Relation of Retinopathy to Coronary Artery Calcification
The Multi-Ethnic Study of Atherosclerosis

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Microvascular disease, reflected by retinal vascular changes, has been shown to predict clinical coronary heart disease. Whether retinal vascular changes are associated with subclinical coronary artery disease is unclear and was examined in this study. The authors conducted a multiethnic, population-based study of 6,147 persons aged 45–84 years, sampled from six US communities in 2002–2004, who were free of clinical cardiovascular disease. Coronary artery calcification (CAC), a noninvasive measure of subclinical coronary artery disease, was assessed by cardiac computed tomography scanning and categorized into three groups of increasing severity: none (average CAC score = 0), mild (1–100), and moderate-to-severe (>100). Retinopathy signs and retinal vascular caliber were graded from retinal photographs following standardized protocols. After adjustment for age, gender, race/ethnicity, blood pressure, diabetes, lipid profile, smoking, and other risk factors, retinopathy was associated with having a moderate-to-severe CAC score (odds ratio = 1.43, 95% confidence interval: 1.18, 1.75). This association remained significant in both men and women and in persons with and without diabetes or hypertension. Variations in retinal vascular caliber were not significantly associated with CAC score. This study shows that retinopathy signs are independently associated with CAC, supporting the concept that common pathophysiologic processes may underlie both micro- and macrovascular disease.

arterioles; atherosclerosis; cardiovascular diseases; coronary disease; diabetic retinopathy; microcirculation; retinal vessels; venules

Abbreviations: CAC, coronary artery calcification; CI, confidence interval; MESA, Multi-Ethnic Study of Atherosclerosis; OR, odds ratio.

There is increasing recognition that microvascular disease plays an important role in the pathogenesis of coronary heart disease (1–4). Coronary microvascular dysfunction, for example, is the underlying mechanism of microvascular angina, in which patients have typical symptoms of myocardial ischemia without angiographic epicardial coronary artery blockage (5).
Coronary artery calcification (CAC), as measured by chest computed tomography scanning, represents evidence of subclinical coronary artery disease and independently predicts future coronary events (6–9). While most studies indicate that CAC scores are correlated with epicardial coronary artery atherosclerosis (10, 11), some studies have reported elevated CAC scores in persons with microvascular angina without epicardial coronary stenosis (12–14). These latter observations raise an important question: Do persons with higher CAC levels have concomitant microvascular disease?

The retinal circulation provides an opportunity to study changes in the microvasculature. Retinal vascular changes (e.g., microaneurysms, retinal hemorrhages, narrower retinal arterioles) are associated with hypertension and diabetes and predict clinical cardiovascular events (15), including myocardial infarction in women (16, 17) and in persons with diabetes (18), and congestive heart failure in the general population (19). We examined the relation of retinal vascular changes to CAC levels using data from the Multi-Ethnic Study of Atherosclerosis (MESA).

**MATERIALS AND METHODS**

**Study population**

MESA is a prospective cohort study of men and women aged 45–84 years without a history of clinical cardiovascular disease in six US communities (20). In brief, investigators at each site planned to examine approximately 1,100 eligible participants according to site-specified race/ethnicity proportions. The baseline examination included 6,814 participants: 1,086 from Baltimore, Maryland; 1,164 from Chicago, Illinois; 1,077 from Forsyth County, North Carolina; 1,319 from Los Angeles County, California; 1,102 from New York, New York; and 1,066 from St. Paul, Minnesota. Institutional review board approval was granted at each study site, and written informed consent was obtained from each participant.

Measurement of CAC was performed at the baseline examination (July 2000–August 2002) (21), and retinal photography was performed at the second examination immediately following baseline (August 2002–January 2004) (22, 23). Of the 6,814 baseline participants, 6,237 returned for the second examination. Of these, 6,176 had retinal photography; 6,147 of these persons had gradable photographs for retinopathy signs and 5,971 had gradable photographs for retinal vascular caliber. Ungradable photographs were ungradable largely because of media opacities (e.g., cataract) and incomplete visualization of the optic disc, which is required for measurement of retinal caliber. The proportions of people with photographs that were ungradable for retinopathy did not differ significantly between Whites (0.5 percent), Blacks (0.5 percent), Hispanics (0.5 percent), and Chinese (0.4 percent) ($p = 0.97$).

