Cerebral White Matter Lesions, Retinopathy, and Incident Clinical Stroke

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With the increasing use of magnetic resonance imaging (MRI) to scan the brain, changes in the cerebral white matter are commonly detected in elderly people.1-3 These white matter lesions (WMLs) are found in 27% to 87% of populations aged 65 years and older.4,5 Despite recent research, the pathogenesis and clinical significance of WMLs are obscure.6-9 These lesions have been hypothesized to be ischemic complications of cerebral microvascular disease,6 based on histopathological studies that demonstrate small-vessel changes in brains with WMLs10-12 and on clinical studies that show associations between WMLs and microvascular risk factors, such as hypertension13-16 and diabetes.17-19 In people with a history of stroke, WMLs have been suggested to increase the risk of recurrent stroke and cognitive decline.20,21

However, existing studies are limited by their small sample sizes and highly selected populations, and it remains uncertain whether WMLs have a microvascular etiology6 and are associated with development of clinical stroke in the general population.8 Retinal arterioles share similar anatomy, physiology, and embryology with the cerebral arterioles.22 Retinal microvascular changes (eg, microaneurysms, retinal hemorrhages) due to aging, hypertension, and other processes appear to reflect cerebral microvascular disease23 and are associated with stroke.24 Thus, the retinal arterioles provide a unique opportunity to study the correlates and consequences of cerebral small-vessel diseases.

The purposes of our current study were to examine the association of ce-
rebral WMLs and retinal microvascular abnormalities and the association of WMLs and incident clinical stroke.

**METHODS**

**Study Population**

The study population consisted of 1684 persons who participated in cerebral MRI and retinal photography in the Atherosclerosis Risk in Communities (ARIC) study. Initiated in 1987 through 1989, the ARIC study is a cohort study of cardiovascular disease among 15792 persons 45 to 64 years of age, selected from 4 US communities. Participants in the study herein underwent a second examination 3 years later in 1990 through 1992 (93% return rate) and a third examination 3 years after the second in 1993 through 1995 (86% return rate).

Cerebral MRI and retinal photography were performed at the third examination, when participants were 51 to 72 years of age. Retinal photography was offered to all participants. Of the 12884 participants at the third examination, 12553 (97.4%) had retinal photography performed. Cerebral MRI was only offered to participants at 2 study sites (Forsyth County, North Carolina; Jackson, Miss) in 1993 and 1994 in the third examination. The MRI examinees could be considered a random sample of the full cohort because examination dates were allocated at baseline through randomly selected induction cycles and, to the degree possible, reexamination visits were scheduled according to the anniversary date. Among individuals screened for eligibility for cerebral MRI (n=2887), we excluded 8 whose race was neither black nor white, 106 who were ineligible, 649 who declined to participate in the MRI study, and 204 with ungradeable MRI. In general, persons who were examined were similar to those who were ineligible or who declined to participate in the MRI examination. Additionally, 50 persons with a history of stroke, 49 with no retinal photographs, and 137 with ungradable photographs were also excluded, leaving 1684 (58.3%) for the current study.

Institutional review boards at each study site, the MRI reading center, and the retinal reading centers approved the study. Informed consent was obtained from all participants.

