C-Reactive Protein and Retinal Microvascular Caliber in a Multiethnic Asian Population

Carol Yim-Lui Cheung, Tien Yin Wong*, Ecosse L. Lamoureux, Charumathi Sabanayagam, Jialiang Li, Jeanette Lee, and E. Shyong Tai

* Correspondence to Prof. Tien Yin Wong, Singapore Eye Research Institute, 11 Third Hospital Avenue, Singapore 168751, Singapore (e-mail: ophwty@nus.edu.sg).

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Retinal microvascular caliber is a risk marker for cardiovascular disease. The authors examined the relation between high-sensitivity C-reactive protein (hsCRP) and retinal microvascular caliber in a multiethnic Asian population (n = 3,583) of Chinese, Malays, and Indians aged 24–95 years residing in Singapore (2003–2007). Retinal arteriolar and venular diameters were measured and summarized as central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE), respectively. Persons with higher levels of hsCRP had wider CRVE (P trend < 0.001). In subgroup analysis stratified for different cardiovascular disease risk factors, the association between hsCRP and CRVE was seen in persons without diabetes (P trend < 0.001) but was absent in persons with diabetes (P trend = 0.200; P interaction = 0.004). No significant interaction between race/ethnicity and hsCRP in relation to retinal vascular caliber was observed. These data suggest that retinal venular caliber is associated with higher levels of hsCRP in Asians, which is consistent with studies in white Caucasian populations, further supporting the concept that retinal venular caliber may be a marker for low-grade systemic inflammation.

C-reactive protein; diabetes mellitus; retinal vessels; Singapore; systemic inflammation; venules

Abbreviations: CRAE, central retinal artery equivalent; CRP, C-reactive protein; CRVE, central retinal vein equivalent; CVD, cardiovascular disease; hsCRP, high-sensitivity C-reactive protein.

The retina allows for noninvasive visualization of the human microcirculation. Advances in digital photographic imaging provide the means to quantify structural characteristics of retinal blood vessels (1–3). Changes in the retinal microvasculature caliber (e.g., narrowing of retinal arterioles and widening of retinal venules) have been shown to be associated with cardiovascular disease (CVD) and its risk factors (e.g., hypertension and diabetes mellitus) and to predict CVD events, including coronary heart disease and stroke (4–12).

Inflammation is now known to be involved in the pathogenesis of CVD (13–15). High-sensitivity C-reactive protein (hsCRP), a specific biomarker of inflammation, has been shown to predict CVD events (16–18). Recent studies have shown that wider retinal venular caliber is associated with elevated levels of hsCRP and other inflammatory markers, suggesting that retinal venular caliber is a possible marker for systemic inflammation (19–22). These findings, however, have been reported only for older persons (aged ≥45 years) and mostly white Caucasian populations. To our knowledge, the relation between retinal vascular caliber and hsCRP in persons under age 40 years and in Asians has not yet been studied. The latter is important in that the relation between vascular risk factors and CVD appears to vary between racial/ethnic groups. For example, the impact of obesity on CVD risk seems to be attenuated in some ethnic minorities in the United States (23), and we have previously reported that diabetes mellitus has a greater effect on the risk of CVD in Asian Indians than it does in Chinese (24). Furthermore, while retinal vascular caliber has been shown to be related to various CVD risk factors such as cigarette smoking (19–21, 25), diabetes (19, 20, 26–30), obesity (20, 31) and dyslipidemia (20, 32), it is unknown whether the association between retinal microvascular caliber and hsCRP is modified by these risk factors.
In the current study, we examined the relation between retinal microvascular caliber and hsCRP in a multietnic Asian population of Chinese, Malays, and Indians with a broad age range of 24–95 years. We further investigated whether the association between retinal vascular caliber and hsCRP is modified by other CVD risk factors, specifically smoking, diabetes, hypertension, overweight, and dyslipidemia.

