Original Investigation

Association of Cerebral Microbleeds With Cognitive Decline and Dementia

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IMPORTANCE Cerebral microbleeds are hypothesized downstream markers of brain damage caused by vascular and amyloid pathologic mechanisms. To date, whether their presence is associated with cognitive deterioration in the general population remains unclear.

OBJECTIVE To determine whether microbleeds, and more specifically microbleed count and location, are associated with an increased risk for cognitive impairment and dementia in the general population.

DESIGN, SETTING, AND PARTICIPANTS The Rotterdam Study, a prospective population-based study set in the general community, assessed the presence, number, and location of microbleeds at baseline (August 2005 to December 2011) on magnetic resonance imaging studies of the brain in 4841 participants 45 years or older. Participants underwent neuropsychological testing at 2 points a mean (SD) of 5.9 (0.6) years apart and were followed up for incident dementia throughout the study period until January 1, 2013. The association of microbleeds with cognitive decline and dementia was studied using multiple linear regression, linear mixed-effects modeling, and Cox proportional hazards.

EXPOSURES Cerebral microbleed presence, location, and number.

MAIN OUTCOMES AND MEASURES Cognitive decline measured by a decrease in neuropsychological test battery scores (Mini-Mental State Examination, Letter Digit Substitution Task, Word Fluency Test, Stroop test, 15-word Verbal Learning Test, and Purdue Pegboard Test) and compound scores (eg, G factor, executive function, information processing speed, memory, motor speed) and dementia.

RESULTS In total, 3257 participants (1758 women [54.7%]; mean [SD] age, 59.6 [7.8] years) underwent baseline and follow-up cognitive testing. Microbleed prevalence was 15.3% (median [interquartile range] count, 1 [1-88]). The presence of more than 4 microbleeds was associated with cognitive decline. Lobar (with or without cerebellar) microbleeds were associated with a decline in executive functions (mean difference in *z* score, −0.31; 95% CI, −0.51 to −0.11; $P = .003$), information processing (mean difference in *z* score, −0.44; 95% CI, −0.65 to −0.22; $P < .001$), and memory function (mean difference in *z* score, −0.34; 95% CI, −0.64 to −0.03; $P = .03$), whereas microbleeds in other brain regions were associated with a decline in information processing and motor speed (mean difference in *z* score, −0.61; 95% CI, −1.05 to −0.17; $P = .007$). After a mean (SD) follow-up of 4.8 (1.4) years, 72 participants developed dementia, of whom 53 had Alzheimer dementia. The presence of microbleeds was associated with an increased risk for dementia after adjustment for age, sex, and educational level (hazard ratio, 2.02; 95% CI, 1.25-3.24), including Alzheimer dementia (hazard ratio, 2.10; 95% CI, 1.21-3.64).

CONCLUSIONS AND RELEVANCE In the general population, a high microbleed count was associated with an increased risk for cognitive deterioration and dementia. Microbleeds thus mark the presence of diffuse vascular and neurodegenerative brain damage.

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Editorial

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With increasing life expectancy, societies are facing a major public health challenge as the number of people living with cognitive impairments and dementia are growing steadily. The need to identify early etiologic markers of cognitive impairment and dementia is growing, because timely implementation of preventive strategies is key to a positive influence on the disease course. Accumulating evidence suggests that vascular pathologic mechanisms have a central role in cognitive deterioration.[1] Studies that have investigated pathologic changes of cerebral small vessels[2-4] emphasized a potential role for these vessels in the pathogenesis of cognitive impairment and dementia. Arteriosclerosis and amyloid angiopathy are the leading causes of cerebral small-vessel disease. The effects of small-vessel disease on brain parenchyma can be visualized by neuroimaging. These lesions can be ischemic (lacunes, white matter lesions) or hemorrhagic (cerebral microbleeds). Although the underlying pathogenic cascade of lacunes and white matter lesions mainly revolves around vascular risk factors (ie, chronic hypertension, smoking, diabetes mellitus),[5] the pathogenesis of microbleeds involves vessel wall damage caused by vascular risk factors and accumulation of β-amyloid.[6] As such, microbleeds may help to explain the overlap between cerebrovascular and neurodegenerative pathologic mechanisms in cognitive dysfunction and dementia.

Although microbleeds do not appear to affect the rate of cognitive decline in patients with Alzheimer disease,[7] whether microbleeds play a role in cognitive deterioration in individuals without cognitive impairment remains unclear. This uncertainty is mainly owing to the lack of longitudinal data and the heterogeneity of cognitive tests used in previous studies. Thus far, a single longitudinal study[8] and a few cross-sectional studies in the general population[9-12] showed that a high microbleed count was associated with lower scores on the Mini-Mental State Examination (MMSE) and on tests sensitive to executive function, processing speed, and motor function. Studies in patients with cerebrovascular disease report inconsistent results, with some reporting only associations between microbleeds and global cognition, and others reporting associations between microbleeds and specific cognitive domains.[13-16] To date, whether community-dwelling elderly individuals with microbleeds are at increased risk for dementia, and more particularly Alzheimer disease, remains unclear. An association of microbleeds with Alzheimer dementia would highlight the role of vascular pathologic mechanisms in the etiology of the disease and build a bridge between the vascular and amyloid hypotheses. In the prospective population-based Rotterdam Study, we assessed whether the presence, number, and location of microbleeds mark a decline in cognitive functioning and are associated with an increased risk for dementia.

Key Points

Question Are microbleeds, and more specifically microbleed count and location, associated with an increased risk for cognitive impairment and dementia in the general population?

Findings In a population-based study, a high microbleed count was associated with an increased risk for cognitive deterioration and dementia.

Meaning Microbleeds may mark the presence of diffuse vascular and neurodegenerative brain damage.

