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Cerebral Microbleeds and Amyloid Pathology Estimates From the Amyloid Biomarker Study

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Abstract

IMPORTANCE Baseline cerebral microbleeds (CMBs) and *APOE* ε4 allele copy number are important risk factors for amyloid-related imaging abnormalities in patients with Alzheimer disease (AD) receiving therapies to lower amyloid-β plaque levels.

OBJECTIVE To provide prevalence estimates of any, no more than 4, or fewer than 2 CMBs in association with amyloid status, *APOE* ε4 copy number, and age.

DESIGN, SETTING, AND PARTICIPANTS This cross-sectional study used data included in the Amyloid Biomarker Study data pooling initiative (January 1, 2012, to the present [data collection is ongoing]). Data from 15 research and memory clinic studies were pooled and harmonized. Participants included individuals for whom data on age, cognitive status, amyloid status, and presence of CMBs were available. Data were analyzed from October 22, 2023, to April 26, 2024.

MAIN OUTCOMES AND MEASURES The main outcomes were age, cognitive status, amyloid status and presence, location, and number of CMBs. Presence of amyloid pathology was determined based on 42 amino acid–long form of amyloid-β peptide ($A\beta_{42}$) levels in cerebrospinal fluid or on amyloid–positron emission tomography. Presence and, in a subset, location (lobar vs deep) and number of CMBs were determined on magnetic resonance imaging (locally with visual rating).

RESULTS Among 4080 participants included in the analysis, the mean (SD) age was 66.5 (8.9) years, and 2241 (54.9%) were female. A total of 2973 participants had no cognitive impairment (cognitive unimpairment [CU]), and 1107 had mild cognitive impairment (MCI) or AD dementia (ADD). One thousand five hundred and thirteen participants (37.1%) had amyloid pathology, 1368 of 3599 (38.0%) with data available were *APOE* ε4 carriers, and 648 (15.9%) had CMBs. In the CU group, amyloid pathology and *APOE* ε4 copy number were not associated with presence of any, no more than 4, or fewer than 2 CMBs but were associated with increased odds of lobar CMBs (odds ratio [OR] for amyloid, 1.42 [95% CI, 1.20-1.69], $P < .001$; OR for 2 vs 0 alleles, 1.81 [95% CI, 1.19-2.74], $P = .006$; OR for 1 vs 0 alleles, 1.10 [95% CI, 0.83-1.46], $P = .49$; and OR for 2 vs 1 allele, 1.64 [95% CI, 0.90-2.97], $P = .11$; overall $P = .02$). In the MCI-ADD group, amyloid pathology was associated with presence of any CMBs (OR, 1.51 [95% CI, 1.17-1.96], $P = .002$), no more than 4 CMBs (OR, 1.44 [95%

(continued)

Key Points

Question What is the prevalence of cerebral microbleeds (CMBs) in association with amyloid status, *APOE* ε4 copy number, and age?

Findings In this cross-sectional study of 4080 participants, prevalence estimates of CMBs ranged from 6% at 50 years of age in a non–*APOE* ε4 allele carrier with no amyloid pathology and no cognitive impairment to 52% at 90 years of age in an *APOE* ε4 homozygote carrier with amyloid pathology and cognitive impairment.

Meaning These results suggest that CMB prevalence estimates may help inform safety evaluations for antiamyloid clinical trials.

+ Supplemental content

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Abstract (continued)

