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10-Year Longitudinal Changes in Retinal Microvascular Lesions: The Atherosclerosis Risk in Communities Study

Gerald Liew, MD, MPH[1,2], **Stephen Campbell, MHS**[3], **Ronald Klein, MD, MPH**[4], **Barbara E. K. Klein, MD, MPH**[4], **A Richey Sharrett, MD, DrPH**[5], **Mary Frances Cotch, PhD**[6], **Jie Jin Wang, PhD**[1,2], and **Tien Y. Wong, MD, PhD**[2,7]

[1] Centre for Vision Research, University of Sydney, NSW, Australia

[2] Centre for Eye Research Australia, University of Melbourne, Victoria, Australia

[3] Department of Biostatistics, University of North Carolina, Chapel Hill, North Carolina, USA

[4] Department of Ophthalmology and Visual Science, University of Wisconsin School of Medicine and Public Health, Madison, USA

[5] Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, USA

[6] Division of Epidemiology and Clinical Applications, National Eye Institute, National Institutes of Health, Bethesda, Maryland, USA

[7] Singapore Eye Research Institute, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

Abstract

Objective—There are limited data on the natural history and longitudinal changes of retinal microvascular lesions. We examined 10-year changes in retinal microvascular lesions, focusing on those related to hypertension and shown to predict development of cardiovascular disease.

Design—Prospective cohort

Participants—1,120 middle-aged participants without diabetes of the Atherosclerosis Risk in Communities (ARIC) Study in 1993–5 and again 10 years later in 2003–5.

Methods—. Retinal microvascular lesions were graded from retinal photographs using the same protocol at both examinations, with changes (incidence or disappearance) adjudicated by a side-by-side comparison of photographs. The study sample was stratified by carotid intima-media thickness (IMT) and ARIC field center; thus all analyses were weighted by these factors. Persons with diabetes were excluded because the frequency and pathophysiology of diabetic retinal lesions is different.

Main Outcome Measures—Incidence and disappearance rates of lesions.

Results—. The 10 year incidence of focal arteriolar narrowing, arteriovenous (AV) nicking, and retinopathy in persons without diabetes was 3.4% (95% confidence intervals 2.3–4.9), 2.5% (1.6–

Correspondence to: Tien Y. Wong, MD, PhD, Centre for Eye Research Australia, University of Melbourne, 32 Gisborne Street, Victoria 3002, Australia, Tel: +61 3 9929 8352, Fax: +61 3 9662 3859, twong@unimelb.edu.au.

No conflicting relationship exists for any author.

3.9), and 2.2% (1.3–3.5) respectively. Over the 10 year period, of 32, 219, and 24 eyes with focal arteriolar narrowing, AV nicking and retinopathy at baseline, 50.3% (28.6–71.9), 40.7% (32.7–49.4) and 65.9% (42.4–83.5), respectively, disappeared. Higher baseline plasma fibrinogen and white cell count were associated with incident focal arteriolar narrowing; antihypertensive medication use associated with incident AV nicking; and higher diastolic blood pressure, carotid IMT and white cell count associated with incident retinopathy. Higher fasting serum glucose was not significantly associated with incident retinopathy, though this may be related to the small number of lesions.(Odds ratio 5.88, 95% confidence interval 0.74–46.64 per standard deviation difference)

Conclusions—In this sample of middle-aged adults, new retinal microvascular lesions appeared at a rate between 2–4% over 10 years. A high percentage of lesions (40% or more) disappeared over the same period, suggesting considerable remodeling in the retinal microvasculature.