Methods

Study Population

This investigation was conducted as part of the prospective population-based Rotterdam Study.[17] After its start in 1990, a total of 7983 people were included in the initial study wave. In 1999, the cohort was expanded with 3011 participants and in 2006 again with 3932 participants. All 14 926 participants who were enrolled were invited to undergo home interviews and various physical and laboratory examinations at the research center every 4 years. Of these, 5074 participants (88.5% of 5733 invitees) without dementia or contraindications to magnetic resonance imaging (MRI) underwent MRI of the brain from August 2005 to December 2011 (considered baseline for this study) for the assessment of microbleeds.[18] We excluded participants if the scans were incomplete or of inadequate quality (n = 129). In addition, we excluded 56 participants with insufficient screening for dementia, and 48 participants for whom follow-up for incident dementia ended before the date of the MRI owing to the absence of automatic linkage between the general practitioner's office and our study database. In total, 4841 participants were included in the dementia analysis. Of these, 3257 participants (without prevalent or incident dementia) underwent baseline and follow-up cognitive testing from April 17, 2002, to June 18, 2014, and were included in the analysis of cognitive decline. Baseline cognition was assessed during the research visit closest to the MRI date (2002-2008) and reassessed at a subsequent visit (2009-2014). Follow-up cognitive tests were unavailable for participants who underwent baseline MRI of the brain from 2009 to 2011.

The Rotterdam Study was approved by the medical ethics committee of the Erasmus MC and by the Ministry of Health, Welfare, and Sport of the Netherlands, implementing the Wet Bevolkingsonderzoek: ERGO (Population Studies Act: Rotterdam Study). All participants provided written informed consent to participate in the study and to obtain information from their treating physicians.

Brain MRI and Markers of Small-Vessel Disease

Participants underwent scanning on a 1.5-T MRI device (GE Healthcare) using a multisequence protocol consisting of T1-weighted, proton density-weighted, fluid-attenuated inversion recovery, and T2-weighted sequences.[18] Trained research physicians (S.A., F.J.W., M.A.I., and M.W.V.), blinded to clinical data, reviewed the MRI scans. Cerebral microbleeds were defined as small, round to ovoid areas of focal signal loss on T2-weighted images. Intraobserver agreement (κ = 0.87) and interobserver agreement (κ = 0.85) were good.[6] Microbleeds were classified manually as lobar microbleeds with or without cerebellar microbleeds (suggestive of cerebral amyloid angiopathy) and deep or infratentorial microbleeds with or without lobar microbleeds (suggestive of hypertensive arteriopathy). In

addition, we classified every microbleed according to its topographic distribution in the brain (frontal, temporal, parietal, and occipital lobe, infratentorial, and deep). The topographic categorization of microbleeds was performed semiautomatically, as described previously.[19] In short, after microbleeds were manually labeled, automated lobe segmentation was performed by nonrigid registration of 6 manually annotated lobe atlases to the participant under investigation using Elastix software.[20] Lobe segmentations were combined with the manually labeled microbleeds to determine the lobar distribution of microbleeds. Infarcts were defined as focal lesions with the same signal intensity as cerebrospinal fluid on all sequences. Infarcts of at least 3 and less than 15 mm were classified as lacunes; infarcts of at least 15 mm, as subcortical infarcts; and infarcts involving cortical gray matter, as cortical infarcts. Brain tissue was segmented into gray matter, white matter, and cerebrospinal fluid using automated postprocessing tools that included conventional k-nearest-neighbor brain tissue classifier extended with white matter lesion segmentation.[21] Intracranial volume was defined as the sum of cerebrospinal fluid, gray matter, white matter, and white matter lesions.

Assessment of Cognitive Functioning

The neuropsychological test battery included the MMSE,[22] Letter Digit Substitution Task (LDST), Word Fluency Test (WFT), Stroop test (consisting of reading, color-naming, and interference subtasks), 15-word Verbal Learning Test (15-WLT), and Purdue Pegboard Test.[23] We computed compound scores for global cognition (mean *z* score of the Stroop interference subtask, LDST, WFT, delayed recall of the 15-WLT, and Purdue Pegboard Test), executive functioning (mean *z* score of the Stroop interference subtask, LDST, and WFT), information-processing speed (mean *z* score of the Stroop reading and color-naming subtasks and LDST), memory (mean *z* score of immediate and delayed recall of the 15-WLT), and motor speed (mean *z* score of the Purdue Pegboard Test).

Assessment of Dementia

We used a 3-step protocol to screen for prevalent and incident dementia. All participants underwent the MMSE (score range, 0-30, with higher scores indicating better cognitive function) and the Geriatric Mental Schedule organic level (score range, 0-3, with higher scores indicating worse cognitive function).[24] Those participants with positive findings on either test (an MMSE score <26 or GMS organic level >0) also underwent an examination and informant interview with the Cambridge Examination for Mental Disorders in the Elderly.[25] Those participants who allegedly had dementia underwent further neuropsychological testing if necessary. In addition, all participants underwent continuous monitoring for dementia by linking the study database to digitized medical records from general health care professionals and the Regional Institute for Outpatient Mental Health Care. If available, clinical neuroimages were used in the diagnostic process. The final diagnosis was made in accordance with international criteria and determined by a consensus panel led by a neurologist (P.J.K.).[26,27] Follow-up for incident dementia started on August 16, 2005, and was completed on January 1, 2013, for 23 177 potential person-years (98.5%).

Assessment of Covariates

Covariates were assessed during the same visit in which baseline cognition was tested. Blood pressure was measured in 2 readings using a random-zero sphygmomanometer in a sitting position, and the mean of both measurements was calculated. Hypertension was defined as a systolic blood pressure of at least 140 mm Hg or a diastolic blood pressure of at least 90 mm Hg or the use of antihypertensives. Serum total and high-density lipoprotein cholesterol levels were measured using an automated enzymatic procedure. Smoking behavior was classified as ever vs never smoked. People were considered to have diabetes when their fasting blood glucose levels were at least 126 mg/dL (to convert to millimoles per liter, multiply by 0.0555) or when they used medication to lower glucose levels. Medication use (antihypertensives or any medication to lower glucose or lipid levels) and educational level were assessed during home visits by standardized interviews. Genotyping of apolipoprotein E (*APOE*) was performed on coded genomic DNA samples.[28] Distribution of *APOE* genotype and allele frequencies in this population were in the Hardy-Weinberg equilibrium.

