Retinal Microvascular Abnormalities Predict Progression of Brain Microvascular Disease

An Atherosclerosis Risk in Communities Magnetic Resonance Imaging Study

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Background and Purpose—Brain microvascular disease leads to leukoaraiosis and lacunar infarcts and contributes to risk of stroke and cognitive decline. Given a shared pathophysiology, retinal microvascular signs are expected to predict brain microvascular disease progression. We investigated if either leukoaraiosis volume progression measured continuously or combined with incident lacunar infarcts would better demonstrate expected associations with retinal disease than has previously been shown.

Methods—Eight hundred thirty participants in the Atherosclerosis Risk in Communities (ARIC) study aged ≥55 years and without previous stroke received an initial brain magnetic resonance imaging, retinal photography, and, 10 years later, a follow-up magnetic resonance imaging. We evaluated retinal vascular sign phenotypes as predictors of (1) leukoaraiosis volume increase, and (2) a new score combining leukoaraiosis volume change and incident lacunar infarcts. Hypertension and diabetes mellitus were evaluated as confounders and effect modifiers.

Results—Individuals with any retinopathy (3.34 cm³; 95% confidence interval [CI], 0.74–5.96) or with arteriovenous nicking (2.61 cm³; 95% CI, 0.80–4.42) each had greater progression of leukoaraiosis compared with those without these conditions. Any retinopathy (odds ratio [OR], 3.18; 95% CI, 1.71–5.89) or its components—microaneurysms (OR, 3.06; 95% CI, 1.33–7.07) and retinal hemorrhage (OR, 3.02; 95% CI, 1.27–7.20)—as well as arteriovenous nicking (OR, 1.93; 95%, CI 1.24–3.02) and focal arteriolar narrowing (OR, 1.76; 95% CI, 1.19–2.59), were associated with a higher quartile of a novel brain microvascular disease score combining leukoaraiosis progression with incident subclinical lacunes.

Conclusions—A novel scoring method revealed associations of retinal signs with leukoaraiosis progression and brain microvascular disease, which have not been shown before. (Stroke. 2014;45:1012-1017.)

Key Words: leukoaraiosis ■ retina

Early detection of cerebral microvascular disease is critical for the prevention of further cerebrovascular injury. However, the earliest brain microvascular pathology precedes detectable changes on magnetic resonance imaging (MRI). It is important, therefore, to identify predictors of cerebral small vessel disease occurring before the detection of brain abnormalities on MRI. As outlined in the Standards for Reporting Vascular Changes on Neuroimaging (STRIVE) position paper, conventional MRI can show distinct forms of cerebral small vessel disease, most typically symptomatic small subcortical infarcts, subclinical lacunes, white matter hyperintensities, and cerebral microbleeds. The microvascular bed of the retina mirrors the cerebral small vessels in embryological origin, anatomic features, and physiological properties. Hypertensive and diabetic retinal signs are associated with incident stroke, independent of blood pressure and other risk factors. Likewise, retinal signs are associated with and may predict subclinical brain microvascular pathology as an intermediary step toward clinical cerebrovascular disease.

Leukoaraiosis and silent lacunar infarcts are 2 variations of subclinical brain microvascular pathology that share pathological features and risk factors. Both predict clinical stroke, dementia, and a worse prognosis after cerebral infarction. Many studies seeking to elaborate the risk factors for these phenomena separate these outcomes in analysis, as have previous Atherosclerosis Risk in Communities (ARIC) studies.
evaluating the relationship between retinal and brain microvascular disease. However, the 2 imaging findings are not always clearly distinguished, particularly when leukoaraiosis or white matter hyperintensity is in areas typical of lacunar infarcts, such as the basal ganglia and thalamus. More importantly, because the 2 share similar pathophysiology, separate analysis of white matter hyperintensities and lacunar infarcts would limit a study’s power to detect statistically significant exposure–outcome relationships in brain microvascular disease.