Keywords

microvascular signs; hypertension; microcirculation; retina; ARIC

INTRODUCTION

Retinal microvascular lesions such as focal arteriolar narrowing, arteriovenous (AV) nicking and retinopathy lesions (e.g., microaneurysms, hemorrhages, and cotton wool spots) are strongly associated with systemic vascular disease such as hypertension[1] and may be markers of cerebral small vessel disease.[2;3] cerebral atrophy and cognitive decline [4–6]. They are also known to predict incident coronary heart disease,[2;7] cardiac failure,[8] stroke[3], and cardiovascular mortality.[9–11] These lesions are present in 2–15% of the general population and appear to be markers of microvascular damage from elevated blood pressure, inflammatory processes and vascular endothelial dysfunction.[12] However, despite their importance as clinical markers of end organ damage, few prospective studies have examined the incidence and disappearance rates of these retinal lesions, or the factors influencing these rates. [13–15] Such data are needed to better understand the evolution of retinal microvascular disease.

We have previously reported cross-sectional data on atherosclerotic risk factor associations of retinal microvascular lesions.[2;16;17] In the present study we describe the 10-year incidence and disappearance of retinal microvascular lesions and their relationship to vascular disease risk factors in participants without diabetes from the same population-based cohort. Participants with diabetes were excluded as the pathophysiology of retinal microvascular lesions, particularly retinopathy, is likely to be different and determined primarily by hyperglycemia.[18]

METHODS

Study Population

The Atherosclerosis Risk In Communities (ARIC) study is a population-based cohort study that included 15,792 women and men 45–64 years of age at recruitment in 1987 through 1989. Further details are published elsewhere [19;20] The current analysis comprises a subgroup of 1,120 persons who participated at the third examination and the Carotid MRI (Magnetic Resonance Imaging) substudy 10 years later, as these were the 2 examinations where retinal photography was performed. Of the 12,887 participants at the third examination (visit 3), 2066 returned for Carotid MRI 10 years later. From these 2066 persons, we excluded 530 and 259 who did not have retinal photographs or had ungradable photographs at visit 3 and Carotid MRI respectively, 150 who had diabetes, and 7 with

missing data on other variables, leaving 1,120 for this analysis. Persons with diabetes were excluded because the prevalence of retinal microvascular lesions is very much higher, and the underlying pathophysiology is different.[18]

Sampling of Carotid MRI substudy

The ARIC Carotid MRI substudy re-examined 2066 surviving participants in 2005–2006 where they underwent repeat retinal photography, carotid ultrasound and brain MRI.[21] The sample was selected to achieve approximately 1200 participants with high carotid intima-media thickness (IMT) values at their last ARIC ultrasound examination and an additional 800 participants randomly sampled from the remainder of the carotid IMT distribution. Field-center-specific cutpoints of carotid IMT were used to achieve this, with 100% sampling above the cutpoint, and a sampling fraction below the cutpoint to achieve the desired 800 participant total. The cutpoints were 1.35, 1.00, 1.28, and 1.22mm IMT at Forsyth County, Jackson, Minneapolis suburbs, and Washington County, respectively, representing the 73rd, 69th, 73rd, and 68th percentiles of maximal IMT. Participants were ineligible for the substudy if they had standard contraindications to MRI or contrast agent, carotid revascularization on either side for the low IMT group or on the side selected for imaging for the high IMT group, or difficulties in completing informed consent. A total of 4306 persons were contacted and invited to participate in the substudy; 1403 refused, 346 were ineligible, 491 reported medical conditions which precluded their participation, and 2066 (48%) participated. Those who refused were more likely to be African American, and have diabetes, hypertension, and obesity, compared to those who participated. [21]

Institutional review boards at each study site and at the University of Wisconsin, Madison where the Ocular Epidemiology Photograph Reading Center is located, approved the study. Informed consent was obtained from all participants and the study was conducted in accordance with the Declaration of Helsinki.

Assessment of Retinal Microvascular Lesions

The retinal photography procedure and grading of retinal microvascular lesions have been described in detail elsewhere.[12;22] Briefly, retinal photographs using film of 1 randomly selected eye of each participant was taken at visit 3. If the eye selected randomly was considered too difficult or not possible to photograph with adequate quality (e.g., inability to dilate the pupil to at least 4 mm, inability to fixate adequately for proper photographic field definition, or opacities of the ocular media preventing a reasonably clear view of the retina), the other eye was photographed instead. Following 5 minutes of dark adaptation, a 45-degree photograph was taken, centered on the region of the optic disc and the macula, using an auto-focus camera. The same eye was re-photographed at carotid MRI about 10 years later.