Statistical Analysis

We investigated the association of microbleed presence, location, and number (a priori–defined categories of 1, 2-4, or >4 microbleeds) with cognitive decline and dementia, using people without microbleeds as a reference group. We first used multiple linear regression to investigate the association of microbleeds with cognitive decline. We examined microbleeds in association with individual neuropsychological test results and afterwards with specific cognitive domains. We calculated *z* scores from baseline and follow-up cognitive test results for each participant. A decline in cognitive scores was studied using cognitive scores at follow-up as the dependent variable and adjusting for baseline test scores in the linear regression models.

Second, we used linear mixed models with added random effects to determine the relationship between microbleed count per topographic distribution in the brain and cognitive decline in specific domains. Third, we determined Cox proportional hazards to study the association between microbleeds and dementia, including Alzheimer dementia. These analyses were also censored for stroke.

All analyses were adjusted for age, sex, and educational level. In addition, regression models were adjusted for *APOE* ε4, a propensity score of cardiovascular risk (hypertension, total and high-density lipoprotein cholesterol levels, smoking status, diabetes mellitus, use of medications to lower lipid levels, and use of antithrombotics), intracranial volume, and other imaging markers of cerebral small-vessel disease (lacunes and white matter lesions). Lacunes were modeled dichotomously. White matter lesion load was naturally transformed because of its skewed distribution and modeled continuously.

Missing covariate data (≤7.0%; educational level, hypertension, total cholesterol level, high-density lipoprotein cholesterol level, smoking, diabetes, and medication to lower lipid levels) were imputed based on age, sex, and cardiovascular risk factors using regression models. Afterwards, logistic regression was used to compute propensity scores for cardiovascular risk. For

Table 1. Characteristics of the Study Population

Characteristic	Cognitive Decline Analysis (n = 3257)		Incident Dementia Analysis (n = 4841)	
	Microbleeds Absent (n = 2780)	Microbleeds Present (n = 477)	Microbleeds Absent (n = 3911)	Microbleeds Present (n = 930)
Age, mean (SD), y	59.0 (7.6)	62.8 (8.5)[a]	62.4 (10.4)	69.8 (71.7)[a]
No. (%) female	1530 (55.0)	252 (52.8)	2171 (55.5)	492 (52.9)
Educational level, No. (%)[b]				
Primary	207 (7.4)	37 (7.8)	339 (8.7)	97 (10.4)[a]
Lower or intermediate general	995 (35.8)	193 (40.9)	1431 (36.6)	361 (38.8)[a]
Intermediate vocational	828 (29.8)	132 (28.0)	1180 (30.2)	280 (30.1)
Higher vocational	728 (26.2)	110 (23.1)	930 (23.8)	185 (19.9)[a]
Hypertension, No. (%)[c]	1446 (52.0)	297 (62.3)[a]	2304 (58.9)	678 (72.9)[a]
Cholesterol level, mean (SD), mg/dL				
Total[d]	216.2 (38.6)	216.2 (42.5)	216.2 (38.6)	208.5 (42.5)[a]
HDL[e]	54.0 (15.4)	54.0 (15.4)	54.0 (15.4)	54.0 (15.4)
Smokers, No. (%)[f]	1900 (68.3)	351 (73.6)[a]	2706 (69.2)	678 (72.9)[a]
Diabetes, No. (%)[g]	210 (7.6)	37 (7.8)	330 (8.4)	98 (10.5)[a]
APOE ε4 carriers, No. (%)[h]	735 (28.2)	141 (31.4)	884 (28.6)	233 (32.0)[a]
Medication use, No. (%)				
Lipid-level lowering[i]	585 (21.0)	108 (22.6)	900 (23.0)	287 (30.9)[a]
Antithrombotic	511 (18.4)	152 (31.9)[a]	945 (24.2)	425 (45.7)[a]
Lacunes, No. (%)	103 (3.7)	46 (9.6)[a]	213 (5.4)	143 (15.4)[a]
Intracranial volume, mean (SD), mL	1126.4 (120.4)	1126.8 (116.8)	1123.6 (121.8)	1127.6 (119.2)
White matter lesion volume, median (IQR), mL[j]	2.2 (1.4-3.8)	3.1 (1.8-5.9)[a]	2.6 (1.5-4.9)	5.0 (2.4-11.9)[a]

Abbreviations: *APOE*, apolipoprotein E; HDL, high-density lipoprotein; IQR, interquartile range.

SI conversion factor: To convert cholesterol levels to millimoles per liter, multiply by 0.0259.

[a] Variables differ significantly (*P* value <.05) for people with and without microbleeds.

[b] Owing to missing data (n = 27), percentages may not total 100.

[c] Data were missing for 22 participants.

[d] Data were missing for 29 participants.

[e] Data were missing for 31 participants.

[f] Data were missing for 13 participants.

[g] Data were missing for 51 participants.

[h] Data were missing for 202 participants.

[i] Data were missing for 27 participants.

[j] Calculated in 3130 participants with reliable white matter lesion volume segmentations.

this analysis, microbleed status (yes vs no) was defined as the dependent variable and the above-mentioned cardiovascular risk factors were considered independent covariates. The estimated propensity score was the derived predicted value of the equation. Finally, we also investigated whether adjustments for age squared would give a better adjustment for confounding by age. One hundred twenty-seven participants with unreliable segmentations of white matter lesion volume (eg, owing to large ischemic areas in the brain or motion artifacts) were excluded in the analysis involving white matter lesion volume and may have contributed to selection bias in the study.

Results

Microbleeds and Cognitive Decline

In total, 3257 participants (1758 women [54.7%]; mean [SD] age, 59.6 [7.8] years) without prevalent or incident dementia underwent baseline and follow-up cognitive testing a mean of 5.9 years apart from April 17, 2002, to June 18, 2014 (**Table 1**). The prevalence of lobar microbleeds (with or without cerebellar microbleeds) and deep or infratentorial microbleeds (with or without lobar microbleeds) was 10.9% (354 of 3257 participants) and 3.8% (123 of 3257 participants), respectively. The topographic distribution of cerebral microbleeds included 210 of 3979 participants (5.3%) with at least 1 microbleed in the frontal lobe, 218 (5.5%) in the temporal lobe, 203 (5.1%) in the parietal lobe, 135 (3.4%) in the occipital lobe, 127 (3.2%) in infratentorial regions, and 139 (3.5%) in the deep hemispheric regions.