MATERIALS AND METHODS

Study population

In the present study, we utilized data from the Singapore Prospective Study Program and Singapore Cardiovascular Cohort Study 2, which included participants from 4 cross-sectional studies: the Thyroid and Heart Study 1982–1984 (33), the National Health Survey 1992 (34), the National University of Singapore Heart Study 1993–1995 (35), and the National Health Survey 1998 (36). All of the studies involved a random sample of persons from the Singapore population aged 24–95 years, with disproportionate sampling by ethnicity to increase the sample sizes of minority ethnic groups (Malays and Indians). The study sample was selected by the Singapore Ministry of Health.

Recruitment of the study population has been reported in detail elsewhere (30) (Figure 1). In brief, from 2003 to 2007, all 10,747 participants were invited to participate in the current study through linkage of their unique national identification numbers with national registries. The study questionnaire, administered by interviewers at participants’
homes, collected data on a wide variety of demographic and lifestyle factors (alcohol intake, smoking) and medical history for 7,744 persons. All 7,744 participants were then invited to undergo a clinic examination that included a systemic and ocular examination, retinal photography, and laboratory investigations; 5,164 persons attended. Logistic constraints due to the availability of 1 retinal camera resulted in only in 1 Chinese participants (the group with the largest sample size) being able to have retinal photography done between March 19, 2005, and February 20, 2006. Retinal photographs were available for 4,098 participants (99.1% response). Participants with ungradable retinal photographs (n = 296) or missing information on hsCRP or other relevant variables (n = 219) were then excluded, leaving 3,383 persons for the final analysis (46.3% of the 7,744 eligible participants). Excluded participants tended to be older and to have a higher high density lipoprotein cholesterol level and systolic blood pressure and a lower low density lipoprotein cholesterol level (all significant at P < 0.05) than included participants.

The Declaration of Helsinki’s tenets were followed, and institutional review board approval was granted at each study site. All participants provided written informed consent.

Measurement of C-reactive protein

Serum C-reactive protein (CRP) concentration was measured in frozen plasma that had been stored at −80°C at the National University Hospital Reference Laboratory, using an immunoturbidimetric assay (intraassay precision, 0.6%–1.3%; interassay precision, 2.3%–3.1%) implemented on a Roche Integra 400 chemistry analyzer (Roche Diagnostics, Rotkreuz, Switzerland). The detection limit of this assay is 0.07 mg/L, and the coefficient of variation is 2.9% at 6.3 mg/L and 3.9% at the mean value of 108 mg/L.

Measurement of retinal vascular caliber

Retinal vascular caliber was measured as previously described (30, 37). In brief, digital fundus photographs were taken using a 45-degree digital retinal camera (Canon CR-DGi with a 10D SLR back; Canon, Tokyo, Japan) after pupil dilation with tropicamide (1%) and phenylephrine (2.5%). Two retinal images of each eye were obtained, one centered at the optic disc and another centered at the fovea, identical to the Early Treatment for Diabetic Retinopathy Study standard fields 1 and 2 (38, 39). Retinal vascular caliber was measured with computer-assisted software according to a standardized protocol (2, 20). A trained grader, masked to the participants’ characteristics, performed the vessel measurements on the optic disc-centered image of the right eye for most participants and on the left eye in persons without gradable right eye images. All arterioles and venules crossing through a specified zone 0.5–1 disc diameter away from the optic disc margin were measured and summarized as the central retinal artery equivalent (CRAE) or central retinal vein equivalent (CRVE). A retinal photograph with fewer than 6 acceptable measurements of either vessel type was considered ungradable. For assessment of reproducibility, 200 randomly selected retinal photographs were regraded by the same assessor; intragraded reliability intra-class correlation coefficients were 0.99 (95% confidence interval: 0.98, 0.99) for CRAE and 0.94 (95% confidence interval: 0.92, 0.96) for CRVE.

Assessment of covariates

Fasting venous blood samples were analyzed on the same day at the National University Hospital Reference Laboratory for biochemical testing of total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol, triglycerides, and fasting plasma glucose. Participants underwent an interview and assessment of CVD risk factors during the course of the study. Current smokers were defined as those who were currently smoking daily or on some days (i.e., current smoking vs. past/never smoking). Alcohol consumption was defined as currently drinking alcoholic beverages daily or on some days (i.e., current drinking vs. past/never drinking).

