The caliber of the retinal vessels has been shown to be associated with stroke events. However, the consistency and magnitude of association, and the changes in predicted risk independent of traditional risk factors, are unclear. To determine the association between retinal vessel caliber and the risk of stroke events, the investigators combined individual data from 20,798 people, who were free of stroke at baseline, in 6 cohort studies identified from a search of the Medline (National Library of Medicine, Bethesda, Maryland) and EMBASE (Elsevier B.V., Amsterdam, the Netherlands) databases. During follow-up of 5–12 years, 945 (4.5%) incident stroke events were recorded. Wider retinal venular caliber predicted stroke (pooled hazard ratio = 1.15, 95% confidence interval: 1.05, 1.25 per 20-μm increase in caliber), but the caliber of retinal arterioles was not associated with stroke (pooled hazard ratio = 1.00, 95% confidence interval: 0.92, 1.08). There was weak evidence of heterogeneity in the hazard ratio for retinal venular caliber, which may be attributable to differences in follow-up strategies across studies. Inclusion of retinal venular caliber in prediction models containing traditional stroke risk factors reassigned 10.1% of people at intermediate risk into different, mostly lower, risk categories.

Each year in the United States, 1 in 18 deaths result from stroke, and approximately 610,000 people will experience their first stroke (1). Many of these stroke events are preventable; however, current methods to identify people at high risk of stroke are limited (2). The retinal and cerebral microcirculations share embryologic, anatomic, and physiologic similarities (3–6), and subtle variation in retinal blood vessel caliber, as measured from retinal photography, has been shown to be independently associated with increased risk of stroke (7–9). These findings have raised the possibility that retinal photography could provide additional information that may be of use in predicting the risk of stroke in asymptomatic people.

Results reported thus far have not been consistent. One study found that a smaller arterio-venular ratio, which may reflect narrower arterioles or wider venules, is associated with incident stroke (9), whereas others report that only wider retinal venules predict stroke (8, 10). Another study suggests that both of these retinal vascular measures (narrower arterioles and wider venules) predict stroke mortality, but only for those younger than 70 years of age (11). A recent meta-analysis using published estimates of different studies reported associations between only wider retinal venular caliber and stroke, with no associations for narrower retinal arteriolar caliber (12). The issue of which microcirculatory changes are related to stroke, and in which subgroups, is important, because these findings may provide insights into the etiology of stroke. Finally, the extent to which retinal vascular imaging changes stroke risk classification when used in conjunction with traditional stroke risk factors is unknown.
To provide robust evidence to address these questions, we conducted a systematic review and an individual-participant meta-analysis to determine the associations of retinal vessel caliber with stroke risk while adjusting for traditional stroke risk factors. We specifically examined whether an individual’s classification of stroke risk as low, intermediate, or high was altered by measurement of retinal vessel caliber in conjunction with traditional risk factors (13).

**MATERIALS AND METHODS**

**Data extraction**

We reviewed the literature to identify all studies conducted in general populations that measured retinal vessel caliber and documented stroke events. A Medline (National Library of Medicine, Bethesda, Maryland) and EMBASE (Elsevier B.V., Amsterdam, the Netherlands) database search was conducted of all studies published between 1950 and July 21, 2009.

The Medline search terms we used were (exp Retinal Diseases/, (retina or retinal).tw., retinopathy.tw., Arteriolar narrowing.tw., Arterio-venous nicking.tw., Arteriovenous nicking.tw., venular dilatation.tw., venular dilation.tw., arterio-venular ratio.tow.) and (Cardiovascular Diseases/exp Heart Diseases/exp Vascular Diseases/,exp Cardiovascular.tw., stroke.tow., mortality.tow.) and (incidence/, exp Mortality/, exp epidemiologic studies/, prognostic.tw., Prognosis/, predict_.mp., course.tw., (score or scoring or scored).tw., observation.mp., risk:.mp., between group:.tw.) and (Photography/, Photomicrography/, photo$.tw., image$.tw.). We then searched the selected papers to identify studies that met the inclusion criteria: they were carried out in general populations, had measured retinal vascular caliber from either 35 mm photographic film or digital photographs using computer-assisted methods, and had recorded stroke events.

