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Microvascular lesions in the brain and retina: The AGES-Reykjavik Study

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Abstract

Objective—To investigate whether the severity and location of cerebral white matter hyperintensities (WMHs) and brain infarcts are correlated with the signs of retinal microvascular abnormalities in the elderly.

Methods—The study included 4176 men and women (mean age, 76 years) who participated in the Age, Gene/Environment Susceptibility (AGES)-Reykjavik Study. Digital retinal images of both dilated eyes were taken and evaluated for the presence of retinal focal arteriolar signs (focal arteriolar narrowing and arteriovenous nicking) and retinopathy lesions (retinal blot hemorrhages and microaneurysms). Brain MRI scans were acquired and evaluated for the presence and distribution of cerebral infarcts and WMHs. Logistic and multinomial logistic models were constructed to estimate the association of retinal microvascular signs to brain lesions.

Results—Controlling for demographic and major cardiovascular risk factors, retinal focal arteriolar signs, but not retinopathy lesions, were significantly associated with an increasing load of subcortical and periventricular WMHs. The strongest association was found between retinal arteriolar signs and a heavier WMH load, specifically in subcortical frontal lobe and periventricular frontal and parietal caps. There was a tendency towards bilateral retinal focal arteriolar narrowing being more strongly associated with the heavier load of subcortical WMHs. Arteriovenous nicking was significantly associated with subcortical infarcts.

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Interpretation—In older adults, retinal focal arteriolar signs, but not retinopathy lesions, are correlated with the load of diffuse WMHs, particularly those located in the subcortical frontal lobe and the periventricular frontal and parietal caps of the brain.

Retinal focal arteriolar signs (e.g., focal arteriolar narrowing and arteriovenous [AV] nicking) and retinopathy lesions (e.g., retinal hemorrhages and microaneurysms) are common retinal vascular lesions among older adults. Among people age 65 years and older, the prevalence was 9.6% for focal arteriolar narrowing, 7.7% for AV nicking, and 8.3% for retinopathy lesions.¹ Similarly, older adults frequently have evidence of diffuse cerebral microvascular disease indicated by white matter hyperintensities (WMHs)^{2,3} and focal vascular disease evidenced by brain infarcts on magnetic resonance images (MRI).^{4,5}

Two large population-based studies suggest that individuals with retinal microvascular lesions are more likely to perform poorly on cognitive tests,^{6–8} and to have an increased risk of dementia.^{7,8} Silent brain infarcts and more severe WMHs also increase the risk of cognitive decline and dementia.^{9–11}

The vasculature in the brain and retina share similar features in anatomy, physiology, and metabolic activity.^{12,13} Therefore, it is of interest to characterize the relation of brain and retinal vascular lesions, and to investigate the predictability of ocular microvascular changes for brain vascular lesions. Studies of middle-aged people suggest that retinal focal arteriolar narrowing and AV nicking, and retinal hemorrhages and microaneurysms in particular, are associated with brain infarcts as well as more severe WMHs.^{14,15} However, findings from two population-based studies of older people are inconsistent with those from studies of middle-aged adults; the Rotterdam Scan Study found no association of focal arteriolar narrowing with the severity of WMHs and lacunar infarcts,¹⁶ and in the Cardiovascular Health Study only AV nicking, but neither focal arteriolar narrowing nor retinopathy, was associated with cerebral white matter changes and small brain infarcts.¹⁷

Here, we investigate whether retinal microvascular lesions are correlated with cerebral WMHs and infarcts in an elderly population. We extend previous research by examining (1) whether an increasing load of cerebrovascular lesions is associated with the burden of retinal microvascular disease, and (2) whether there are particular locations of cerebrovascular lesions that are more highly correlated with retinal microvascular changes.

