007$) and smaller CPF (mean percentage [SD]=71 [4] of TIV, $P=0.026$) than those without CMBs (Table 1). They were also more likely to have an SBI (with CMBs 20% vs without CMBs 7%, $P=0.002$) and less likely to take diabetes medications (with CMBs 7% vs without CMBs 21%, $P=0.019$), although blood glucose levels were not significantly associated with CMBs ($P=0.432$). CMB prevalence did not differ by race/ethnicity or other risk factors (Table 1).

Unadjusted analyses were performed based on CMB location (Table 1). Participants with mixed CMBs were older (mean [SD]=83 [10] years, $P<0.0001$) and had greater WMHV (mean [SD]=1.8 [2.0] % of TIV, $P<0.0001$) than those with only deep or only lobar CMBs. Those with SBIs were more likely to have only lobar CMBs (only lobar CMBs 23% vs only deep CMBs 18% vs mixed CMBs 14%, $P=0.016$).

In a multivariable adjusted analysis, older participants (OR [95% CI]=1.09 [1.04, 1.15]) and those with SBIs (OR [95% CI]=2.58 [1.01, 6.589]) were more likely to have CMBs, and those who were not on diabetes medication were less likely to have CMBs (OR [95% CI]=0.25 [0.07, 0.86]) (Table 2). There were no associations between triglyceride levels, DBP, antihypertensive medication use, WMHV, or CPF and CMB presence.

**Discussion**

CMB prevalence was greater among older participants and those with MRI evidence of cerebral small vessel disease but not across sex or race/ethnicity. Those taking diabetes medication were less likely to have a CMB, suggesting a potential protective effect of diabetes control that needs to be examined in larger studies. Our data suggest CMB presence may indicate vascular disease severity in urban multiethnic populations.

We found a lower prevalence of CMBs (5%) than some other studies.1–3,12,24 The Washington Heights/Inwood Columbia Aging Project (WHICAP) reported a higher prevalence in the same location, but the sample was older, did not exclude participants with stroke, and used a different sampling method than NOMAS.3 The WHICAP also found no differences in CMB prevalence between races/ethnicities. The Atahualpa Project in rural Ecuador found a higher CMB prevalence in a similarly aged cohort to NOMAS.24

Consistent with previous studies, older participants were more likely to have CMBs.1,2,11,24 Aging may weaken vessel walls, increasing blood leakage into surrounding tissues. Diabetes medication use was negatively associated with CMBs, but fasting blood glucose was not. Larger studies are warranted to elucidate if those with medication-controlled diabetes had fewer CMBs than the uncontrolled group. Previous studies suggest that a prediabetic state or a family history of diabetes may be related to vascular endothelial dysfunction and damage to the walls of vessels.25 Prediabetic participants or those with a family history of diabetes may or may not have been categorized as taking diabetes medications, which may explain why those who were on diabetes medications were less likely to have CMBs. Because we do not have family history or prediabetes data in our cohort, we were unable to assess this potential mechanism, but future analysis regarding this relationship is warranted. The main underlying cause of CMBs in this sample may be vascular rather than amyloid angiopathy because participants with SBIs had more CMBs than those without, and those with APOE e4 and smaller cerebral volume did not.

There are important limitations to this study. Causality and temporality cannot be determined in this observational, cross-sectional study. Due to the small sample size of those with CMBs, statistical power was limited, and stratification by race...
was not possible. Misclassification of lesions is possible, and small round paramagnetic, diamagnetic, or ferromagnetic deposits could have the appearance typical of CMB. Not all CMBs may have been detectable at 1.5 T.26 A healthy cohort effect similar to other MRI studies may have led to an underestimate of the prevalence. Variability in CMB prevalence across studies could also be explained by CMB detection methods.27

