Prevalence and risk factors of cerebral microbleeds

The Rotterdam Scan Study

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ABSTRACT

Background: Cerebral microbleeds are focal deposits of hemosiderin that can be visualized with MRI. Little is known on their prevalence in the general population and on their etiology. It has been suggested that, in analogy to spontaneous intracranial hemorrhage, the etiology of microbleeds differs according to their location in the brain, with lobar microbleeds being caused by cerebral amyloid angiopathy and deep or infratentorial microbleeds resulting from hypertension and atherosclerosis. We investigated the prevalence of and risk factors for microbleeds in the general population aged 60 years and older.

Methods: This study is based on 1,062 persons (mean age 69.6 years) from the population-based Rotterdam Scan Study. MRI was performed at 1.5 T and included a sequence optimized to increase the conspicuity of microbleeds. We assessed the relation of *APOE* genotype, cardiovascular risk factors, and markers of small vessel disease to the presence and location of microbleeds with multiple logistic regression.

Results: Overall prevalence of cerebral microbleeds was high and increased with age from 17.8% in persons aged 60-69 years to 38.3% in those over 80 years. *APOE* ε4 carriers had significantly more often strictly lobar microbleeds than noncarriers. In contrast, cardiovascular risk factors and presence of lacunar infarcts and white matter lesions were associated with microbleeds in a deep or infratentorial location but not in a lobar location.

Conclusion: The prevalence of cerebral microbleeds is high. Our data support the hypothesis that strictly lobar microbleeds are related to cerebral amyloid angiopathy, whereas microbleeds in a deep or infratentorial location result from hypertensive or atherosclerotic microangiopathy.
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GLOSSARY

CAA = cerebral amyloid angiopathy; **FLAIR** = fluid-attenuated inversion recovery; **GRE** = gradient-recalled echo; **ICH** = intracerebral hemorrhage; **PD** = proton density.

Cerebral microbleeds are focal lesions that can be visualized on MRI.[1] Histopathological analysis shows that these are hemosiderin deposits from red blood cells that presumably have leaked out of small brain vessels.[2] In patients with symptomatic intracranial hemorrhage or ischemic stroke, the prevalence of cerebral microbleeds reportedly ranges from 20% to 70%.[3,4] In clinical series, microbleeds were associated with an increased risk of stroke recurrence and with hemorrhagic transformation after ischemic stroke.[5,6]

Little is known on microbleed prevalence, risk factors, and clinical correlates in the general population. Prevalence estimates are highly dependent on the sensitivity of the MRI sequence used,[7] and microbleeds may be more frequent in the general population than was thought previously. Furthermore, the exact etiology of microbleeds is still unclear. Because microb-

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leeds often seem to accompany spontaneous intracerebral hemorrhage (ICH),[8,9] they are thought to be the asymptomatic counterpart of ICH, of which the etiologic mechanisms are better understood. Typically, ICHs that are restricted to a lobar location result from cerebral amyloid angiopathy (CAA).[10] This in contrast to ICHs in the basal ganglia, cerebellum, or pons, which are mainly attributed to hypertension.[11] If this parallel between ICH and cerebral microbleeds is indeed true, one would expect the risk factors for microbleeds to also differ according to their location in the brain. Established risk factors for lobar ICHs are the ε2 and ε4 alleles of the *APOE* gene,[11-13] which would suggest that *APOE* allele status would also be primarily related to the presence of microbleeds in a lobar location. In contrast, cardiovascular risk factors and classic markers of ischemic small vessel disease, such as lacunar infarcts and white matter lesions, may preferentially relate to microbleeds in deep or infratentorial brain regions.

Therefore, in the population-based Rotterdam Scan Study, we investigated the prevalence of cerebral microbleeds and studied how *APOE* genotype, cardiovascular risk factors, and markers of ischemic small vessel disease related to the presence of microbleeds and their location within the brain.