**Retinal photography**

Fundus photography was performed at each site using a standardized protocol (22, 23). Participants were seated in a darkened room, and both eyes were photographed using a 45-degree digital nonmydriatic camera. Two photographic fields were taken of each eye (24). Images were evaluated by graders masked to participant characteristics at the University of Wisconsin (Madison, Wisconsin).

Retinopathy was graded using a standardized protocol. Retinopathy was considered present if any characteristic lesion, as defined by the Early Treatment Diabetic Retinopathy Study severity scale (24), was present: microaneurysms, hemorrhages, cotton wool spots, intraretinal microvascular abnormalities, hard exudates, venous beading, and new vessels. Retinal arteriovenous nicking and focal arteriolar narrowing were similarly defined from photographs.

The caliber of retinal arterioles and venules was measured using a computer-based program (25–27). Caliber was summarized as the average central arteriolar and venular “equivalents,” using formulas developed by Hubbard et al. (25) and Knudtson et al. (28). The equivalents are a summary of diameters for the central retinal vessels measured away from the optic disc. Photographs in the right eye were selected for measurement. If measurements could not be performed in the right eye (e.g., ungradable photographs from media opacities, or incomplete visualization of the zones surrounding the optic disc required for these measurements), the retinal vascular caliber of the left eye was measured. Previous studies have shown that correlations of measurements between the right and left eyes are high (24). Reproducibility of retinal measurements has been reported, with intra- and intergrader intraclass correlation coefficients ranging from 0.78 to 0.99 (25–27).

**Measurement of CAC**

CAC was assessed by chest computed tomography using either a cardiac-gated electron-beam computed tomography scanner (29) (Chicago, Los Angeles, and New York field centers) or a multidetector computed tomography system (30) (Baltimore, Forsyth County, and St. Paul field centers), according to standardized protocols (21). The participants were scanned twice over phantoms of known physical calcium concentration, and the scans were analyzed centrally at the Los Angeles Biomedical Research Institute (Harbor-UCLA Medical Center, Torrance, California) to identify and quantify coronary calcification, calibrated according to the readings of the calcium phantom. Scans were read in a masked fashion with respect to scan pairs and to other participant data using a computer interactive scoring system following a protocol described previously (21). Calcium scores were adjusted with a standard calcium phantom that was scanned along with the participant (31). The average Agatston score for the two scans was used in all analyses (32).

**Assessment of cardiovascular risk factors**

Participants underwent an interview and assessment of cardiovascular risk factors at both baseline and the second examination (20, 33). Variables for this analysis were based on data collected at the second examination, unless data
were not available, in which case data from the first examination were used. Resting blood pressure was measured three times with the participant in the seated position, and the average of the last two measurements at both the first and the second examination was used to control for the confounding effects of blood pressure on the associations. Height and weight were measured with the participant wearing light clothing and no shoes, and body mass index was calculated as weight divided by the square of height (kg/m²). A detailed questionnaire was used to obtain information about medical history (e.g., hypertension, diabetes), cigarette smoking, alcohol consumption, and medication use.

Fasting (>8 hours) blood samples were drawn from participants and analyzed for plasma total and high density lipoprotein cholesterol, plasma triglycerides, serum glucose, glycosylated hemoglobin, and C-reactive protein. High density lipoprotein cholesterol was calculated with the Friedewald equation. Details of these methods, including coefficients of variation, are provided elsewhere (33). Hypertension was defined as systolic blood pressure >140 mmHg, diastolic blood pressure ≥90 mmHg, or current use of antihypertensive medication. Diabetes mellitus was defined as fasting glucose level ≥7.0 mmol/liter (>126 mg/dl) or use of insulin or oral hypoglycemic medication. Carotid artery intima-media thickness was assessed using high-resolution B-mode ultrasonography as described previously (34).

Statistical analysis

Retinopathy, retinal arteriovenous nicking, and focal arteriolar narrowing were defined as present or absent. Retinal arteriolar and venular calibers were categorized into quartiles, with the first quartile representing the narrowest caliber and the fourth quartile representing the widest. CAC was categorized into three ordinal groups of increasing calcified plaque burden: no CAC (average Agatston CAC score = 0), mild CAC (average score 1–100), and moderate-to-severe CAC (average score >100) (35, 36).