Compared with no microbleeds, the presence of any microbleed was not associated with a decline in cognition. We did, however, observe that the presence of more than 4 microbleeds was associated with worse performance on the LDST (mean difference in *z* score, −0.32; 95% CI, −0.53 to −0.10; *P* = .004), WFT (mean difference in *z* score, −0.35; 95% CI, −0.62 to −0.08; *P* = .01), Stroop reading (mean difference in *z* score, −0.60; 95% CI, −0.89 to −0.31; *P* < .001) and naming (mean difference in *z* score, −0.35; 95% CI, −0.57 to −0.13; *P* = .002) subtasks, immediate 15-WLT (mean difference in *z* score, −0.31; 95% CI, −0.58 to −0.03; *P* = .03), and Purdue Pegboard Test (mean difference in *z* score, −0.33; 95% CI, −0.64 to −0.03; *P* = .03) neuropsychological testing during follow-up. Furthermore, presence of multiple lobar microbleeds were specifically associated with worse performance on WFT (mean difference in *z* score, −0.52; 95% CI, −1.88 to −0.15; *P* = .006), Stroop reading (mean difference in *z* score, −0.87; 95% CI, −1.26 to −0.47; *P* < .001) and naming (mean difference in *z* score, −0.35; 95% CI, −0.65 to −0.05; *P* = .02) subtasks, and immediate 15-WLT (mean difference in *z* score, −0.38; 95% CI, −0.76 to −0.002; *P* = .04). The presence of multiple deep or infratentorial microbleeds was associated with worse performance on the Purdue Pegboard Test (mean difference in *z* score, −0.61; 95% CI, −1.05 to −0.17; *P* = .007) (**Table 2**). In accordance, lobar microbleeds were the strongest determinant for decline in information processing speed (mean difference in *z* score, −0.44; 95% CI, −0.65 to −0.22; *P* < .001), whereas deep or infratentorial microbleeds were most strongly associated with a decline in motor speed (mean difference in *z* score, −0.61; 95% CI, −1.05 to −0.17; *P* = .007) (**Figure**). Adjusting for *APOE* ε4 and

Table 2. Cerebral Microbleeds and Cognitive Decline Expressed as Decline in Neuropsychological Test Battery Scores

Type and No. of Microbleeds	No. of Participants	Neuropsychological Test, Mean Difference in *z* Score (95% CI)[a]								
		LDST	WFT	Stroop Reading Subtask	Stroop Naming Subtask	Stroop Interference Subtask	15-WLT Immediate Recall	15-WLT Delayed Recall	15-WLT Recognition	Purdue Pegboard Test
No	2780	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Any										
Any	477	−0.05 (−0.12 to 0.02)	0.02 (−0.06 to 0.11)	0.01 (−0.08 to 010)	−0.03 (−0.10 to 0.04)	−0.07 (−0.14 to 0.00)	−0.01 (−0.09 to 0.08)	0.04 (−0.07 to 1.14)	0.03 (−0.07 to 0.14)	−0.03 (−0.13 to 0.06)
1	326	−0.02 (−0.09 to 0.06)	0.04 (−0.06 to 0.14)	0.06 (−0.04 to 0.17)	−0.02 (−0.10 to 0.06)	−0.07 (−0.15 to 0.01)	0.0004 (−0.10 to 0.10)	0.08 (−0.04 to 0.20)	0.04 (−0.10 to 0.17)	−0.01 (−0.12 to 0.11)
2-4	107	−0.05 (−0.18 to 0.09)	0.09 (−0.08 to 0.26)	0.07 (−0.11 to 0.25)	0.05 (−0.08 to 0.19)	−0.02 (−0.16 to 0.11)	0.08 (−0.09 to 0.25)	−0.01 (−0.21 to 0.20)	−0.09 (−0.31 to 0.14)	−0.01 (−0.20 to 0.18)
>4	44	−0.32 (−0.53 to −0.10)[b]	−0.35 (−0.62 to −0.08)[b]	−0.60 (−0.89 to −0.31)[b]	−0.35 (−0.57 to −0.13)[b]	−0.20 (−0.42 to 0.02)	−0.31 (−0.58 to −0.03)[b]	−0.20 (−0.54 to 0.14)	−0.13 (−0.49 to 0.24)	−0.33 (−0.64 to −0.03)[b]
Lobar[c]										
Any	354	−0.05 (−0.13 to 0.03)	0.001 (−0.10 to 0.10)	−0.01 (−0.11 to 0.10)	−0.03 (−0.11 to 0.05)	−0.06 (−0.13 to 0.02)	−0.01 (−0.11 to 0.09)	0.04 (−0.08 to 0.17)	0.06 (−0.06 to 0.19)	−0.05 (−0.16 to 0.06)
1	253	−0.02 (−0.11 to 0.07)	0.03 (−0.08 to 0.14)	0.05 (−0.07 to 0.17)	−0.05 (−0.14 to 0.04)	−0.08 (−0.17 to 0.01)	0.02 (−0.10 to 0.13)	0.10 (−0.04 to 0.24)	0.09 (−0.06 to 0.24)	−0.03 (−0.16 to 0.09)
2-4	78	−0.07 (−0.23 to 0.08)	0.05 (−0.15 to 0.24)	0.03 (−0.18 to 0.23)	0.07 (−0.09 to 0.23)	0.04 (−0.12 to 0.20)	−0.01 (−0.21 to 0.19)	−0.06 (−0.30 to 0.19)	−0.16 (−0.43 to 0.11)	−0.11 (−0.32 to 0.11)
>4	23	−0.33 (−0.62 to −0.03)[b]	−0.52 (−0.88 to −0.15)[b]	−0.87 (−1.26 to −0.47)[b]	−0.35 (−0.65 to −0.05)[b]	−0.22 (−0.52 to 0.08)	−0.38 (−0.76 to −0.002)[b]	−0.34 (−0.81 to 0.15)	−0.14 (−0.64 to 0.37)	−0.09 (−0.50 to 0.33)
Deep or Infratentorial[d]										
Any	123	−0.05 (−0.17 to 0.08)	0.08 (−0.08 to 0.23)	0.08 (−0.09 to 0.24)	0.001 (−0.13 to 0.13)	−0.11 (−0.23 to 0.01)	0.002 (−0.16 to 0.16)	0.02 (−0.16 to 0.20)	−0.05 (−0.23 to 0.14)	0.04 (−0.14 to 0.21)
1	73	0.002 (−0.16 to 0.16)	0.09 (−0.11 to 0.29)	0.12 (−0.09 to 0.33)	0.09 (−0.07 to 0.25)	−0.05 (−0.20 to 0.11)	−0.05 (−0.25 to 0.15)	−0.001 (−0.23 to 0.22)	−0.15 (−0.40 to 0.10)	0.10 (−0.13 to 0.32)
2-4	29	0.01 (−0.25 to 0.27)	0.21 (−0.11 to 0.53)	0.19 (−0.16 to 0.53)	0.0004 (−0.26 to 0.26)	−0.23 (−0.48 to 0.03)	0.31 (−0.02 to 0.63)	0.14 (−0.23 to 0.51)	0.12 (−0.29 to 0.53)	0.26 (−0.10 to 0.63)
>4	21	−0.31 (−0.63 to 0.01)	−0.18 (−0.57 to 0.22)	−0.28 (−0.71 to 0.14)	−0.35 (−0.66 to −0.03)[b]	−0.19 (−0.50 to 0.12)	−0.23 (−0.63 to 0.17)	−0.06 (−0.51 to 0.39)	−0.11 (−0.61 to 0.39)	−0.61 (−1.05 to −0.17)[b]