In this study, we evaluated the extent of cerebral microvascular disease found in ARIC participants with and without retinal microvascular signs. We evaluated volumetric measurements of white matter hyperintensity progression (WMP) instead of a categorical rating of white matter disease. We combined incident lacunar infarcts with this measure of WMP, hypothesizing that retinal microvascular signs would be more likely to demonstrate associations with this combined measure than with separate cerebral microvascular measures.

Methods

Study Population
ARIC is a prospective cohort study designed to assess the risk factors for cardiovascular disease and the natural history of atherosclerosis. ARIC was approved by the institutional review board for each institution associated with each field center, and participants gave informed consent. Participants were middle-aged predominantly black and white men and women from 4 US communities: Forsyth County, NC; Jackson, MS; suburbs of Minneapolis, MN; and Washington County, MD. In all, 15,792 participants, aged 45 to 64, were enrolled at visit 1 (1988–1989), with follow-up at visit 2 (1990–1993), visit 3 (1993–1995), and visit 4 (1996–1999). Participants >55 years old at visit 3 were invited to undergo an initial brain MRI, and a subset had a follow-up MRI in 2004–2006. Participants with prevalent stroke in 2004–2006 were excluded from analysis.

Visit 3 MRI
As described elsewhere,19 1930 subjects drawn from 2 sites (Forsyth and Jackson) underwent MRI. The proton density-weighted images were graded for severity of leukoaraiosis on a scale of 0 to 9 developed for the Cardiovascular Health Study (CHS).20 Lacunar infarcts were defined as infarct-like lesions hyperintense to grey matter on T2 or hypointense on T1 with size >3 mm but <20 mm, in the caudate, lenticular nucleus, internal capsule, thalamus, brain stem, deep cerebellar white matter, centrum semiovale, or corona radiate.

Follow-Up MRI
For follow-up MRI, 1134 participants returned. As reported elsewhere,19 those who returned were more likely black than in the total ARIC sample and predominantly women.19 CHS grades were assigned to scans as in visit 3. Scans also underwent a semiautomated volumetric analysis of leukoaraiosis using fluid-attenuated inversion recovery images and were standardized to an intracranial volume of 1500 mL. Incident lacunes were present if seen on the follow-up but not visit MRI.

White Matter Hyperintensity Change
WMP has been more strongly associated with cognitive decline than with baseline leukoaraiosis.12,13 However, because leukoaraiosis volume from visit 3 MRIs was not directly measured volumetrically (thin section images were not obtained on the baseline study), a direct volumetric calculation of WMP was not possible. Instead, we imputed visit 3 leukoaraiosis volumes using a previously published prediction quadratic equation ($\beta^2=0.80$) relating CHS score and leukoaraiosis at the follow-up-MRI visit. WMP volume was calculated as: follow-up MRI–visit 3 volumes. Progression of leukoaraiosis using the CHS score was defined as increase in score >2.

Brain Microvascular Disease Score
Lacunar infarcts and WMP were combined into 1 score. We used associations with cumulative systolic blood pressure (SBP) as a measure of validity, given the strong relationships previously observed in the literature between cumulative SBP and brain microvascular disease.10 We created linear regression models, regressing SBP onto different combinations of lacunes and WMP, and, using the likelihood ratio test, selected the model with the lowest Akaike Information Criteria scores. We used this model’s $\beta$-coefficients to derive our scoring system for cumulative brain microvascular disease (Figure) and also rounded these $\beta$-coefficients for ease of use.

Retinal Variables
Retinal photographs were taken at visit 3 of all participants, as described elsewhere.1 Trained readers, masked to clinical history and risk factors, assessed the photographs for the presence of microvascular abnormalities using standardized protocols. Any retinopathy was defined as the presence of any of the following: retinal microaneurysms, hemorrhages, soft exudates, hard exudates, macular edema, or optic disk swelling. Standardized definitions were also provided for retinal arteriovenous (AV) nicking, focal arteriolar narrowing, central retinal arteriolar equivalents (CRAE), and central retinal venular equivalents (CRVE). Quality control, grading, and definition of these lesions were based on a standard protocol.21 The reliability of retinal microvascular sign assessment was moderate to high in the ARIC study for most lesions, with repeated grading of photographs during earlier visits showing intragrader and intergrader weightings of 0.57 and 0.56 for AV nicking, 0.62 and 0.29 for focal arteriolar narrowing, and ranging from 0.81 to 1.00 for retinopathy lesions.14 Intraindividual reliability coefficients were generally high.13