Subjects and Methods

Participants

Participants were from the Age, Gene/Environment Susceptibility (AGES)-Reykjavik Study, which is a continuation of the Reykjavik Study. The Reykjavik Study was initiated in 1967 by the Icelandic Heart Association and included men and women who were born in 1907–1935 and were living in the Reykjavik area.¹⁸ The original cohort of the Reykjavik Study was divided into six subcohorts each examined from one to six times according to a schedule that allowed longitudinal as well as cross-sectional analyses over the 30-year follow-up period. The last examination (1991–1996) was focused on cohort members 70 years and older. Surveillance for vital events and cardiovascular disease of the cohort has been continual since 1967. In 2002 when the AGES-Reykjavik Study began, 11549 previously examined cohort members were still alive and 5764 persons, randomly chosen from the survivors, were examined for the AGES-Reykjavik Study during 2002–2006. The AGES-Reykjavik Study was aimed at investigating the genetic and environmental factors contributing to the aging phenotype of clinical and subclinical disease. The study design and initial assessments of the cohort have been described elsewhere.¹⁸ As part of the

assessments at the Reykjavik research center, a questionnaire was administered, a clinical examination was performed, and images were acquired of the brain and retina.

The AGES-Reykjavik Study was approved by the Icelandic National Bioethics Committee, which acts as the Institutional Review Board for the Icelandic Heart Association, and by the Institutional Review Board for the US National Institute on Aging, National Institutes of Health. Informed consent was obtained from all participants.

Assessment of Retinal Microvascular Signs

RETINAL PHOTOGRAPHY PROCEDURE—Digital retinal images were taken directly from the fundus of both eyes following a standardized procedure as fully described elsewhere.^{19,20} Briefly, after maximal pharmacologic pupil dilation, two 45-degree digital retinal images, centered on the optic disc and the macula, were taken using a 6.3-megapixels Canon CR6 nonmydriatic digital camera with a Canon D-60 camera back. Retinal image quality was assessed by the photographer, and images judged to be of suboptimal quality were immediately retaken. Feedback on image quality from the Ocular Epidemiology Reading Center in Madison, Wisconsin was provided to all photographers on a routine basis.

ASSESSMENT OF RETINAL MICROVASCULAR SIGNS—All retinal images were independently assessed by three certified graders at the Ocular Reading Center using a validated protocol,²¹ without knowledge of subjects' characteristics. All images were graded twice; discrepant findings were subject to adjudication and resolution by a senior grader. The following retinal vascular lesions were evaluated and included in this analysis: focal arteriolar narrowing, AV nicking, and retinopathy lesions. Focal arteriolar narrowing was graded definite when the involved arteriole was $\geq 40 \mu\text{m}$ in diameter and $\geq 250 \mu\text{m}$ in length, and the constricted area had a caliber $\leq 1/2$ that of proximal and distal segments. Probable focal arteriolar narrowing was graded when a constricted vessel was $< 40 \mu\text{m}$ in diameter or $< 250 \mu\text{m}$ in length. Tapering or narrowing of the venular blood column on three or four sides of the crossing was required for definite AV nicking; if the narrowing appeared on only two sides of the crossing, probable AV nicking was graded. Each quadrant of both eyes was assessed. Retinal focal arteriolar signs were considered present if the lesions were graded definite or probable in any quadrant of either eye. Retinopathy lesions were defined as having probable or definite lesions of either retinal blot hemorrhages or microaneurysms.

QUALITY CONTROL PROCEDURE FOR GRADING RETINAL IMAGES—The quality control procedure used for grading retinal images was similar to those reported elsewhere.^{22,23} For the AGES-Reykjavik Study, the unweighted κ statistics for intra-observer variability ranged 0.31–0.63 for focal arteriolar narrowing, 0.45–0.52 for AV nicking, and 0.81–1.00 for retinal hemorrhages and microaneurysms. The corresponding statistics for inter-observer variability were 0.33–0.41, 0.41–0.76, and 0.87–1.00, respectively. All instances of discrepant grading were edited by a third grader, and if still discrepant, were adjudicated by co-director of the Ocular Reading Center without knowledge of the participant's health status.

