

# Retinal and Cerebral Microvascular Signs and Diabetes

## The Age, Gene/Environment Susceptibility-Reykjavik Study

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**OBJECTIVE**—Diabetes increases the risk for microvascular disease. The retina and the brain both have intricate microvascular systems that are developmentally similar. We sought to examine whether microvascular lesions in the retina and in the brain are associated and whether this association differs among people with and without diabetes.

**RESEARCH DESIGN AND METHODS**—The analysis included 4,218 participants of the Icelandic population-based Age, Gene/Environment Susceptibility-Reykjavik Study who were born in 1907–1935 and who were previously followed as a part of the Reykjavik Study. Retinal focal arteriolar narrowing, arteriovenous (AV) nicking, and microaneurysms/hemorrhages were evaluated on digital retinal images of both eyes. Cerebral microbleeds (CMBs) were evaluated from magnetic resonance images. Data were analyzed with logistic and multinomial logistic regression models controlling for demographics, major cardiovascular risk factors, cerebral infarcts, and white matter lesions.

**RESULTS**—Evidence of brain microbleeds was found in 485 (11.5%) people, including 192 with multiple ( $\geq 2$ ) microbleeds. Subjects with signs of retinal microvascular lesions were at a significantly increased likelihood for having multiple CMBs. People with diabetes in combination with the presence of either retinal AV nicking (odds ratio [OR] 2.47 [95% CI 1.42–4.31]) or retinal microaneurysms/hemorrhages (2.28 [1.24–4.18]) were significantly more likely to have multiple CMBs.

**CONCLUSIONS**—Retinal microvascular abnormalities and brain microbleeds may occur together in older adults. People with both diabetes and signs of retinal microvascular lesions (AV

nicking and microaneurysms/hemorrhages) are more likely to have multiple microbleeds in the brain. Microvascular disease in diabetes extends to the brain. *Diabetes* 57:1645–1650, 2008

Developmentally, the retina is an outgrowth of the brain and shares with the brain similar microvascular properties in anatomy, physiology, and metabolic activities (1,2). Microvascular systems in both the retina and the brain may be affected by atherosclerotic, hemodynamic, or other metabolic factors that affect large, small, and microblood vessels (3,4). Population-based epidemiological studies have shown that retinal microvascular abnormalities, such as arteriovenous (AV) nicking, microaneurysms, and hemorrhages, are associated with an increased risk of clinical stroke and cerebral white matter lesions (WMLs) (5–8), a marker for small-vessel disease. To date, no population-based studies have examined the relation of retinal microvascular signs to cerebral microbleeds (CMBs), which indicate the presence of hemorrhagic microvascular lesions or microangiopathy in the brain (9). CMBs are histopathologically confirmed signals on magnetic resonance image (MRI) that signify hemosiderin deposits due to frank minor hemorrhages or blood leakage through small blood vessels (10). Clinical studies suggest that CMBs are associated with an increased risk for intracerebral hemorrhages and serve as the basis for a clinical diagnosis of cerebral amyloid angiopathy (9,11,12).

Individuals with diabetes are known to be at an increased risk for microvascular lesions of both the retina and the brain. Diabetes also is associated with cognitive disorders (13–15) and with brain structural changes in large and small vessels (16,17). Therefore, it is biologically plausible to hypothesize that the strength of association between retinal and cerebral microvascular lesions may be greater in people with diabetes compared with those without the disease.

In this population-based study of older adults, we sought to investigate whether retinal microvascular signs are associated with microbleeds in the brain and whether the association between retinal microvascular lesions and brain microbleeds varies by diabetes status.