Covariates
Cardiovascular risk factors were ascertained at each ARIC visit through interview, physical examination, blood sample, and ECG. Diabetes mellitus was defined as fasting glucose $\geq$126 mg/dL, nonfasting glucose $\geq$200 mg/dL, or a self-reported history of physician-diagnosed diabetes mellitus or use of medications for diabetes mellitus. Three blood pressure measurements were taken with 5 minutes of rest between each measurement; the second and third measurements were averaged for that visit. Hypertension was defined as SBP $\geq$140 mm Hg, diastolic BP $\geq$90 mm Hg, or antihypertensive medication use <2 weeks. Cumulative SBP was calculated as time-weighted average of the second and third blood pressure readings from all 5 visits and can be interpreted as the mean daily SBP for the entire period. If any participant reported antihypertensive medication use at >50% of study visits, 10 mm Hg of SBP was added to his/her cumulative SBP.20 Other covariates in the fully adjusted model included age, sex, race, study center, total cholesterol, high-density lipoprotein cholesterol, blood sugar, body mass index, cigarette pack-years, and prevalent coronary heart disease. Other than cumulative SBP, visit 3 covariates were used in our analysis.

Statistical Analysis
Stata version 12.0 for Macintosh was used. WMP volume was analyzed continuously. Retinal vascular signs were analyzed in separate models as binary variables except for CRAE and CRVE, which are continuous measures (in microns) of retinal vessel caliber. Using linear regression, we tested the association between retinal variables and continuous WMP and used ordinal logistic regression of brain microvascular disease progression score on retinal variables. Based on small numbers in some score categories, we combined scores based on quartile distribution. Multinomial logistic regression and ordinal logistic regression were used to compare combined groups of scores (quartiles) with a reference group of a score from 0 to 3. We used ordinal logistic regression models for total score distribution, but proportional odds assumptions were violated for some retinal variables (results not shown).

Interactions between diabetes mellitus and hypertension, each, were evaluated with the presence of retinal disease, by introducing an interaction term. We also stratified models by diabetes mellitus and hypertension status.
Results

Participant Characteristics

A total of 830 participants in our study had interpretable baseline and follow-up MRIs, gradable retinal photography, and were without prevalent stroke at visit 3. Of these, 157 participants had lacunes on follow-up MRI, 147 of which were incident. Median WMP >10 years was 2.5 cm³. The numbers of participants with each retinal sign were as follows: A V nicking (n=108), focal arteriolar narrowing (n=121), and any retinopathy (n=50) or its components—retinal hemorrhage (n=24) and microaneurysms (n=28). Other signs of retinopathy were seen less frequently. Four participants had retinopathy, A V nicking, and focal arteriolar narrowing. Participants with 2 MRIs (versus only 1) did not differ with respect to age, sex, or race, but had less hypertension and diabetes mellitus and more retinopathy.

Participants with retinopathy were more likely men, black, hypertensive, and with diabetes mellitus compared with participants without retinopathy (Table 1). Individuals with focal arteriolar narrowing were older than those without (62.4 versus 61.2 years; P=0.005) and more likely to have hypertension (52.9% versus 40.1%; P=0.008) compared with persons without focal arteriolar narrowing. Sex, race, and frequency of diabetes mellitus were not significantly different between the groups with and without focal narrowing.

WMP and Retinal Signs

Table 2 shows the results of each linear regression between WMP (defined both as a volumetric change, in cm³, and as a categorical change—an increase of ≥2 categories using the CHS scale) and separate retinal variables. As a continuous variable, in separate adjusted models, continuous WMP was higher in the presence of AV nicking or any retinopathy. In contrast, when WMP was treated as an ordinal variable using the CHS rating scale, WMP was significantly associated only with AV nicking in unadjusted models.

