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Cerebral Microbleeds and risk of Incident Dementia: The Framingham Heart Study

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Abstract

Cerebral microbleeds (CMB) are MRI markers attributed to the most common cerebral angiopathies in the elderly and in patients with dementia: hypertensive and cerebral amyloid angiopathy (CAA). CMB detection in asymptomatic persons may help identify those at risk for dementia, and may influence preventive strategies and design of clinical trials testing treatments for dementia. We studied the association of CMB with risk of incident dementia in community dwelling individuals. 1296 dementia-free Framingham Heart Study participants (mean age 72years; 54% women) with available brain MRI and incident dementia data during a mean follow-up period of 6.7 years were included. Using Cox-proportional hazards models we related CMB presence to incident dementia. Multivariable models were adjusted for age, sex, APOE status, and education, with additional models adjusting for vascular risk factors and MRI markers of ischemic brain injury. CMB were observed in 10.8% and incident dementia in 85 participants (6.6% over study period). Participants with any CMB had 1.74 times higher risk of dementia (HR 1.74, 95% CI 1.00–3.01), while those with deep and mixed CMB had a three-fold increased risk (HR 2.99, 95% CI 1.52–5.90). The associations were independent of vascular risk factors, and for deep and mixed CMB also independent of MRI markers of ischemia (HR 2.44, 95% CI 1.22–4.88). Purely lobar CMB were not associated with incident dementia. Our findings support a role for hypertensive vasculopathy and the interplay of hypertensive and CAA in risk of dementia, and suggest that CMB presence can identify individuals at risk of dementia.

Introduction

Dementia is a major public health concern affecting millions of individuals worldwide and its prevalence is expected to increase tremendously over the next few decades.(Hebert et al.,

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2013) Detection in early stages is an essential task to address this problem. Cerebral microbleeds (CMBs) detected using brain MRI are emerging as a marker to allow identification of individuals at risk of dementia in the preclinical stages of disease.(Akoudad et al., 2016) CMB are associated with stroke,(Charidimou et al., 2013, Chen et al., 2008, Fan et al., 2003, Wardlaw et al., 2006) poor cognition(Charidimou and Werring, 2012, Cordonnier et al., 2006, Poels et al., 2012, Werring et al., 2004, Yakushiji et al., 2008) and mortality risk.(Akoudad et al., 2013, Benedictus et al., 2015) CMBs represent the most common forms of hemorrhage-prone cerebral small vessel disease in the elderly and in persons with dementia: hypertensive arteriopathy and/or cerebral amyloid angiopathy based on their brain location.(Jansen et al., 2015) Autopsy studies have reported presence of hypertensive arteriopathy (arteriolosclerosis) in 10% of elderly persons and in 35% of AD patients,(Toledo et al., 2013) and CAA in 10 to 30% of elderly persons and 80 to 90% of all persons with dementia (25 to 41% moderate to severe CAA).(Jellinger, 2002, Rensink et al., 2003, Toledoet al., 2013) In prior cross-sectional studies and selected samples CMB have been associated with risk of prevalent dementia.(Cordonnieret al., 2006, Pettersen et al., 2008) In selected hospital or clinic samples, CMB have also been related to incident dementia,(Miwa et al., 2014) and more recently in a community based study.(Akoudadet al., 2016) Since CMB have been strongly associated with traditional modifiable risk factors, (Romero et al., 2014) increased risk of ischemic events,(Charidimouet al., 2013) and ischemic small vessel disease (covert brain infarcts and extensive white matter hyperintensities)(Akoudad et al., 2014) the independent contribution of CMB per se to incident dementia is not entirely clear. Study of the relation of CMB and incident dementia will advance our understanding of the pathophysiology of various forms of dementia, help elucidate the vascular contributions to dementia, and may inform subsequent preventive strategies, including guidelines for clinicians and eligibility criteria for clinical trials. We studied the association of CMB with incident dementia in a large sample of asymptomatic participants dwelling in the community, and evaluated whether this association is independent of ischemic brain MRI measures of small vessel disease and traditional vascular risk factors.