### RESEARCH DESIGN AND METHODS

The study population included all participants of the Icelandic Age, Gene/Environment Susceptibility (AGES)-Reykjavik Study, a population-based study aimed to investigate genetic and environmental factors contributing to diseases of older people. The study design and assessments of the cohort have been described previously (18). Briefly, the study population of the AGES-Reykjavik Study consisted of a cohort of men and women born 1907–1935 and living in the Reykjavik area when the Reykjavik Study (1967–1996) was launched by the Icelandic Heart Association (IHA). Since the beginning, the

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AGES, Age, Gene/Environment Susceptibility; AV, arteriovenous; CMB, cerebral microbleed; FLAIR, fluid-attenuated inversion recovery; FOV, field of view; FSE, fast spin-echo; GRE-EPI, gradient-echo type echo planar image; IHA, Icelandic Heart Association; MMSE, mini-mental state examination; MRI, magnetic resonance image; NIH, National Institutes of Health; WML, white matter lesion.

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cohort of the Reykjavik Study has been under surveillance for vital status and coronary heart disease. From February 2002 to February 2006, survivors of the original cohort were invited for the AGES-Reykjavik Study, and a total number of 5,764 subjects participated in the study. The cohort of participants has been previously described and compared with the total cohort of the AGES-Reykjavik Study (18).

The AGES-Reykjavik Study has been approved by the Icelandic National Bioethics Committee (VSN-00-063), which acts as the Institutional Review Board for the IHA, and by the Institutional Review Board for the U.S. National Institute on Aging, National Institutes of Health. Written informed consent was obtained from all participants.

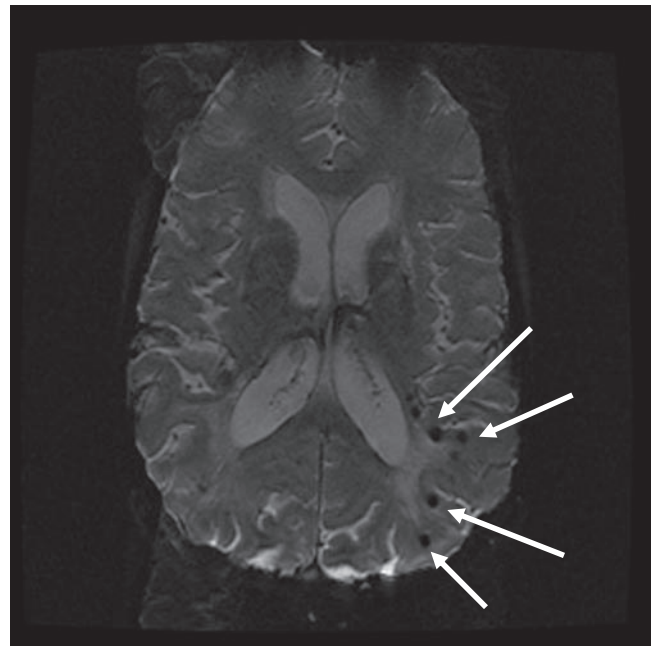
#### Retinal photography and assessment of retinal microvascular signs.

Two 45-degree digital retinal images, centered on the optic nerve (field 1) and the macula (field 2), were taken through the pharmacologically dilated pupil of each of both eyes using a Canon CR6 nonmydriatic camera with a Canon D60 camera back. The digital retinal images were evaluated for the presence of retinal microvascular signs by certified graders at the Ocular Epidemiology Reading Center (Madison, WI) as described previously (19). The retinal microvascular lesions that were analyzed in this study included focal arteriolar narrowing, AV nicking, and signs of retinopathy (microaneurysms and hemorrhages). The images were evaluated according to standardized protocols using EyeQ Lite image processing software. Graders were masked to subjects' health status. In each eye, a grid was placed over the optic nerve that divided the retina into four distinct quadrants, i.e., superior temporal, superior nasal, inferior nasal, and inferior temporal. Retinal focal arteriolar narrowing and AV nicking were assessed in each of the four quadrants, excluding the area within 1/2 of the disc diameter (zone A). Retinal microvascular signs were defined as present if the lesion was graded definite or probable in any quadrant of either eye. Definite focal arteriolar narrowing (in field 1 only) was graded when the involved vessel was at least 40  $\mu\text{m}$  in diameter, or about one-third of the diameter of a vein at the disc margin, and the constricted area had a caliber less than or equal to one-half the caliber of proximal and distal vessel segments. The focal "pinch" had to be at least 250  $\mu\text{m}$  in length to be considered definite. If the grader observed constriction in vessels <40  $\mu\text{m}$  in diameter or if a subtle constriction of vessels was present or a definite pinch was present but the length was <250  $\mu\text{m}$  long, such constriction was graded as probable focal arteriolar narrowing. When assessing abnormalities of AV crossings (AV nicking), both fields 1 and 2 were assessed. Crossings within 1/2 DD of the disc margins (zone A) were excluded, as were the atypical crossings where the venules crossed over the arterioles. Definite AV nicking was defined as tapering or narrowing of the venular blood column on three or all four sides of the crossing. If the tapering appeared on only two sides of the crossing, AV nicking was defined as probable.