METHODS

Participants. The study is based on participants from the population-based Rotterdam Study.[14] From August 2005 to May 2006, we randomly selected 1,073 members of the Rotterdam Study Plus cohort[14] (at that time all ≥60 years of age) for participation in the Rotterdam Scan Study, a prospective brain MRI study. In addition, we invited all participants who had undergone brain imaging (not including microbleed assessment) in 1995 in the context of a previous round of the Rotterdam Scan Study (n = 302).[15] The institutional review board approved the study. We excluded individuals who were demented (n = 4) or had MRI contraindications (n = 142). Of 1,229 eligible persons, 1,114 (91%) participated and gave written informed consent. Due to physical inabilities, imaging could not be performed in 16 individuals. Of 1,098 complete MRI examinations, 36 scans had to be excluded because of motion artifacts or susceptibility artifacts, leaving 1,062 scans to be analyzed.

Brain MRI. We performed a multisequence MRI protocol on a 1.5-T scanner (GE Healthcare). For microbleed detection, we used a custom-made accelerated three-dimensional T2*-weighted gradient-recalled echo (three-dimensional T2* GRE) sequence with high spatial resolution and long echo time,[7] which was previously shown to detect microbleeds nearly twice as often as conventional 2D T2* GRE imaging.[7] The other sequences in the imaging protocol consisted of three high-resolution axial scans, i.e., a T1-weighted sequence, a proton density (PD) weighted sequence, and a fluid-attenuated inversion recovery (FLAIR) sequence.[16] Slice position of the T1-weighted and three-dimensional T2* GRE scans was matched.

Rating of cerebral microbleeds. All three-dimensional T2* GRE scans were reviewed by one of two trained raters (M.W.V., M.A.I.; both 2.5 years of experience in microbleed rating) who recorded the presence, number, and location of cerebral microbleeds. Both raters were blinded to the other MRI sequences and to clinical data, and the three-dimensional T2* GRE scan did not reveal the presence of infarcts and white matter lesions. Microbleeds were defined as focal areas of very low signal intensity, smaller than 10 mm in size.[17,18] They were categorized into one of three locations: lobar (cortical gray and subcortical or periventricular white matter), deep (deep gray matter: basal ganglia and thalamus, and the white matter of the corpus callosum, internal, external, and extreme capsule), and infratentorial (brainstem and cerebellum).[17,18] Signal voids caused by sulcal vessels, symmetric calcifications in the basal ganglia, choroid plexus, and pineal calcifications, and signal averaging from bone were excluded. All scans that were rated positive in the initial rating, mixed with a random selection of scans that had been rated negative, were reviewed by an experienced neuroradiologist (A.v.d.L.). The neuroradiologist did not confirm 2% of the initial positive ratings, and no additional microbleeds were detected on the scans that had been rated negative. The neuroradiologist additionally used the T1-weighted scan to confirm the location of the microbleed and to differentiate from ventricular calcification or from sulcal vessels. Intraobserver (n = 500, one rater) and interobserver (n = 300) reliabilities were $\kappa = 0.87$ and $\kappa = 0.85$, which corresponds to very good agreement.

Ischemic small vessel disease on MRI. Infarcts were rated on FLAIR, PD-weighted, and T1-weighted sequences by the two raters who had scored cerebral microbleeds, after an interval of at least two weeks. Both raters were blinded to all clinical data and to the presence of cerebral microbleeds. Lacunar infarcts were defined as focal lesions ≥3 mm and <15 mm in size with the same signal characteristics as CSF on all sequences, and (when located supratentorially) with a hyperintense rim on the FLAIR sequence.[19] Lesions ≥15 mm in size, but otherwise similar, were rated as subcortical infarcts. Infarcts showing involvement of cortical gray matter were classified as cortical infarcts. All infarcts were reviewed in a consensus meeting with an experienced neuroradiologist (A.v.d.L.).

White matter lesion volume was quantified with a validated tissue classification technique.[20] Manual editing of classification results was necessary in 86 scans (8%), mainly because of motion artifacts. In two persons, excessive motion necessitated exclusion from analysis. One other person was excluded because of a large meningioma, which complicated white matter lesion classification. White matter lesion volumes (milliliters) were calculated by summing all voxels of the white matter lesion-class across the whole brain.

Apolipoprotein E genotyping. *APOE* genotyping was performed on coded genomic DNA samples[21] and was available in 1,000 participants. The distributions of *APOE* genotype and allele frequencies in this population were in Hardy-Weinberg equilibrium.