CI, 1.18-1.82], *P* = .002), and fewer than 2 CMBs (OR 1.34 [95% CI, 1.03-1.74], *P* = .03) but not lobar CMBs. *APOE* ε4 copy number was associated with presence of any (OR for 2 vs 0 alleles, 1.72 [95% CI, 0.88-3.35], *P* = .11; OR for 1 vs 0 alleles, 0.78 [95% CI, 0.59-1.04], *P* = .09; and OR for 2 vs 1 allele, 2.20 [95% CI, 1.32-3.67], *P* = .002; overall *P* < .001) and no more than 4 CMBs (OR for 2 vs 0 alleles, 1.31 [95% CI, 0.64-2.68], *P* = .45; OR for 1 vs 0 alleles, 0.75 [95% CI, 0.54-1.04], *P* = .08; and OR for 2 vs 1 allele, 1.76 [95% CI, 0.97-3.19], *P* = .06; overall *P* = .03) but not with fewer than 2 or lobar CMBs. Prevalence estimates of CMBs ranged from 6% at 50 years of age in a non–*APOE* ε4 allele carrier with no amyloid pathology and no cognitive impairment to 52% at 90 years of age in an *APOE* ε4 homozygote carrier with amyloid pathology and cognitive impairment.

CONCLUSIONS AND RELEVANCE In this cross-sectional study of 4080 participants, prevalence estimates of CMBs were associated with amyloid status, *APOE* ε4 copy number, and age. CMB prevalence estimates may help inform safety evaluations for antiamyloid clinical trials.

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Introduction

Amyloid-related imaging abnormalities (ARIAs) are clinically important adverse events observed in antibody therapy clinical trials to reduce amyloid-β plaque levels in patients with Alzheimer disease (AD). Risk factors for ARIAs include *APOE* ε4 allele carrier status, cerebral microbleeds (CMBs), and cerebral amyloid angiopathy (CAA).[1] As high numbers of lobar CMBs are thought to reflect the presence of CAA and risk for ARIAs, the Alzheimer Association Research Roundtable Workgroup recommended excluding participants with more than 4 CMBs from AD clinical trials of antiamyloid therapies.[1] Emerging data have sparked discussion as to whether this criterion should be more stringent and should be adapted to excluding participants with 2 or more CMBs.[2]

However, information on the background prevalence rate of CMBs considering amyloid biomarker status and *APOE* ε4 carriership is not yet readily available. This information may help inform safety evaluations for amyloid-β plaque–reducing clinical trials and improve our understanding of the association between CMBs and amyloid pathology. The aims of the present study, therefore, were to (1) examine the association of amyloid pathology and *APOE* ε4 carriership with CMBs in individuals with no cognitive impairment (cognitive unimpairment [CU] group) and those with mild cognitive impairment or AD dementia (MCI-ADD group) included in the Amyloid Biomarker Study and to (2) provide prevalence estimates of CMBs in association with amyloid status, *APOE* ε4 copy number, and age. To evaluate the relevant subgroups under consideration for trial inclusion criteria, we considered the presence of both no more than 4 and fewer than 2 CMBs as secondary outcomes.

Methods

Participants

Data for this cross-sectional study were obtained from the Amyloid Biomarker Study data pooling initiative (January 1, 2012, to the present [data collection is ongoing]), including 95 studies.[3-5] For the present study, we selected all participants for whom information on age, cognitive status, amyloid status, and presence of CMBs was available, with a maximum interval of 1 year between CMB and amyloid assessments. This resulted in the inclusion of 4080 participants from 15 research and memory clinic studies (992 were excluded due to missing information on CMBs) (eTable 1 in Supplement 1). A total of 2973 participants were in the CU group as defined by normal scores on cognitive tests and 1107 participants were in the MCI-ADD group.[6,7] Information on number of *APOE*

ε4 alleles was available for 2513 participants (84.5%) in the CU group and 890 (80.4%) in the MCI-ADD group.

All individual sites contributing to the Amyloid Biomarker Study obtained local ethical approval, and the Amyloid Biomarker Study was approved by the Medical Ethics Committee of the Maastricht University Medical Center, which declared that the Medical Research Involving Human Subjects Act does not apply to the study and waived the informed consent requirement because deidentified data were used. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Amyloid Pathology

Presence or absence of amyloid pathology was determined based on cerebrospinal fluid (CSF) concentrations of the 42 amino acid–long form of amyloid-β peptide ($A\beta_{42}$; 10 centers) or an amyloid–positron emission tomography (PET) scan (5 centers) using predefined cutoffs.[3] Data-driven cutoffs from gaussian mixed modeling were applied to dichotomize data for 2592 participants (CSF), and center-specific cutoffs were used to dichotomize data for 1488 participants (452 with CSF measurements and 1036 with PET scans).