For logistical reasons, 4,981 (86.4%) of the 5,764 participants were evaluated with retinal photography for both eyes, and 4,851 (84.2%) had gradable retinal images for all three measures of retinal microvascular abnormalities.

**MRI procedure and definition of CMBs.** All eligible participants were offered a high-resolution MRI examination that was acquired on a 1.5T Signa Twinspeed system (General Electric Medical Systems, Waukesha, WI). The image protocol consisted of the following pulse sequences (20): T1-weighted three-dimensional spoiled gradient-echo sequence (time to echo 8 ms; repetition time 21 ms; flip angle 30°; field of view [FOV] 240 mm; matrix 256  $\times$  256), a proton density/T2-weighted fast spin-echo (FSE) sequence (time to echo 1, 22 ms; time to echo 2, 90 ms; repetition time 3,220 ms; echo train length 8; flip angle 90°; FOV 220 mm; matrix 256  $\times$  256), and a fluid-attenuated inversion recovery (FLAIR) sequence (time to echo 100 ms; repetition time 8,000 ms; inversion time 2,000 ms; flip angle 90°; FOV 220 mm; matrix 256  $\times$  256). To detect CMBs, a T2\*-weighted gradient-echo type echo planar (GRE-EPI) sequence (time to echo 50 ms; repetition time 3,050 ms; flip angle 90°; FOV 220 mm; matrix 256  $\times$  256) sensitive to hemosiderin was used. The acquisition of these sequences was performed with 3-mm-thick interleaved slices. All images were acquired to give full brain coverage, and slices were angled parallel to the anterior-posterior commissure line to give reproducible image views in the oblique-axial plane.

Two neuroradiologists blinded to subjects' clinical information assessed the presence of CMBs on the T2\*-weighted GRE-EPI and T2-weighted FSE images. CMBs were defined as focal areas of signal void within the brain parenchyma that 1) are visible on T2\*-weighted GRE-EPI images, 2) are smaller or invisible on T2-weighted FSE images ("blooming effect"), 3) are not abutting a parenchymal defect, and 4) do not show any other structure in the area of signal void (Fig. 1) (20). Using these criteria, microbleeds can be differentiated from areas of signal void based on vascular flow voids (which do not show the "blooming effect"), from past larger hematomas associated with parenchymal defects, and from cavernomas (which are in general associated with areas of increased signal on T1- and T2-weighted images within the flow void). Areas of symmetric hypointensities of the globus pallidus and putamen,



**FIG. 1. CMBs on MRI: signal voids within brain parenchyma that are not associated with parenchymal defects and do not show any other structures in the areas of signal voids or focal signal loss on the T2\*-weighted gradient-echo image.**

likely to represent calcification or nonhemorrhagic iron deposits, were excluded.