Cardiovascular risk factors. Cardiovascular risk factors were examined by interview and laboratory and physical examination at the preceding regular visit of study participants to the research center. Sitting blood pressure was measured twice on the right arm with a random-zero sphygmomanometer. We used the average of these two measurements. We calculated pulse pressure by subtracting diastolic blood pressure from systolic blood pressure. We defined two categories of severity of hypertension according to WHO criteria.[22] First, persons who had a systolic blood pressure ≥140 mm Hg and <160 mm Hg or a diastolic blood pressure ≥90 mm Hg and <100 mm Hg, or used blood pressure–lowering medication, were classified as mild hypertensive (grade 1 of 2003 WHO criteria[22]). Second, individuals with a systolic blood pressure ≥160 mm Hg or a diastolic blood pressure ≥100 mm Hg regardless of the use of blood pressure–lowering medication were classified as severe hypertensive (grades 2 and 3 of 2003 WHO criteria[22]). Smoking habits were classified as "ever" or "never" smoking. Alcohol use was categorized as "never," "former," or "current" use (intake of alcohol within the past 12 months). Current alcohol use was further categorized into "light" (less than one drink per day), "moderate" (one or more than one drink per day but less than four drinks per day), and "heavy" (four or more drinks per day). Diabetes was considered present when a person used oral antidiabetic drugs or insulin, or when fasting blood glucose was ≥7.0 mmol/L. Serum total cholesterol and high-density lipoprotein (HDL-cholesterol) were determined using an automated enzymatic procedure (Hitachi analyzer, Roche Diagnostics). The use of lipid-lowering drugs and blood pressure–lowering medication was assessed by interview and house visits during which medication use was registered.

Data analysis. We calculated the prevalence of cerebral microbleeds for three age categories (60–69, 70–79, and 80–97 years). To test our hypothesis that lobar microbleeds have a different etiology, and hence different risk factors, than deep or infratentorial microbleeds, we categorized persons based on microbleed location. According to the Boston criteria[23] for CAA, persons aged ≥55 years with primary ICH restricted to lobar regions can be diagnosed as having "possible" (one hemorrhage) or "probable" (more than one hemorrhage) CAA-related hemorrhage. Accordingly, we made a separate category ("strictly lobar microbleeds") of persons who had one or more microbleeds restricted to a lobar location. Persons with microbleeds in a deep or infratentorial location, with or without one or more lobar microbleeds, were assigned to the category "deep or infratentorial microbleeds." We additionally analyzed this group excluding persons with lobar microbleeds to investigate whether results were different for persons with "strictly" deep or infratentorial microbleeds.

We analyzed the relation of *APOE* allele status and cardiovascular risk factors to the presence and location of microbleeds using multiple logistic regressions, adjusted for age and, when appropriate, sex. We additionally adjusted analyses of *APOE* genotype and microbleeds for serum levels of cholesterol. Also, we dichotomized serum total cholesterol at the 10th percentile (4.42 mmol/L) and analyzed the association of very low cholesterol level with presence of microbleeds at different locations.

We used multiple logistic regression models, adjusting for age and sex and additionally for cardiovascular risk factors (blood pressure, smoking, alcohol use, diabetes, total serum cholesterol and HDL-cholesterol), to analyze whether cerebral microbleeds were more frequent in persons with brain infarcts or white matter lesions. Because the distribution of white matter lesion volume was skewed leftward, we used the natural log-transformed variable. Finally, we repeated all analyses after exclusion of persons with cortical infarcts on MRI. All analyses were performed using the statistical software package SPSS (version 11.0.1).

RESULTS Table 1 shows the characteristics of the study population. Mean age was 69.6 years, and 543 (51%) were women. The prevalence of microbleeds was high and increased strongly with age, as did the proportion of participants with multiple microbleeds (table 2). Of those with microbleeds (n = 250), 146 (58.4%) had microbleeds in a strictly lobar location. Of these, 44 had multiple strictly lobar microbleeds. There were 104 (41.6%) persons who had microbleeds located in

Table 1 Characteristics of the study population (N = 1,062)