Methods

Sample

Framingham Original and Offspring Cohort participants were eligible for the present study if they attended the closest exam cycle to MRI (exams 26/28 for Original, and exams 7/8 for Offspring participants), were aged 60 years or older, free of prevalent dementia, and had available CMB data, APOE genotyping and follow up information for incident dementia. Among the participants who attended the respective exam cycle above, 2085 participants had brain MRI including CMB measurements. A total of 1501 participants were aged 60 years or older and had APOE genotyping. An additional 40 participants were excluded for having prevalent dementia and 126 participants for lack of follow up information, yielding a study sample of 1296 participants (Supplementary Figure 1 shows a flow chart of sample selection). Framingham Heart Study participants are of predominant White race, 91% across all cohorts. The Institutional Review Board of Boston University Medical Center approved the study protocol and informed consent was obtained from all subjects.

Brain MRI

A 1.5-tesla MR machine (Siemens Magnetom) was used to obtain the following sequences: coronal T2-weighted 2470/20 to 80 (TR/TE), echo train length 8, field of view 22 cm, acquisition matrix 192×256 interpolated to 256×256 with 1 excitation, 4-mm slice thickness from nasion to occiput, sagittal Tl-weighted 11.4/4.4, 3D FLASH, 192 mm slab, 128 slices of 1.5-mm thickness, 12-degree flip angle and axial T2*gradient echo 656/26 (TR/TE), field of view 22cm, acquisition matrix 144×256, 30-degree flip angle, 19 slices of 5-mm thickness, and 2 mm gap. MRI data were analyzed using QUANTA 2 on a Linux operating system, blind to the subject's demographic and clinical characteristics, and outcome ascertainment.

CMB definition—CMB were defined using standard criteria (Greenberg et al., 2009) as rounded or ovoid hypointense lesions on $T2^{*}$-GRE weighted sequence. The lesions measured 10mm or less in diameter and were surrounded by brain parenchyma over at least half the circumference of the lesion. CMB mimics were excluded. Reliability measures for CMB readings have been published.(Romeroet al., 2014) The intra-rater reliability based on blinded reading of 200 scans on two separate occasions was excellent (kappa statistic 0.78). Inter-rater reliability comparing two independent readers in a subset of 200 scans was excellent (Kappa 0.78). CMB location in the brain was classified into subgroups based on assumed pathophysiology (cerebral amyloid angiopathy [CAA] and hypertensive vasculopathy). Details for the CMB topography grouping are provided in the supplementary material.

Ischemic brain MRI markers (white matter hyperintensities, covert brain infarcts), hippocampal and total brain volume—Methods and definitions for extensive white matter hyperintensities (LWMH), presence of covert brain infarcts, hippocampal volume and total brain to cranial volume ratio measurements have been described in detail.(DeCarli et al., 2005, Jeerakathil et al., 2004)

Assessment of Incident Dementia

Methods for surveillance of incident dementia in the Framingham Heart Study have been published.(Seshadri et al., 2011, Seshadri et al., 1997) Briefly, ongoing surveillance for dementia is carried through Framingham heart study clinic evaluations, biennial questionnaires, annual telephone health history updates, report by participants, their relatives or care providers. A concern of cognitive symptoms can be raised by the participant, family member, Framingham Heart Study staff or physician, by a drop in mini-mental status exam of >3 points in sequential visits, >5 points across all visits or a score below an education specific cut point. Such concerns trigger further detailed evaluation including review of all records, comprehensive neurological assessment and neuropsychological evaluation including a comprehensive battery of cognitive testing, interview of family members and in some cases review of autopsy data when available. Details of neuropsychological test battery are provided in the supplemental material (Supplementary Table 1). Potential incident dementia cases are then adjudicated by a panel including at least 1 neurologist and 1 neuropsychologist. Dementia is defined using Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM IV) criteria.(American-Psychatric-Association., 2000) A

diagnosis of clinical AD was based on the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the AD and Related Disorders Association for definite, probable, or possible AD.(McKhann et al., 1984) The diagnosis of vascular dementia was based on the National Institute of Neurological Disorders, and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria.(Roman et al., 1993) Participants with evidence of both clinical AD and vascular dementia were classified as having both diseases. All-cause dementia included dementia cases of any type, including AD, vascular dementia or other.

The follow up interval spans from entry to present study (time of MRI) until December 31, 2013. Participants who did not develop dementia during follow-up (including those who died during follow-up) were censored at the date last known to be dementia free.