We contacted the principal or lead investigators of the chosen studies and obtained individual-participant data from each of the studies to enable investigation of heterogeneity in published results and, if appropriate, to calculate pooled estimates of the associations between retinal vascular caliber and stroke risk. Study investigators who agreed to participate in this collaborative project were then requested to provide original recorded data on the following variables: individual retinal vessel caliber measurements, fatal and nonfatal stroke events and time to these events, baseline measurements of the traditional risk factors (age, sex, systolic blood pressure, serum total cholesterol, high density lipoprotein cholesterol, current smoking status, use of blood-pressure-lowering medications, prevalent coronary heart disease), the presence of diabetes, and previous stroke.

We excluded people with diabetes from this meta-analysis. Current guidelines for primary stroke prevention already recommend tight control of blood pressure and lipid levels among this group (2), so measurement of these additional risk factors may be of limited use (14).

**Statistical analysis**

The standard deviation for the means of arteriolar and venular caliber was approximately 20 µm. We estimated hazard ratios associated with a 20-µm decrease in arteriolar caliber and a 20-µm increase in venular caliber, each adjusted for the other retinal vessel caliber and adjusted for the traditional risk factors. These were estimated separately for each study by using a proportional hazards model. Data were then combined for all studies, and a stratified proportional hazards model was used to test interaction between the study stratification variable and retinal vessel caliber variables, as well as the traditional risk factors. Doing so tests heterogeneity across studies in associations with retinal vessel caliber. When no heterogeneity was present, we obtained a pooled hazard ratio adjusted for the traditional risk factors. The stratified proportional hazards model allows the baseline hazard function to differ between the studies but assumes that the effect of the retinal vessel caliber and the other variables is fixed.

Fatal events in all studies were identified from searches of death registers supplemented by contact with relatives and/or local medical providers in all studies (11, 15–18). For nonfatal stroke outcomes, the Australian Diabetes, Obesity and Lifestyle (AusDiab) study; Beaver Dam Eye Study (BDES); and Blue Mountains Eye Study (BMES) identified nonfatal stroke events among only those who returned for subsequent study visits (19). These participants were asked whether they had had a stroke event. In BMES and AusDiab, this question was then verified from participants’ medical records, but not in BDES. In AusDiab, 82% of participants returned for the follow-up examination (20); in BMES and BDES, 75% returned for the 5-year follow-up visit (19, 21). The remaining 3 studies—the Atherosclerosis Risk in Communities (ARIC) study, Cardiovascular Health Study, and the Rotterdam Study—identified nonfatal events by using a process of continuous monitoring, which included regular telephone interviews and contacts with general practitioners and local hospitals (15, 17, 18). In all of the studies except BDES, stroke events were validated by clinician review of available medical records. Transient ischemic attack was not included in the definition of stroke for this meta-analysis.

In each study, the appropriate functional form of each of the continuous variables in the models was assessed by using fractional polynomials, and the proportional hazards assumption was tested by using plots of the Schoenfeld residuals and by testing for the effect of adding time-dependent covariates (22).

We conducted a number of sensitivity analyses to assess the robustness of the results to different methods of analysis. We repeated the main analysis by 1) standardizing the retinal vessel caliber measurements by dividing them by the study-specific standard deviations to allow for different means and standard deviations of the retinal vessel caliber measurements in the different studies (23) and 2) estimating the pooled hazard ratio by using a 2-stage process. First, the hazard ratios for the retinal caliber were estimated separately for each study; second, these estimates were pooled by using a random-effects model (23).