**Cerebral MRI**

Cerebral MRI scanning and image interpretation have been previously described. In brief, T1- and T2-weighted magnetic resonance images were obtained. Axial images were angled to be parallel to the anterior commissure–posterior commissure line. Trained and certified MRI readers, who were masked to participants' clinical condition and retinal photography findings, evaluated the digitized scan data on a personal display workstation at the MRI reading center. When evaluating for WMLs, focal abnormalities were ignored. Thus, if one or both sides of the brain were focally abnormal, estimates were based on the uninvolved or unaffected areas. The spin-density images (repetition time, 3000 milliseconds; echo time, 30 seconds) were used to estimate the overall volume of periventricular and subcortical white matter signal abnormality. These were coded on a scale from 0 to 9, based on “pattern matching” of a scan to a set of reference standards, which are described in detail elsewhere. The reference standards are: no white matter signal abnormalities (grade 0); discontinuous periventricular rim or minimal “dots” of subcortical white matter (grade 1); thin continuous periventricular rim or few patches of subcortical WMLs (grade 2); thicker continuous periventricular rim with scattered patches of subcortical WMLs (grade 3); thicker, shaggier periventricular rim with mild subcortical WMLs—may have minimal confluent periventricular lesions (grade 4); mild periventricular confluence surrounding the frontal and occipital horns (grade 5); moderate periventricular confluence surrounding the frontal and occipital horns (grade 6); periventricular confluence with moderate involvement of the centrum semiovale (grade 7); periventricular confluence involving most of the centrum semiovale (grade 8); and all white matter involved (grade 9). The ARIC MRI standard images were graded 1 through 8: anything less than grade 1 was considered grade 0 and anything more than grade 8 was considered grade 9 (FIGURE). Quality control procedures, described elsewhere, showed that interreader and intrareader intraclass correlation coefficients were 0.68 and 0.71, respectively.

**Retinal Photography**

Retinal photography procedures are described elsewhere. Briefly, photographs of the retina were taken of 1 randomly selected eye after 5 minutes of dark adaptation. Trained graders at the retinal reading center who were masked to participant characteristics evaluated the photographic slides for presence of microvascular abnormalities using a standardized protocol. Retinopathy was defined as present if any of the following lesions were detected: microaneurysms, retinal hemorrhages, soft exudates, and other less common lesions (eg, hard exudates, macular edema, optic disc swelling). Arteriovenous nicking and focal arteriolar narrowing were separately defined as present if graded definite or probable. To estimate the severity of generalized retinal arteriolar narrowing, photographs were digitized and diameters of individual retinal vessels coursing through a specified area were measured on the computer and summarized as the arteriole-to-venule ratio (AVR). A smaller AVR represents narrower arterioles (since venular diameters vary little), with generalized arteriolar narrowing defined as the lowest 20th percentile of the sample AVR distribution. As previously reported, intragrader and intergrader k statistics for retinopathy, arteriovenous nicking, and focal narrowing ranged from 0.61 to 1.00. For AVR, intragreader and intergrader reliability coefficients were 0.84 and 0.79, respectively.

**Ascertainment of Incident Stroke**

Incident stroke was defined to include strokes occurring between the time of
a participant’s MRI scan (1993 to 1994) and December 31, 1998, using previously described methods of ascertainment and diagnosis.28 Strokes were identified by contacting participants and their families annually to identify hospitalizations and deaths from stroke during the previous year, and by surveying discharge lists from local hospitals and death certificates from state vital statistics offices. When a potential stroke was identified, a trained nurse sent hospital records for abstraction. A computer algorithm classified each case according to standardized criteria. A physician independently classified cases and a second physician-reviewer adjudicated disagreements between the first physician and computer classification. Details on quality assurance are presented elsewhere.28 For analysis, strokes were further categorized as ischemic (thrombotic or embolic brain infarction), hemorrhagic (subarachnoid or intracerebral hemorrhage), or combined.28

**Definition of Risk Factors**

Participants had a standardized interview, clinical examination, and laboratory investigations.29 Cigarette smoking was ascertained from interview. Blood pressure was determined using a random-zero sphygmomanometer and the mean of the last 2 measurements was used. Mean arterial blood pressure was computed as two thirds of the diastolic plus one third of the systolic value and the average of this over the first 3 examinations (ie, 6-year mean arterial blood pressure) was used as a covariate for adjustment of blood pressure. Hypertension was defined as systolic blood pressure of 140 mm Hg or greater, diastolic blood pressure of 90 mm Hg or greater, or use of antihypertensive medication during the previous 2 weeks. Diabetes mellitus was defined as a fasting glucose level of at least 126 mg/dL (7.0 mmol/L), a nonfasting glucose level of at least 200 mg/dL (11.1 mmol/L), or a self-reported history of physician-diagnosed diabetes or treatment for diabetes. Average intimal-media wall thickness (IMT) was measured using B-mode ultrasonograms.29 Collection of fasting blood samples and assays of total cholesterol, high-density lipoprotein cholesterol, and glucose levels are described elsewhere.29 All data were from the third examination (considered baseline in this study), except for 6-year mean arterial blood pressure.