Vascular risk factors

Systolic and diastolic blood pressures were each taken as the average of the Framingham clinic physician's two measurements. Hypertension was defined by the JNC-7 classification (SBP ≥140mm Hg and/or DBP ≥90mm Hg, or use of antihypertensive medications). Current cigarette smoking was defined as self-reported use in the year prior to the examination. Total cholesterol was measured on fasting specimens in the Offspring cohort, and random samples in the Original cohort. We defined diabetes as a random blood glucose ≥200 mg/dl (≥11.1 mmol/L) for the Original cohort, fasting glucose ≥126mg/dl (≥7 mmol/L) for the Offspring cohort or use of insulin or oral hypoglycemic medications for either cohort. Prevalent cardiovascular disease (CVD) included stroke, transient ischemic attack, coronary heart disease, heart failure and peripheral arterial disease.

Medication use was assessed by self-report, including antiplatelet agents, anticoagulant therapies, and statin use.

APOE ε4 status was analyzed using any ε4 allele versus none, based on previously reported stronger association of this allele with risk dementia(Raber et al., 2004) and lobar CMB. (Maxwell et al., 2011)

Statistical Analysis

Baseline characteristics of study participants were evaluated overall and by CMB status, presented in tables 1 and Supplementary table 1. Incidence rates (per 1,000 person-years), stratified by CMB status, were calculated for each type of event (all-cause dementia, AD type, and vascular dementia) by dividing the total number of events by the total follow-up time. We used multivariable cox proportional hazards regression analyses to obtain hazards ratios (HR) and 95% confidence intervals (95% CI) for all-cause dementia and dementia subtype, and examined overall CMB presence as well as CMB topography given that CMB in different brain regions may represent a different vasculopathy. Because the brain location of CMB reflects a different underlying cerebral angiopathy, we performed separate analyses comparing each of the following CMB groups to the referent group of those with no CMB: those with any CMB; only lobar CMB; deep and/or mixed CMB, and lobar plus mixed CMB. Three multivariable models were evaluated: model 1, adjusted for age, sex, educational level and APOE e4; model 2 additionally adjusted for ischemic cerebral small

vessel disease markers on MRI (covert brain infarcts and white matter hyperintensities); model 3, adjusted for the covariates in model 1 and additionally for hypertension, diabetes and prevalent CVD. In exploratory analyses we included interaction terms to assess effect modification in the association between lobar CMB and dementia risk by each of APOE e4 allele presence and hypertension treatment use. We evaluated CMB burden by creating a three-category variable (≥2 CMBs, 1 CMB, and no CMB [referent]) and examined its association with each of the incident dementia categories. All statistical analyses were performed using SAS version 9.4 (Cary, NC).

Results

We observed CMB in 10.8% of participants (n=140), 64% were located in lobar regions only (n=90) and 36% in deep and mixed regions (n=50); 64.2% participants had single and 35.8% multiple CMB. Participants with CMB were older, more likely to be men, had greater prevalence of hypertension, diabetes and cardiovascular disease, greater mean systolic blood pressures and greater proportion of APOE ε4 allele (Table 1). Among CMB subgroups (Supplementary Table 2), those with CMB in deep only regions had greater prevalence of hypertension, diabetes and higher mean systolic blood pressures than those with strictly lobar CMB. Participants with deep and mixed location CMB had the greatest prevalence of CVD, while those with lobar only CMB had the lowest prevalence. The proportion of APOE ε4 was greater among those with lobar only CMB. Supplementary Figure 2 shows the proportion of hypertension and hypertension treatment use according to CMB location.

Over the follow up period (mean [SD] period of 6.7 [2.7] years), 85 participants developed incident dementia of any cause, 63 had AD type dementia and 21 participants developed vascular dementia. Incidence rates were higher among persons with CMB, and within CMB subgroups participants with deep and deep and mixed location CMB had the highest incidence rates (Table 2).

All cause dementia

We observed that participants with any CMB had 1.7 times the risk of all cause dementia (HR 1.74, 95% CI 1.00–3.01) compared to those without CMB. The increased risk was independent of vascular risk factors and prevalent stroke (HR 1.89, 95% CI 1.04–3.44), but was attenuated after adjusting for ischemic brain MRI measures (Table 3). In stratified analyses by CMB location, we observed that participants with deep and mixed location CMB had nearly three-fold higher risk of all cause dementia compared to those without CMB (HR 2.99, 95% CI 1.52–5.90). The association was independent of vascular risk factors (HR 3.49, 95% CI 1.72–7.10) and ischemic brain MRI measures (HR 2.44, 95% CI 1.22–4.88). Lobar CMB were not associated with higher risk of dementia, although participants with lobar and mixed location CMB had slightly higher hazard ratios of dementia in all models.