**Reclassification of participants when adding retinal caliber to the risk prediction model**

Among people without prevalent coronary heart disease, we calculated the difference between the 5-year risk of
Table 1. Characteristics of Study Participants Included in the Meta-Analysis

<table>
<thead>
<tr>
<th>Study (Reference No.)</th>
<th>No. of Participants Included in the Meta-Analysis</th>
<th>No. of Stroke Events</th>
<th>No. of Participants with Retinal Vessel Caliber Measurement</th>
<th>Study (Reference No.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARIC (9)</td>
<td>9,083</td>
<td>9,082</td>
<td>52,301</td>
<td>BDES (45)</td>
</tr>
<tr>
<td>AusDiab (44)</td>
<td>1,002</td>
<td>1,002</td>
<td>10,020</td>
<td>BMES (19)</td>
</tr>
<tr>
<td>BDES (45)</td>
<td>3,047</td>
<td>3,047</td>
<td>30,470</td>
<td>CHS (8)</td>
</tr>
<tr>
<td>BMES (19)</td>
<td>1,842</td>
<td>1,842</td>
<td>18,420</td>
<td>Rotterdam (10)</td>
</tr>
<tr>
<td>CHS (8)</td>
<td>1,285</td>
<td>1,285</td>
<td>12,850</td>
<td></td>
</tr>
<tr>
<td>Rotterdam (10)</td>
<td>4,539</td>
<td>4,539</td>
<td>45,390</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ARIC, Atherosclerosis Risk in Communities; AusDiab, Australian Diabetes, Obesity and Lifestyle; BDES, Beaver Dam Eye Study; BMES, Blue Mountains Eye Study; CHS, Cardiovascular Health Study; HDL, high density lipoprotein; IQR, interquartile range.

RESULTS

Characteristics of the studies identified

Our initial search strategy found 3,952 papers. Twenty-five studies were then identified that had performed retinal assessments or vessel caliber measurements and had followed participants over time to monitor stroke events. Eighteen of these studies recorded only the presence of retinopathy and not retinal vessel caliber or they were conducted exclusively among people with diabetes or recorded only fatal events (25–42). This exclusion process resulted in 7 studies that met our inclusion criteria. One study, the Multi-Ethnic Study of Atherosclerosis (MESA), did not have sufficient outcome data available at the time of the analysis (43). Investigators from all 6 of the other studies agreed to provide data for the individual-participant meta-analysis. These 6 studies were ARIC (9), the Cardiovascular Health Study (8), the AusDiab study (44), BMES (19), BDES (45), and the Rotterdam Study (10).

Table 1 shows the characteristics of 20,798 participants without diabetes from each of the 6 studies included in the analysis. Measurement of retinal vessel caliber was similar in each study, with some slight variations (44, 46–50). Briefly, for participants of each study, retinal photographs (film or digital) were taken for a single eye or both eyes, centered on the optic disc and macula. BDES and BMES used the Zeiss FF3 camera and 30° fields (11), ARIC and the Cardiovascular Health Study used the Canon CR6-45NM camera with 45° fields (46, 49), AusDiab used the Canon CR45UAF camera with 45° fields (44), and the Rotterdam Study used the Topcon TRC-SS2 camera with 20° fields (10). In BDES, BMES, AusDiab, and the Rotterdam Study, stereoscopic images were taken; in ARIC and the Cardiovascular Health Study, single images were taken. In the AusDiab study, a digital image was captured, whereas in the other studies the color slide or transparency was digitized by using a scanner. BDES, BMES, and the Rotterdam Study all took retinal photographs following pharmacologic mydriasis, whereas ARIC, AusDiab, and the Cardiovascular Health Study took nonmydriatic photographs (44, 46–50). The Rotterdam Study used the photograph with the best image quality from either eye to measure retinal vessel...
caliber; in all other studies, a prespecified eye (usually the right eye) was used for the measurement and analysis of retinal vessel caliber, which was replaced with the measurement from the other eye (usually the left eye) only if the image of the first eye was not usable (44, 46–50). In a random subsample of 100 participants, the Rotterdam Study found no difference in summary measures for the right and left eyes (10).

Optic disc photographs were then viewed by trained graders masked to participant characteristics. Graders measured the diameters of all arterioles and venules coursing through a zone surrounding the optic disc, one-half to one disc diameter away from the optic disc margin, using a computer-assisted software program. The measurement module was custom programmed in Khoros (public domain image processing software from the University of New Mexico, Albuquerque) and utilized the green channel of the digital image to enhance contrast of the retinal vessels against the retinal pigment epithelium. The ARIC, BDES, and BMES studies used an earlier version of this software to measure retinal vessel caliber, whereas AusDiab, the Cardiovascular Health Study, and the Rotterdam Study used a later version of the same software. Both versions are available on request from the authors or from the Wisconsin Fundus Photograph Reading Center, University of Wisconsin-Madison. The individual mean retinal vessel calibers provided by each study were summarized for the present meta-analysis by using the Parr-Hubbard formula (46).