Age, y, mean ± SD	69.6 ± 7.2
Women, n (%)	543 (51.1)
Systolic blood pressure, mean ± SD	144.4 ± 18.7
Diastolic blood pressure, mean ± SD	80.2 ± 10.3
Mild hypertension, n (%)	541 (51.5)
Severe hypertension, n (%)	214 (20.4)
Smoking (ever), n (%)	755 (72.2)
Alcohol use, n (%)	
Former	65 (6.2)
Current light (<1 drink per day)	417 (39.9)
Current moderate (≥1 drink per day, <4 drinks per day)	446 (42.6)
Current heavy (≥4 drinks per day)	60 (5.7)
Diabetes, n (%)	95 (9.2)
Serum total cholesterol, mean ± SD	5.67 ± 0.96
Serum HDL cholesterol, mean ± SD	1.44 ± 0.38
APOE ε2 allele carrier, n (%)	155 (15.5)
APOE ε4 allele carrier, n (%)	273 (27.3)
Cortical infarct on MRI, n (%)	37 (3.5)
Lacunar infarct on MRI, n (%)	93 (8.8)
Subcortical infarct on MRI, n (%)	2 (0.2)
White matter lesions on MRI, mL, median (interquartile range)	3.4 (2.0–7.3)

Data are missing for blood pressure/hypertension (n = 11), smoking (n = 17), alcohol use (n = 16), diabetes (n = 24), serum cholesterol (n = 17), *APOE* genotype (n = 62), and white matter lesion (n = 3).
HDL = high-density lipoprotein.

Table 2 Age-specific prevalence of cerebral microbleeds

Age range	No. of persons	Cerebral microbleeds, % (n)	Multiple cerebral microbleeds, % (n)
60–69 y	670	17.8 (119)	5.4 (36)
70–79 y	272	31.3 (85)	16.5 (45)
80–97 y	120	38.3 (46)	23.3 (28)

a deep or infratentorial brain region. Of these, 58 persons also had one or more lobar microbleeds.

The prevalence of microbleeds increased with age for all locations and did not differ between men and women (table 3). Carriers of the *APOE* ε4 allele had cerebral microbleeds significantly more often in a strictly lobar location when compared with persons with the ε3/ε3 genotype [age-adjusted OR = 1.87, 95% CI (1.25–2.81) (table 3)]. This was even more pronounced for persons with multiple strictly lobar microbleeds: OR = 2.68, 95% CI (1.37–5.27). We did not find an association between *APOE* ε2 allele carriership and presence of microbleeds in either location. However, although based on very few cases, we did find an association for the ε2/ε2 genotype with strictly lobar microbleeds [OR = 10.70, 95% CI (2.29–50.11)]. When we analyzed persons with deep or infratentorial microbleeds excluding those with additional lobar microbleeds, results did not markedly change, yet the association with *APOE* ε4 allele carriership attenuated further [OR = 0.61, 95% CI (0.26–1.42)]. Additional adjustment for serum cholesterol did not change any of these associations. High systolic blood pressure, high pulse pressure, and smoking were associated with presence of microbleeds in a deep or infratentorial brain location (table 4). Associations of blood pressure with deep or infratentorial microbleeds were stronger after exclusion of persons who also had lobar microbleeds [age- and sex-adjusted OR for systolic blood pressure (per SD increase) = 1.65, 95% CI (1.24–2.19) and for pulse pressure OR = 1.77, 95% CI (1.29–2.43)]. With increasing serum total cholesterol, the prevalence of microbleeds decreased (table 4). When we subsequently analyzed serum cholesterol as a variable dichotomized at the 10th percentile (<4.42 mmol/L vs higher values), we found a strong association of very low serum cholesterol level with the presence of strictly lobar microbleeds (table 4).

Cortical infarcts on MRI were not related to the presence of cerebral microbleeds; however, both lacunar infarcts and white matter lesion volume where strongly associated with microbleeds in a deep or infratentorial location but not with those in a lobar location (table 5). Additional adjustment for cardiovascular risk factors did not change these results.

Finally, exclusion of persons with cortical infarcts on MRI (n = 37) did not change any of the above-described results.

Table 3 *APOE* allele status and the presence of cerebral microbleeds

	Odds ratio (95% CI)		
	Any microbleed (n = 250)	Strictly lobar microbleeds (n = 146)	Deep or infratentorial microbleeds‡ (n = 104)
Age, per year*	1.06 (1.04–1.08)	1.05 (1.03–1.08)	1.07 (1.04–1.10)
Women, vs men†	1.01 (0.76–1.35)	1.14 (0.80–1.63)	0.83 (0.55–1.26)
APOE ε4, vs ε3/ε3†	1.53 (1.09–2.14)	1.87 (1.25–2.81)	1.17 (0.70–1.93)
APOE ε2, vs ε3/ε3†	1.31 (0.86–1.99)	1.40 (0.83–2.35)	1.19 (0.65–2.16)

*Adjusted for sex.
†Adjusted for age.
‡With or without lobar microbleeds.