Cerebral Microbleeds

Presence of any CMBs (yes or no) was determined on magnetic resonance imaging (MRI) (locally with visual rating). Susceptibility-weighted imaging (SWI) sequences were used in 7 centers and T2-weighted sequences were used in 4 centers. Three centers made use of both. Information on CMB location (lobar vs deep) and count was available for a subset of 2329 (78.3%) and 2457 (82.6%) participants, respectively, in the CU group and 969 (87.5%) and 1044 (94.3%) participants, respectively, in the MCI-ADD group. MRI acquisition methods and assessment details are provided in eTable 2 in Supplement 1, and availability of CMB data across centers is summarized in eTable 3 in Supplement 1.

Statistical Analysis

Data were analyzed from October 22, 2023, to April 26, 2024. We used marginal models to assess the association of amyloid pathology and *APOE* ε4 copy number with CMBs and compute prevalence estimates using generalized estimating equations as the method of estimation and assuming a logit link function for binary outcomes with an exchangeable working correlation matrix and robust variance estimators to account for within-cohort correlation.

We first evaluated the association of amyloid pathology with presence of any CMBs (0 vs ≥1) as the dependent variable. We then examined the added effect of *APOE* ε4 copy number by including it in the model. In secondary analyses, to evaluate the relevant subgroups under consideration for clinical trial inclusion criteria,[1,2] we repeated these steps using the presence of no more than 4 CMBs (0 vs ≤4; excluding participants with >4 CMBs) or the presence of fewer than 2 CMBs (0 vs <2; excluding participants with ≥2 CMBs) as the dependent variable, as well as the presence of lobar CMBs (0 vs ≥1). All models were corrected for age (centered at the mean). We then computed prevalence estimates for presence of any, no more than 4, and less than 2 CMBs based on models including age, amyloid pathology, and *APOE* ε4 copy number as predictive factors associated with outcome using probabilities and 95% CIs that were estimated by generalized estimating equations for figures and tables. Finally, we examined the possible interaction of amyloid measurement modality (ie, CSF or PET) and MRI sequence used to determine presence of CMBs (SWI vs T2 weighted, excluding centers that used both measurements) in post hoc analyses.

Analyses were conducted using IBM SPSS statistics, version 28 (IBM Corporation), and figures were created using R, version 4.3.2 (R Project for Statistical Computing). The significance level was set at $P < .05$ for unpaired, 2-sided tests. We used the Bonferroni adjustment to correct for multiple comparisons when evaluating the primary outcomes. We report uncorrected *P* values and note if the association was no longer present after correction for multiple comparisons.

Results

Participant Characteristics

Participant characteristics of the 4080 participants are presented in **Table 1**. Overall mean (SD) age was 66.5 (8.9) years; 2241 participants (54.9%) were female and 1839 (45.1%) were male. One thousand five hundred and thirteen participants (37.1%) had amyloid pathology, 1368 of 3599 with data available (38.0%) were *APOE* ε4 carriers, and 648 (15.9%) had CMBs.

The mean (SD) age of the 2973 participants in the CU group was 65.9 (9.1) years; 1705 (57.3%) were female and 1268 (42.7%) were male; 872 (29.3%) had amyloid pathology; and 949 of 2708 with available data (35.0%) were *APOE ε4* carriers. Two thousand forty-eight of 2457 participants in the CU group (83.4%) had no CMBs, 257 (10.4%) had 1 CMB, 111 (4.5%) had 2 to 4 CMBs, and 41 (1.7%) had 5 or more CMBs. Participants in the CU group with amyloid pathology were older, more likely to be non-Hispanic White, more likely to be *APOE ε4* carriers, and more likely to have hypertension, lobar CMBs, and 2 or more CMBs than those without amyloid pathology.