We also tested the association of retinal signs with WMP across strata defined by the presence or absence of hypertension and diabetes mellitus (Tables I and II in the online-only Data Supplement). With smaller numbers in each stratum, the associations were attenuated and fewer were statistically significant. In linear regression models for each separate retinal sign, however, the direction of associations was similar across strata with no significant interactions between most retinal signs and hypertension or diabetes mellitus. The exception was for AV nicking, where a significant (multivariable P interaction=0.003) interaction was found for the association of AV nicking and diabetes mellitus with WMP.

Retinal Associations With Cumulative Microvascular Disease Score

Among the different combinations of lacunar infarcts and WMP tested for the strength of association with cumulative SBP, dividing WMP into quintiles and treating lacunes as present or absent yielded the lowest Akaike Information Criteria scores (Table 3); we, therefore, used the score resulting from this regression equation as the end point for evaluating the associations of small vessel disease with retinal disease.
Table 4 shows the associations between retinal variables and grouped new cumulative brain microvascular disease scores using multinomial and ordinal logistic regression. Results using the rounded scoring system (Figure) were identical to the results using the exact score. AV nicking, focal arteriolar narrowing, and any retinopathy or its individual components, microaneurysms and retinal hemorrhage, were all significantly associated with composite brain microvascular disease. Associations with CRAE and CRVE remained nonsignificant.

Discussion
In our study, we aimed to improve the characterization of brain microvascular disease as an outcome so that we would be more likely to detect associations with signs of retinal disease. We predicted that by converting WMP into a continuous measurement rather than an ordinal score and by combining WMP and lacunar infarcts into a cumulative brain microvascular disease score, more retinal signs would be significantly associated with brain microvascular disease in a manner meeting a priori expectations. Indeed, more retinal signs were associated with brain microvascular disease using these methods than has been shown in previous studies. WMP alone was associated with AV nicking and with any retinopathy. The cumulative score was associated with AV nicking, focal arteriolar narrowing, and any retinopathy as well as its components.

A previous ARIC study evaluated retinal microvascular pathology in association with silent lacunar infarcts and WMP as separate outcomes.

Table 1. Baseline Characteristics of Participants

Table 2. Regression Models Evaluating Distinct Signs of Retinal Microvascular Disease, Each, With MRI Small Vessel Disease

AV indicates arteriovenous; CRAE, central retinal arteriolar equivalent; CRVE, central retinal venular equivalent; and WMP, white matter hyperintensity progression.

*Results for lacunes (incident) and categorical progression of WMP are odds ratios (ORs) with 95% confidence intervals, because these were derived from logistic regressions.

†Volume changes in WMP results are \( \beta \)-coefficients from linear regressions (with 95% confidence interval).

‡Adjusted for age, sex, race, study center; total and high-density lipoprotein-cholesterol, body mass index, pack-years, cumulative systolic blood pressure, blood glucose, and presence of coronary heart disease.

§Values represent statistically significant associations (\( P \text{-value} \leq 0.05 \)).
findings can be explained by a lower number of WMP events and lacunes coupled with the infrequency of retinal changes, limiting the power to detect associations with WMP. By using a quadratic model to impute white matter volume from CHS scores,10 this created a measure of WMP with a greater ability to discriminate small changes in disease burden, allowing us to detect the additional association between any retinopathy and WMP. Our cumulative brain microvascular disease score also allows us to identify associations between brain microvascular disease and retinal changes not previously identified, by combining lacunar infarcts and WMP.