**Statistical Analysis**

We classified persons with WMLs of grade 3 or higher as having “WML” and of grade 2 or lower as having “little or no WML” (cutoff corresponds to the 90th percentile of WML scores in the sample).15,26 We used logistic regres-
sion to determine the odds ratios (ORs) and their 95% confidence intervals (CIs) for WMLs in the presence vs absence of a specific retinal abnormality. Polytomous logistic regression models were also used to determine a possible graded effect by treating WML grade as a nominal outcome (ie, grades 0-1 [reference], grade 2, grade 3, and grades 4-9). 30

To examine prospectively the association of WMLs to incident clinical stroke, we used the Kaplan-Meier method to estimate the 5-year cumulative incidence of stroke (defined as 100 × [1-Kaplan-Meier estimators]) according to presence vs absence of WMLs. Follow-up time was defined as the number of days from the MRI examination to the hospital admission date of the first stroke, death, last contact, or December 31, 1998, whichever occurred first. We used Cox regression to estimate the relative risk (RR) of stroke associated with WMLs. To determine the separate and joint effects of WMLs and retinopathy on the risk of stroke, we stratified the population into 4 groups (ie, people with neither lesion, WMLs only, retinopathy only, and both WMLs and retinopathy) and calculated the stroke incidence for each group and the RR of stroke of a particular group vs the group with neither lesion.

All models were adjusted for age, sex, and race. In multivariable models, we further adjusted for 6-year mean arterial blood pressure, antihypertensive medication use (yes, no), diabetes (yes, no), levels of fasting glucose and total cholesterol, carotid IMT, and cigarette smoking (ever, never).

RESULTS

In the study population, 186 (11.0%) persons had cerebral WMLs (grade 3 or more) and 153 (9.1%) persons had retinopathy. TABLE 1 shows the baseline characteristics comparing the presence vs absence of cerebral WMLs and retinopathy. In general, cerebral WMLs were significantly associated with increasing age, black race, and—after adjusting for age, sex, and race—with higher blood pressure and increased carotid IMT. Retinopathy was significantly associated with black race and, after similar adjustment, with higher systolic blood pressure and fasting glucose level, diabetes, and increased carotid IMT.

TABLE 2 shows the distribution of WML grades by presence vs absence of retinopathy and other microvascular abnormalities. Persons with each of the retinal abnormalities were significantly more likely to have higher grades of WML than persons without retinal abnormalities. Logistic regression models of the association between cerebral WML (grade 3 or higher) and specific retinal abnormalities are shown in TABLE 3. After controlling for age, sex, and race, persons with retinal abnormalities were 1.5 to 3.6 times more likely to have cerebral WMLs than persons without these retinal abnormalities. These associations were not substantially altered with further adjustment for blood pressure and other risk factors, with the exception of generalized retinal arteriolar narrowing (which was no longer significant).

Analyses repeated using polyclomous logistic regression with WML categorized as a nominal outcome (grades 0-1 [reference], 2, 3, and 4-9) indicated a stronger association between the presence of retinal abnormalities and higher grades of WML (data not shown). For example, the multivariable-adjusted OR (95% CI) for WML grade 4 through 9 vs grade 0 through 1 was 5.0 (2.6-9.5) for retinopathy, 4.4 (2.4-8.0) for arteriovenous nicking, and 3.6 (1.9-6.7) for focal arteriolar narrowing.

Over a median follow-up of 4.7 years (maximum, 5.8 years), 32 persons developed a clinical stroke. The 5-year cumulative incidence of stroke was 6.8% in persons with WMLs compared with 1.4% in those without. After adjustment for age, sex, race, and vascular risk factors, persons with WMLs were 3.4 times as likely to develop a stroke than...
persons without WMLs (Table 4). Retinopathy, as previously reported,24 was also an independent predictor of stroke.