The mean (SD) age of the 1107 participants in the MCI-ADD group was 68.2 (8.3) years; 536 (48.4%) were female and 571 (51.6%) were male; 641 (57.9%) had amyloid pathology; and 419 of 891 with available data (47.0%) were *APOE ε4* carriers. Eight hundred and forty-five of 1044 participants

Table 1. Participant Characteristics

Characteristic	Participant group, No. (%)							
	CU group				MCI-ADD group			
	Total (n = 2973)	No amyloid pathology (n = 2101)	Amyloid pathology (n = 872)	*P* value, absent vs present[a]	Total (n = 1107)	No amyloid pathology (n = 466)	Amyloid pathology (n = 641)	*P* value, absent vs present[a]
Age, mean (SD), y	65.9 (9.1)	65.1 (8.9)	67.9 (9.2)	.001	68.2 (8.3)	66.6 (8.0)	69.4 (8.3)	.001
Sex								
Female	1705 (57.3)	1221 (58.1)	484 (55.5)	.19	536 (48.4)	222 (47.6)	314 (49.0)	.66
Male	1268 (42.7)	880 (41.9)	388 (44.5)		571 (51.6)	244 (52.4)	327 (51.0)	
Educational level, mean (SD), y[b]	14.5 (3.9)	14.5 (3.8)	14.3 (4.0)	.12	12.8 (4.1)	12.9 (4.0)	12.7 (4.1)	.50
Non-Hispanic White[c]	1982 (90.6)	1338 (87.7)	644 (97.1)	<.001	297 (73.5)	129 (65.5)	168 (81.2)	<.001
APOE ε4 carrier[d]	949 (35.0)	537 (27.8)	412 (53.0)	<.001	419 (47.0)	102 (26.2)	317 (63.3)	.001
APOE ε4 copy number[e]								
0	1629 (64.8)	1296 (72.0)	333 (46.7)	<.001	472 (53.0)	288 (73.8)	184 (36.8)	<.001
1	784 (31.2)	477 (26.5)	307 (43.1)		330 (37.1)	98 (25.1)	232 (46.4)	
2	100 (4.0)	27 (1.5)	73 (10.2)		88 (9.9)	4 (1.0)	84 (16.8)	
Hypertension[f]	792 (29.9)	539 (28.7)	253 (32.6)	.047	330 (32.9)	153 (35.4)	177 (31.1)	.15
CMBs	439 (14.8)	295 (14.0)	144 (16.5)	.08	209 (18.9)	66 (14.2)	143 (22.3)	<.001
No. of CMBs[g]								
0	2048 (83.4)	1475 (84.3)	573 (80.9)	.043	845 (80.9)	378 (85.7)	467 (77.4)	.08
1	257 (10.4)	191 (10.9)	66 (9.3)		110 (10.5)	40 (9.1)	70 (11.6)	
2-4	111 (4.5)	61 (3.5)	50 (7.1)		55 (5.3)	16 (3.6)	39 (6.5)	
≥5	41 (1.7)	22 (1.3)	19 (2.7)		34 (3.3)	7 (1.6)	27 (4.5)	
Location of CMBs[h]								
Lobar	143 (6.5)	87 (5.6)	56 (8.9)	.004	73 (8.0)	24 (6.0)	49 (9.5)	.05
Deep	176 (8.0)	127 (7.9)	49 (7.9)	.97	66 (7.2)	24 (6.0)	42 (8.3)	.19

Abbreviations: ADD, Alzheimer disease dementia; CMB, cerebral microbleed; CU, cognitive unimpairment (ie, no cognitive impairment); MCI, mild cognitive impairment.

[a] Differences were assessed using independent sample *t* tests for continuous variables or χ^2 tests for categorical variables.

[b] Data were missing for 20 (0.7%) in the CU group and 18 (1.6%) in the MCI-ADD group.

[c] Data were missing for 785 (26.4%) in the CU group and 703 (63.5%) in the MCI-ADD group.