Table 1. Sample Characteristics Stratified by CMB Presence and Location*

|                     | All N=935 | With CMB N=46 | Without CMB N=889 | P Value† | Only Deep N=17 | Mixed N=7 | Only Lobar N=22 | P Value‡ |
|---------------------|-----------|---------------|-------------------|----------|----------------|-----------|----------------|----------|
| Frequency (%)       |           |               |                   |          |                |           |                |          |
| Sex                 |           |               |                   |          |                |           |                |          |
| Male                | 369 (39)  | 17 (37)       | 352 (40)          | 0.721    | 6 (35)         | 2 (29)    | 9 (41)         | 0.920    |
| Female              | 566 (61)  | 29 (63)       | 537 (60)          |          | 11 (65)        | 5 (71)    | 13 (59)        |          |
| Race/ethnicity      |           |               |                   |          |                |           |                |          |
| Black               | 138 (15)  | 8 (17)        | 130 (14)          | 0.784    | 3 (18)         | 2 (29)    | 3 (14)         | 0.218    |
| Hispanic            | 652 (70)  | 29 (63)       | 623 (70)          |          | 12 (71)        | 4 (57)    | 13 (59)        |          |
| White               | 127 (14)  | 8 (17)        | 119 (13)          |          | 2 (12)         | —         | 6 (27)         |          |
| Other               | 18 (2)    | 1 (2)         | 17 (2)            |          | —              | 1 (14)    | —              |          |
| Smoking             |           |               |                   |          |                |           |                |          |
| Current             | 144 (15)  | 5 (11)        | 139 (16)          | 0.727    | —              | 2 (29)    | 3 (14)         | 0.295    |
| Former              | 345 (37)  | 20 (43)       | 325 (37)          |          | 5 (29)         | 2 (29)    | 13 (59)        |          |
| Never               | 446 (48)  | 21 (46)       | 425 (48)          |          | 12 (71)        | 3 (43)    | 6 (27)         |          |
| Moderate alcohol consumption | 394 (42) | 15 (33)      | 379 (43)          | 0.179    | 7 (41)         | 2 (29)    | 6 (27)         | 0.454    |
| APOE genotype       |           |               |                   |          |                |           |                |          |
| APOE e2             | 99 (11)   | 8 (17)        | 91 (10)           | 0.222    | 3 (18)         | 1 (14)    | 4 (18)         | 0.506    |
| APOE e3             | 568 (61)  | 24 (52)       | 544 (61)          |          | 10 (59)        | 4 (57)    | 10 (45)        |          |
| APOE e4             | 214 (23)  | 13 (28)       | 201 (23)          |          | 4 (24)         | 1 (14)    | 8 (36)         |          |
| Taking antiplatelets/anticoagulants§ 522 (57) | 30 (67) | 492 (56) | 0.168 | 10 (59) | 5 (71) | 15 (71) | 0.460 |
| Taking cholesterol medications 274 (30) | 11 (25) | 263 (31) | 0.435 | 3 (18) | 3 (43) | 5 (25) | 0.551 |
| Taking antihypertensive medications 547 (61) | 28 (65) | 519 (60) | 0.527 | 7 (44) | 7 (100) | 14 (70) | 0.065 |
| Taking diabetes medications 189 (21) | 3 (7) | 186 (21) | 0.019 | 2 (12) | — | 1 (5) | 0.114 |
| Presence of subclinical brain infarcts 72 (8) | 9 (20) | 63 (7) | 0.002 | 3 (18) | 1 (14) | 5 (23) | 0.016 |
| Mean (SD)           |           |               |                   |          |                |           |                |          |
| Age at MRI, y       | 70 (9)    | 76 (9)        | 70 (9)            | <0.0001  | 72 (10)        | 83 (10)   | 78 (6)         | <0.0001  |
| LDL-C, mg/dL        | 115 (36)  | 109 (31)      | 115 (36)          | 0.232    | 106 (34)       | 106 (25)  | 110 (32)       | 0.657    |
| HDL-C, mg/dL        | 53 (17)   | 57 (17)       | 53 (17)           | 0.125    | 60 (19)        | 59 (22)   | 53 (14)        | 0.237    |
| Triglycerides, mg/dL | 128 (79) | 114 (46) | 128 (80) | 0.065 | 111 (56) | 116 (45) | 116 (39) | 0.714 |
| Blood glucose, mg/dL | 101 (32)| 97 (29) | 101 (33) | 0.432 | 102 (35) | 89 (9) | 97 (28) | 0.719 |
| BMI, kg/m²          | 29 (5)    | 28 (5)        | 29 (5)            | 0.382    | 27 (5)         | 28 (4)    | 28 (6)         | 0.734    |
| SBP, mm Hg          | 136 (17)  | 138 (15)      | 136 (17)          | 0.473    | 132 (12)       | 144 (20)  | 140 (15)       | 0.340    |
| DBP, mm Hg          | 78 (10)   | 77 (10)       | 78 (10)           | 0.596    | 77 (10)        | 86 (9)    | 75 (9)         | 0.061    |
| WMHV§               | 0.7 (0.8) | 1.2 (1.4)     | 0.6 (0.8)         | 0.007    | 1.2 (1.5)      | 1.8 (2.0) | 1.0 (1.1)      | <0.0001  |
| CPF§                | 72 (4)    | 71 (4)        | 72 (4)            | 0.026    | 72 (4)         | 70 (2)    | 71 (3.6)       | 0.116    |