Systolic and diastolic blood pressures were measured using a digital automatic blood pressure monitor (Dinamap model Pro100V2; Criticon GmbH, Norderstedt, Germany), after the subject had been seated for at least 5 minutes. Hypertension was defined as systolic blood pressure of 140 mm Hg or more or diastolic blood pressure of 90 mm Hg or more at examination, a reported history of physician-diagnosed hypertension or a self-reported history of antihypertension medication use, or both. Mean arterial blood pressure was calculated as two-thirds of the diastolic value plus one-third of the systolic value.

Diabetes mellitus was identified from a fasting plasma glucose level of 7 mmol/L or more, self-reported use of diabietic medication, or physician-diagnosed diabetes. Body mass index was calculated as body weight (in kilograms) divided by body height (in meters) squared. Overweight was defined as a body mass index of 25 or more. Dyslipidemia was defined as a total cholesterol level of 6.2 mmol/L or more, a low density lipoprotein cholesterol level of 4.1 mmol/L or more, a high density lipoprotein cholesterol level less than 1.0 mmol/L, a triglyceride level of 2.3 mmol/L or more, a reported history of physician-diagnosed dyslipidemia, or a self-reported history of antidysslipidemia medication use.

Statistical analysis

All statistical analyses were performed using SPSS, version 17.0 (SPSS, Inc., Chicago, Illinois). Characteristics of the participants were compared within racial/ethnic groups by analysis of variance or chi-squared test. We used analyses of covariance to estimate mean retinal caliber in association with quartiles of hsCRP level. We performed analyses incorporating the sampling weights to adjust for the unequal probability sampling from the 3 racial/ethnic groups using the weighting methods of Palta (40). CRAE and CRVE were analyzed as a continuous variable, and hsCRP level was analyzed as a categorical variable (tertiles and quartiles). Linear models were fitted with CRAE/CRVE as dependent variables and hsCRP level and other predictors as independent variables. For each fitted model, we conducted diagnostic analysis by producing scatterplots, distribution histograms, Q-Q plots, P-P plots, and standardized residuals to test the model assumptions, including the linearity assumption, distribution normality, and homogeneity of
variance. We tested for trend by treating quartiles of hsCRP level as continuous ordinal variables.

To test multiple hypotheses simultaneously, we implemented Tukey’s test for multiple comparisons to control the type I error. We performed these analyses for the total population using 3 multivariable models: 1) Model 1 included adjustment for age, gender, and race/ethnicity; 2) model 2 included adjustment for age, gender, race/ethnicity, smoking, mean arterial blood pressure, diabetes, alcohol consumption, total cholesterol, high density lipoprotein cholesterol, triglyceride, and body mass index; and 3) model 3 included adjustment for all of the variables in model 2, plus CRAE in models for CRVE and vice versa, which accounted for potential confounding from fellow vascular caliber (41). We performed a formal interaction analysis to test for racial/ethnic differences in the relation between hsCRP and CRAE/CRVE by including cross-product interaction terms (i.e., race/ethnicity × quartile of hsCRP) as independent variables in the analysis of covariance for the total population. No statistically significant interaction was observed (e.g., for CRVE, P values for interaction were 0.112, 0.134, and 0.899 for models 1, 2, and 3, respectively). Therefore, all analyses were performed for the total population and adjusted for race/ethnicity.

We further divided the population into tertiles of hsCRP level and performed subgroup analyses stratified by CVD risk factors (smoking, diabetes, hypertension, overweight, and dyslipidemia). We also tested for statistical interactions by CVD risk factors in the association between CRVE and hsCRP by including cross-product interaction terms as independent variables (e.g., tertile of hsCRP × diabetes status) in the linear models adjusted for age, gender, and race/ethnicity.

In supplementary analyses, we stratified the population into 2 age groups (24–39 years and 40–95 years) to examine the association between retinal vascular caliber and hsCRP and repeated all analyses after excluding participants with hsCRP levels suggestive of clinical inflammation (>10 mg/L).

Statistical interactions were deemed significant if the P value for interaction was less than 0.1.