Alzheimer Dementia

Similar to findings with all cause dementia, we found higher risk of AD type dementia among participants with any CMB presence (HR 1.92, 95% CI 1.02–3.61), which was

independent of prevalent cardiovascular disease and vascular risk factors, but attenuated after adjustment for ischemic brain MRI measures (Table 3). Deep and mixed CMB were strongly associated with higher risk of AD (HR 3.29, 95% CI 1.54–7.06), independent of vascular risk factors, prevalent CVD and ischemic brain MRI measures. Lobar CMB were not associated with risk of dementia, though again we noted slightly higher hazard ratios among participants with lobar and mixed location CMB.

Vascular Dementia

Analyses of pure vascular dementia type were limited as only 4 events occurred in this subgroup thus limiting further statistical analyses.

Overall, the relations of deep only CMB and risk of dementia were similar to those observed in the group of participants with deep and mixed CMB. When we excluded participants with prevalent stroke, the associations remained strong, especially among participants with deep and mixed CMB (data not shown).

Given that prior studies have related lobar CMB to dementia risk, and strictly lobar CMB are thought to reflect CAA, we conducted additional exploratory analysis to evaluate this relation. We related CMB to prevalent dementia to assess if participants with lobar CMB had dementia earlier and therefore were excluded from analysis, but lobar CMB were not associated with prevalent dementia. We performed analyses stratified by APOE ε4 allele presence but did not observe differences in participants with or without APOE e4 alleles among those with lobar CMB. We evaluated the role of blood pressure control and antihypertensive treatment as possible effect modifiers of the relation of lobar CMB and dementia risk. Although overall there did not appear to be an association between presence of strictly lobar CMB and incident dementia, this exploratory analysis suggested that the effect may be modified by hypertension/hypertension treatment. Participants with normotension (BP<140/90) and not taking hypertensive treatment had a higher hazard ratio for all cause dementia (HR 3.27, 95% CI 0.91 – 11.79) whereas those with hypertension taking antihypertensive treatment had a lower hazard ratio (0.56, 95% CI 0.17–1.82); however this subgroup analysis was limited by the small sample. Lastly, we assessed the relation of hippocampal volume (as marker of neurodegeneration) and CMB presence overall and by brain topography (Supplementary Table 3). We found that hippocampal volumes were significantly lower in participants with deep and mixed location CMB, independent of vascular risk factors and ischemic MRI measures (β −0.015, SE 0.007, p-value 0.038). Participants with deep and mixed location CMB also had descriptively lower total brain volumes (total brain to cranial volume ratio) although the association was not statistically significant (β −0.221, SE 0.444, p-value ns).

Analyses of CMB burden (number of CMB single vs. multiple) showed higher crude incidence rates of all dementia and AD type dementia for persons with multiple CMB compared to single CMB, and higher rates in participants with single CMB compared to no CMB. However, adjusted multivariate analyses showed that there was no difference for single versus multiple CMB (supplementary Tables 4 and 5).

Discussion

Our study included asymptomatic individuals in the community, and showed that CMB may be detectable years before occurrence of incident dementia, thereby offering the potential for identification of individuals at high risk.

Our results support the notion that subclinical cerebrovascular disease contributes to dementia of all types, and concurs with the hypothesis that neurodegenerative pathology is more likely to manifest clinically in the presence of cerebrovascular disease, and at earlier stages.(Toledoet al., 2013) We observed that the higher risk of dementia was mainly among persons with deep and mixed location CMB, and that there was no association among persons with lobar CMB. These findings are consistent with prior reports in a selected sample of patients at high cardiovascular risk.(Miwaet al., 2014) Our results concur with a recent report from Rotterdam study investigators showing increased risk of incident dementia among persons with CMB, with higher risks observed among non-lobar CMB. (Akoudadet al., 2016) The lack of association of lobar CMB with dementia in our study was not explained by the distribution of APOE ε4 alleles, or occurrence of dementia earlier, but additional analysis suggested effect modification by hypertension and hypertension treatment use. However, this observation needs replication and further evaluation in larger samples. Persons with strictly lobar CMB may have lower burden of hypertensive arteriopathy (represented by deep CMB) and may require a longer period to develop dementia (requiring longer follow up for detection); conversely, cumulative exposure to vascular risk factors and the resulting hypertensive arteriopathy reflected by deep and deep and mixed CMB may promote manifestation of clinical dementia earlier. The slightly higher hazard ratio among persons with lobar and mixed CMB, and the clearly higher risk observed in those with mixed and deep, and deep only CMB suggests this may be the case. Further, data from the prospective Honolulu Heart Program/Honolulu Asia Aging Study suggests that midlife blood pressure modifies Aβ-related risk for dementia: participants with higher midlife blood pressure had lower plasma levels of Aβ and higher risk of dementia,(Shah et al., 2012)

Our results do not exclude a potential association of lobar CMB with impaired cognition in other samples, as suggested by prior studies showing impaired global cognitive and executive function among persons with lobar CMB.(Chung et al., 2016) It is also conceivable that disruption of cortico-nigrostriatal and thalamo-cortical pathways by strategically placed deep/mixed CMBs could contribute to cognitive decline.