Trained graders masked to participant characteristics at the Ocular Epidemiology Photograph Reading Center, University of Wisconsin-Madison, examined the photographs for the presence of retinal vascular abnormalities, including (1) focal arteriolar narrowing (2) arteriovenous (AV) nicking and (3) retinopathy lesions (such as microaneurysms, retinal hemorrhages, cotton wool spots and hard exudates). The grading and definition of these lesions were based on a standard protocol described in other reports, and identical between visit 3 and follow-up.[22] Incidence was defined as the appearance of a retinal microvascular sign at the carotid MRI examination in persons who did not have that sign 10 years earlier at the visit 3 examination. Disappearance was defined as the absence at carotid MRI of a previously documented lesion at visit 3. When a lesion appeared or disappeared, side-by-side grading, masked by subject information, was performed by another grader to ensure the

change was real and not due to differences in the photographic field, quality of the photograph, or grader error.

Quality control procedures for retinal photography and grading have been previously reported.[22] The reliability of retinal microvascular sign assessment is moderate to high in the ARIC study for most lesions, with repeated grading of photographs during earlier visits (3 and 4) showing intra-grader and inter-grader weight kappas 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.[12] Intra-individual reliability coefficients were generally high.[23]

Definition of Other Variables

Participants underwent standardized evaluations at each examination.[19] At each examination, blood pressures were taken with a random-zero sphygmomanometer, and the mean of the last 2 of 3 measurements was used for analysis. Hypertension and diabetes history, cigarette smoking, alcohol consumption, and use of anti-hypertensive and diabetic medications were ascertained by questionnaire. Hypertension was defined as systolic blood pressure (BP)≥140 mmHg, diastolic BP≥90 mmHg, or use of anti-hypertensive medication during the previous 2 weeks. Mean arterial BP was defined as 2/3 systolic BP + 1/3 diastolic BP. Diabetes mellitus was defined as a fasting glucose ≥126 mg/dl (≥7.0 mmol/L), a non-fasting glucose ≥200mg/dl (≥11.1 mmol/L), or a self-reported history of physician-diagnosed diabetes or pharmaceutical treatment for diabetes. Total plasma cholesterol and triglycerides were measured by enzymatic methods, High Density Lipoprotein (HDL) cholesterol was measured after dextran-magnesium precipitation of the non-HDL lipoproteins, and glucose was measured by the modified hexokinase/glucose-6-phosphate dehydrogenase procedure. Platelet and white blood cell counts were measured by Coulter counter. Venous blood was drawn after an 8-hour fast for measuring fibrinogen, factor VIII, and von Willebrand factor (vWF) antigen at visit 1. Fibrinogen was measured by thrombin-time titration; factor VIII activity, by clotting time with the use of factor VIII–deficient plasma; and vWF antigen, by ELISA kits. Height and weight were measured for calculation of body mass index (BMI). Mean carotid intima media thickness (IMT) was derived from standardized B-mode ultrasonograms at visit 3 or imputed from readings taken at visit 4.[24] Other variables were based on the visit 3 examination at the time of retinal photography.

Statistical methods

All analyses were based on methods appropriate for stratified random sampling. Analyses were weighted by the inverse of the sampling fractions in the 8 sampling strata (2 IMT strata X 4 field centers) - e.g., the sampling weight for a given individual was the reciprocal of (the number participating from a given IMT stratum at a given field center/the number from the same stratum at the same field center who were invited to participate). Continuous risk factors such as blood pressure were standardized using 1 standard deviation of exposure. We constructed logistic models adjusted for age (continuous), race, and gender, to examine the association between single risk factors and arteriovenous nicking, focal arteriolar narrowing, and diabetic retinopathy. SAS software (version 9.1, SAS Institute) was used for analysis of descriptive statistics and SUDAAN (RTI International) was used for logistic regression. (Details of variance and parameter estimation are given in Sections 4.8 and 10.9 of Research Triangle Institute (2004). *SUDAAN Language Manual, Release 9.0*. Research Triangle Park, NC.).