Abbreviations: LDST, Letter Digit Substitution Test; WFT, Word Fluency Test; 15-WLT, 15-Word Verbal Learning Test.

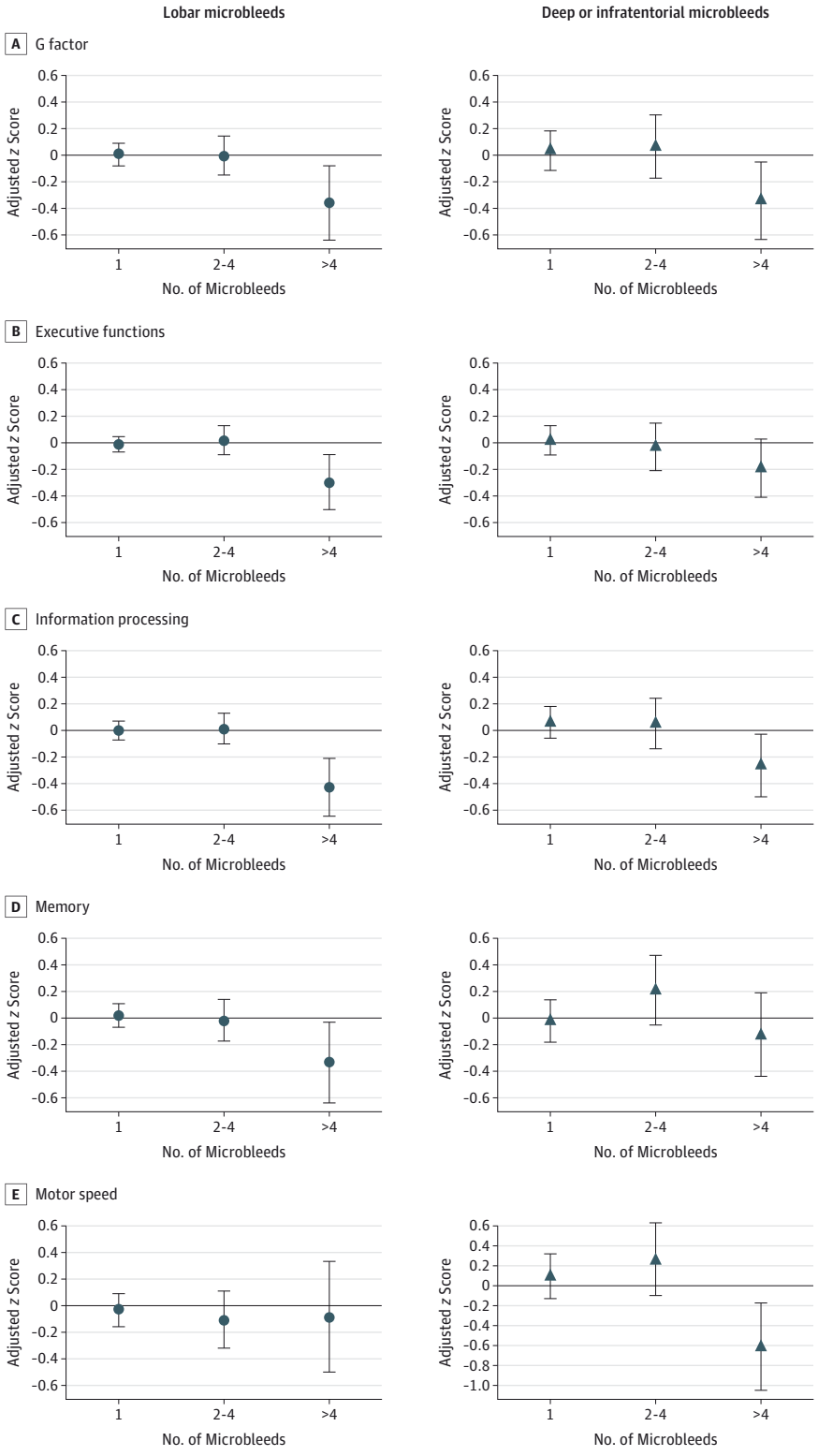
[a] Values are adjusted for age, sex, educational level, baseline cognitive tests score, and time from baseline to follow-up visit. Values represent the mean differences in the *z* score of various cognitive tests in participants with microbleeds compared with those without microbleeds.

[b] Decline in neuropsychological test scores differ significantly ($P < .05$) compared with participants without microbleeds.