[d] Data were missing for 265 (8.9%) in the CU group and 216 (19.5%) in the MCI-ADD group.

[e] Data were missing for 460 (15.5%) in the CU group and 217 (19.6%) in the MCI-ADD group.

[f] Data were missing for 321 (10.8%) in the CU group and 105 (9.5%) in the MCI-ADD group.

[g] Data were missing for 516 (17.4%) in the CU group and 63 (5.7%) in the MCI-ADD group.

[h] Data were missing for 782 (26.3%) in the CU group and 189 (17.1%) in the MCI-ADD group.

in the MCI-ADD group (80.9%) had no CMBs, 110 (10.5%) had 1 CMB, 55 (5.3%) had 2 to 4 CMBs, and 34 (3.3%) had 5 or more CMBs. Participants in the MCI-ADD group with amyloid pathology were older, more likely to be non-Hispanic White, more likely to be *APOE ε4* carriers, and more likely to have CMBs than those without amyloid pathology.

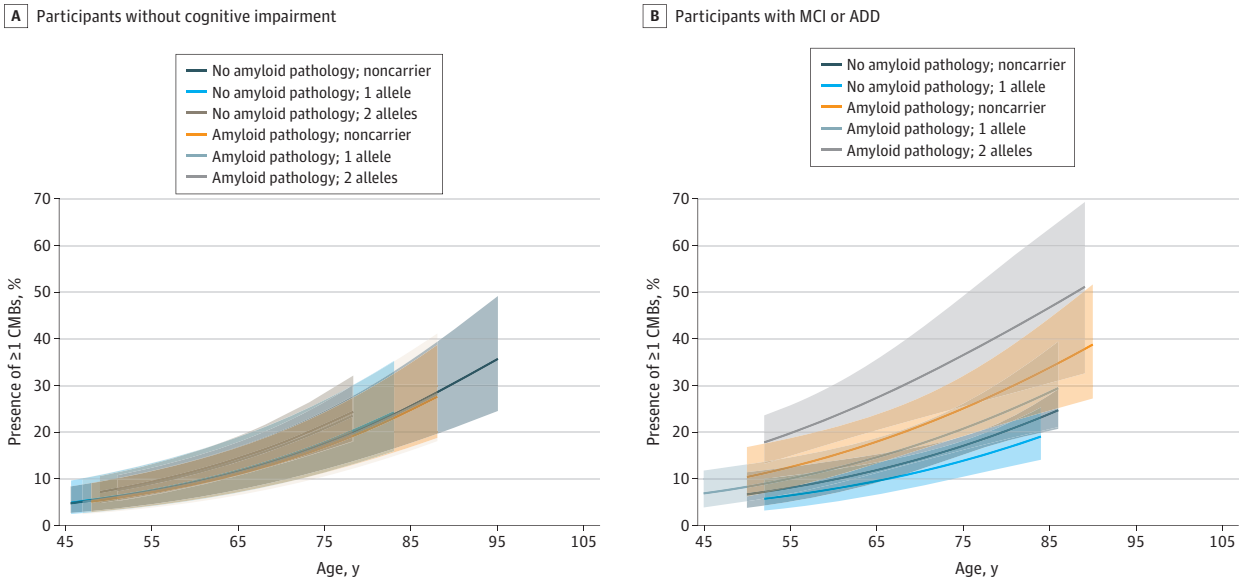
Associations of Amyloid Pathology and *APOE* ε4 Carriership With CMBs in the CU Group