Other groups have proposed combining lacunar infarcts and white matter disease into 1 measure. In the Women’s Health Initiative, Haan et al16 summed volumes of lacunar infarcts and white matter disease across different brain regions, combining both types of brain microvascular disease. Our method of combining lacune and WMP information involved exploring the relative strength of associations of different combinations in SBP. Although our definition of lacune does not exactly match that recently recommended by the STRIVE Initiative, Haan et al16 summed volumes of lacunar infarcts and white matter disease across different brain regions, combining both types of brain microvascular disease. Our method of combining lacune and WMP information involved exploring the relative strength of associations of different combinations with SBP. Although our definition of lacune does not exactly match that recently recommended by the STRIVE group1 (we used a maximum lacunar size of 20 mm, versus 15 mm in STRIVE), we used it consistently throughout the study, allowing for assessment of incident lacunes over time.

We think our combined index represents a measure of brain microvascular disease reflecting the shared pathophysiology between these 2 MRI-detected signs. This score is, therefore, more likely to detect true risk factors for brain microvascular disease than when the risk factors are evaluated with either lacunar infarcts or white matter disease alone. Moreover, if this score is a more sensitive measure of microvascular disease as an exposure, it might have greater value as a risk factor for cognitive decline, incident stroke, and stroke prognosis. If retinal microvascular changes precede the progression of cerebral microvascular disease, this might indicate a point at which aggressive preventive therapies (eg, aimed at control of hypertension or diabetes mellitus) might be implemented, which could even lead to reduction in brain microvascular disease and possibly, in turn, in mild cognitive impairment and dementia. Future studies might evaluate the utility of retinal screening as an indicator of a need for more aggressive vascular risk factor control.

Our score includes the MRI components (lacunes, WMP) that are most strongly driven by microvascular disease. We did not include measures of cerebral atrophy or enlarged perivascular spaces, although these may also represent a form of cerebral small vessel disease.17,18 The study of retinal microvascular disease in association with cerebral atrophy might allow for a better understanding of vascular contribution to cerebral atrophy, but atrophy is not pathognomonic for microvascular disease, and although it might be at least partially due to small vessel disease, it is probably a multifactorial process. We were not able to evaluate the progression of microbleeds, which is another likely sign of brain microvascular disease, because evaluation for these had not been included in MRI scans presented here.

Although we controlled for major cardiovascular risk factors in our regression models, unmeasured confounders may still exist. In addition, the sample of participants who were included and underwent 2 MRIs had less retinopathy and less comorbidity compared with those with only 1 MRI; however, this might dilute the true findings, so our estimates would be conservative. Measurements of our neuroimaging end points could also be a limitation. By imputing volumes at visit 3

### Table 3. Distinct Models Comparing White Matter Hyperintensity Progression (WMP; mL) and Incident Lacunes (Present vs Absent)

<table>
<thead>
<tr>
<th>Model</th>
<th>AIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>WMP</td>
<td>6557</td>
</tr>
<tr>
<td>Lacunes</td>
<td>6657</td>
</tr>
<tr>
<td>WMP + Lacunes</td>
<td>6447</td>
</tr>
<tr>
<td>WMP + Lacunes + WMP* Lacunes</td>
<td>6442</td>
</tr>
<tr>
<td>Quintiles of WMP + Lacunes</td>
<td>6429</td>
</tr>
<tr>
<td>Quartiles of WMP + Lacunes</td>
<td>6431</td>
</tr>
<tr>
<td>Sextiles of WMP + Lacunes</td>
<td>6431</td>
</tr>
</tbody>
</table>

WMP*Lacunes is an interaction term. Cumulative SBP is regressed onto each set of variables in separate models. Akaike information criteria (AIC) scores derived from likelihood ratio tests comparing the model to a null model with no independent variables. Quintiles of WMP + Lacunes selected for lowest AIC.