We used multinomial logistic regression to determine the odds of increasing CAC severity (none, mild, moderate-to-severe) associated with the presence or absence of retinopathy, retinal arteriovenous nicking, and focal arteriolar narrowing or with quartile extremes of retinal vascular caliber (narrower arteriolar caliber (first quartile vs. fourth quartile) and larger venular caliber (fourth quartile vs. first quartile); these measures have been shown to predict cardiovascular events). We constructed three models. Model 1 included adjustment for age, gender, race/ethnicity, and study center; model 2 included adjustment for the variables in model 1 plus systolic blood pressure at examination 1 and 2, use of antihypertensive medication, diabetes status, serum glucose, body mass index, total and high density lipoprotein cholesterol, triglycerides, current cigarette smoking, pack-years of smoking, and C-reactive protein; and model 3 included adjustment for all of the variables in model 2 plus common carotid intima-media thickness. In all models for retinal arteriolar caliber, we adjusted for venular caliber and vice versa (37).

In supplementary analysis, we performed the following. First, we repeated the analyses using different CAC categories. We defined coronary calcification as absent (CAC score = 0) versus present (CAC score > 0), as absent or mild (CAC score 0–100) versus moderate-to-severe (CAC score > 100), and as mild-to-moderate (CAC score 1–400) versus severe (CAC score > 400). We repeated the above analysis using binary logistic regression models of these new CAC categories. Second, we analyzed retinal vascular caliber and CAC score as continuous variables using linear regression models. Since CAC scores were not normally distributed, we log-transformed the data after adding a value of 1 to all participants’ CAC scores (to allow inclusion of participants with a CAC score of 0). In the regression models, we analyzed for possible nonlinear relations with spline models; however, there was no clear nonlinear pattern in the relations, with no distinct cutpoints that allowed us to apply spline models (data not shown). Finally, we examined in binary logistic regression models the odds of moderate-to-severe CAC (CAC score > 100 vs. 0–100) for retinal signs, adjusting for potential confounders (model 2 covariates) in subgroups stratified by gender, race/ethnicity, diabetes, and hypertension status. Potential interactions with these variables and age were also tested. All analyses were performed using the Statistical Package for the Social Sciences, version 12.0.1 (SPSS, Inc., Chicago, Illinois).

RESULTS

Baseline characteristics of the study population across different CAC categories are shown in table 1. In our study population, 16.5 percent had retinopathy. Participants with positive CAC scores (either mild CAC or moderate-to-severe CAC) were more likely to be male, to be older, to have hypertension and/or diabetes, and to have a higher systolic blood pressure, a higher serum glucose level, and a different lipid profile than participants with no coronary artery calcified plaque. Participants with retinopathy were more likely to be older, to have hypertension and/or diabetes, to have a higher systolic blood pressure, body mass index, and serum glucose level, and to have a lower serum cholesterol level than participants without retinopathy (data not shown).

Table 2 shows that participants with retinopathy, retinal arteriovenous nicking, and narrower retinal arteriolar and venular caliber were more likely to have higher CAC scores. In multinomial logistic regression adjusting for age, gender, race/ethnicity, and center (model 1) and additionally adjusting for cardiovascular risk factors (model 2) and carotid intima-media thickness (model 3), retinopathy was associated with higher CAC scores (table 3). Retinal arteriovenous nicking was associated with higher CAC scores in multivariate analysis, although the association was weaker, with borderline statistical significance. In general, retinal arteriolar caliber and venular caliber were not associated with CAC scores.

In supplementary analyses (data not shown), we repeated the analyses in binary logistic regression using different CAC score categories (no CAC (CAC score = 0) vs. any CAC (CAC score > 0)) and obtained similar results. The presence of retinopathy was associated with the presence of any CAC (odds ratio (OR) = 1.22, 95 percent confidence
interval (CI): 1.04, 1.43) in a multivariable-adjusted model (model 2). Retinal arteriolar (OR = 1.13, 95 percent CI: 0.91, 1.41) and venular (OR = 0.95, 95 percent CI: 0.77, 1.18) calibers were not associated with the presence of any

### TABLE 1. Characteristics of participants according to category of coronary artery calcification, Multi-Ethnic Study of Atherosclerosis, 2002–2004