Participants in all studies completed baseline questionnaires on previous medical history, and traditional stroke risk factors were measured. ARIC, Cardiovascular Health Study, and Rotterdam Study participants underwent a more extensive clinical examination than participants in the other studies (17, 18, 51). All studies used standard methods to measure the traditional cerebrovascular disease risk factors of systolic blood pressure, smoking status, serum total cholesterol, and high density lipoprotein cholesterol. The only differences between studies were that BMES recorded systolic blood pressure taken from one measurement at the baseline visit, whereas all other studies used the average of at least 2 measurements taken at the baseline visit (52). In addition, the Rotterdam Study and BDES measured nonfasting cholesterol and high density lipoprotein cholesterol levels; all other studies measured fasting values (11, 50).

Assessment of proportional hazards assumption

No evidence of a nonlinear relation was found in any of the studies between any covariates and the log-hazard function, so all covariates were fitted as linear in the proportional hazards model. The proportional hazards assumption was satisfied in all data sets.

Assessment of heterogeneity of hazard ratios between studies

Table 2 provides hazard ratios for the stroke events outcomes among people without diabetes in each study, adjusted for the traditional risk factors. The hazard ratios for arteriolar caliber were not significant in any of the studies. Four of the 6 hazard ratios for venular caliber were greater than 1, with 2 of the studies showing a significant association. The 2 studies with hazard ratios of less than 1 had the smallest number of events and also recorded nonfatal stroke events among only those who returned for a subsequent visit at 5 years. There was weak evidence that the effect of retinal venular caliber was heterogeneous between studies ($P = 0.06$). Excluding the AusDiab and BMES studies removed any evidence of

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Participants$^b$ Included in Stroke-events Meta-Analysis</th>
<th>No. of Stroke Events</th>
<th>Retinal Arteriolar Caliber$^d$</th>
<th>Retinal Venular Caliber$^d$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Retinal Arteriolar Caliber$^d$</td>
<td>Retinal Venular Caliber$^d$</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>HR 95% CI</td>
<td>HR 95% CI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARIC</td>
<td>9,083</td>
<td>226</td>
<td>0.92 0.76, 1.12</td>
<td>1.18 0.97, 1.43</td>
</tr>
<tr>
<td>AusDiab</td>
<td>1,002</td>
<td>4</td>
<td>1.17 0.48, 2.84</td>
<td>0.80 0.27, 2.36</td>
</tr>
<tr>
<td>BDES</td>
<td>3,047</td>
<td>138</td>
<td>0.98 0.80, 1.22</td>
<td>1.04 0.84, 1.28</td>
</tr>
<tr>
<td>BMES</td>
<td>1,842</td>
<td>33</td>
<td>1.02 0.68, 1.54</td>
<td>0.74 0.48, 1.13</td>
</tr>
<tr>
<td>CHS</td>
<td>1,285</td>
<td>102</td>
<td>1.06 0.82, 1.36</td>
<td>1.37 1.05, 1.81</td>
</tr>
<tr>
<td>Rotterdam</td>
<td>4,539</td>
<td>442</td>
<td>1.00 0.88, 1.34</td>
<td>1.16 1.03, 1.31</td>
</tr>
<tr>
<td>Pooled cohort</td>
<td>20,798</td>
<td>945</td>
<td>1.00 0.92, 1.08</td>
<td>1.15 1.05, 1.25</td>
</tr>
</tbody>
</table>

$^a$ The traditional risk factors are age, systolic blood pressure, serum cholesterol, current use of antihypertensive medication, and prevalent coronary heart disease. The hazard ratios were also adjusted for the other retinal vessel caliber.

$^b$ Excluding people with diabetes or previous stroke.

$^c$ Per 20-$\mu$m decrease in arteriolar caliber.