### Table 4. Multinomial and Ordinal Logistic Regression Results for Each Retinal Disease Phenotype, Comparing Higher Scores on the Cumulative Brain Microvascular Disease With the Lowest Possible Scores

<table>
<thead>
<tr>
<th>Retinal Finding</th>
<th>Multinomial Logistic Regression</th>
<th>Unadjusted Ordinal Logistic Regression OR per Higher Category</th>
<th>Adjusted Ordinal Logistic Regression OR per Higher Score Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any retinopathy</td>
<td>Score 0–3: 1.0 0.86 (0.25–2.97)</td>
<td>Score 5–6: 3.57 (1.26–10.13)*</td>
<td>Score 8–9: 4.21 (1.54–11.45)*</td>
</tr>
<tr>
<td>AV nicking</td>
<td>1.0 0.57 (0.25–1.29)</td>
<td>1.04 (0.50–2.17)</td>
<td>2.31 (1.26–4.26)*</td>
</tr>
<tr>
<td>Focal arteriolar narrowing</td>
<td>1.0 1.71 (0.91–3.21)</td>
<td>2.45 (1.29–4.65)*</td>
<td>2.08 (1.12–3.86)*</td>
</tr>
<tr>
<td>CRAE/10 (Central Retinal Arteriolar Equivalent)</td>
<td>1.0 0.99 (0.95–1.04)</td>
<td>1.01 (0.97–1.05)</td>
<td>1.02 (0.98–1.06)</td>
</tr>
<tr>
<td>Microaneurysms</td>
<td>1.0 0.34 (0.05–2.19)</td>
<td>3.24 (0.78–13.38)</td>
<td>3.39 (0.89–12.88)</td>
</tr>
<tr>
<td>Retinal hemorrhage</td>
<td>1.0 0.92 (0.18–4.74)</td>
<td>2.55 (0.58–11.21)</td>
<td>4.20 (1.07–16.52)*</td>
</tr>
</tbody>
</table>

Adjusted as in Table 2. ORs (95% confidence interval) are displayed. A score of 0 to 3 is the reference group. AV indicates arteriovenous; CRAE, central retinal arteriolar equivalent; CRVE, central retinal venular equivalent; and OR, odds ratio.

*Values represent statistically significant associations (P<0.05).
MRI, there is a possibility of measurement error or erroneous predicted associations. Moreover, we were only able to define lacunes as present or absent, and disallowed anyone with any lacune at visit 3 from having incident lacunes at the follow-up MRI, although additional lacunes could in fact be incident. Lastly, we validated our cumulative brain microvascular disease score (via the strength of association with cumulative SBP) using the same data set we used to test associations between our score and retinal disease. Ideally, we would validate this in a separate sample in the future. It is possible that by finding a score that is highly associated with SBP, we are only representing 1 type of small vessel disease. Future evaluation of composite scores might evaluate these in regard to other vascular risk factors as well.

Conclusions

These data are consistent with previous reports that retinal microvascular signs predict white matter disease and lacunar infarcts. In treating WMP as a continuous measure and combining it with lacunar infarcts, we see associations between brain microvascular disease and retinal signs that, though expected based on common pathophysiology, were not seen before. The cumulative brain microvascular disease score that we developed could be a useful research tool in further studies seeking to elaborate on risk factors and outcomes associated with lacunar infarcts and white matter disease.

Acknowledgments

We thank the staff and participants of the Atherosclerosis Risk in Communities study for their important contributions.

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Disclosures

Dr Knopman serves as Deputy Editor for Neurology; serves on a Data Safety Monitoring Board for Lundbeck Pharmaceuticals and for the Dominantly Inherited Alzheimer’s Disease Treatment Unit. He has served on a Data Safety Monitoring Board for Lilly Pharmaceuticals (completed 2012); served as a consultant to Tau RX (completed 2012), was an investigator in clinical trials sponsored by Baxter and Elan Pharmaceuticals in the past 2 years (both completed in 2012); and receives research support from the NIH.

References

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SUPPLEMENTAL MATERIAL

Supplemental Table I. Linear regression results, stratified by hypertension, demonstrating beta coefficients for the progression in white matter hyperintensity (WMP) over ten years, associated with the presence of different retinal signs. Adjusted for age, gender, race, study center, total cholesterol, HDL cholesterol, BMI, pack years, cumulative systolic BP, blood glucose, and presence of CHD.