RESULTS

Table 1 shows the characteristics of included and excluded participants without diabetes, based on their baseline values at visit 3. Participants who were included were slightly

younger, less likely to be African-American, and less likely to have hypertension and other cardiovascular risk factors. Over the 10-year period between visit 3 and carotid MRI, the weighted incidence of focal arteriolar narrowing, AV nicking and retinopathy lesions in persons without diabetes was 3.4% (95% confidence interval 2,3–4.9), 2.5% (1.6–3.9) and 2.2% (1.3–3.5) respectively (Table 2). A substantial percentage of retinal microvascular lesions observed at visit 3 had disappeared by carotid MRI, ranging from 40.7% (32.7–49.4) for AV nicking, to 50.3% (28.6–71.9) for focal arteriolar narrowing, to 65.9% (42.4–83.5) for retinopathy in persons without diabetes. Incidence and disappearance rates were similar in white and African American participants.

Table 3 examines odds ratios associated with per SD differences of individual risk factors, considered separately and adjusted for age, gender and race. Higher plasma fibrinogen and white blood cell count were associated with higher incidence of focal arteriolar narrowing; antihypertensive medication use was associated with higher incidence of arteriovenous nicking; and higher diastolic BP, higher carotid IMT and higher white cell count were associated with higher incidence of retinopathy (Table 3). Systolic BP (Odds Ratio 1.46, 95% confidence interval 0,90–2.39) mean arterial BP (1.54, 0.97–2.42) and fasting glucose (5.88, 0.74–46.64) were not associated with incidence of any of these lesions,. None of the factors in Table 3 was associated with disappearance of retinal microvascular lesions over 10 years, as compared to participants with these signs persisting from visit 3 to follow-up. (data not shown)

DISCUSSION

The retinal microcirculation can be directly visualized and provides an opportunity to assess longitudinal changes in microvascular structure. In this cohort of middle-aged individuals free from diabetes, we report that the 10-year incidence of new retinal microvascular lesions is between 2–4%. In persons with existing lesions at baseline, close to half or more of these lesions (40–66%) disappeared over the same period of time.

In the ARIC study, we previously reported 2.9% incidence of retinopathy in persons without diabetes over 3 years in a subsample of 981 participants who had retinal photography at visit 3 and visit 4.[25] We now report that the 10-year incident retinopathy rate in a different ARIC subsample of 1120 individuals appears to be slightly lower at 2.2% (1.3–3.5), though still within the 95% confidence interval estimates. The lower 10-year incidence estimate may be due to lower prevalence of hypertension (29% vs 44%), and more stringent side by side grading performed for this analysis. Additionally, the lower 10-year incidence rates may also reflect the high rate of regression, with almost 2 in 3 nondiabetic participants with retinopathy at baseline found to have no lesions after 10 years. Thus, it is possible that 2–3% represents a steady state of “incidence” and “disappearance” of these lesions. This possibility is supported by the difference in 10-year prevalence of retinopathy in the baseline ARIC, Beaver Dam and Blue Mountains Eye studies, which show a 2–3% higher prevalence of retinopathy per higher decade.[12;14;26]