RESULTS

Characteristics of the study participants, overall and by race/ethnicity, are shown in Table 1. The mean age of the

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**Table 1.** Characteristics of Study Participants, Overall and by Race/Ethnicity, Singapore Prospective Study Program and Singapore Cardiovascular Cohort Study 2, Singapore, 2003–2007

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Participants (n = 3,583)</th>
<th>Chinese (n = 2,069)</th>
<th>Malays (n = 796)</th>
<th>Indians (n = 718)</th>
<th>P Valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% (Mean (SD))</td>
<td>% (Mean (SD))</td>
<td>% (Mean (SD))</td>
<td>% (Mean (SD))</td>
<td></td>
</tr>
<tr>
<td>Female gender</td>
<td>53.50 (55.24)</td>
<td>50.88 (51.39)</td>
<td>51.39 (52.00)</td>
<td>0.052</td>
<td></td>
</tr>
<tr>
<td>Current smoking</td>
<td>12.56 (10.63)</td>
<td>17.84 (12.26)</td>
<td>40.53 (47.99)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>39.38 (36.49)</td>
<td>45.85 (40.53)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>11.53 (6.81)</td>
<td>14.20 (22.14)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>33.46 (44.22)</td>
<td>6.66 (32.17)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>49.38 (11.21)</td>
<td>49.90 (10.89)</td>
<td>51.05 (10.36)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Body mass indexb</td>
<td>24.24 (4.45)</td>
<td>22.84 (4.71)</td>
<td>25.99 (4.73)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>131.60 (20.23)</td>
<td>129.41 (19.91)</td>
<td>136.42 (20.16)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>77.74 (10.63)</td>
<td>76.84 (10.62)</td>
<td>79.42 (10.53)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Serum glucose level, mmol/L</td>
<td>5.21 (1.61)</td>
<td>4.98 (1.18)</td>
<td>5.34 (1.83)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Cholesterol level, mmol/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>5.24 (0.95)</td>
<td>5.16 (0.91)</td>
<td>5.48 (1.01)</td>
<td>5.19 (0.92)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High density lipoprotein cholesterol</td>
<td>1.32 (0.34)</td>
<td>1.40 (0.34)</td>
<td>1.29 (0.32)</td>
<td>1.15 (0.29)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low density lipoprotein cholesterol</td>
<td>3.29 (0.86)</td>
<td>3.17 (0.80)</td>
<td>3.49 (0.97)</td>
<td>3.39 (0.81)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglyceride level, mmol/L</td>
<td>1.37 (0.94)</td>
<td>1.29 (0.85)</td>
<td>1.53 (1.24)</td>
<td>1.44 (0.74)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High-sensitivity C-reactive protein level, mg/L</td>
<td>2.87 (6.12)</td>
<td>2.14 (5.63)</td>
<td>3.22 (4.71)</td>
<td>4.59 (8.15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Retinal arteriolar caliber (CRAE), μm</td>
<td>144.00 (14.10)</td>
<td>143.80 (14.09)</td>
<td>145.41 (13.70)</td>
<td>143.02 (14.46)</td>
<td>0.003</td>
</tr>
<tr>
<td>Retinal venular caliber (CRVE), μm</td>
<td>221.05 (20.61)</td>
<td>219.87 (20.12)</td>
<td>226.84 (20.66)</td>
<td>218.01 (20.76)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Abbreviations: CRAE, central retinal artery equivalent; CRVE, central retinal vein equivalent; SD, standard deviation.

a Difference by race/ethnicity, based on 1-way analysis of variance or chi-squared test as appropriate.

b Weight (kg)/height (m)^2.
Table 2. Relation of Retinal Vascular Caliber With High-Sensitivity C-Reactive Protein Level, Singapore Prospective Study Program and Singapore Cardiovascular Cohort Study 2, Singapore, 2003–2007a