The presence and number of CMBs and the slice number of each CMB were assessed and recorded by neuroradiologists. Subsequently, trained raters accessed the database and recorded the anatomical location and size of each CMB, up to 30 CMBs. Anatomical locations of CMBs included cerebral lobes (frontal, parietal, temporal, and occipital), external capsule, basal ganglia (internal capsule, putamen, globus pallidus, and thalamus), and the infratentorium (cerebellum, medulla oblongata, pons, and mesencephalon). Inter-rater reliability based on MRI readings of 96 participants by two observers was good (weighted  $\kappa = 0.71$  and  $0.73$ ). Intra-rater reliability based on two ratings by one observer of the total number of CMBs in 19 brains with a 1-week interval was excellent (weighted  $\kappa = 1$ ) (20).

WMLs were assessed on the T2-weighted FSE and FLAIR images. The WML load in the subcortical and periventricular areas was separately evaluated using the previously described scales with known properties (21). A semi-quantitative estimate of subcortical WMLs was obtained by integrating the number and size of the lesions: small ( $\leq 3$  mm), medium (4–10 mm), and large ( $\geq 11$  mm). A fixed diameter per size category was used to weight each lesion, and all lesions were summed to get the total score. Periventricular WML load was rated semiquantitatively by lesion size around frontal caps, parietal caps, and bands on a scale of 0 (absent), 1 ( $\leq 4$  mm), 2 (5–10 mm), and 3 ( $\geq 11$  mm) for the right and left sides of the brain. A high load of subcortical and periventricular WMLs was defined as being in the highest quartile of the respective distributions. Cerebral infarcts were evaluated and recorded based on the T2-weighted FSE/proton density images and the FLAIR images.

Of all 5,764 participants, 5,483 (95.1%) had no contraindications for MRI scans, and 4,668 (81.0%) had the MRI sequences needed to score CMBs. The reasons for lack of MRI data on 481 (8.3%) eligible participants were refusal ( $n = 283$ ) and subjects only participating in home visits ( $n = 198$ ).

**Covariates.** Data on demographics and other factors potentially related to both retinal lesions and CMBs were obtained during examination visits to the study center (18). Global cognitive functioning was assessed with the minimal state examination (MMSE). Current use of medications (e.g., blood pressure-lowering drugs, antidiabetic drugs, anticoagulants, and aspirin) was recorded based on presentation of vials at the clinic. Cigarette smoking was assessed with a standard questionnaire and was dichotomized as current versus noncurrent (never or former) smokers. Systolic and diastolic (phase V) blood pressures were measured with a standard mercury sphygmomanometer, and the mean of two measurements on separate occasions was used for the analysis. Height, weight, fasting blood glucose, and total serum cholesterol were measured following standard procedures (18,22). BMI was calculated as measured weight (kg) divided by height squared ( $\text{m}^2$ ). Diabetes was ascer-

TABLE 1  
 Characteristics of study participants ( $n = 4,218$ ) CMBs: the AGES-Reykjavik Study