APOE indicates apolipoprotein E; BMI, body mass index; CPF, cerebral parenchymal fraction; DBP, diastolic blood pressure; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; MRI, magnetic resonance imaging; SBP, systolic blood pressure; WMHV, white matter hyperintensity volume.

*Prevalence of risk factor in each group.
†P-values derived from chi-square tests for categorical variables and Student t tests for continuous variables.
‡Warfarin or aspirin.
§Percentage of TIV.

DOI: 10.1161/JAHA.116.003477
Cerebral Microbleeds: NOMAS

Pharmaceuticals, and Sano of CMB Presence*

DOI: 10.1161/JAHA.116.003477

investigators in clinical trials (P29993), private foundation support (American Heart Association/American Stroke Association. He

and stroke litigation) and Hi-Tech; and serves on the National,

chapters. Dr Elkind receives compensation for providing

receives royalties from UpToDate for 2 vascular dementia

model.

*Reference group: No CMBs. All variables were mutually adjusted in a logistic regression

hyperintensity volume.

CMBs correlate with age, SBI, and diabetes medication use. Further studies are needed to understand the pathogenesis of CMBs in racially and ethnically diverse samples.

Sources of Funding

This work was supported by grants from the National Institute of Neurological Disorders and Stroke (R01 NS 29993 to R.L.S.) and the Evelyn F. McKnight Brain Institute.

Disclosures

Dr Wright receives federal grant support (K02 NS 059729, R01 HL 108623, SPRINT MRI WFUHS 330214, R01 NS 29993) and private foundation support (American Heart Association Bugher Center project 14BFSC17690003). He receives royalties from UpToDate for 2 vascular dementia chapters. Dr Elkind receives compensation for providing consultative services for BioTelemetry/Cardionet, BMS-Pfizer Partnership, Boehringer-Ingelheim, Daiichi-Sankyo, Janssen Pharmaceuticals, and Sanofi-Regeneron Partnership; receives research support from diaDexus, Inc., Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership, and the NIH/NINDS; has given expert legal opinions on behalf of Organan (NuvaRing® and stroke litigation) and Hi-Tech; and serves on the National, Founders Affiliate, and New York City chapter boards of the American Heart Association/American Stroke Association. He receives royalties from UpToDate for chapters related to stroke. Dr Sacco receives federal grant support (R01 NS 29993), private foundation support (American Heart Association Bugher Center), and pharma research support (Boehringer Ingelheim). Dr Dequatre and Dr Cordonnier were investigators in clinical trials (Pfizer, Pierre Fabre, Astra-Zeneca). Dr Cordonnier served on scientific boards for Bayer and Medtronic. There was no personal funding; all honoraria were paid to Adrinord or to the research account of the Lille University Hospital. Dr Cordonnier is a member of the Institut Universitaire de France. For the remaining authors, no conflicts of interest were declared.

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Table 2. Multivariable Adjusted Model Examining Correlates of CMB Presence*

| Variable                  | OR (95% CI) | P Value |
|---------------------------|-------------|---------|
| Age at MRI                | 1.09 (1.04, 1.15) | 0.0003 |
| Triglycerides             | 1.00 (0.99, 1.00) | 0.592  |
| DBP                       | 1.00 (0.97, 1.03) | 0.900  |
| Antihypertensive medication | 1.05 (0.52, 2.14) | 0.891  |
| Diabetes medication       | 0.25 (0.07, 0.86) | 0.028  |
| WMHV                      | 1.22 (0.90, 1.65) | 0.212  |
| SBI                       | 2.58 (1.01, 6.59) | 0.048  |
| CPF                       | 1.07 (0.97, 1.18) | 0.159  |

CPF indicates cerebral parenchymal fraction; DBP, diastolic blood pressure; MRI, magnetic resonance imaging; SBI, subclinical infarcts; WMHV, white matter hyperintensity volume.

*Reference group: No CMBs. All variables were mutually adjusted in a logistic regression model.
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