We performed the following supplementary analyses. First, analysis repeated with WMLs categorized into grades 0 through 1, 2, 3, and 4 through 9 showed higher risk of stroke with increasing grades of WML. Compared with grades 0 through 1, the multivariable-adjusted RR (95% CI) of stroke was 2.0 (0.7-5.6) for grade 2, 5.7 (2.0-16.2) for grade 3, and 4.9 (1.2-13.9) for grades 4 through 9 (P<.001 for trend). Second, of the 32 incident strokes, 25 were ischemic, 5 were hemorrhagic, and 2 were combined ischemic and hemorrhagic. In general, the association between WMLs and risk of ischemic stroke was similar to the association for all strokes (multivariable-adjusted RR, 3.2; 95% CI, 1.2-8.3).

Finally, we examined the separate and joint effects of WMLs and retinopathy on risk of stroke. The 5-year cumulative incidence of stroke was 1.4% in persons without WMLs or retinopathy, 4.0% in those with WMLs only, 4.7% in those with retinopathy only, and 20.0% in those with both WMLs and retinopa-

Table 2. Distribution of Different Grades of Cerebral WMLs, by Retinal Microvascular Characteristics*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Status</th>
<th>No. at Risk</th>
<th>Grade 0-1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4-9</th>
<th>P Value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinopathy</td>
<td>Present</td>
<td>153</td>
<td>82 (53.6)</td>
<td>36 (23.5)</td>
<td>12 (7.8)</td>
<td>23 (15.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>1531</td>
<td>1024 (66.9)</td>
<td>356 (23.3)</td>
<td>105 (6.8)</td>
<td>46 (3.0)</td>
<td></td>
</tr>
<tr>
<td>Microaneurysm</td>
<td>Present</td>
<td>80</td>
<td>40 (50.0)</td>
<td>19 (23.8)</td>
<td>4 (5.0)</td>
<td>17 (21.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>1416</td>
<td>961 (67.9)</td>
<td>325 (23.0)</td>
<td>93 (6.6)</td>
<td>37 (2.6)</td>
<td></td>
</tr>
<tr>
<td>Retinal hemorrhage</td>
<td>Present</td>
<td>76</td>
<td>39 (51.3)</td>
<td>18 (23.7)</td>
<td>8 (10.5)</td>
<td>11 (14.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>1515</td>
<td>1017 (67.1)</td>
<td>352 (23.2)</td>
<td>99 (6.5)</td>
<td>47 (3.1)</td>
<td></td>
</tr>
<tr>
<td>Soft exudate</td>
<td>Present</td>
<td>33</td>
<td>19 (57.6)</td>
<td>5 (15.2)</td>
<td>3 (9.1)</td>
<td>6 (18.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>1597</td>
<td>1062 (66.5)</td>
<td>374 (23.4)</td>
<td>108 (6.8)</td>
<td>53 (3.3)</td>
<td></td>
</tr>
<tr>
<td>Arteriovenous nicking</td>
<td>Present</td>
<td>234</td>
<td>123 (52.6)</td>
<td>65 (27.8)</td>
<td>23 (9.8)</td>
<td>23 (9.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>1401</td>
<td>952 (68.0)</td>
<td>318 (22.7)</td>
<td>92 (6.6)</td>
<td>39 (2.8)</td>
<td></td>
</tr>
<tr>
<td>Focal arteriolar narrowing</td>
<td>Present</td>
<td>238</td>
<td>129 (64.2)</td>
<td>61 (25.6)</td>
<td>25 (10.5)</td>
<td>23 (9.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>1354</td>
<td>923 (68.2)</td>
<td>310 (22.9)</td>
<td>82 (6.1)</td>
<td>39 (2.9)</td>
<td></td>
</tr>
<tr>
<td>Generalized arteriolar narrowing</td>
<td>Present</td>
<td>300</td>
<td>185 (61.7)</td>
<td>73 (24.3)</td>
<td>25 (8.3)</td>
<td>17 (5.7)</td>
<td>.01</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>1201</td>
<td>813 (67.7)</td>
<td>271 (22.6)</td>
<td>80 (6.7)</td>
<td>37 (3.1)</td>
<td></td>
</tr>
</tbody>
</table>

*WML indicates white matter lesion.
†Denotes percentage distribution of grades of WML in presence vs absence of a specific retinal microvascular lesion (row totals for percentages may not add to 100 because of rounding).
‡Based on χ² test of trend across grades of WML.