Characteristics	CMBs			<i>P</i> value*
	No	Single	Multiple ( $\geq 2$ )	
<i>n</i>	3,733	293	192	
Age (years)	76.0 $\pm$ 5.4	77.3 $\pm$ 5.2	78.1 $\pm$ 5.3	<0.001
Systolic BP (mmHg)	141.9 $\pm$ 20.2	144.3 $\pm$ 19.9	145.4 $\pm$ 20.2	0.035
Diastolic BP (mmHg)	73.9 $\pm$ 9.6	73.6 $\pm$ 9.9	76.4 $\pm$ 9.7	<0.001
BMI (kg/m <sup>2</sup> )†	27.0 $\pm$ 4.4	26.7 $\pm$ 4.1	26.2 $\pm$ 3.6	0.070
Fasting blood glucose (mmol/l)	5.8 $\pm$ 1.1	5.7 $\pm$ 0.9	5.9 $\pm$ 1.4	0.191
Total serum cholesterol (mmol/l)	5.6 $\pm$ 1.1	5.6 $\pm$ 1.3	5.4 $\pm$ 1.2	0.015
Female sex	2,206 (59.1)	138 (47.1)	81 (42.2)	<0.001
Elementary education†	854 (23.0)	66 (22.8)	49 (25.8)	0.831
Current smoker	448 (12.0)	28 (9.6)	25 (13.0)	0.540
Diabetes	403 (10.8)	33 (11.3)	33 (17.2)	0.013
Use of BP-lowering drugs	2,290 (61.4)	211 (72.0)	136 (71.2)	0.001
Use of anticoagulants/aspirin†	948 (28.1)	90 (32.8)	67 (37.2)	0.012
MMSE score <24	384 (10.3)	35 (11.9)	38 (19.8)	0.011
High subcortical WML load†	851 (22.9)	92 (31.5)	101 (52.6)	<0.001
High periventricular WML load†	768 (21.0)	87 (30.4)	92 (49.7)	<0.001
Cerebral infarcts	1,044 (28.0)	136 (46.4)	118 (61.5)	<0.001
Focal arteriolar narrowing	644 (17.3)	57 (19.5)	49 (25.5)	0.054
AV nicking	1,529 (41.0)	139 (47.4)	104 (54.2)	0.001
Microaneurysms/hemorrhages	687 (18.4)	71 (24.2)	59 (30.7)	<0.001

Data are means  $\pm$  SD or *n* (%). \*All *P* values were adjusted for age. †Information was missing in 4 persons for BMI, in 27 for education, in 394 for anticoagulants or aspirin, in 25 for subcortical WMLs, and in 85 for periventricular WMLs. In subsequent analysis, missing values were replaced with mean value for continuous variables and with a code of referent group for categorical variables. BP, blood pressure.

tained by integrating the information of the self-reported history of diabetes, use of antidiabetic drugs, or a fasting blood glucose level  $\geq 7.0$  mmol/l (23).

In the analyses, we also controlled for the presence of cerebral infarcts and severity of subcortical and periventricular WMLs because previous studies showed that these brain lesions were associated with both retinal microvascular changes and CMBs (6,9,24–26).

**Statistical analysis.** Of the 5,764 participants, 4,218 (73.2%) with both gradable retinal photographs and the MRI sequences needed for scoring CMBs were included in the current analysis. Subjects not included ( $n = 1,546$ ) were older (79.3  $\pm$  6.5 vs. 76.2  $\pm$  5.4 years [means  $\pm$  SD],  $P < 0.001$ ) and more likely to have diabetes (17.9 vs. 11.1%, age-adjusted  $P < 0.001$ ) and a slightly higher BMI (27.2  $\pm$  4.7 vs. 27.0  $\pm$  4.3 kg/m<sup>2</sup>, age-adjusted  $P < 0.001$ ) and to take anticoagulants or aspirin (34.8 vs. 28.9%, age-adjusted  $P = 0.005$ ); but the two groups had no significant difference in the distribution of sex, education, history of smoking, hypertension, serum total cholesterol, and history of using blood pressure-lowering drugs.

We compared the characteristics of participants with no, a single, and multiple ( $\geq 2$ ) CMBs by  $\chi^2$  test for categorical variables and by ANOVA for continuous variables adjusting for age. With logistic regression, we estimated the odds ratio (OR) and 95% CI of CMBs associated with retinal microvascular abnormalities. Two-way multiplicative statistical interaction was assessed by incorporating the independent variables and their cross-product term into the same model. Multinomial logistic regression analysis was used to examine the association of retinal microvascular signs with a single and multiple microbleeds in the brain. Finally, we assessed the joint additive effect of two factors (A and B) by specifying their joint exposure status as having neither A nor B (reference), only A, only B, and both A and B.

We presented the results from two models. The first model was adjusted for age and sex, and in the second model, additional adjustment was made for more covariates, as described above, that might explain or modify the association between retinal microvascular signs and CMBs (10,27). All analyses were completed with the statistical software SPSS 15.0 for Windows (SPSS, Chicago, IL).