DISCUSSION We found in a general population of persons aged 60 years and older a high prevalence of cerebral microbleeds, which increased with age. Determinants of the presence of cerebral microbleeds differed according to microbleed location in the brain, suggesting different etiologies for microbleeds in different locations.

Major strengths of our study are its population-based design and large sample size of elderly persons. We used an MRI sequence that was optimized for the detection of cerebral microbleeds.[7] Despite our very high response rate among eligible Rotterdam Study participants, there is a possibility of selection bias. Persons who refuse to participate or those with MRI contra-indications are generally older than participants.[24] However, this will likely have led us to underestimate the actual prevalence of cerebral microbleeds. We should consider potential misclassification of cerebral microbleeds. Deoxygenated blood in small veins and cerebral calcifications may resemble microbleeds on MRI. However, on our high-resolution MR images, vessels can be identified clearly as linear structures and will never present as a single dot. Moreover, cerebral calcifications have a typical location and shape, and when located in the basal ganglia are usually symmetric in distribution. We therefore believe that we did not misclassify other structures as cerebral microbleeds and thus did not overestimate the prevalence of microbleeds.

We found a three- to fourfold higher overall prevalence of cerebral microbleeds as compared

Table 4 Cardiovascular determinants and the presence of cerebral microbleeds

	Odds ratio (95% CI)		
	All microbleeds (n = 250)	Strictly lobar microbleeds (n = 146)	Deep or infratentorial microbleeds‡ (n = 104)
Systolic BP,* per SD increase	1.16 (1.00–1.35)	1.08 (0.91–1.29)	1.29 (1.05–1.58)
Diastolic BP,* per SD increase	1.15 (0.99–1.35)	1.19 (0.98–1.44)	1.12 (0.90–1.40)
Pulse pressure,* per SD increase	1.10 (0.95–1.29)	0.99 (0.82–1.20)	1.28 (1.03–1.59)
Hypertension			
Mild, vs none	1.07 (0.75–1.52)	0.97 (0.63–1.49)	1.24 (0.73–2.10)
Severe, vs none	1.33 (0.87–2.02)	1.15 (0.69–1.92)	1.66 (0.91–3.05)
Smoking, ever vs never	1.45 (1.02–2.07)	1.29 (0.84–1.98)	1.70 (0.98–2.93)
Alcohol use			
Former, vs never	0.94 (0.43–2.07)	1.06 (0.41–2.76)	0.75 (0.25–2.26)
Current light, vs never	0.61 (0.33–1.14)	0.75 (0.35–1.61)	0.43 (0.18–1.03)
Current moderate, vs never	0.81 (0.44–1.51)	0.83 (0.39–1.77)	0.73 (0.31–1.69)
Current heavy, vs never	0.66 (0.27–1.58)	0.51 (0.16–1.68)	0.76 (0.24–2.39)
Diabetes, yes vs no	0.88 (0.53–1.48)	0.87 (0.46–1.65)	0.91 (0.44–1.90)
Serum total cholesterol,† per SD increase	0.85 (0.72–1.00)	0.87 (0.71–1.07)	0.83 (0.65–1.05)
Serum HDL cholesterol,† per SD increase	0.91 (0.78–1.07)	0.85 (0.70–1.04)	1.01 (0.80–1.27)
Serum total cholesterol,† <4.42 mmol/L vs higher	2.01 (1.24–3.26)	2.28 (1.28–4.06)	1.67 (0.85–3.31)

All values are age- and sex-adjusted.
*Additionally adjusted for the use of blood pressure–lowering medication.
†Additionally adjusted for the use of lipid-lowering drugs.
‡With or without lobar microbleeds.
BP = blood pressure; HDL = high-density lipoprotein.