Among participants in the CU group, we did not find an association of amyloid pathology with presence of any (odds ratio [OR], 1.00 [95% CI, 0.85-1.20] *P* = .95), no more than 4 (OR, 1.00 [95% CI, 0.78-1.28]; *P* = .98), or fewer than 2 CMBs (OR, 0.78 [95% CI, 0.53-1.15]; *P* = .21) (**Figure** and eTable 4 in Supplement 1). However, when restricting analyses to presence of lobar CMBs, we found that amyloid pathology was associated with increased odds of lobar CMBs (OR, 1.42 [95% CI, 1.20-1.69]; *P* < .001). We did not find an association of *APOE ε4* copy number with presence of any, no more than 4, or fewer than 2 CMBs (eTable 5 in Supplement 1). *APOE ε4* copy number was associated with increased odds of lobar CMBs (OR for 2 vs 0 alleles, 1.81 [95% CI, 1.19-2.74], *P* = .006; OR for 1 vs 0 alleles, 1.10 [95% CI, 0.83-1.46], *P* = .49; and OR for 2 vs 1 allele, 1.64 [95% CI, 0.90-2.97], *P* = .11; overall *P* = .02) (eTable 5 in Supplement 1). Age was associated with increased odds of any (β = 0.049 [95% CI, 0.034-0.064], *P* < .001), no more than 4 (β = 0.045 [95% CI, 0.034-0.057]; *P* < .001), less than 2 (β = 0.038 [95% CI, 0.027-0.049]; *P* < .001), and lobar (β = 0.055 [95% CI, 0.039-0.071]; *P* < .001) CMBs. Prevalence estimates are provided in eTable 6 in Supplement 1). Prevalence estimates of CMBs ranged from 6% at 50 years of age in a non–*APOE ε4* allele carrier with no amyloid pathology to 35% at 90 years of age in an *APOE ε4* homozygote with amyloid pathology.

Associations of Amyloid Pathology and *APOE* ε4 Carriership With CMBs in the MCI-ADD Group

In participants in the MCI-ADD group, we found that amyloid pathology increased the odds of any (OR, 1.51 [95% CI, 1.17-1.96]; *P* = .002), no more than 4 (OR, 1.44 [95% CI, 1.18-1.82]; *P* = .002), and fewer than 2 (OR, 1.34 [95% CI, 1.03-1.74]; *P* = .03) CMBs (Figure and eTable 4 in Supplement 1). We did not find an association of amyloid pathology with the presence of lobar CMBs (OR, 1.47; 95% CI,

Figure. Prevalence of Any Cerebral Microbleeds (CMBs) by Amyloid Status and *APOE* ε4 Copy Number (Alleles)



Data for participants with no cognitive impairment, amyloid pathology present, and 2 *APOE* ε4 alleles were not visualized, as only 4 were in this subgroup. ADD indicates Alzheimer disease dementia; MCI, mild cognitive impairment. Shading represents 95% CIs.

0.95-2.27; *P* = .08) (eTable 4 in Supplement 1). *APOE ε4* copy number was associated with presence of any CMBs (OR for 2 vs 0 alleles, 1.72 [95% CI, 0.88-3.35], *P* = .11; OR for 1 vs 0 alleles, 0.78 [95% CI, 0.59-1.04], *P* = .09; and OR for 2 vs 1 allele, 2.20 [95% CI, 1.32-3.67], *P* = .002; overall *P* < .001) and no more than 4 CMBs (OR for 2 vs 0 alleles, 1.31 [95% CI, 0.64-2.68], *P* = .45; OR for 1 vs 0 alleles, 0.75 [95% CI, 0.54-1.04], *P* = .08; and OR for 2 vs 1 allele, 1.76 [95% CI, 0.97-3.19], *P* = .06; overall *P* = .03) CMBs (eTable 5 in Supplement 1), but not with presence of fewer than 2 CMBs or lobar CMBs (eTable 5 in Supplement 1). Age was associated with increased odds of any (β = 0.042 [95% CI, 0.021-0.064]; *P* < .001), no more than 4 (β = 0.043 [95% CI, 0.024-0.062]; *P* < .001), and lobar (β = 0.037 [95% CI, 0.016-0.058]; *P* < .001) CMBs. Prevalence estimates are provided in **Table 2**. Prevalence estimates of CMBs ranged from 7% at 50 years of age in a non–*APOE ε4* allele carrier with no amyloid pathology to 52% at 90 years of age in an *APOE* ε4 homozygote with amyloid pathology.