<table>
<thead>
<tr>
<th></th>
<th>No CAC* (CAC score = 0) (n = 3,148)</th>
<th>Mild CAC (CAC score 1–100) (n = 1,598)</th>
<th>Moderate-to-severe CAC (CAC score &gt;100) (n = 1,401)</th>
<th>p value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>No. 1,160 36.8</td>
<td>No. 840 52.6</td>
<td>No. 931 66.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1,223 38.9</td>
<td>862 53.9</td>
<td>935 66.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>373 11.8</td>
<td>246 15.4</td>
<td>302 21.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current cigarette smoking</td>
<td>367 11.7</td>
<td>182 11.4</td>
<td>158 11.3</td>
<td>0.71</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Mean (SD) 59.6 (9.0)</td>
<td>Mean (SD) 65.4 (9.5)</td>
<td>Mean (SD) 70.2 (8.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum glucose level (mg/dl)</td>
<td>102.8 (29.5)</td>
<td>107.0 (32.9)</td>
<td>108.7 (30.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>120.9 (20.4)</td>
<td>126.5 (20.2)</td>
<td>129.9 (21.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index‡</td>
<td>28.4 (5.7)</td>
<td>28.4 (5.3)</td>
<td>28.3 (5.1)</td>
<td>0.85</td>
</tr>
<tr>
<td>Total cholesterol level (mg/dl)</td>
<td>193.4 (35.9)</td>
<td>191.7 (35.2)</td>
<td>186.3 (35.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High density lipoprotein cholesterol level (mg/dl)</td>
<td>53.4 (15.3)</td>
<td>50.6 (14.3)</td>
<td>49.8 (14.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglyceride level (mg/dl)</td>
<td>128.5 (84.1)</td>
<td>133.8 (77.8)</td>
<td>135.6 (82.0)</td>
<td>0.01</td>
</tr>
<tr>
<td>C-reactive protein level (mg/liter)</td>
<td>1.89 (3.25)</td>
<td>1.92 (3.11)</td>
<td>1.83 (3.13)</td>
<td>0.56</td>
</tr>
</tbody>
</table>

* CAC, coronary artery calcification; SD, standard deviation.
† p value based on chi-squared tests or one way analysis of variance, comparing different levels of CAC.
‡ Weight (kg)/height (m²).

### TABLE 2. Relation of retinal microvascular signs to coronary artery calcification, Multi-Ethnic Study of Atherosclerosis, 2002–2004

<table>
<thead>
<tr>
<th></th>
<th>No CAC* (CAC score = 0) (n = 3,148)</th>
<th>Mild CAC (CAC score 1–100) (n = 1,598)</th>
<th>Moderate-to-severe CAC (CAC score &gt;100) (n = 1,401)</th>
<th>p value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinopathy</td>
<td>No. %</td>
<td>No. %</td>
<td>No. %</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>2,697 85.7</td>
<td>1,323 82.8</td>
<td>1,110 79.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Present</td>
<td>451 14.3</td>
<td>275 17.2</td>
<td>291 20.8</td>
<td></td>
</tr>
<tr>
<td>Retinal arteriovenous nicking</td>
<td>No. %</td>
<td>No. %</td>
<td>No. %</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>2,598 82.8</td>
<td>1,247 78.8</td>
<td>1,041 75.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Present</td>
<td>541 17.2</td>
<td>335 21.2</td>
<td>344 24.8</td>
<td></td>
</tr>
<tr>
<td>Retinal arteriolar caliber</td>
<td>No. %</td>
<td>No. %</td>
<td>No. %</td>
<td></td>
</tr>
<tr>
<td>Quartile 1 (&lt;136 μm) (narrowest)</td>
<td>666 21.4</td>
<td>425 27.5</td>
<td>403 30.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Quartile 2 (136–&lt;144 μm)</td>
<td>774 24.9</td>
<td>386 25.0</td>
<td>334 25.3</td>
<td></td>
</tr>
<tr>
<td>Quartile 3 (144–152 μm)</td>
<td>810 26.1</td>
<td>390 25.2</td>
<td>295 22.3</td>
<td></td>
</tr>
<tr>
<td>Quartile 4 (&gt;152 μm) (widest)</td>
<td>857 27.6</td>
<td>346 22.4</td>
<td>290 21.9</td>
<td></td>
</tr>
<tr>
<td>Retinal venular caliber</td>
<td>No. %</td>
<td>No. %</td>
<td>No. %</td>
<td></td>
</tr>
<tr>
<td>Quartile 1 (&lt;199 μm) (narrowest)</td>
<td>729 23.5</td>
<td>405 26.1</td>
<td>361 27.4</td>
<td>0.005</td>
</tr>
<tr>
<td>Quartile 2 (199–&lt;214 μm)</td>
<td>782 25.2</td>
<td>371 23.9</td>
<td>341 25.9</td>
<td></td>
</tr>
<tr>
<td>Quartile 3 (214–228 μm)</td>
<td>798 25.7</td>
<td>396 25.5</td>
<td>299 22.7</td>
<td></td>
</tr>
<tr>
<td>Quartile 4 (&gt;228 μm) (widest)</td>
<td>797 25.7</td>
<td>378 24.4</td>
<td>318 24.1</td>
<td></td>
</tr>
</tbody>
</table>