MRI Acquisition and Assessment of Brain Lesions

MRI ACQUISITION—The standard criteria of contraindications for receiving an MRI scan (e.g., having heart pacemaker, cerebral aneurysm clips, and neurostimulator) were followed.²⁴ All eligible participants were offered brain MRI scans with a 1.5T system (General Electric Medical Systems, Waukesha, WI). The core image protocol consisted of a proton density/T2-weighted fast spin-echo sequence [time to echo (TE)₁, 22 ms; TE₂, 90 ms; repetition time (TR), 3220 ms; echo train length, 8; flip angle (FA), 90°; field of view (FOV), 220 mm; matrix, 256×256] and a fluid attenuated inversion recovery (FLAIR)

sequence (TE, 100 ms; TR, 8000 ms; inversion time, 2000 ms; FA, 90°; FOV, 220 mm; matrix, 256×256), with 3-mm thick interleaved slices. Additional images were acquired with a T1-weighted 3D spoiled gradient-echo sequence (TE, 8 ms; TR, 21 ms; FA, 30°; FOV, 240 mm; matrix, 256×256; 1.5-mm thick slices). Full brain coverage was given for all sequences.

MRI READING PROTOCOL—All MRI images were read by a neuroradiologist for clinical alerts and for the identification of brain infarcts. Trained radiographers further evaluated the infarcts and scored WMH load in detail.

White matter hyperintensities were defined as visible hyperintense lesions on T2-weighted and FLAIR images. The load of WMHs in subcortical and periventricular regions was separately rated following a validated scale.²⁵ Subcortical WMHs were scored separately for the right and left hemispheres and in the frontal, occipitoparietal, and temporal lobes. The scale provides a semi-quantitative ‘volumetric’ estimation for WMH load by taking into account the size and number of lesions in the subcortical area. Periventricular WMHs were those adjacent to ventricular lining and in the frontal caps, parietal caps, and bands. The scale was based on lesion size: 0 (absent), 1 (≤5 mm), 2 (6–10 mm), and 3 (>10 mm). Scores for all three areas on both hemispheres were summed to get the total periventricular WMH load.

Cortical and subcortical infarcts were defined as lesions ≥4 mm in the maximum diameter over a vascular distribution with typical MRI characteristics (e.g., a signal intensity that was isointense to that of cerebrospinal fluid), and were distinguished from WMHs. Infarcts in cerebellum had no size criteria since lesions in this area can be very small. A neuroradiologist first examined the images for presence of cortical, subcortical, and cerebellar infarcts. Then, the radiographers characterized the infarcts in more detail.

QUALITY CONTROL PROCEDURE FOR GRADING MRI IMAGES—Readers in the Reykjavik research center were required to re-read a set of randomly selected scans after six months of the MRI acquisition. The weighted κ statistics for intra-observer variability were 0.91 for subcortical WMHs and 0.90 for brain infarcts; the corresponding κ statistics for inter-observer variability were 0.72 and 0.70. In addition, a sample (5% of all MRI scans) was re-read by experts in the Leiden University Medical Center. Any discrepancies among readers in the two centers were discussed and resolved on a routine basis.

Covariates

Data on demographic and other factors potentially related to both retinal and cerebral lesions were collected through a questionnaire survey and clinical examination. Global cognitive function was assessed with the Mini-Mental State Examination (MMSE). The questionnaire survey collected information on health history, use of blood pressure lowering drugs, and smoking.¹⁸ Systolic and diastolic (phase V) pressure were measured with a standard mercury sphygmomanometer, and the mean of two measurements on separate occasions was used for analysis. Body mass index (BMI) was defined as measured weight (kg) divided by height squared (m²). Fasting blood glucose was measured following a standard procedure. Diabetes was defined according to self-reported history of diabetes, use of blood glucose lowering drugs, or fasting blood glucose level ≥7.0 mmol/L.^{26,27}

Statistical Analysis

Of the 5764 participants, 762 (13.2%) did not have MRI scans due to contraindications (n=281), refusal or claustrophobia (n=283), or only participating in a home visit (n=198); 4616 (80.1%) had the MRI sequences needed for the evaluation of brain infarcts and

WMHs. Retinal images were not acquired on 316 subjects, due to either refusal or logistic reasons. Additional 124 persons were not included because photos were not gradable for retinal microvascular signs in at least one eye, leaving 4176 individuals for the current analysis. Compared to people who were included, those excluded from this analysis (27.6%) were older and less educated, and had poorer performance on global cognitive function, but the two groups did not differ either by gender or by any of the three retinal lesions of interest.