Table 3. Odds Ratio of Cerebral WMLs, by Retinal Microvascular Characteristics*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Status</th>
<th>No. at Risk</th>
<th>Prevalence, No. (%)</th>
<th>Age-, Sex-, Race-Adjusted†</th>
<th>Multivariable-Adjusted‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinopathy</td>
<td>Present</td>
<td>153</td>
<td>35 (22.9)</td>
<td>2.5 (1.6-3.9)</td>
<td>2.5 (1.5-4.0)</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>1531</td>
<td>151 (9.9)</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Microaneurysm</td>
<td>Present</td>
<td>80</td>
<td>21 (26.3)</td>
<td>3.6 (2.0-6.5)</td>
<td>4.0 (2.1-7.8)</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>1416</td>
<td>130 (9.2)</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Retinal hemorrhage</td>
<td>Present</td>
<td>76</td>
<td>19 (25.0)</td>
<td>2.6 (1.4-4.8)</td>
<td>2.4 (1.2-4.7)</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>1515</td>
<td>146 (9.6)</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Soft exudate</td>
<td>Present</td>
<td>33</td>
<td>9 (27.3)</td>
<td>2.2 (0.9-5.4)</td>
<td>2.6 (1.0-7.0)</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>1597</td>
<td>161 (10.1)</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Arteriovenous nicking</td>
<td>Present</td>
<td>234</td>
<td>46 (19.7)</td>
<td>2.5 (1.7-3.7)</td>
<td>2.1 (1.4-3.2)</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>1401</td>
<td>131 (9.4)</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Focal arteriolar narrowing</td>
<td>Present</td>
<td>238</td>
<td>48 (20.2)</td>
<td>2.5 (1.7-3.7)</td>
<td>2.1 (1.4-3.1)</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>1354</td>
<td>121 (8.9)</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Generalized arteriolar narrowing</td>
<td>Present</td>
<td>300</td>
<td>42 (14.0)</td>
<td>1.5 (1.0-2.2)</td>
<td>1.2 (0.8-1.9)</td>
</tr>
<tr>
<td></td>
<td>Absent</td>
<td>1201</td>
<td>117 (9.7)</td>
<td>Reference</td>
<td>Reference</td>
</tr>
</tbody>
</table>

*WML indicates white matter lesion; OR, odds ratio; and CI, confidence interval.
†Odds ratio (95% CI) of cerebral WML, comparing presence vs absence of a specific retinal microvascular lesion.
‡Additional adjustment for 6-year mean arterial blood pressure, antihypertensive medication use, diabetes, levels of fasting glucose and total cholesterol, carotid intima-media thickness, and cigarette smoking.

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Both Retinopathy only 118 5 4.7 3.7 (1.2-11.8) 4.0 (1.3-12.2)
Cerebral WML only
Neither cerebral WML

WML indicates white matter lesion; RR, relative risk; and CI, confidence interval.
†Cerebral WML defined as grade 3 or higher.
‡Comparing presence vs absence of cerebral WML and retinopathy (same model). See Table 3 footnote for list of covariates.
§Comparing presence vs absence of cerebral WML and retinopathy, adjusted for age, sex, and race (separate models).
¶Multivariable-adjusted RR for stroke was 2.1 for WMLs alone, 2.6 for WMLs only, 3.7 for retinopathy alone, and 11.5 for both WMLs and retinopathy.

Although population-based data indicate that up to 80% of these people may have changes in their cerebral white matter,1-3 the pathogenesis and clinical consequences of these cerebral changes are uncertain.