* CAC, coronary artery calcification.
† p value based on chi-squared testing.
CAC. Similar results were seen in analyses of absent or mild CAC (CAC score 0–100) versus moderate-to-severe CAC (CAC score >100) and mild-to-moderate CAC (CAC score 1–400) versus severe CAC (CAC score >400) (data not shown). Second, we analyzed retinal vascular caliber and CAC scores as continuous variables using linear regression models. Similarly, we found no significant associations of retinal arteriolar \( (p = 0.42) \) or venular \( (p = 0.30) \) caliber with CAC scores after adjusting for model 2 covariates. Finally, in stratified analyses, the pattern of associations for retinopathy remained consistent across different subgroups. In particular, the association between retinopathy and moderate-to-severe CAC was present in all ethnic groups and remained significant in both men and women and in persons with and without diabetes or hypertension. Finally, we tested interaction terms for these stratified variables as well as age and found no significant interaction.

**DISCUSSION**

CAC represents the presence of subclinical coronary artery disease, is correlated with total atherosclerotic plaque burden, and predicts clinical coronary events independently of traditional risk factors. Our current study of a large cohort that was free of clinical cardiovascular disease provides the first population-based evidence that microvascular disease in the retina, reflected as retinopathy signs, is associated with subclinical coronary macrovascular disease, reflected as increased coronary calcification, independently of age, gender, race/ethnicity, blood pressure, and other traditional and nontraditional risk factors. This association was present in men and women and was largely similar in all four racial/ethnic groups and in people with and without diabetes or hypertension. The association was weaker for retinal arteriovenous nicking, but we found no independent association of focal arteriolar narrowing or variations in retinal vascular caliber with coronary calcification.

Our finding of an association between retinopathy and increased coronary calcification is consistent with other studies carried out among persons with diabetes (18, 38, 39) and in the general population (16, 40). These studies have largely focused on the association of retinopathy with clinical cardiovascular events (16, 19, 40). Population-based data from the Cardiovascular Health Study and the

<table>
<thead>
<tr>
<th>Retinopathy</th>
<th><strong>Model 1</strong>§</th>
<th><strong>Model 2</strong>¶</th>
<th><strong>Model 3</strong>#</th>
</tr>
</thead>
<tbody>
<tr>
<td>No CAC* (CAC score 0)†</td>
<td>1.00</td>
<td>1.22</td>
<td>1.03, 1.45</td>
</tr>
<tr>
<td>Mild CAC (CAC score 1–100) (n = 1,598)</td>
<td>1.00</td>
<td>1.12</td>
<td>0.93, 1.34</td>
</tr>
<tr>
<td>Moderate-to-severe CAC (CAC score &gt;100) (n = 1,401)</td>
<td>1.00</td>
<td>1.11</td>
<td>0.93, 1.33</td>
</tr>
</tbody>
</table>