We compared characteristics of participants by retinal microvascular signs using *chi-square* tests for categorical variables and analysis of variance for continuous variables adjusting for age. Taking into account their respective distributions, we categorized subcortical WMH load into quartiles, and periventricular WMH load into tertiles. For brain locations, the WMH load in frontal and occipitoparietal lobes was categorized into quartiles; the WMH load was dichotomized (≥ 0.36 vs. < 0.36 ml) in temporal lobe as there were few visible WMHs in that area. The WMH load in periventricular frontal caps, parietal caps, and the bands was trichotomized. To account for the larger size of frontal lobe, we re-categorized the WMH load by using comparable cut-offs for various lobes, i.e., 1.00–2.99 or ≥ 3.00 vs. < 1.00 ml for both frontal and occipitoparietal lobes, and ≥ 1.00 vs. < 1.00 ml for temporal lobe. This categorization yielded results similar to those obtained when using lobe-specific cut-offs (data not shown). We dichotomized the variables of brain infarcts (yes vs. no) in the whole brain and by locations of cortical, subcortical, and cerebellar areas. The burden of retinal vascular lesions was defined as no lesion, one eye affected, and both eyes affected.

Logistic regression analysis was used to estimate the odds ratio (OR) and 95% confidence interval (CI) of retinal vascular lesions related to cerebral WMHs and infarcts. Multinomial logistic models were used to relate burden and type of retinal vascular lesions to brain lesions. We present the results from two separate models: Model 1 was adjusted for age and sex, and in Model 2 additional adjustment was made for education, smoking, systolic pressure, use of blood pressure lowering drugs, diabetes, and BMI. For the analysis of WMH load we also controlled for cerebral infarcts. All analyses were completed with the statistical software SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA).

Role of the Funding Source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or report writing. The corresponding authors had full access to all data in this study and had final responsibility for the decision to submit for publication.

Results

Of the 4176 participants, 17.7% had focal arteriolar narrowing, 41.9% had AV nicking, and 19.3% had retinopathy lesions in at least one eye. All three measures were significantly related to older age and high blood pressure (Table 1). Furthermore, people with focal narrowing were more likely to be female and to have a heavier WMH load, but less likely to have diabetes, take blood pressure lowering drugs, or smoke; AV nicking was related to a slightly higher BMI and a heavier WMH load; the presence of retinopathy lesions was significantly associated with diabetes and subcortical WMHs. After controlling for age, none of the three retinal measures was significantly associated with education, MMSE score, or total brain infarcts.

Focal arteriolar narrowing was significantly associated with a heavier load of subcortical and periventricular WMHs (Table 2). Further, bilateral focal arteriolar narrowing was more strongly associated with a higher load of subcortical WMHs, but not of periventricular WMHs (Figure 1). AV nicking was associated with a heavier load of subcortical and

periventricular WMHs in a dose-response manner that did not vary substantially by the burden of AV nicking (Table 2, Figure 1). After controlling for major potential confounders, retinopathy lesions were not significantly associated with the severity of WMHs.

In further analysis, all participants were categorized into four groups according to type of retinal microvascular lesions: having only retinopathy lesions (retinal blot hemorrhages or microaneurysms, $n=321$), having only retinal focal arteriolar signs (arteriolar narrowing or AV nicking, $n=1597$), having both retinopathy and focal arteriolar signs ($n=484$), and having no retinal lesions ($n=1774$). Multinomial logistic regressions analysis, controlling for multiple potential confounders, suggested that the increasing load of subcortical and periventricular WMHs was significantly associated with an increasing OR of retinal arteriolar signs alone or in combination with retinopathy lesions, but not with retinopathy lesions alone (Figure 2).

An increasing load of subcortical WMHs in the *frontal* area was associated with an increasing likelihood of having focal arteriolar narrowing (p for trend=0.01) and AV nicking (p for trend=0.02) (see supplementary Table 1). For example, the multi-adjusted OR (95% CI) of focal arteriolar narrowing related to the second, the third, and the fourth quartiles of subcortical frontal WMHs, in comparison with the first quartile, was 1.38 (1.05–1.80), 1.50 (1.12–2.01), and 1.56 (1.11–2.19), respectively. Similarly, a heavier WMH load in periventricular frontal and parietal caps was significantly associated with a higher likelihood of AV nicking (p for trend<0.01); focal arteriolar narrowing was related to the heavier load of WMHs in parietal caps (p for trend<0.01). Finally, the presence of retinopathy lesions (retinal hemorrhages and microaneurysms) was not significantly related to WMH load in any brain locations.