Post Hoc Analyses

There was no interaction between modality (CSF vs PET) and amyloid pathology in either the CU (β = 0.180 [95% CI, −0.281 to 0.640], *P* = .45) or the MCI-ADD (β = 0.406 [95% CI, −0.014 to 0.825]; *P* = .06) group. There was no significant effect of MRI sequence used (SWI vs T2- weighted) with correction for age on presence of any CMBs in either the CU group (β = −0.053 [95% CI, −0.866 to 0.760]; *P* = .90) or the MCI-ADD group (β = −0.537 [95% CI, −1.564 to 0.490]; *P* = .31).

Discussion

In this cross-sectional study, we found that amyloid pathology and, additively, *APOE* ε4 copy number were associated with higher odds of CMBs in participants in the MCI-ADD group and with higher odds of lobar CMBs only in the CU group. Prevalence estimates of CMBs ranged from 6% at 50 years of age in a non–*APOE* ε4 allele carrier with no amyloid pathology and no cognitive impairment to 52% at 90 years of age in an *APOE* ε4 homozygote carrier with amyloid pathology and cognitive impairment.

Generally, our findings are in line with those of previous studies identifying positive associations between amyloid pathology and (lobar) CMBs,[8-16] which were primarily performed in participants with MCI and probable AD. The observation that amyloid pathology was associated with presence of lobar CMBs in participants without but not those with cognitive impairment may be due to differences in statistical power or differences in vascular risk profiles (ie, unexplained variance) between our CU and MCI-ADD groups.

While prevalence estimates of CMBs in relation to amyloid status and *APOE* ε4 copy number have not, to our knowledge, been reported before, our estimates by age seem to correspond with those observed in earlier studies; for example, in the Rotterdam Scan Study,[17] 6.5% in persons aged 45 to 50 years to 35.7% in those 80 years or older, and in the Mayo Clinic Study of Aging,[13] 11.0% in persons aged 60 to 69 years to 39% in those 80 years or older. In our MCI-ADD group, the estimated prevalence of any and no more than 4 CMBs increased with age and was associated with amyloid pathology and *APOE* ε4 copy number. In contrast, there was no association between having fewer than 2 CMBs and age or *APOE* ε4 copy number in participants with cognitive impairment.

Limitations

This study has limitations. Although pooling of data resulted in a large and multinational dataset that was uniquely situated to study amyloid-CMB associations and provide robust prevalence estimates, data pooling may also have introduced sources of variance, especially due to heterogeneity in CMB assessment. Moreover, the present study did not allow for detailed or full examination of vascular risk burden, medication use, the spatial distribution of amyloid burden, or other imaging findings that may suggest the presence of CAA or inform exclusion from clinical trials, as this information was not available across all centers.

Table 2. Estimated Prevalence of Presence of CMBs by Age, Amyloid Pathology, and *APOE* ε4 Copy Number in the MCI-ADD Group