<table>
<thead>
<tr>
<th>Quartile and High-Sensitivity C-Reactive Protein Level, mg/L</th>
<th>Retinal Arteriolar Caliber (CRAE), μm</th>
<th>Retinal Venular Caliber (CRVE), μm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model 1b</td>
<td>Model 2c</td>
</tr>
<tr>
<td>All participants (n = 3,583)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (&lt;0.5)</td>
<td>147.01 (4.18)</td>
<td>146.90 (4.00)</td>
</tr>
<tr>
<td>2 (0.5–1.2)</td>
<td>147.16 (4.16)</td>
<td>147.32 (3.98)</td>
</tr>
<tr>
<td>3 (1.2–3.1)</td>
<td>147.14 (4.14)</td>
<td>147.90 (3.96)</td>
</tr>
<tr>
<td>4 (≥3.1)</td>
<td>146.69 (4.16)</td>
<td>147.79 (3.98)</td>
</tr>
<tr>
<td>P for trenda</td>
<td>0.661</td>
<td>0.178</td>
</tr>
<tr>
<td>Younger participants (ages 25–39 years) (n = 664)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (&lt;0.5)</td>
<td>151.49 (3.84)</td>
<td>152.95 (3.95)</td>
</tr>
<tr>
<td>2 (0.5–1.2)</td>
<td>153.55 (3.85)</td>
<td>155.86 (3.96)</td>
</tr>
<tr>
<td>3 (1.2–3.1)</td>
<td>150.90 (3.77)</td>
<td>153.65 (3.86)</td>
</tr>
<tr>
<td>4 (≥3.1)</td>
<td>150.86 (3.86)</td>
<td>153.62 (4.03)</td>
</tr>
<tr>
<td>P for trenda</td>
<td>0.330</td>
<td>0.967</td>
</tr>
<tr>
<td>Older participants (ages 40–95 years) (n = 2,919)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (&lt;0.5)</td>
<td>143.11 (0.67)</td>
<td>144.00 (0.79)</td>
</tr>
<tr>
<td>2 (0.5–1.2)</td>
<td>142.87 (0.51)</td>
<td>143.88 (0.65)</td>
</tr>
<tr>
<td>3 (1.2–3.1)</td>
<td>143.34 (0.48)</td>
<td>144.93 (0.60)</td>
</tr>
<tr>
<td>4 (≥3.1)</td>
<td>142.81 (0.48)</td>
<td>144.76 (0.60)</td>
</tr>
<tr>
<td>P for trenda</td>
<td>0.871</td>
<td>0.222</td>
</tr>
</tbody>
</table>

Abbreviations: CRAE, central retinal artery equivalent; CRVE, central retinal vein equivalent.

a Mean (standard error).

b Results were adjusted for age, gender, and race/ethnicity.

c Results were adjusted for age, gender, race/ethnicity, smoking, mean blood pressure, diabetes, alcohol consumption, total cholesterol level, high density lipoprotein cholesterol level, triglyceride level, and body mass index.

d Results were adjusted for all of the variables in model 2, as well as for CRVE (in models for CRAE) or CRAE (in models for CRVE).

e P value for ordinal trend across categories of high-sensitivity C-reactive protein level.

total cohort was 49.4 years (standard deviation, 11.2; range, 24.6–94.9). There were significant differences in the frequency and distribution of risk factors among the 3 racial/ethnic groups. Malays were more likely to be smokers, had a higher body mass index, and had higher levels of total cholesterol, low density lipoprotein cholesterol, triglycerides, systolic blood pressure, diastolic blood pressure, mean CRAE, and mean CRVE than Chinese and Indians (P < 0.005). Chinese were more likely to be alcohol drinkers. Indians were more likely to be older, had a higher prevalence of diabetes, had a higher hsCRP level, and had a lower level of high density lipoprotein cholesterol than Chinese and Malays (Table 1).

The association of mean retinal vascular caliber with quartile of hsCRP level was estimated by analysis of covariance (Table 2). There was no significant association between CRAE and hsCRP in any of the models (all P’s for trend ≥ 0.178). In contrast, wider CRVE was strongly related to higher levels of hsCRP in the whole population in all 3 models. The P value for hsCRP from analysis of covariance was less than 0.001. Tukey’s test further indicated that the mean CRVE in the first quartile of hsCRP was significantly different from that in the other 3 quartiles (P = 0.034, P < 0.001, and P < 0.001, respectively) and the mean CRVE in the second quartile of hsCRP was significantly different from that in the third and fourth quartiles (P = 0.038 and P = 0.003, respectively), but the mean CRVE in the third quartile of hsCRP was not significantly different from that in the fourth quartile (P = 0.340). This trend remained significant after multivariate adjustment (model 2) and after multivariate adjustment plus CRAE (model 3) for CRVE (all P’s for trend < 0.001). The adjusted R² values for models 1, 2, and 3 were 0.083, 0.104, and 0.335, respectively. In the supplementary analysis, when we stratified the population into younger (25–39 years) and older (40–95 years) age groups, the associations between CRVE (all P’s for trend < 0.008) and hsCRP were similar to those for the whole population in all 3 models (Table 2).