None of the three retinal measures was significantly associated with total brain infarcts. For the location of brain infarcts, only AV nicking was significantly associated with infarcts in the subcortical region (multi-adjusted OR, 1.33; 95% CI, 1.09–1.62) (see supplementary Table 2).

Overall, there was no significant sex difference in the associations of retinal microvascular lesions to brain lesions. However, there was one exception; women in the upper tertile of periventricular WMH load had a marginally higher OR of retinopathy lesions (multi-adjusted OR, 1.30; 95% CI, 0.99–1.70; $p=0.06$), whereas no statistically significant association was observed in men (multi-adjusted OR, 0.88; 95% CI, 0.64–1.21).

To address to what extent the probable and definite retinal microvascular lesions were differently associated with brain lesions, we performed multinomial logistic regression analysis, in which retinal microvascular lesions as outcomes were categorized into no lesion (reference), probable lesion, and definite lesion. Overall, an increasing load of subcortical and periventricular WMHs was significantly or marginally associated with an elevated OR of both definite and probable retinal arteriolar lesions, although the associations with definite lesions were slightly stronger than those of with probable lesions. The load of WMHs and brain infarcts were not significantly associated with either probable or definite retinopathy lesions (retinal blot hemorrhages and microaneurysms) (see supplementary Table 3).

Finally, neither presence nor absence of hypertension (i.e., systolic pressure ≥ 140 mm Hg or diastolic pressure ≥ 90 mm Hg or use of blood pressure lowering drugs; 79.6% persons had hypertension) or diabetes significantly modified these results.

Discussion

In this large-scale community-based study of older adults we found that retinal focal arteriolar changes (focal arteriolar narrowing and AV nicking) are correlated with the severity and specific location of cerebral WMHs. However, burden of these retinal arteriolar lesions was only weakly associated with WMH load. Older adults with a heavier WMH load in the *frontal* region were more likely to have retinal arteriolar changes. We also found that only retinal AV nicking was associated with brain infarcts in the subcortical region, but not in other brain areas. Interestingly, retinopathy signs (retinal blot hemorrhages and microaneurysms) were not associated with WMHs nor with brain infarcts.

This study has two major strengths. First, retinal microvascular signs were detected on digital images taken directly from the fundus of both eyes after pharmacologic pupil dilation. With this procedure, we detected much higher prevalence rates of retinal microvascular lesions compared to previous studies using the film-based acquisition methods, where only one eye had been photographed after dark adaptation to facilitate pupil dilation.^{1,6} Second, we used sensitive MRI-FLAIR sequences and a validated semi-quantitative scale to define the severity of WMHs taking into account brain locations. As a result, we could address burden of retinal vascular lesions in relation to both the severity and location of WMH load.

This cross-sectional study is also subject to limitations. First, a temporal relation of retinal and brain lesions, if there is one, cannot be established. Second, the cross-sectional association may also be subject to selective survival or participation/exclusion bias that could occur when the retinal and brain vascular lesions are differently associated with survival and participation of the study. However, there is no evidence to suggest this is the case. Third, although we did not find significant effect modification of hypertension and diabetes on our primary analyses, sample size differences in those with or without these conditions may make it more difficult to study these effects.

The Atherosclerosis Risk in Communities Study based on middle age adults found that retinal focal arteriolar signs and retinopathy lesions were associated with the MRI-defined subclinical brain infarcts, mainly in persons with hypertension.²⁸ By contrast, in the Cardiovascular Health Study of persons older than 65 years, AV nicking, but not retinal focal arteriolar narrowing or retinopathy signs, were associated with prevalent and incident brain infarcts.¹⁷ Also, the Rotterdam Study found no association of smaller retinal arteriolar diameters with the risk of brain infarcts.²⁹ The differences in characteristics of study participants (e.g., age, race, and morbidity) as well as variations in methods of assessing retinal (e.g., digital versus film) and brain lesions (e.g., MRI sequences and rating scales) might contribute to the inconsistent findings among different studies.