$^d$ Per 20-$\mu$m increase in venular caliber.
heterogeneity. There was evidence that the effect of systolic blood pressure on stroke risk varied between studies ($P = 0.01$). However, accounting for this interaction had no effect on the hazard ratios for retinal arteriolar caliber. There was no evidence that the effect of the other traditional risk factors on risk of stroke varied between studies.

**Pooled hazard ratios for stroke**

We found evidence that wider venular caliber was associated with an increased risk of stroke (hazard ratio = 1.15, 95% confidence interval: 1.05, 1.25 per 20-μm increase in caliber), and there was no evidence of an association between arteriolar caliber and risk of stroke (hazard ratio = 1.00, 95% confidence interval: 0.92, 1.08 per 20-μm decrease in caliber) (Table 2). Study-specific and pooled hazard ratios are summarized in Figures 1 and 2.

Table 3 shows the pooled hazard ratios for retinal venular caliber and stroke in subgroups stratified by age, sex, and hypertension status. We found no evidence that the effect of retinal vessel caliber differed by sex and hypertension status. There was weak evidence that the effect of the retinal calibers differed by age ($P = 0.07$).

Findings were similar when the retinal caliber measurements were standardized by using the study-specific standard deviations and also when the study-specific hazard ratios were combined by using a random-effects model.

**Reclassification of participants when adding retinal caliber to the risk prediction model**

Figure 3 shows that, for people who changed risk categories when retinal vessel caliber was added to the prediction model,
their risk predicted by the traditional risk factors tended to be close to a boundary where risk categories change (2% and 5%). Figure 4 displays the percentage who changed risk category for each level of risk predicted by the traditional risk factors. The largest amount of reclassification occurred in the intermediate risk category, where 10.1% were reclassified. Among the 3,600 participants at intermediate risk, 250 (6.9%) were reclassified down and 115 (3.2%) were reclassified up.

Table 3. Relation of Retinal Venular Caliber and Incident Stroke in Subgroups of the Pooled Population, Adjusted for Traditional Risk Factors

<table>
<thead>
<tr>
<th>Age, years</th>
<th>No. at Risk</th>
<th>No. of Stroke Events</th>
<th>Retinal Arteriolar Caliber</th>
<th>Retinal Venular Caliber</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;60</td>
<td>8,543</td>
<td>131</td>
<td>1.10 (0.86, 1.40)</td>
<td>1.36 (1.07, 1.73)</td>
</tr>
<tr>
<td>60–69</td>
<td>7,860</td>
<td>372</td>
<td>0.94 (0.82, 1.08)</td>
<td>1.09 (0.94, 1.25)</td>
</tr>
<tr>
<td>70–79</td>
<td>3,432</td>
<td>314</td>
<td>1.06 (0.92, 1.23)</td>
<td>1.20 (1.04, 1.38)</td>
</tr>
<tr>
<td>≥80</td>
<td>963</td>
<td>128</td>
<td>0.78 (0.62, 0.98)</td>
<td>0.91 (0.73, 1.15)</td>
</tr>
<tr>
<td>Male</td>
<td>8,797</td>
<td>426</td>
<td>1.01 (0.89, 1.15)</td>
<td>1.18 (1.04, 1.35)</td>
</tr>
<tr>
<td>Female</td>
<td>12,001</td>
<td>519</td>
<td>0.98 (0.87, 1.10)</td>
<td>1.11 (0.99, 1.24)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>9,677</td>
<td>667</td>
<td>0.96 (0.87, 1.06)</td>
<td>1.10 (0.99, 1.22)</td>
</tr>
<tr>
<td>No hypertension</td>
<td>11,121</td>
<td>278</td>
<td>1.06 (0.90, 1.25)</td>
<td>1.23 (1.05, 1.45)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio.

DISCUSSION

In this individual-participant-level meta-analysis of 20,798 participants without diabetes, we showed that retinal venular caliber predicts an increased risk of incident stroke, independent of traditional stroke risk factors. Addition of information on retinal venular caliber reclassified 1 in 10 persons at intermediate risk into different risk categories. In
contrast, retinal arteriolar caliber was not associated with stroke. There was weak evidence of heterogeneity in the hazard ratio for retinal venular caliber, which may be attributable to differences in follow-up strategies across studies. Summarized results were consistent among subgroups stratified by age, sex, and the presence of hypertension.