The current study provides key insights into the underlying pathogenic mechanisms and clinical significance of WMLs in a community-based cohort of middle-aged persons who were initially free of stroke. First, we demonstrate a strong independent association between retinal microvascular abnormalities, as detected on retinal photographs, and WMLs, as defined from cerebral MRI. Persons with retinopathy and other arteriolar abnormalities (arteriovenous nicking and focal arteriolar narrowing) were 2.1 to 4.0 times as likely to have WMLs than persons without these retinal signs, independent of age and vascular risk factors. Second, we show that WMLs were independently associated with risk of clinical stroke. After controlling for blood pressure, diabetes, cigarette smoking, and other stroke risk factors, persons with WMLs were 3.4 times as likely to develop a clinical stroke than those without WMLs in the ensuing 5 years. In addition, we found a multiplicative interaction between retinopathy and WMLs on the risk of stroke. In the presence of retinopathy, persons with WMLs were 18.1 times as likely to develop stroke than those without either WMLs or retinopathy.

Retinal microvascular abnormalities result from small-vessel damage from aging, elevated blood pressure,
and other microvascular processes. Studies have shown that retinal microvascular flow is reduced in persons with WMLs and lacunar infarction and that retinal and cerebral arterioles share similar histopathology in stroke decrements. In the ARIC study, these retinal abnormalities, as detected from photographs, were related to concurrent blood pressure and independently to past blood pressure and markers of inflammation, but not to measures of atherosclerosis. Thus, the strong independent association between these retinal abnormalities and WMLs provides further evidence that microvascular processes (due to hypertension, inflammation, and other factors) may contribute to the occurrence of WMLs, supporting previous pathological studies that have reported small-vessel abnormalities in brains with WMLs, and clinical studies that show associations of WMLs with hypertension and diabetes, but not consistently with atherosclerosis.

Our finding that WMLs predict incident stroke may have important clinical implications. In persons with previous stroke or vascular dementia, these lesions have been reported to predict future episodes of stroke. Fewer data are available regarding stroke risk associated with WMLs in healthy people. In the Cardiovascular Health Study, 11.1% of participants aged 65 years and older with MRI-defined WMLs developed a stroke as compared with 3.5% of participants with normal MRI results. The current data offer additional evidence that asymptomatic persons with WMLs appear to be at increased risk of stroke, independent of other risk factors. Additionally, the risk of stroke associated with WMLs appears to be substantially elevated in the presence of retinopathy. The multiplicative interaction between WMLs and retinopathy on the risk of stroke suggests that cerebral microvascular pathology is more severe in persons with both WMLs and retinopathy. Another possible explanation is that WMLs reflect heterogeneous entities, and the presence or absence of retinopathy distinguishes “pathological” WMLs (with much higher risk of stroke) from those more “benign” in nature.

These data raise the possibility that asymptomatic people with WMLs detected by MRI may benefit from a retinal evaluation for purposes of stroke risk stratification. However, the MRI scans and retinal photographs in the ARIC study were evaluated in a standardized setting, which may not be easily translated to clinical practice. Future investigations using a more simplified WML grading system might increase the practical utility of these data.

The strengths of our study include a population-based cohort, standardized and masked evaluation of MRI and retinal photographs, and validated ascertainment of incident stroke. Limitations should also be noted. First, hypertension is a common risk factor for WMLs, retinal microvascular abnormalities, and stroke, and the effect of blood pressure on these results may be considerable. However, these associations remained highly significant despite controlling for the average of 3 blood pressure measurements over a 6-year period and for use of antihypertensive medications. Second, the small numbers of incident stroke may reduce the precision of the RR estimates presented and may even introduce bias in multivariable models with many covariates. Nevertheless, the observed associations seen were strong and robust in an alternate model with fewer covariates. A longer follow-up with more stroke events may eventually provide a clearer picture.

In conclusion, these population-based data show that WMLs are independently associated with retinal microvascular abnormalities, providing evidence that small-vessel diseases are linked to the pathogenesis of WMLs. Persons with WMLs are at increased risk of developing a clinical stroke, independent of conventional stroke risk factors, particularly when retinopathy is also present.


Epidemiology: Liao.

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Acknowledgment: We thank the staff and participants in the ARIC study for their important contributions.

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Now what I want is, Facts . . . Facts alone are wanted in life.
—Charles Dickens (1812-1870)