We observed higher proportions of hypertension among participants with deep and deep and mixed CMB; however vascular risk factors alone didn’t completely explain the results given that the associations persisted after adjustment for vascular risk factors; CMB representing cumulative exposure may be better suited to identify persons at high risk than single blood pressure measurements. The risk of dementia observed in persons with deep and mixed CMB was independent of ischemic MRI measures of cerebral small vessel disease (i.e. white matter hyperintensity and covert brain infarcts), highlighting the independent role of CMB as markers of adverse neurological outcomes including dementia risk. In addition, the slightly higher risk of dementia observed among persons with deep and mixed CMB

compared to those with deep only CMB suggests that CMB burden may play a role increasing further the risk as the former group had multiple CMB and the latter single lesions. Analyses by CMB burden were limited by small number of events in subgroups. The observation of smaller hippocampal volumes, and lower total brain volumes (albeit not statistically significant), among participants with deep and mixed CMB suggests that small vessel disease is associated with neurodegeneration.

In view of the recent report of decreasing incidence of dementia among FHS participants, which was in part attributed to improved vascular risk factor control,(Satizabal et al., 2016) our results suggest that CMB may be a measure to consider for detection of individuals at residual high risk. However, clinical trials of long enough duration are required to investigate if vascular risk factor treatment, blood pressure control in particular, may reduce incident dementia in asymptomatic individuals. For instance, the SPS3 trial studying strict blood pressure control in patients with stroke due to small vessel disease did not show effects on cognition, but duration of follow up was less than 5 years.(Pearce et al., 2014) CMB may be one measure to consider in such trials, for identification of persons at highest risk and more likely to benefit from blood pressure lowering.

Our study has several strengths including its prospective cohort design, with thorough characterization of covariates that may affect the outcome, as well as inclusion of brain MRI markers of ischemic cerebrovascular disease to assess the independent role of hemorrhagic and ischemic cerebral small vessel disease. Incident dementia ascertainment was confirmed using reliable sources and accurately characterized. We included a large sample of participants individuals free of dementia, dwelling in the community. Brain MRI measurements were reliable and blinded to clinical, demographic characteristics and outcome ascertainment.

Although participants who underwent brain MRI are generally healthier than those who did not have MRI, selection of participants into the study is unrelated to the exposure or outcome, thus the effect estimates are expected to be unbiased with respect of selection of participants. While it may be argued that more sensitive MR scanner strength and methods (such as SWI or higher magnetic field strength) may increase CMB proportions, we submit that any potential resulting misclassification of exposure would be considered non-differential thus more likely to underestimate true effects. We used MR scanner strength (1.5 T) and protocol that resemble those used in current clinical practice, thus findings are more likely to represent those that would be observed routinely during evaluation of patients. Our analyses involving pre-specified subgroups of CMB among participants with vascular dementia type are limited by the smaller sample and fewer events among these subgroups. Lastly, our study includes Framingham Heart Study participants of primarily European ancestry thus preventing generalization of results to other ethnic or racial groups.

Conclusions

Our results suggest that CMB overall, and deep and mixed CMB in particular, are associated with increased risk of dementia, independent of ischemic brain MRI measures of small vessel disease. CMBs are useful subclinical markers of adverse neurological outcomes likely

reflecting the interplay of hypertensive and cerebral amyloid angiopathy. Further studies are needed to clarify if CMB could assist in identification of asymptomatic individuals at risk of dementia, development of preventive strategies and in clinical trials of long duration testing treatments (especially with blood pressure lowering) for dementia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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- Dementia is an increasing public health problem.
- Early identification of persons at risk is essential to develop preventive strategies.
- Cerebral microbleeds were associated with increased risk of incident dementia.
- Cerebral microbleeds may help identify asymptomatic persons at risk of dementia.