## RESULTS

Of the 4,218 subjects, evidence of CMBs was found in 485 (11.5%) people, including 293 (6.9%) with a single CMB and 192 (4.6%) with multiple CMBs. Compared with people having no CMB, people with a single or multiple CMBs were older; more often men; more likely to have high systolic and diastolic pressure, diabetes, cerebral infarcts, high load of WMLs, cognitive impairment, slightly low total

serum cholesterol, and low BMI; and more likely to use blood pressure-lowering drugs and anticoagulants/aspirin (Table 1).

After controlling for demographics and major vascular factors, the likelihood of having a single CMB (adjusted OR 0.90 [95% CI 0.61–1.33]) was not higher in people with diabetes compared with those without diabetes. However, people with diabetes were significantly more likely to have multiple CMBs (1.58 [1.04–2.39]) than those without diabetes. Diabetes status was not statistically related to retinal focal arteriolar narrowing and AV nicking but was significantly associated with retinal microaneurysms/hemorrhages (multi-adjusted OR 2.32 [1.86–2.89]).

Overall, the presence of CMBs was significantly associated with retinal AV nicking (multi-adjusted OR 1.29 [95% CI 1.06–1.57]) and microaneurysms/hemorrhages (1.48 [1.18–1.86]); the association with retinal focal arteriolar narrowing was statistically marginal (1.25 [0.98–1.60];  $P = 0.077$ ). No multiplicative statistical interaction was detected between diabetes status and signs of retinal microvascular lesions on CMBs.

In multinomial logistic regression analysis, focal arteriolar narrowing and AV nicking were not significantly associated with a single CMB, whereas even controlling for major potential confounders, signs of both retinal arteriolar lesions were significantly associated with a ~45% increased OR for multiple CMBs (Table 2). The presence of retinal microaneurysms/hemorrhages was marginally associated with 33% increased likelihood for a single CMB and significantly associated with 75% increased likelihood for multiple CMBs (Table 2).

In the analysis of joint additive effect, compared with subjects with neither diabetes nor microaneurysms/hemorrhages, individuals having both disorders had a more than twofold increased likelihood for having multiple CMBs after controlling for multiple potential confounders (Table 3). Similarly, people with both diabetes

TABLE 2

Single and multiple microbleeds in the brain related to retinal microvascular signs from multinomial logistic regression models: the AGES-Reykjavik Study\*

Retinal microvascular abnormalities	Single microbleed			Multiple microbleeds		
	Cases	Model 1†	Model 2‡	Cases	Model 1†	Model 2‡
Focal arteriolar narrowing						
No	236	1.00 (Reference)	1.00 (Reference)	143	1.00 (Reference)	1.00 (Reference)
Yes	57	1.08 (0.80–1.47)	1.14 (0.83–1.56)	49	1.49 (1.06–2.10)	1.45 (1.01–2.09)
AV nicking						
No	154	1.00 (Reference)	1.00 (Reference)	88	1.00 (Reference)	1.00 (Reference)
Yes	139	1.25 (0.98–1.59)	1.22 (0.95–1.55)	104	1.60 (1.19–2.14)	1.44 (1.06–1.95)
Microaneurysms/hemorrhages						
No	222	1.00 (Reference)	1.00 (Reference)	133	1.00 (Reference)	1.00 (Reference)
Yes	71	1.35 (1.02–1.78)	1.33 (1.00–1.77)	59	1.82 (1.32–2.51)	1.75 (1.25–2.45)

Data are *n* or OR (95% CI). \*Total *n* = 4,218. Participants with no brain microbleed (*n* = 3,733) held as referent category for multinomial logistic modeling. †Model 1 was adjusted for age and sex, and in model 2, additional adjustment was made for education, systolic pressure, diastolic pressure, smoking, diabetes, use of blood pressure lowering drugs, use of anticoagulants/ aspirin, total serum cholesterol, cerebral infarcts, and a heavy load of subcortical and periventricular WMLs.

and retinal AV nicking, in comparison with subjects having neither condition, were significantly more likely to have multiple CMBs (multi-adjusted OR 2.47 [95% CI 1.42–4.31]). There appeared to be no joint effect between diabetes and focal arteriolar narrowing on CMBs (Table 3).