There are no studies that have examined the association of retinal microvascular lesions to different locations of brain infarcts. Our study indicates that the association of retinal and cerebral lesions may be more specific for subcortical infarcts. The findings that lesions in the subcortical area are more consistently associated with AV nicking support the hypothesis that retinal arteriolar changes better correlate with cerebral small, rather than large, vessel disease. We have also reported that AV nicking is more strongly associated with cerebral microbleeds.²⁷

The biological mechanisms underlying the association of retinal arteriolar signs with brain WMHs are not fully understood. Focal arteriolar narrowing and AV nicking both reflect early or mild retinal microvascular changes due to hypertension;^{30–32} focal arteriolar narrowing is thought to be a transient marker for the severity of concurrent hypertension, whereas AV nicking is considered to be a marker of microvascular damage from long-

standing high blood pressure. These retinal arteriolar signs represent intimal thickening, medial hyperplasia, and sclerosis.^{13,30} Similarly, WMHs reflect ischemic microvascular lesions in the brain due largely to chronic hypertension and other atherosclerotic factors.^{33,34} Therefore, retinal arteriolar signs and brain WMHs could be concomitant lesions as parts of systemic microvascular changes.

Retinal focal arteriolar signs may also be linked to the changes of cerebral microcirculation through arterial stiffness.^{35,36} Population-based imaging studies indicate that carotid arterial stiffness, atherosclerosis, and arteriosclerosis are associated with retinal arteriolar lesions as well as with cerebral WMHs.^{37,38} The internal carotid artery supplies the retina and the anterior part of the brain (e.g., frontal and parietal cortex). Thus, it is plausible to find the selective association of retinal arteriolar lesions with WMH load in brain locations such as frontal cortex and frontal and parietal caps.

Finally, it is of interest to note that retinopathy lesions (retinal blot microaneurysms and microbleeds) were not associated with cerebral WMH load or infarcts. This suggests that retinal microvascular bleeds reflect the predominance of different mechanisms, for instance, the effects of hyperglycemia more than hypertension, but this needs further investigation.

In summary, retinal focal arteriolar signs, but not retinopathy lesions, are associated with the severity and specific location (e.g., frontal lobe) of diffuse cerebral WMHs in the elderly. Further investigation is needed to determine whether retinal arteriolar lesions are associated with the functional correlates that follow from cerebral diffuse WMHs. There is also evidence that retinal microvascular lesions are correlated to small focal infarcts, particularly in the subcortical area of the brain. These data suggest further study to investigate whether retinal lesions can be used as a marker for diffuse and focal cerebral small-vessel lesions and to identify individuals who may be at an increased risk for the sequelae of these lesions, such as clinical stroke, cognitive impairment, and dementia.

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Fig 1.

Burden (one eye or both eyes affected vs. no lesion) of retinal focal arteriolar narrowing (A), AV nicking (B), and retinopathy lesions (C) in relation to the severity of cerebral white matter hyperintensities (WMHs) in subcortical (quartiles) and periventricular (tertiles) areas: odds ratios were derived from multi-adjusted multinomial logistic models, in which people with no retinal lesion held as reference for the modeling.

Reference group; * $p < 0.05$; § $p < 0.01$.

Fig 2.

Retinal focal arteriolar changes (arteriolar narrowing or AV nicking) and retinopathy lesions (retinal hemorrhages or microaneurysms), each alone or in combination, in relation to the severity of cerebral white matter hyperintensities (WMHs) in subcortical (quartiles) and periventricular (tertiles) areas: odds ratios were derived from multi-adjusted multinomial logistic models, in which people with no retinal lesion held as reference for the modeling.

Reference group; § $p < 0.01$.

Table 1
Characteristics of Study Participants (n=4176) by Retinal Microvascular Lesions: The AGES-Reykjavik Study