The incidence rates of retinal microvascular lesions in ARIC are lower than reported from other studies, although studies are not directly comparable. Table 4 is intended to provide an overview of the estimates from different studies, but it should be noted that methodological differences may underlie the different rates reported. In the Beaver Dam Eye Study (US), [13] about 6–10% of participants without diabetes developed incident retinal microvascular lesions over a 5-year period. In the Blue Mountains Eye Study (Australia)[14], 10% of an older population without diabetes developed incident retinopathy after 5 years, while in the Hoorn Study (Netherlands) [15], 7.3% of persons without diabetes developed incident retinopathy over 9.4years. In the ARIC study, we used a 45° non-mydriatic retinal

photograph of only 1 eye to define presence or absence of retinopathy lesions, while the Beaver Dam Eye Study used 30° stereoscopic mydriatic photographs of 2 eyes,[13] the Blue Mountains Eye Study defined retinopathy from six-field 30° stereoscopic retinal photographs of 2 eyes,[14] and the Hoorn study used 45° mydriatic retinal photographs of 2 eyes.[15] Additionally, both the Blue Mountains and Beaver Dam Eye studies validated incident cases by a side-by-side assessment of the retinal photographs performed at baseline and follow up of patients who developed incident retinopathy. Differences in study participant characteristics (e.g., age and prevalence of risk factors between studies) may also contribute to the variation in incidence rates of retinopathy. Nonetheless our data is valuable as we report both incidence and disappearance of lesions, and relate them to carefully measured cardiovascular risk factors from a study designed to measure these risk factors.

We considered the possibility that the high rate of apparent regression of retinal microvascular lesions may be due to misclassification at the carotid MRI grading and thus re-examined simultaneously side by side photos with lesions at both visit 3 and follow-up. This showed minimal misclassification (net 1 out of 219 AV nicking lesions at baseline was reclassified) that was unlikely to meaningfully influence our results. The same high rate of regression of retinopathy was also reported in the Blue Mountains Study,[14] earlier ARIC data showing 64% of retinopathy in persons without diabetes regressed over 3 years [25] as well as a clinic study which documented over 50% regression of microaneurysms (graded from fundus fluorescein angiograms) over 2 years in persons with diabetes.[27] These results highlight the transient nature of retinopathy lesions and is consistent with their known biology, as microaneurysms can become nonperfused and hemorrhages and exudates are resorbed over a period of months. A study in persons with malignant hypertension found almost complete resolution of retinopathy lesions within 6–12 months once elevated BP is controlled, although focal arteriolar narrowing and AV nicking persisted.[28] In our study, the high disappearance rate of focal arteriolar narrowing and AV nicking may be related to the long follow up, and less severe lesions as the majority of participants had only mild or no hypertension. It should be noted that we defined retinopathy to be consistent and comparable with earlier studies. In preliminary analyses the incidence of more severe forms of retinopathy involving at least 1 microaneurysm was lower, around 1.5%.

Antihypertensive medication use, which may indicate more severe hypertension, was associated with increased incidence of AV nicking but not with other lesions. Higher diastolic BP, carotid IMT and white cell count was associated with incident retinopathy. The association of higher carotid IMT with incident retinopathy is consistent with clinic studies showing increased prevalence of retinopathy lesions in persons with severe carotid occlusive disease.[29] Carotid IMT is a measure of subclinical atherosclerosis, with higher values indicating more advanced disease. Retinopathy lesions in such individuals may be due to embolization to the retinal microvasculature or the ocular ischemic syndrome, which is usually associated with >75% stenosis of the carotid artery.[29] White cell count is a marker for systemic inflammation, and the Hoorn study has reported that other inflammatory markers such as C-reactive protein are associated with prevalent retinopathy in persons without diabetes.[30] The Hoorn study also reported an association of endothelial dysfunction[30] with retinopathy and it is noteworthy that our results indicate a weak association of von Willebrand factor with incident retinopathy. The pathogenesis of retinopathy in persons without diabetes is poorly understood and our findings suggest a role for elevated diastolic BP, carotid disease and inflammation. Although fasting glucose was not significantly associated with incident retinopathy, the OR of 5.88 (0.74, 46.64) per SD change in fasting glucose is highly suggestive, while lack of statistical significance is likely related to the small number of incident lesions and the limited number of individuals with high fasting glucose in this nondiabetic sample. This is consistent with the known moderate association of retinopathy and incident diabetes.[13] Higher white cell count and fibrinogen