No. of *APOE* ε4 alleles	Prevalence (95% CI) by age, %[a]								
	50 y	55 y	60 y	65 y	70 y	75 y	80 y	85 y	90 y
Any CMBs (n = 890)									
Amyloid pathology absent									
0	7 (4-11)	8 (5-13)	10 (7-14)	12 (9-15)	14 (12-17)	17 (15-19)	20 (18-23)	24 (20-28)	28 (22-35)
1	5 (3-10)	6 (4-11)	8 (5-12)	10 (7-14)	12 (8-16)	14 (10-18)	17 (13-22)	20 (14-26)	23 (16-32)
2	11 (6-20)	13 (7-23)	16 (9-27)	19 (11-31)	22 (13-36)	26 (15-42)	30 (17-49)	35 (19-55)	40 (22-62)
Amyloid pathology present									
0	10 (6-17)	13 (8-19)	15 (11-21)	18 (13-24)	21 (16-27)	25 (19-32)	29 (22-38)	34 (25-44)	39 (27-52)
1	8 (5-13)	10 (7-15)	12 (9-16)	15 (11-19)	17 (14-22)	21 (16-26)	24 (18-32)	29 (21-38)	33 (23-45)
2	17 (12-22)	20 (15-26)	23 (18-30)	27 (20-36)	32 (23-42)	37 (26-49)	42 (28-57)	47 (31-64)	52 (33-71)
≤4 CMBs (n = 828)									
Amyloid pathology absent									
0	6 (4-9)	7 (5-10)	9 (7-11)	11 (9-13)	13 (12-15)	16 (14-18)	19 (16-22)	23 (18-28)	27 (20-34)
1	5 (3-8)	6 (4-9)	7 (5-10)	8 (6-11)	10 (8-13)	12 (9-16)	15 (11-20)	18 (13-25)	21 (14-30)
2	8 (4-14)	10 (5-17)	12 (6-20)	14 (7-25)	17 (9-29)	20 (10-35)	24 (12-42)	28 (13-48)	32 (15-56)
Amyloid pathology present									
0	9 (6-14)	11 (7-16)	13 (10-18)	16 (12-21)	19 (15-24)	22 (17-28)	26 (20-34)	31 (23-40)	36 (25-48)
1	7 (5-10)	8 (6-11)	10 (8-13)	12 (10-15)	15 (12-18)	18 (15-21)	21 (17-26)	25 (19-32)	29 (21-39)
2	11 (8-16)	14 (10-19)	17 (12-23)	20 (14-28)	23 (15-34)	28 (17-41)	32 (19-48)	37 (22-55)	42 (24-63)
<2 CMBs (n = 787)									
Amyloid pathology absent									
0	6 (3-9)	6 (4-9)	7 (6-9)	8 (7-9)	9 (8-11)	11 (8-13)	12 (8-17)	13 (8-21)	15 (8-26)
1	4 (2-7)	4 (3-7)	5 (3-7)	6 (4-8)	6 (4-9)	7 (5-11)	8 (5-13)	9 (5-16)	10 (5-20)
2	4 (2-7)	5 (2-8)	5 (3-10)	6 (3-12)	7 (3-15)	8 (3-19)	9 (3-23)	10 (3-28)	11 (3-34)
Amyloid pathology present									
0	9 (5-18)	11 (6-18)	12 (8-18)	14 (10-18)	15 (12-19)	17 (13-22)	19 (14-25)	21 (15-30)	24 (15-36)
1	6 (3-13)	7 (4-13)	8 (5-13)	9 (7-13)	11 (8-14)	12 (9-15)	13 (10-18)	15 (10-22)	17 (10-26)
2	7 (5-10)	8 (6-11)	9 (6-13)	10 (6-15)	11 (7-19)	13 (7-23)	14 (7-29)	16 (7-34)	18 (7-41)

Abbreviations: ADD, Alzheimer disease dementia; CMBs, cerebral microbleeds; MCI, mild cognitive impairment.

[a] Probabilities and 95% CIs were estimated by generalized estimating equations and based on models including age, amyloid, and *APOE* ε4 copy number as predictive factors.

Conclusions

The results of this cross-sectional study provide further evidence for associations among age, amyloid pathology, *APOE ε4* carriership, and CMBs. Improving our understanding of these associations and generating robust prevalence estimates of CMB, given AD biomarker and vascular risk status, will help inform safety evaluations for antiamyloid trials.

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SUPPLEMENT 1.

eTable 1. Cohort Characteristics
eTable 2. MRI Acquisition and Assessment
eTable 3. Availability of Data Across Centers
eTable 4. Odds Ratios for the Effect of Amyloid on the Presence of CMBs
eTable 5. Odds Ratios for the Effect of APOE ε4 Copy Number on the Presence of CMBs
eTable 6. Estimated Prevalence of Presence of CMBs by Age, Amyloid Pathology, and APOE ε4 Copy Number in Participants Without Cognitive Impairment
eAppendix. FACEHBI and BIOFACE Contributor List

eReferences

SUPPLEMENT 2.
Data Sharing Statement