Characteristics	Focal Arteriolar Narrowing		Retinal AV Nicking		Retinopathy Lesions	
	No (n=3436)	Yes (n=740)	No (n=2427)	Yes (n=1749)	No (n=3371)	Yes (n=805)
Age (years), mean (SD)	75.8 (5.2)	77.9 (5.6) [†]	75.8 (5.4)	76.6 (5.3) [†]	76.0 (5.3)	77.0 (5.6) [†]
Female sex, %	56.8	61.4*	58.5	56.3	58.3	54.8
Elementary school [‡] , %	22.4	25.5	22.2	24.0	22.7	24.0
Current smoking, %	12.5	9.6*	11.7	12.3	12.0	11.9
BMI (kg/m ²) [‡] , mean (SD)	27.0 (4.3)	26.8 (4.3)	26.9 (4.3)	27.1 (4.3)*	27.0 (4.3)	27.0 (4.4)
Systolic pressure (mm Hg), mean (SD)	140.9 (19.9)	148.1 (19.9) [†]	140.5 (19.6)	144.5 (20.5) [†]	141.2 (19.6)	145.9 (21.7) [†]
Diastolic pressure (mm Hg), mean (SD)	73.4 (9.4)	76.4 (10.1) [†]	73.4 (9.5)	74.7 (9.7) [†]	74.0 (9.5)	74.0 (10.0)
Use of blood pressure lowering drugs, %	64.2	53.6 [†]	61.4	63.6	61.7	65.0
Diabetes mellitus, %	11.7	8.8*	10.8	11.8	9.2	19.6 [†]
MMSE score <24, %	10.2	13.8	10.0	12.1	10.8	11.1
Subcortical WMHs (Quartiles, ml), %						
Q1 (<0.58)	26.4	18.5	28.0	20.8	25.8	21.5
Q2 (0.58–2.03)	25.5	22.7	25.7	24.0	25.5	22.9
Q3 (2.04–5.83)	24.2	29.5	24.5	26.1	24.4	28.3
Q4 (≥5.84)	23.9	29.3 [†]	21.8	29.1 [†]	24.3	27.3*
Periventricular WMHs (Tertiles), %						
T1 (<5)	29.9	22.4	32.2	23.6	29.2	26.1
T2 (5–6)	37.2	34.2	36.4	37.0	37.1	34.5
T3 (≥7)	32.9	43.4 [†]	31.4	39.4 [†]	33.7	39.4
MRI-defined brain infarcts, %	29.6	32.7	28.8	32.0	29.2	33.9

BMI = body mass index; MMSE = Mini-Mental state Examination; SD = standard deviation; WMHs = white matter hyperintensities.

* Age-adjusted $p < 0.05$.

[†] Age-adjusted $p < 0.01$.

[‡] Information was missing in 28 subjects for education and in four subjects for body mass index.

Table 2
Odds Ratios (95% Confidence Intervals) of Retinal Microvascular Signs Related to the Severity of Cerebral White Matter Hyperintensities (WMHs): The AGES-Reykjavik Study

Load of WMHs	No. of Subjects	Retinal Focal Arteriolar Narrowing		Retinal AV Nicking		Retinopathy Lesions	
		No.	Model 1 *	Model 2 *	No.	Model 1 *	Model 2 *
Subcortical (ml)							
Q1 (<0.58)	1043	137	1.00 (reference)	363	1.00 (reference)	173	1.00 (reference)
Q2 (0.58–2.03)	1043	168	1.15 (0.90–1.47)	419	1.23 (1.03–1.47)	184	1.04 (0.82–1.30)
Q3 (2.04–5.83)	1051	218	1.48 (1.17–1.88)	457	1.39 (1.16–1.66)	228	1.31 (1.05–1.64)
Q4 (≥5.84)	1039	217	1.38 (1.09–1.76)	510	1.71 (1.43–2.05)	220	1.24 (0.99–1.55)
<i>p</i> for trend		0.002	0.003	<0.001	<0.001	0.017	0.185
Periventricular							
T1 (<5)	1194	166	1.00 (reference)	413	1.00 (reference)	210	1.00 (reference)
T2 (5–6)	1530	253	1.14 (0.92–1.42)	647	1.35 (1.15–1.58)	278	0.99 (0.81–1.21)
T3 (≥7)	1452	321	1.45 (1.17–1.79)	689	1.61 (1.37–1.89)	317	1.19 (0.97–1.45)
<i>p</i> for trend		<0.001	0.002	<0.001	<0.001	0.075	0.243

* Odds ratios (95% confidence intervals) derived from Model 1 were adjusted for age and sex, and those from Model 2 were additionally adjusted for education, smoking, systolic pressure, use of blood pressure lowering drugs, diabetes, MRI-defined brain infarcts, and body mass index.