were associated with incident focal arteriolar narrowing. The first 2 parameters are inflammatory markers and may be associated with impaired endothelium dependent vasodilation,[31] leading to vasoconstriction seen clinically as focal arteriolar narrowing. Little data is available on the disappearance of focal arteriolar narrowing and AV nicking. Focal arteriolar narrowing secondary to localized vasoconstriction may attenuate over years leading to loss of this lesion, or it could have progressed from focal narrowing to overall generalized narrowing so that "disappearance" was not necessarily indicative of "regression". AV nicking is traditionally related to compression of venules within a common adventitial sheath due to arteriolar sclerosis and medial thickening at AV crossings.[32] Resolution of this lesion is thus somewhat surprising and suggests a high degree of remodeling of vessel walls or the adventitial sheath over a period of years. Our study did not identify any factors associated with lesion disappearance, a likely consequence of the limited number of lesions at baseline, although AV nicking was one of the more frequent lesions at baseline. To our knowledge, this is the first study to report regression rates of focal narrowing and AV nicking.

Our study has several strengths including a prospective design with 10-year follow up and standardized measurement of a range of retinal microvascular lesions including side by side grading. Several limitations should be considered. First, although the initial sample was population based, the sampling 10 years later was stratified according to carotid IMT and ARIC field center. We applied sampling weights and robust variance estimation in all analyses to adjust for the effects of stratification. Nonetheless, such statistical adjustment may be less robust than true random sampling of the follow-up population, and should be considered when interpreting our findings. Secondly, we only graded and examined the changes in retinal microvascular lesions from 1 eye. This would underestimate the incidence of new lesions and may partly account for the lower rates reported from our study. Thirdly, the number of some lesions at baseline, particularly focal arteriolar narrowing and retinopathy, is low and the estimates of incidence and disappearance are thus imprecise with wide confidence intervals. For the same reason, the associations observed here could have occurred by chance. Fourthly, retinal microvascular signs are associated with increased mortality,[2;10;11] and a form of survival bias may have influenced our results whereby persons with more severe retinal lesions were more likely to die and thus not be included in the follow-up. Without knowing the natural history of retinal lesions in persons with high mortality, it is not possible to be certain how this effect may bias our results, but we speculate that more severe lesions may be less likely to regress, and thus this may help explain part of the high rate of lesion disappearance.

With these limitations in mind, our findings have clinical implications as prevalent retinal microvascular lesions are known to be independent markers of increased risk of developing hypertension and cardiovascular disease risk.[2;17] It remains unclear whether the disappearance of these lesions modifies the risk of developing hypertension or other cardiovascular diseases. Continuing surveillance of this ARIC cohort may help determine if disappearance of lesions is associated with decreased cardiovascular risk. The high rate of lesion disappearance also suggests that a high degree of microvascular remodeling occurs over time. Future research to identify factors associated with this phenomenon is warranted.

In summary, we report in this selected sample of middle-aged adults the 10-year incidence of new retinal microvascular lesions (focal arteriolar narrowing, AV nicking and retinopathy) is between 2–4%. A high percentage of lesions (40–66%), disappeared over the same time period, suggesting a considerable degree of microvascular remodeling. Some cardiovascular risk factors including use of antihypertensive medication, higher diastolic BP, markers of inflammation and higher carotid IMT were associated with incidence of new

lesions. Our findings help clarify the natural history of retinal microvascular lesions in persons without diabetes.