Because microbleeds in the lobar superficial areas are more likely to indicate the presence of cerebral amyloid angiopathy, whereas CMBs in other locations of the brain more reflect the consequence of hypertension (11,12), we performed multinomial logistic regression analysis by separating CMBs in lobar from other areas; the associations between CMBs and retinal microvascular lesions did not vary substantially by locations of CMBs (data not shown).

## DISCUSSION

In this study of a large community-based cohort of older adults, we found that retinal focal arteriolar narrowing, AV nicking, and microaneurysms/hemorrhages were associated with the presence of multiple microbleeds in the brain. In particular, people having diabetes together with retinal AV nicking or microaneurysms/hemorrhages were more likely to have multiple CMBs. The association was present independent of major potential confounders, including high blood pressure, ischemic brain lesions, and other vascular factors. These findings are consistent with the hypothesis that common mechanisms, besides hypertension, are involved in the pathological processes leading to ocular and cerebral microvascular lesions.

There are several strengths of this study. It was conducted in a large community-based cohort of older men and women. Retinal microvascular signs were evaluated following standardized protocols from images directly acquired from both eyes after pharmacological pupil dilation and without knowledge of subjects' health status. This approach improves the ability to detect any retinal lesions and the reproducibility of grading retinal arteriolar lesions (3), compared with most previous community-based studies (3–8), in which only one eye was examined with no pharmacological pupil dilation.

However, some limitations related to the cross-sectional design deserve mentioning. First, measures on retinal and cerebral lesions were taken almost at the same time, and a temporal relationship cannot be established. Second, the cross-sectional association may not be generalizable from this older northern European cohort to populations of

other age or ethnic groups—if these factors affect survival. Finally, there was a potential for selection bias because subjects not included in this analysis were older and more likely to have diabetes than those included. However, if these individuals were more likely to have retinal lesions and CMBs, the observed associations are conservative.

Several community-based studies of middle-aged and older population have shown an association of retinal microvascular signs, especially microaneurysms/hemorrhages, with clinical stroke, cerebral infarcts, and MRI-WMLs (5–8,24), which are indicators of large and small-vessel disease in the brain. To the best of our knowledge, this is the first community-based study to show an association of signs of retinal arteriolar changes (i.e., focal narrowing and AV nicking) and retinopathy lesions (i.e., microaneurysms and hemorrhages) with brain microbleeds in an older population. Furthermore, we found that older people with diabetes, especially in combination with signs of retinal microvascular lesions, were more likely to have multiple CMBs. These findings emphasize the importance of screening for diabetic retinopathy lesions as suggested in the guidelines (27).

Microvascular lesions in both the retina and the brain may occur concomitantly as parts of generalized systemic vascular disease resulting from common pathophysiological mechanisms. Retinal focal arteriolar narrowing and AV nicking are both associated with high blood pressure. Focal arteriolar narrowing is thought to be a transient marker for the severity of concurrent hypertension, whereas retinal AV nicking is thought to be a marker of damage to the microvasculature from long-standing high blood pressure (28,29). Therefore, retinal arteriolar signs and cerebral microvascular disease may reflect the consequence of concurrent and chronic hypertension (1,28–32). However, when we controlled for high blood pressure, the associations remained, suggesting that other common mechanisms may have led to microvascular bleeds in both the brain and the retina. One such mechanism may be insulin dysregulation and the subsequent toxic effects that might have on the brain (33). Advanced glycation end products may also link microvascular changes in the retina to those in the brain (34,35). In addition, previous studies reveal that diabetes is related to cerebral amyloid angiopathy, especially among carriers of apolipoprotein E  $\epsilon$ 4

allele (13,36), and CMBs are associated with the  $\epsilon 4$  allele (20), suggesting that common genetic susceptibility may play a role in the association between diabetes and CMBs. Furthermore, histopathological studies show evidence of amyloid  $\beta$  deposition in the degenerative retina associated with age-related macular degeneration (37), which has been linked to retinal microvascular signs (38).