[c] Indicates with or without cerebellar microbleeds.

[d] Indicates with or without lobar microbleeds.

Figure. Cerebral Microbleeds and Decline in Specific Cognitive Domains



Age-, sex-, educational level–, and baseline cognition-adjusted *z* scores are shown for decline in specific cognitive domains for categories of lobar and deep or infratentorial microbleed count compared with a reference group without cerebral microbleeds. The cognitive domains are described in the Assessment of Cognitive Functioning subsection of the Methods section. Error bars represent 95% CIs.

a propensity score of cardiovascular risk factors weakened the associations of lobar microbleeds with various cognitive domains. In addition, the association between deep or infratentorial microbleeds and information processing speed was no longer significant (mean difference in *z* score, −0.22; 95% CI, −0.45 to −0.02; *P* = .07) (**Table 3**, model 2). Lobar micro-

Table 3. Cerebral Microbleeds and Decline in Compound Scores of Neuropsychological Tests of Specific Cognitive Domains

Type and No. of Microbleeds by Model	Cognitive Domain, Mean Difference in *z* Score (95% CI)[a]				
	G Factor	Executive Function	Information Processing	Memory	Motor Speed
Model 1[b]					
Lobar[c]	−0.02 (−0.09 to 0.05)	−0.03 (−0.10 to 0.04)	−0.03 (−0.10 to 0.04)	−0.02 (−0.11 to 0.08)	−0.05 (−0.16 to 0.06)
1 CMB	0.0003 (−0.08 to 0.08)	−0.02 (−0.08 to 0.05)	−0.001 (−0.07 to 0.06)	0.01 (−0.08 to 0.10)	−0.03 (−0.16 to 0.09)
2-4 CMBs	−0.01 (−0.15 to 0.13)	0.02 (−0.09 to 0.13)	0.01 (−0.11 to 0.12)	−0.02 (−0.17 to 0.14)	−0.11 (−0.32 to 0.11)
>4 CMBs	−0.37 (−0.65 to −0.09)[d]	−0.31 (−0.51 to −0.11)[d]	−0.44 (−0.65 to −0.22)[d]	−0.34 (−0.64 to −0.03)[d]	−0.09 (−0.50 to 0.33)
Deep or infratentorial[e]	−0.02 (−0.13 to 0.10)	−0.03 (−0.14 to 0.08)	0.01 (−0.11 to 0.13)	0.02 (−0.13 to 0.17)	0.03 (−0.15 to 0.20)
1 CMB	0.03 (−0.11 to 0.18)	0.02 (−0.09 to 0.12)	0.06 (−0.06 to 0.17)	−0.02 (−0.18 to 0.14)	0.10 (−0.13 to 0.32)
2-4 CMBs	0.06 (−0.17 to 0.29)	−0.03 (−0.21 to 0.14)	0.05 (−0.14 to 0.24)	0.21 (−0.05 to 0.47)	0.26 (−0.10 to 0.63)
>4 CMBs	−0.34 (−0.62 to −0.05)[d]	−0.20 (−0.41 to 0.02)	−0.26 (−0.50 to −0.03)[d]	−0.13 (−0.44 to 0.19)	−0.61 (−1.05 to −0.17)[d]
Model 2[f]					
Lobar[c]	−0.02 (−0.09 to 0.05)	−0.03 (−0.09 to 0.04)	−0.02 (−0.09 to 0.05)	−0.02 (−0.11 to 0.08)	−0.05 (−0.16 to 0.06)
1 CMB	0.002 (−0.08 to 0.08)	−0.01 (−0.07 to 0.05)	0.001 (−0.07 to 0.07)	0.01 (−0.08 to 0.10)	−0.03 (−0.16 to 0.09)
2-4 CMBs	0.002 (−0.14 to 0.14)	0.03 (−0.08 to 0.13)	0.02 (−0.09 to 0.14)	−0.02 (−0.18 to 0.14)	−0.10 (−0.32 to 0.12)
>4 CMBs	−0.35 (−0.62 to −0.07)[d]	−0.29 (−0.49 to −0.09)[d]	−0.41 (−0.63 to −0.19)[d]	−0.34 (−0.65 to −0.04)[d]	−0.07 (−0.49 to 0.35)
Deep or infratentorial[e]	−0.003 (−0.12 to 0.11)	−0.02 (−0.13 to 0.09)	0.02 (−0.09 to 0.14)	0.02 (−0.14 to 0.17)	0.04 (−0.14 to 0.22)
1 CMB	0.04 (−0.11 to 0.18)	0.02 (−0.09 to 0.13)	0.06 (−0.06 to 0.18)	−0.02 (−0.18 to 0.14)	0.10 (−0.12 to 0.32)
2-4 CMBs	0.08 (−0.15 to 0.32)	−0.02 (−0.19 to 0.16)	0.07 (−0.12 to 0.26)	0.21 (−0.05 to 0.46)	0.29 (−0.08 to 0.65)
>4 CMBs	−0.29 (−0.57 to −0.002)[d]	−0.16 (−0.37 to 0.06)	−0.22 (−0.45 to 0.02)	−0.14 (−0.45 to 0.18)	−0.56 (−1.00 to −0.11)[d]
Model 3[g]					
Lobar[c]	−0.02 (−0.09 to 0.05)	−0.03 (−0.09 to 0.04)	−0.01 (−0.09 to 0.06)	−0.02 (−0.12 to 0.08)	−0.05 (−0.16 to 0.06)
1 CMB	−0.01 (−0.09 to 0.07)	−0.02 (−0.08 to 0.04)	0.01 (−0.06 to 0.07)	0.01 (−0.08 to 0.10)	−0.04 (−0.16 to 0.09)
2-4 CMBs	−0.01 (−0.16 to 0.13)	0.02 (−0.08 to 0.13)	0.03 (−0.09 to 0.14)	−0.03 (−0.19 to 0.13)	−0.10 (−0.33 to 0.12)
>4 CMBs	−0.29 (−0.57 to 0.002)	−0.24 (−0.45 to −0.03)[d]	−0.40 (−0.62 to −0.17)[d]	−0.28 (−0.60 to 0.04)	−0.01 (−0.43 to 0.42)
Deep or infratentorial[e]	0.03 (−0.09 to 0.15)	0.02 (−0.10 to 0.13)	0.04 (−0.08 to 0.16)	0.05 (−0.11 to 0.21)	0.08 (−0.10 to 0.27)
1 CMB	0.04 (−0.11 to 0.18)	0.02 (−0.09 to 0.13)	0.05 (−0.07 to 0.17)	−0.01 (−0.17 to 0.15)	0.10 (−0.12 to 0.32)
2-4 CMBs	0.10 (−0.14 to 0.33)	−0.01 (−0.18 to 0.17)	0.08 (−0.12 to 0.27)	0.23 (−0.03 to 0.49)	0.31 (−0.05 to 0.67)
>4 CMBs	−0.13 (−0.45 to 0.20)	0.006 (−0.24 to 0.25)	−0.17 (−0.44 to 0.10)	−0.05 (−0.41 to 0.32)	−0.48 (−0.98 to 0.03)