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Table 1

Baseline (visit 3) characteristics of participants without diabetes in the Atherosclerosis Risk in Communities Study who had retinal images available at visits 3 and follow-up.(Carotid Magnetic Resonance Imaging)

Characteristics	Included (n=1,120)	Excluded (n=9,357)
Age (years)	58.3	59.9
African-American (%)	15.0	20.3
Hypertension (%)	29.1	36.6
Current Smoker (%)	12.0	17.9
Former Smoker (%)	39.7	40.4
Antihypertensive medication use (%)	20.1	27.2
Systolic Blood Pressure (mmHg)	119.5	123.4
Diastolic Blood Pressure (mmHg)	71.9	71.9
Mean of visit 1,2,3 MABP (mmHg)	86.7	88.4
Fasting glucose (mg/dl)	96.1	98.6
Total cholesterol (mg/dl)	205.4	207.3
Triglycerides (mg/dl)	123.5	135.2
LDL Cholesterol (mg/dl)	124.7	126.7
HDL Cholesterol (mg/dl)	56.0	53.9
BMI (kg/m^2)	27.2	28.0
Waist to hip ratio	0.92	0.93
Carotid IMT (mm)	0.77	0.77
Fibrinogen levels (mg/dl)	288.0	295.7
White blood cell count (1000 cells/mm^3)	5.8	6.0
Von Willebrand factor (%)	110.4	113.3
Factor VIII (%)	123.7	126.2

MABP=mean arterial blood pressure; LDL=low density lipoprotein; HDL=high density lipoprotein; BMI=body mass index; IMT=intima media thickness.

Table 2

Incidence and disappearance of vascular lesions over 10 years (visit 3 to Carotid Magnetic Resonance Imaging) in 1,120 participants without diabetes.

Lesion	Incidence			Disappearance			Unchanged		
	Number of incident lesions	(%) of entire population	95% CI for %	Number which disappeared	(%) of population with prevalent lesions	95% CI for %	Number which remained unchanged	(%) of population with prevalent lesions	95% CI for %
All participants									
Focal arteriolar narrowing	42	3.4	(2.3, 4.9)	16	50.3	(28.6, 71.9)	16	49.7	(28.1, 71.4)
Arteriovenous nicking	28	2.5	(1.6, 3.9)	89	40.7	(32.7, 49.4)	130	59.3	(50.7, 67.3)
Retinopathy	28	2.2	(1.3, 3.5)	16	65.9	(42.4, 83.5)	8	34.1	(16.5, 57.6)
Whites									
Focal arteriolar narrowing	39	3.7	(2.5, 5.5)	16	51.1	(29.0, 72.8)	15	48.9	(27.2, 71.0)
Arteriovenous nicking	24	2.5	(1.5, 4.0)	73	39.6	(30.9, 49.1)	111	60.4	(50.9, 69.1)
Retinopathy	23	2.2	(1.3, 3.7)	12	70.1	(40.2, 89.0)	5	30.0	(11.0, 59.8)
African-Americans									
Focal arteriolar narrowing	3	1.3	(0.3, 4.9)	0	0.0	(N/A)	0	0.0	(N/A)
Arteriovenous nicking	4	2.9	(1.0, 7.9)	16	47.6	(28.5, 67.5)	18	52.4	(32.5, 71.5)
Retinopathy	5	2.0	(0.6, 5.9)	4	56.4	(21.4, 85.9)	3	43.7	(14.1, 78.6)

Counts are unweighted, but percentages are weighted (see Methods). CI=confidence interval.

Table 3

Risk factors assessed at baseline (visit 3) and incident retinal microvascular lesions over 10 years (visit 3 to Carotid Magnetic Resonance Imaging) in participants without diabetes.