The temporality of these associations needs to be investigated in longitudinal studies, as does the long-term physical and cognitive functional implication of combined cerebral and retinal microvascular lesions (39,40). Finally, the association of retinal microvascular lesions with CMBs suggests that additional research is imperative to determine what the diagnostic implications of retinal assessments are for identifying individuals at risk for cerebral microvascular lesions and how these associations are linked to microvascular disease in the kidney and peripheral neuropathy.

In summary, this large-scale, community-based study shows that signs of retinal arteriolar changes and retinopathy lesions, such as focal arteriolar narrowing, AV nicking, and retinal microaneurysms/hemorrhages, are associated with multiple microbleeds in the brain. These associations appear to be stronger in diabetic people, a group that is vulnerable to systemic microvascular disease. This study provides additional evidence of a growing body of literature on the vulnerability of people with diabetes to brain changes, most of which have been demonstrated to have an adverse effect in function.

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**TABLE 3**  
Single and multiple cerebral microbleeds associated with joint exposure to diabetes and retinal microvascular lesions from multinomial logistic regression models: the AGES-Reykjavik Study\*

Status of joint exposure to diabetes and retinal microvascular lesions	Single microbleed		Multiple microbleeds	
	Cases	Model 1†	Cases	Model 2‡
Diabetes	No	1.00 (Reference)	114	1.00 (Reference)
	Yes	0.97 (0.64–1.47)	29	1.68 (1.07–2.64)
	No	1.06 (0.77–1.47)	45	1.58 (1.08–2.32)
Diabetes	Yes	1.24 (0.52–2.92)	4	1.24 (0.42–3.65)
	No	1.00 (Reference)	75	1.00 (Reference)
	Yes	0.86 (0.50–1.50)	13	1.10 (0.58–2.07)
Diabetes	No	1.21 (0.94–1.56)	84	1.32 (0.95–1.84)
	Yes	1.37 (0.82–2.30)	20	2.47 (1.42–4.31)
	No	1.00 (Reference)	115	1.00 (Reference)
Diabetes	Yes	0.79 (0.48–1.33)	18	1.35 (0.78–2.31)
	No	1.27 (0.92–1.73)	44	1.77 (1.21–2.57)
	Yes	1.55 (0.90–2.66)	15	2.28 (1.24–4.18)
Diabetes	No	1.00 (Reference)	115	1.00 (Reference)
	Yes	0.79 (0.41–1.18)	18	1.48 (0.88–2.48)
	No	1.25 (0.91–1.71)	44	1.75 (1.22–2.52)
Diabetes	Yes	1.30 (0.74–2.27)	15	2.54 (1.43–4.50)
	No	1.00 (Reference)	115	1.00 (Reference)
	Yes	0.79 (0.41–1.18)	18	1.48 (0.88–2.48)
Diabetes	No	1.27 (0.92–1.73)	44	1.75 (1.22–2.52)
	Yes	1.55 (0.90–2.66)	15	2.54 (1.43–4.50)

Data are  $n$  or OR (95% CI). \*Total  $n = 4,218$ . Participants with no brain microbleed ( $n = 3,733$ ) held as referent category for multinomial logistic modeling. †Model 1 was adjusted for age and sex, and in model 2, additional adjustment was made for education, smoking, systolic and diastolic pressure, use of blood pressure-lowering drugs, use of anticoagulants/aspirin, total serum cholesterol, cerebral infarcts, and a heavy load of subcortical and periventricular WMHs.

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