Our results confirm the recent observation from some studies, and a recent meta-analysis, that wider retinal venular caliber, rather than narrower retinal arteriolar caliber, is related to risk of stroke. This association supports increasing evidence that venules may play a key role in pathogenesis of stroke more than merely reflecting passive conductance vessels, and it highlights the importance of viewing the venular microvasculature as a dynamic component responsive to changes in circulatory flow. The mechanisms linking wider retinal venules with increased risk of stroke are unclear but may be related to concurrent circulatory phenomena such as altered vessel wall stresses, cerebral hypoxia (53), or venous insufficiency in both the retina and brain (54). It is also possible that retinal venular caliber is a more precise measure than arteriolar caliber of retinal microvascular flow. It has been shown that wider retinal venules are associated with carotid artery disease (50) and reduced arterial wall compliance, another marker of stroke risk that influences blood pressure and hemodynamics (55). Other investigators have suggested that wider retinal venular caliber is related to systemic markers of inflammation (43, 50, 56) and may be an indicator of impaired cerebral oxygen perfusion (56), which is consistent with clinical observations that ocular ischemic syndrome from carotid occlusion leads to mural hypoxia and retinal venular dilation (57). Our findings thus support the continuing research in a relatively unexplored area—the study of venular pathophysiology in both the retina and brain—that may provide further insights into the etiology of microvascular stroke (54, 58).

Estimation of stroke risk using traditional risk factors is currently recommended in the primary prevention of stroke (2), and it has recently been proposed that the predicted risks be stratified and that those persons at intermediate risk may benefit from further testing to help guide treatment (13). Adding retinal vessel caliber measurements to prediction models containing only traditional risk factors reassigned 10.1% of persons at intermediate risk. Most of those reassigned were moved into lower risk categories. At the individual level, the absolute change in predicted risks for individuals who changed risk categories was small and would be unlikely to influence treatment strategies. At the population level, whether reassigning 10.1% of those at intermediate risk would result in a cost-effective improvement in outcomes has yet to be determined. Further work on the costs of implementing retinal vessel imaging and whether preventive therapies significantly improve outcomes is required before this reassignment can be recommended.

Stroke is a heterogenous disorder with multiple etiologies (59). Some forms of stroke, such as lacunar stroke and deep cerebral hemorrhages, are believed to be primarily due to cerebral small vessel disease, and studying the retinal vascular changes in these subtypes may provide valuable clues to their pathophysiology. Our meta-analysis did not examine the relation of retinal vascular caliber to specific stroke subtypes because few of the studies had these data available. A large, multicenter cohort study is currently under way to examine the relation of retinal vascular calibers to specific stroke subtypes (e.g., ischemic, hemorrhagic, lacunar) (60).
The strengths of this meta-analysis are that we identified and analyzed all known population studies to date that have measured retinal vessel calibers and stroke outcomes, resulting in a large sample of 20,798 individuals and 945 stroke events. We were also able to include unpublished data from some studies (ARIC and AusDiab) of the relation between individual retinal vessel calibers and incident stroke. Because measurement of retinal vessel caliber using retinal photography is a relatively new technique, we were able to collaborate with all of the researchers worldwide who have reported using this technology in cohort studies that have recorded stroke events. We thus think that publication bias is highly unlikely to be present in our review and meta-analysis. We were able to standardize inclusion criteria for study subjects, the method of analysis of retinal vessel caliber, covariates adjusted for, and definitions for stroke events because we had access to individual-participant data records. This strategy provides more accurate risk estimates than meta-analyses do, which rely on published estimates (12).