Risk factors		Age-gender-race adjusted Odds Ratio for Incident lesions (95% Confidence Interval)		
		Focal arteriolar narrowing	Arteriovenous Nicking	Retinopathy
Systolic blood pressure	Per SD (17.0 mmHg) higher	0.98 (0.66, 1.46)	1.12 (0.64, 1.98)	1.46 (0.90, 2.39)
Diastolic blood pressure	Per SD (10.2 mmHg) higher	1.14 (0.77, 1.69)	0.89 (0.58, 1.36)	**1.84 (1.04. 3.24)**
Antihypertensive medications	Yes vs no	0.86 (0.36, 2.06)	**3.29 (1.24, 8.71)**	0.59 (0.15, 2.27)
Mean of visit 1,2,3 MABP (mmHg)	Per SD (13.0 mmHg) higher	1.02 (0.65, 1.58)	1.02 (0.60, 1.74)	1.54 (0.97, 2.42)
Fasting glucose (mg/dl)	Per SD (31.4 mg/dl) higher	0.60 (0.19, 1.90)	0.81 (0.13, 5.23)	5.88 (0.74, 46.64)
Former smoker	Yes vs no	0.94 (0.40, 2.18)	0.48 (0.16, 1.47)	0.92 (0.28, 3.00)
Current smoker	Yes vs no	1.12 (0.36, 3.47)	1.26 (0.41, 3.89)	1.65 (0.47, 5.79)
Total serum cholesterol	Per SD (35.4 mg/dl) higher	1.19 (0.79, 1.78)	0.83 (0.60, 1.14)	1.33 (0.82, 2.17)
HDL cholesterol	Per SD (18.9 mg/dl) higher	0.92 (0.54, 1.58)	1.19 (0.60, 2.38)	1.36 (0.87, 2.13)
Plasma triglycerides	Per SD (62.6 mg/dl) higher	1.03 (0.70, 1.50)	1.19 (0.66, 2.16)	1.10 (0.65, 1.87)
Cholesterol-lowering medications	Yes vs no	1.24 (0.33, 4.63)	0.23 (0.03, 1.74)	0.60 (0.13, 2.68)
Body Mass Index	Per SD (5.1 kg/m^2) higher	0.71 (0.49, 1.02)	1.22 (0.74, 2.02)	1.15 (0.61, 2.19)
Waist-to-hip ratio	Per SD (0.08) higher	1.03 (0.72, 1.48)	1.05 (0.55, 2.00)	.086 (0.55, 1.36)
Imputed carotid IMT	Per SD (0.15 mm) higher	0.80 (0.49, 1.30)	0.85 (0.58, 1.26)	**1.28 (1.06, 1.53)**
Plasma fibrinogen	Per SD (59.9 mg/dl) higher	**1.42 (1.03, 1.97)**	1.34 (0.93, 1.94)	1.21 (0.79, 1.86)
White blood cell count	Per SD (2000 cells/mm^3) higher	**1.16 (1.01, 1.35)**	1.05 (0.92, 1.21)	**1.20 (1.01, 1.42)**
Von Willebrand Factor	Per SD (43.1 %) higher	1.30 (0.85, 1.98)	1.08 (0.58, 2.02)	1.37 (0.96, 1.96)
Factor VIII	Per SD (34.5 %) higher	1.34 (0.89, 2.01)	1.05 (0.70, 1.57)	1,04 (0.76, 1.43)

SD=standard deviation; MABP=mean arterial blood pressure; LDL=low density lipoprotein; HDL=high density lipoprotein; BMI=body mass index; IMT=intima media thickness;

Table 4

Incidence of retinal microvascular lesions in persons without diabetes, published studies.

	Length of follow up	Focal arteriolar Narrowing (%)	Arteriovenous Nicking (%)	Retinopathy (%)	Factors associated with incident retinopathy
Beaver Dam Eye Study [13]	5 years	9.9	6.5	6.0	Hypertension
Blue Mountains Eye Study [14]	5 years	--	--	9.7	Age
Hoorn [15]	9.4 years	--	--	7.3	Hyperglycemia, hypertension, abdominal obesity
Atherosclerosis Risk in Communities[25]	3 years	--	--	2.9	Hyperglycemia, hypertension
Atherosclerosis Risk in Communities	10 years	3.4	2.5	2.2	Carotid IMT, white cell count

IMT=intima media thickness. The incidence data are not directly comparable across studies due to methodological differences – see text for further details.