* CAC, coronary artery calcification; OR, odds ratio; CI, confidence interval.
† Reference category.
‡ Multinomial logistic regression analysis of CAC severity according to retinopathy (present vs. absent), narrower arteriolar caliber (first quartile vs. fourth quartile), or larger venular caliber (fourth quartile vs. first quartile).
§ Model 1: adjusted for age, gender, race/ethnicity, and study center.
¶ Model 2: adjusted for the variables in model 1 plus systolic blood pressure at examinations 1 and 2, use of antihypertensive medication, diabetes, serum glucose level, body mass index, total and high density lipoprotein cholesterol level, triglyceride level, C-reactive protein level, current cigarette smoking, and pack-years of smoking.
# Model 3: adjusted for all of the variables in model 2 plus common carotid artery intima-media thickness. Models for arteriolar caliber included additional adjustment for venular caliber and vice versa.
Atherosclerosis Risk in Communities Study, for example, have indicated associations of retinopathy signs with prevalent coronary heart disease (18, 40), incident coronary heart disease (16), and congestive heart failure (19) that were independent of traditional risk factors. In the Milan Study on Atherosclerosis and Diabetes, Faglia et al. (38) reported that among persons with type 2 diabetes, retinopathy was an independent predictor of cardiac death, myocardial infarction, resting angina, and effort angina (hazard ratio = 5.47, 95 percent CI: 2.43, 12.29). Note that these associations with coronary heart disease or heart failure may relate to the myocardial microvasculature rather than to the epicardial coronary arteries. Few investigators have evaluated the association between retinopathy and subclinical coronary artery disease. Yoshida et al. (41) reported that diabetic persons with retinopathy had a significantly higher CAC score than diabetic persons without retinopathy. That study was limited by a small sample size and a lack of adjustment for other cardiovascular risk factors. Another study among diabetic patients showed an independent association of retinopathy, detected on indirect ophthalmoscopic examinations, with more extensive coronary atherosclerosis as defined on angiogram (39). Our study has now demonstrated an association of retinopathy with CAC that was independent of measured risk factors in the larger community, in persons with and without diabetes.

The association of retinopathy with CAC supports the concept that shared pathophysiologic processes may contribute to both microvascular and macrovascular disease. Retinopathy signs assessed here largely represent microvascular damage, not only from increased age, hypertension, and diabetes but also possibly from inflammation and endothelial dysfunction (27, 42, 43). Similar processes may also contribute to the development of coronary calcified plaque.

There is a growing body of literature suggesting that changes in retinal vascular caliber, including narrower arteriolar caliber and larger venular caliber, are predictive of both subclinical and clinical coronary heart disease. In the Rotterdam Study, Ikram et al. (44) described an association of larger venular caliber with carotid atherosclerosis. Prospective data from the Blue Mountains Eye Study and the Cardiovascular Health Study indicate associations of larger retinal venular caliber with incident clinical coronary heart disease and coronary heart disease-related mortality that are independent of traditional risk factors (17, 45). Our data, however, do not support an independent association between larger retinal venular caliber and CAC.

The stronger association of retinopathy, rather than other retinal vascular changes, with CAC scores is possibly due to the fact that retinopathy signs (e.g., microaneurysms, retinal hemorrhages) are definitive pathologic vascular lesions that reflect generalized endothelial dysfunction, which in the coronary circulation may promote atherogenesis. The weaker associations of other retinal vascular changes (e.g., variations in retinal vascular caliber) with CAC scores in our study are in keeping with their less consistent associations with clinical cardiovascular disease shown in previous studies. While measurement errors either from the assessment of retinal vascular signs or CAC may also have contributed to the weaker associations, both retinal vascular signs and CAC in MESA were quantified on the basis of standardized protocols with excellent reliability.

The strengths of this study include its multiethnic and population-based design, with all participants being free of clinical cardiovascular disease at baseline; the high proportion of gradable digital fundus photographs; and the use of validated techniques to assess retinal microvascular signs. However, the study had several limitations. First, we cannot be sure that our associations are not attributable to residual confounding, and we could not adjust for potential risk factors related to both retinopathy and CAC, such as endothelial dysfunction and oxidative damage. Second, the cross-sectional design of the analysis limits our ability to determine the temporal sequence of the associations reported. Third, although similar recruitment methods were used in all ethnic groups, the participation rate varied among those screened for the study: 70 percent for Whites, 61 percent for Blacks, 59 percent for Hispanics, and 48 percent for Chinese. Exclusion of persons with symptomatic cardiovascular disease could also have operated differentially across ethnic groups owing to differences in access to care and diagnosis of disease. Once participants were recruited into the study, however, there were no significant ethnic differences in participation between visit 1, when data on the systemic variables were collected, and visit 2, when retinal vascular caliber was measured.

In conclusion, we have shown, in a multiethnic cohort free of clinical cardiovascular disease, an association of retinopathy with coronary artery calcified plaque as measured by cardiac computed tomography, independent of conventionally measured cardiovascular risk factors. These data suggest that common pathophysiologic processes may underlie both microvascular and macrovascular disease.

ACKNOWLEDGMENTS

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Conflict of interest: none declared.

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