with other population-based studies.[17,18,25] A factor that potentially contributes to this difference in prevalence is the higher mean age of our participants compared with previous studies.[17,18,25] Furthermore, the magnetic field strength that we used (1.5 T) was higher than in the Framingham Study.[18] However, the most important explanation for this difference is that we used a custom-made accelerated three-dimensional T2* GRE sequence that has shown a higher sensitivity in detecting cerebral microbleeds when compared with conventional 2D T2*GRE sequences,[7] because of its higher spatial resolution and longer echo time.[17,18]

We found the *APOE* ε4 allele to be strongly associated with the presence of (multiple) strictly lobar microbleeds. As in Alzheimer disease, the *APOE* ε4 allele is a known risk factor for lobar ICH and CAA.[11,12,26] The *APOE* ε4 allele was previously found to be more frequent in patients with CAA when compared with controls[12] and was furthermore associated with an increased risk of recurrent hemorrhage in CAA patients.[26] Although the exact molecular mechanism is not clear, *APOE* ε4 carriership is presumed to lead to hemorrhage by increased vascular deposition of β-amyloid.[26,27] Our data also seem to indicate an association of the ε2/ε2 genotype and lobar microbleeds. This is again in line with data from CAA patients[13,26,28] and with a single other study that took into account microbleed location in

Table 5 Cerebral vascular disease and the presence of cerebral microbleeds

	Odds ratio (95% CI)		
	All microbleeds (n = 250)	Strictly lobar microbleeds (n = 146)	Deep or infratentorial microbleeds† (n = 104)
Cortical infarcts, vs no infarct	1.03 (0.48-2.21)	1.36 (0.59-3.12)	0.56 (0.13-2.42)
Lacunar infarcts, vs no infarct	2.58 (1.60-4.17)	1.25 (0.61-2.55)	4.75 (2.71-8.34)
White matter lesion volume,* per SD	1.32 (1.13-1.53)	1.12 (0.93-1.35)	1.67 (1.34-2.08)

All values are age- and sex-adjusted.
*ln-transformed.
†With or without lobar microbleeds.

non-CAA patients.[29] It is thought that *APOE* ε2 accelerates the development of vasculopathic changes leading to hemorrhage of amyloid-laden vessels in CAA.[13,28] The associations we found between *APOE* genotype and presence of strictly lobar microbleeds, especially for persons with multiple lobar microbleeds, are thus in line with clinical studies in CAA patients and further support that strictly lobar microbleeds in the general population may be an indicator of CAA.

APOE genotype was not related to deep or infratentorial microbleeds. Rather, microbleeds in these locations were associated with cardiovascular factors such as high systolic blood pressure, pulse pressure, and smoking. The lack of a clear association with hypertension is in contrast to some studies that analyzed the overall prevalence of microbleeds regardless of their location[17,30] but is in line with others.[18,31] Yet, deep and infratentorial microbleeds were furthermore strongly related to lacunar infarcts and white matter lesions, both classic markers of ischemic cerebral small vessel disease. These findings suggest that microbleeds in deep or infratentorial locations are etiologically different from those that are strictly lobar in location, and that they are rather attributable to hypertensive or atherosclerotic microangiopathy.

In our study, serum total cholesterol levels were inversely related to the presence of cerebral microbleeds. There has been a single other study that found similar results.[32] Our results also fit previous reports of a higher risk of spontaneous hemorrhagic stroke in persons with low cholesterol levels or who use high-dose statins.[33-35] Although it seems possible that serum cholesterol might play a role in vessel wall integrity, the underlying mechanism of this association is still unknown.

The high prevalence of cerebral microbleeds in our study as well as the finding that risk factors vary according to microbleed location has major importance in view of previous reports from small clinical series suggesting that microbleeds may reflect an increased risk of recurrence of stroke and hemorrhagic transformation of ischemic stroke.[5,6] Although the relationship between microbleeds and therapy-induced bleeding complications has not been uniformly confirmed in all clinical series,[36,37] it is important to further investigate whether the choice for thrombolytic treatment in persons with ischemic vascular disease or the installment of antiplatelet therapy as primary prevention in asymptomatic persons should depend on the coexistence of cerebral microbleeds in certain locations.[38] In addition, a potential relation of microbleeds with impaired cognition[39] or with severity of small vessel disease[40] suggests a clinical relevance of these lesions.

As such, our study offers new insights into risk factors for microbleeds and warrants further investigation into the prognosis of microbleeds in the general population, focusing on strictly lobar and deep or infratentorial microbleeds separately.

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