This meta-analysis has a number of limitations. Error in measurement of the retinal vessel calibers and the traditional risk factors was not taken into account and may have resulted in overestimation or underestimation of the true association between retinal vessel caliber and stroke (61). These errors may differ between the studies because of the different photographic procedures and software used. In addition, in our study, we summarized retinal vessel caliber using the Parr-Hubbard formula because all 6 studies provided this data (46). A revised formula is available; however, use of this formula has been shown not to affect the estimated associations between retinal vessel caliber and cardiovascular disease outcomes (62). Finally, there was some variability in the collection of data on stroke outcomes across studies. Three of the studies (AusDiab, BDES, and BMES) recorded nonfatal events among only those who returned for a subsequent visit and responded positively to a question on stroke events. These 3 studies had the lowest hazard ratios. Removal of these studies from our analysis removed any evidence of heterogeneity and increased the pooled hazard ratio. People in poorer health, and so at greater risk of stroke, may not have returned for the follow-up visit. It is possible that the less stringent assessment of stroke events in these 3 studies reduced the ability of these studies to detect an association.

In summary, our meta-analysis utilizing individual data records on 20,798 middle- to older-aged individuals without diabetes confirmed that wider retinal venular caliber is independently associated with an increased risk of stroke events. No association with narrower retinal arteriolar caliber was observed. Our findings suggest that if retinal vessel caliber assessments are added to the traditional risk factors, 1 in 10 people without diabetes at intermediate risk would be reclassified from their current risk categories. The applicability and clinical utility of using retinal imaging for stroke risk prediction requires further study, but our results highlight the importance of examining venular widening in understanding pathophysiologic associations of the retinal and cerebral microcirculations.

ACKNOWLEDGMENTS

Author affiliations: Screening and Test Evaluation Program, School of Public Health, University of Sydney, Sydney, New South Wales, Australia (Kevin McGeechan, Petra Macaskill, Les Irwig); Centre for Vision Research, Department of Ophthalmology, Westmead Millennium Institute, University of Sydney, Sydney, New South Wales, Australia (Gerald Liew, Jie Jin Wang, Paul Mitchell); Department of Ophthalmology and Visual Sciences, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin (Ronald Klein, Barbara E. K. Klein); Centre for Eye Research Australia, University of Melbourne, Melbourne, Victoria, Australia (Jie Jin Wang, Tien Y. Wong); Department of Epidemiology and Biostatistics, Erasmus Medical Center, Rotterdam, the Netherlands (Johannes R. Vingerling, Jacqueline C. M. Witteman, Monique M. B. Breteler); Department of Ophthalmology, Erasmus Medical Center, Rotterdam, the Netherlands (Johannes R. Vingerling, Paulus T. V. M. de Jong); Department of Ophthalmomgenetics, The Netherlands Institute for Neuroscience, Royal Netherlands Academy of Arts and Sciences, Amsterdam, the Netherlands (Paulus T. V. M. de Jong); Department of Ophthalmology, Academic Medical Center, Amsterdam, the Netherlands (Paulus T. V. M. de Jong); Department of Ophthalmomgenetics, The Netherlands Institute for Neuroscience, Royal Netherlands Academy of Arts and Sciences, Amsterdam, the Netherlands (Paulus T. V. M. de Jong); Baker IDI Heart and Diabetes Institute, Melbourne, Victoria, Australia (Jonathan Shaw, Paul Zimmet); and Singapore Eye Research Institute, Yong Loo Lin School of Medicine, National University of Singapore, Singapore (Tien Y. Wong).

This work was supported by the Australian National Health and Medical Research Council (program grants 402764 and 358395). The research reported in this article was supported by contracts N01-HC-85079 through N01-HC-85086, N01-HC-35129, N01 HC-15103, N01 HC-55222, N01-HC-75150, N01-HC-45133, grant U01 HL080295 from the National Heart, Lung, and Blood Institute, with an additional contribution from the National Institute of Neurological Disorders and Stroke. The ARIC study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts N01-HC-55015, N01-HC-55016, N01-HC-55018, N01-HC-55019, N01-HC-55020, N01-HC-55021, and N01-HC-55022.

The authors thank the staff of the ARIC study for their important contributions.

Kevin McGeechan had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Ruth Mitchell provided advice on the construction of the Medline and EMBASE search strategies.

A full list of principal Cardiovascular Health Study investigators and institutions can be found at http://www.chs-nhlbi.org/pi.htm.

Conflict of interest: none declared.

REFERENCES