Table 1

Sample Characteristics

Clinical Characteristics	All N=1296	No CMB N=1156	CMB N=140
Age (years) at exam closest to MRI	72±8	71±8	76±7
Men	46%	44%	55%
Follow up period, years, mean (SD)	6.7±2.7	6.8±2.7	5.8±2.8
Education No High School degree High School degree Some college College degree	5% 30% 30% 35%	5% 29% 31% 35%	5% 39% 27% 29%
Vascular risk factors			
Systolic blood pressure, mm Hg	131±19	131±19	135±21
Diastolic Blood pressure, mm Hg	72±10	72±10	71±11
Hypertension	64%	62%	76%
Hypertension treatment	53%	52%	67%
Current smokers	6%	6%	6%
Diabetes	13%	13%	17%
Prevalent cardiovascular disease	20%	18%	35%
Total Cholesterol (mg/dL)	189±36	190±36	180±37
APOE Status			
Any ε4 allele	21%	21%	26%
MRI			
Log-White Matter Hyperintensities volume	−6.7 ± 1.2	−6.8 ± 1.1	−6.1 ± 1.3
Covert Brain infarcts	17%	15%	31%

Values are mean (SD) for continuous variables and n (%) for categorical variables.

Table 2

Crude incidence rates for all cause dementia and dementia type (All cause, Alzheimer and Vascular dementia) by CMB location.

Outcome	Measure	CMB Status					
		No CMB	Any (≥1) CMB	Only Lobar CMB	Lobar + mixed	Deep Only	Deep+Mixed CMB
AllDementia		N=1156	N=140	N=90	N=112	N=28	N=50
	N events/Person-years of follow-up	68/7880	17/807	7/530	12/649	5/158	10/278
	Incidence rate	8.6	21.1	13.2	18.5	31.6	36.0
AD	N events/Person-years of follow-up	50/7880	13/807	5/530	9/649	4/158	8/278
	Incidence rate	6.3	16.1	9.4	13.9	–	28.8
VaD	N events/Person-years of follow-up	17/7880	4/807	2/530	2/649	2/158	2/278
	Incidence rate	2.2	–	–	–	–	–

*Incidence rate per 1,000 person-years. Rates are not presented where there were fewer than 5 events.AD=Alzheimer's type dementia, VaD= vascular dementia type.

Table 3

Cox Proportional Hazard Analysis of Risk of Incident dementia (all-cause and Alzheimer type) according to CMB presence and location

	All-cause dementia			Alzheimer Dementia		
	Model 1	**Model 2**	**Model 3**	**Model 1**	**Model 2**	**Model 3**
CMB location	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
Any	1.74 [1.00−3.01] P=0.049	1.44 [0.82−2.54] P= n.s.	1.89 [1.04−3.44] P=0.038	1.92 [1.02−3.61] P=0.044	1.69 [0.88−3.25] P= n.s.	2.30 [1.16−4.55] P=0.017
Lobar only	1.01 [0.46−2.23] P= n.s.	0.85 [0.38−1.90] P= n.s.	0.89 [0.35−2.27] P= n.s.	1.07 [0.42−2.73] P= n.s.	0.95 [0.37−2.47] P= n.s.	1.10 [0.38−3.15] P= n.s.
Lobar + mixed	1.48 [0.79−2.78] P= n.s.	1.21 [0.63−2.31] P= n.s.	1.51 [0.75−3.05] P= n.s.	1.65 [0.79−3.44] P= n.s.	1.43 [0.67−3.03] P= n.s.	1.90 [0.86−4.22] P= n.s.
Deep only	2.50 [1.00−6.30] P=0.05	2.16 [0.85−5.48] P= n.s.	2.85 [1.10−7.36] P=0.03	2.68 [0.95−7.52] P= n.s.	2.55 [0.89−7.17] P= n.s.	3.27 [1.12−9.59] P=0.03
Deep + mixed	2.99 [1.52−5.90] P=0.002	2.44 [1.22−4.88] P=0.01	3.49 [1.72−7.10] P<0.001	3.29 [1.54−7.06] P=0.002	2.95 [1.36−6.42] P=0.006	4.15 [2.23−7.73] P<0.001

Reference group is no CMB. P= p-value, n.s. = non-significant, >0.05.

Model 1 adjusted for age, sex, education and APOE4.

Model 2 additionally adjusted for ischemic MRI markers: log-white matter hyperintensity volume, covert brain infarcts.

Model 3. Model 1 additionally adjusted for hypertension, diabetes, and prevalent cardiovascular disease