Abbreviation: CMB, cerebral microbleeds.

[a] Values represent mean differences in *z* score of various cognitive domains in participants with microbleeds compared with those without microbleeds. The cognitive domains are described in the Assessment of Cognitive Functioning subsection of the Methods section.

[b] Adjusted for age, sex, educational level, baseline domain tests scores, and time from baseline to follow-up visit.

[c] Indicates lobar microbleeds with or without cerebellar microbleeds.

[d] Decline in compound scores of neuropsychological tests differ significantly ($P < .05$) compared with participants without microbleeds.

[e] Indicates deep or infratentorial microbleeds with or without lobar microbleeds.

[f] Adjusted for the covariates in model 1 and *APOE* ε4 allele and a propensity score of cardiovascular risk factors that included hypertension, total and high-density lipoporotein cholesterol levels, smoking status, diabetes, and use of lipid level–lowering medication and antithrombotics.

[g] Adjusted for the covariates in model 1 and additionally for lacunes, intracranial volume, and white matter lesion volume.

bleeds were associated with a decline in executive functioning (mean difference in *z* score, −0.24; 95% CI, −0.45 to −0.03; $P = .003$) and information processing speed (mean difference in *z* score, −0.40; 95% CI, −0.62 to −0.17; $P < .001$), even after correcting for other imaging markers of cerebral small-vessel disease (Table 3, model 3). The additional adjustment for age squared did not change any of the results. Regarding the topographic distribution of cerebral microbleeds, microbleeds in distinct anatomical brain regions were associated nonspecifically with the decline in various cognitive domains (eTable in the Supplement).

Microbleeds and Dementia

Follow-up for dementia was complete in 4841 participants (2663 women [55.0%]; mean [SD] age, 63.8 [10.9] years) (Table 1). During a mean [SD] follow-up of 4.8 (1.4) years, 72 participants developed dementia, of whom 53 had Alzheimer dementia. The presence of microbleeds– lobar and deep or infratentorial–was associated with an increased risk for dementia (age-, sex-, and educational level-adjusted hazard ratio [HR] for dementia in people with any microbleeds, 2.02; 95% CI, 1.25-3.24; $P = .004$) (**Table 4**). Associations remained after censoring for stroke (HR, 1.70; 95% CI, 1.00-2.87; $P = .05$). Lobar and deep or infratentorial microbleeds were associated with an increased risk for Alzheimer dementia in the same magnitude as that of non-Alzheimer dementia. Significance was lost after adjusting for the *APOE* ε4 allele and a propensity score of cardiovascular risk (Table 4, model 2). Associations remained for deep or infratentorial microbleeds, after adjusting for other imaging markers of cerebral small-vessel disease (Table 4, model 3).

Table 4. Cerebral Microbleeds and the Risk of Dementia

Presence of Microbleeds by Model and Type	Dementia[a]		Alzheimer Dementia[a]	
	No./Total No.	HR (95% CI)	No./Total No.	HR (95% CI)
Model 1[b]				
No microbleeds	39/3911	1 [Reference]	28/3911	1 [Reference]
Any microbleeds	33/930	2.02 (1.25-3.24)[c]	25/930	2.10 (1.21-3.64)[c]
Lobar[d]	21/648	1.81 (1.05-3.11)[c]	17/648	2.00 (1.08-3.71)[c]
Deep or infratentorial[e]	12/282	2.39 (1.23-4.61)[c]	8/282	2.15 (0.97-4.78)
Model 2[f]				
No microbleeds	26/3088	1 [Reference]	18/3088	1 [Reference]
Any microbleeds	21/728	1.59 (0.88-2.89)	16/728	1.67 (0.83-3.36)
Lobar[d]	15/512	1.65 (0.86-3.17)	11/512	1.66 (0.77-3.59)
Deep or infratentorial[e]	6/216	1.40 (0.55-3.52)	5/216	1.58 (0.56-4.45)
Model 3[g]				
No microbleeds	36/3743	1 [Reference]	26/3743	1 [Reference]
Any microbleeds	28/868	1.73 (1.03-2.90)[c]	21/868	1.83 (1.00-3.33)[c]
Lobar[d]	17/603	1.55 (0.86-2.81)	14/603	1.70 (0.87-3.32)
Deep or infratentorial[e]	11/265	2.42 (1.18-4.96)[c]	7/265	2.34 (0.98-5.63)

Abbreviation: HR, hazard ratio.

[a] Values represent adjusted HR (95% CI) for incident dementia in participants with microbleeds compared with those without microbleeds. Numbers differ for models 1 to 3 because missing values for apolipoprotein E (*APOE*) genotype in model 2 were not imputed, and because white matter lesion volume was calculated in 4611 participants in model 3.

[b] Adjusted for age, sex, and educational level.

[c] Risk for dementia differs significantly ($P < .05$) compared with participants without microbleeds.

[d] Indicates with or without cerebellar microbleeds.

[e] Indicates with or without lobar microbleeds.

[f] Adjusted for the covariates in model 1 and *APOE* ε4 allele and a propensity score of cardiovascular risk factors that included hypertension, total and high-density lipoporotein cholesterol levels, smoking status, diabetes, and use of lipid level–lowering medication and antithrombotics.