<table>
<thead>
<tr>
<th>Retinal Disease</th>
<th>WMP with HTN (cm³)</th>
<th>95% CI</th>
<th>WMP without HTN (cm³)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any retinopathy</td>
<td>3.17</td>
<td>(-.81, 7.15)</td>
<td>3.05</td>
<td>(-.69, 6.79)</td>
</tr>
<tr>
<td>AV nicking</td>
<td>3.72</td>
<td>(.88, 6.55)</td>
<td>1.51</td>
<td>(-.80, 3.82)</td>
</tr>
<tr>
<td>Focal Arteriolar Narrowing</td>
<td>2.21</td>
<td>(-.55, 4.97)</td>
<td>1.27</td>
<td>(-.77, 3.31)</td>
</tr>
<tr>
<td>CRAE/10</td>
<td>-0.15</td>
<td>(-2.74, 2.45)</td>
<td>-0.04</td>
<td>(-1.18, 1.10)</td>
</tr>
<tr>
<td>CRVE/10</td>
<td>0.35</td>
<td>(-2.64, 3.34)</td>
<td>0.11</td>
<td>(-.97, 1.18)</td>
</tr>
<tr>
<td>Microaneurysms</td>
<td>1.37</td>
<td>(-3.69, 6.43)</td>
<td>0.76</td>
<td>(-5.49, 7.01)</td>
</tr>
<tr>
<td>Retinal Hemorrhage</td>
<td>2.81</td>
<td>(-2.32, 7.93)</td>
<td>2.93</td>
<td>(-2.95, 8.81)</td>
</tr>
</tbody>
</table>

Abbreviations: WMP: white matter hyperintensity progression; BP: blood pressure; HDL: high density lipoprotein; BMI: body mass index; CHD: coronary heart disease; HTN: hypertension; AV: arteriovenous; CRAE: central retinal arteriolar equivalent; CRVE: central retinal venular equivalent; CI: confidence interval.
Supplemental Table II. Linear regression results, stratified by diabetes, demonstrating beta coefficients for the progression in white matter hyperintensity (WMP) over ten years, associated with the presence of different retinal signs. Adjusted for age, gender, race, study center, total cholesterol, HDL cholesterol, BMI, pack years, cumulative systolic BP, blood glucose, and presence of CHD.

<table>
<thead>
<tr>
<th>Retinal Disease</th>
<th>WMP with diabetes (cm³)</th>
<th>95% CI</th>
<th>WMP without diabetes (cm³)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any retinopathy</td>
<td>2.95</td>
<td>(-2.65, 8.55)</td>
<td>3.86</td>
<td>(.77, 6.94)</td>
</tr>
<tr>
<td>AV nicking</td>
<td>-4.27</td>
<td>(-10.17, 1.63)</td>
<td>3.73</td>
<td>(1.82, 5.65)</td>
</tr>
<tr>
<td>Focal Arteriolar Narrowing</td>
<td>3.31</td>
<td>(-2.25, 8.88)</td>
<td>1.60</td>
<td>(-1.17, 3.38)</td>
</tr>
<tr>
<td>CRAE/10</td>
<td>0.39</td>
<td>(-6.64, 7.42)</td>
<td>0.38</td>
<td>(-1.07, 1.83)</td>
</tr>
<tr>
<td>CRVE/10</td>
<td>0.46</td>
<td>(-5.84, 6.76)</td>
<td>0.88</td>
<td>(-.74, 2.50)</td>
</tr>
<tr>
<td>Microaneurysms</td>
<td>3.59</td>
<td>(-2.17, 9.34)</td>
<td>1.73</td>
<td>(-3.15, 6.62)</td>
</tr>
<tr>
<td>Retinal Hemorrhage</td>
<td>4.19</td>
<td>(-2.32, 10.70)</td>
<td>3.06</td>
<td>(-1.43, 7.56)</td>
</tr>
</tbody>
</table>

Abbreviations: WMP: white matter hyperintensity progression; BP: blood pressure; HDL: high density lipoprotein; BMI: body mass index; CHD: coronary heart disease; HTN: hypertension; AV: arteriovenous; CRAE: central retinal arteriolar equivalent; CRVE: central retinal venular equivalent; CI: confidence interval.