[g] Adjusted for the covariates in model 1 and additionally for lacunes, intracranial volume, and white matter lesion volume.

Discussion

In this population-based study of middle-aged and elderly people, we found that a high microbleed count (ie, >4) was associated with cognitive decline. Also, the presence of microbleeds was associated with an increased risk for dementia.

The presence of multiple microbleeds affected cognition in all domains in our population-based study. Previous cross-sectional studies[9-12] in healthy adults already demonstrated that microbleeds, especially in large numbers, are related to lower MMSE scores, worse information processing, and worse executive functioning. Longitudinal studies are very scarce. The only longitudinal study performed in healthy individuals[8] focused merely on lobar microbleeds in approximately 200 study participants and found an association between multiple lobar microbleeds and decline in executive functioning. Similar findings were reported in a smaller study of patients with stroke.[29] Another longitudinal study[30] performed in patients with the genetic small-vessel disease (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) found that microbleeds were associated with a decline in global cognition, executive function, and memory, but also did not investigate this association separately for different microbleed locations. Cross-sectional studies in patients with or at increased risk for cerebrovascular disease reported inconsistent results on the associations of microbleeds with worse performance on global cognition, tests for executive function, tests for memory function, and tests for psychomotor speed.[13-16] In addition, in memory clinic populations,[31,32] microbleeds were associated with worse MMSE scores (as a measure of global cognition) and several cognitive domains, with the exception of language skills, although most of the studies[33-36] were unable to demonstrate any association. For our study, memory was defined as a compound of immediate and delayed recall scores. Therefore, a decline in memory could be ascribed to afflicted temporal lobes but also to damaged frontal brain regions, because memory may be affected via executive function or attention.

Mechanisms by which microbleeds influence cognitive function remain speculative and may be causal or noncausal.[37] Microbleeds located strategically in the brain may cause focal damage to neurologic tracts that lead to impairment in specific cognitive domains.[15] On the other hand, microbleeds may represent a proxy measure of cerebral vascular disease at large, and their presence may influence cognition indirectly. The latter hypothesis is supported by our findings, because we found associations with multiple microbleeds in widespread areas, rather than with single or multiple microbleeds clustered in a specific brain region. In addition, microbleeds in nonstrategic topographic brain regions were associated with impairments in executive functioning, information processing, and memory. Also, these associations were attenuated after adjusting for white matter lesions and lacunes, indicating that these lesions have a shared effect on cognition. Indeed, previous evidence also suggests that these lesions often coexist, share risk factors, and even indicate a single pathologic continuum.[38-43] Microbleeds are less likely to be a sole causal determinant of cognitive deterioration but rather a downstream product of severe vascular and neurodegenerative disease.

Lobar microbleeds were associated with a decline in distinct cognitive domains when compared with microbleeds in other locations. The association of lobar microbleeds with memory might be explained in part by the fact that multiple lobar microbleeds had a predilection for the temporal lobes in our study.[44] In turn, deep or infratentorial microbleeds could strategically affect infratentorial and deep hemispheric brain regions (including basal ganglia and the internal capsule) to influence motor function. However, participants with deep or infratentorial microbleeds often had a higher microbleed count and more mixed microbleed locations (ie, microbleeds in lobar and nonlobar brain regions). Hence, microbleed count per topographic brain region may be more informative than the categorizations per presumed underlying vasculopathy in assessing cognitive deterioration. In contrast to other studies,[34,45] the prevalence of microbleeds in anterior brain regions was relatively high. The most likely explanation for this discrepancy is a difference in selection of participants contrasting a cognitively impaired population vs the general population.

Microbleeds are found in 18% to 32% of patients with Alzheimer disease,[46] and most patients exhibit a predominance for cortical-subcortical microbleeds.[34] One longitudinal study[47] showed that lobar microbleeds were associated with cognitive decline in cognitively impaired individuals and patients with Alzheimer disease. In the general population, we found that microbleeds related to an increased risk for dementia, including Alzheimer dementia. We found strong associations for deep or infratentorial microbleeds. Our study underscores the role of vascular disease in the pathogenesis of dementia, including Alzheimer dementia. The question remains how vascular disease interacts with amyloid pathologic features to cause clinical cognitive deterioration and dementia. In principle, the relationship could move in either of the following 2 directions: vascular amyloid deposition adversely affects reactivity of cerebral microvasculature and causes loss of function with ischemic and hemorrhagic damage, or hypertensive damage to small vessels leads to disturbances in amyloid clearance and increases the amyloid deposits in vessel walls.[46] Accumulating evidence suggests that vascular damage may be of particular importance in the initiation of neurodegenerative disease, whereas the influence of β-amyloid becomes more prominent in the clinical disease stage.[48,49]

Strengths of our study include the longitudinal population-based design with a large sample size, the use of an extensive neuropsychological test battery, and the virtually complete screening for incident dementia. Some limitations of our study also have to be mentioned. First, we applied multiple statistical tests in our study, increasing the chance of type I errors. However, correcting for multiple testing seems inappropriate because cognitive tests or domains were not independent from one another, and microbleeds in different locations are correlated. Second, selection bias may have influenced our results, because healthier people without subjective memory complaints were more likely to receive follow-up cognitive testing. This likelihood would most likely have biased our results toward the null. Third, the microbleed number rated may not reflect the true biological number because microbleed detection strongly depends on technical imaging methods used (ie, field strength). Fourth, the small number of incident dementia cases in our relatively young cohort hampered our ability to control for all potential confounders, and residual confounding may have affected our results. Specifically, residual confounding by age may have biased the associations presented in our study. Fifth, in our general population, we may have a suboptimal dementia phenotyping because molecular biomarkers were often lacking. Finally, we did not study the relationship between incident microbleeds and cognitive decline. Future studies should include these analyses to further elucidate how progression of small-vessel disease relates to cognitive impairment over time.

Conclusions

Microbleeds are associated with cognitive decline and dementia in the general population. A high microbleed count may represent a proxy for diffuse vascular and neurodegenerative brain damage, which predisposes to progressive cognitive deterioration.

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