Figure 2 shows the distribution of CRVE according to CVD risk factors (smoking, diabetes, hypertension, overweight, and dyslipidemia). The association between CRVE and hsCRP differed between participants with and without diabetes (P for interaction = 0.004) (Figure 2, part B). In
participants without diabetes, a higher level of hsCRP was associated with CRVE widening ($P$ for trend $< 0.001$); in participants with diabetes, this association was not found at all, and the differences observed were not significant ($P$ for trend $= 0.200$). The association between CRVE and hsCRP was consistent across categories of smoking, hypertension, overweight, and dyslipidemia without significant interaction (all $P$’s for interaction $\geq 0.1$).

We excluded participants with hsCRP levels greater than 10 mg/L ($n = 174$) and repeated the analyses. The relation between retinal venular caliber and hsCRP was not substantially altered (data not shown). For example, wider CRVE was strongly related to higher levels of hsCRP in all 3 models (all $P$’s for trend $\leq 0.001$), and the association was modified in persons with diabetes ($P$ for interaction $= 0.004$).

**DISCUSSION**

In this population-based study with a multiethnic Asian population aged 24–95 years, wider retinal venular caliber was significantly associated with elevated levels of hsCRP. This relation was similar across the 3 major Asian racial/ethnic groups (Chinese, Malays, and Indians) but was modified by diabetes status, such that associations were present in persons without diabetes but absent in those with diabetes.
To the best of our knowledge, ours is the first study to have examined the relation between microvascular caliber changes in the retina and markers of systemic inflammation in Asian populations and younger people. Our primary finding of an association between retinal venular caliber and CRP adds to the findings of other population-based studies carried out in largely white populations (20–22), which found that wider retinal venular caliber is strongly associated with elevated levels of CRP and other inflammatory markers (e.g., fibrinogen and interleukin-6). We now extend these findings to persons aged 24–39 years, which suggests that the relation is not modified by age. While our study was not designed to determine underlying mechanisms of this association, we and other investigators (19–22) have hypothesized that venular vessel dilation with an elevated level of inflammatory markers may be related to disruption of the endothelial surface layer by oxidized low density lipoproteins or activated leukocytes (42).

We also examined whether different CVD risk factors may modify the association between retinal venular caliber and CRP. The effect of inflammation on retinal venular caliber was consistently seen regardless of smoking status, hypertension, overweight, and dyslipidemia status. However, a new finding was that elevated CRP was not associated with retinal venular caliber in participants with diabetes \( (P \text{ for interaction} = 0.004) \). Wider retinal venular caliber has been previously shown to be strongly linked with diabetes (19, 20, 26–30). Our findings now may suggest that in persons with diabetes, retinal venular caliber may have already been altered/widened, and therefore the additive effect of inflammation may not be sufficient to further modify retinal venular caliber. Similarly, in a previous study of retinal vascular caliber, Wong et al. (43) reported stronger effects of blood pressure on retinal arteriolar narrowing in persons without diabetes, but such an association was weaker in people with diabetes, again reflecting the fact that in persons with diabetes, retinal arteriolar narrowing is already present. Further studies would be useful for examining the underlying pathophysiologic mechanisms and relations between diabetes, inflammation, and microvascular disease.

The strengths of our study include a large population-based sample with 3 racial/ethnic groups and information on a variety of potential confounders. This study also had limitations that should be considered. First, the analyses were cross-sectional, which did not allow us to make inferences regarding causation between retinal vascular caliber and CRP. Second, because only 1 inflammatory marker (hsCRP) was used, it is uncertain whether there are any associations of retinal vascular caliber with other inflammatory markers in Asians. Furthermore, there may be residual factors (e.g., ocular factors) we could not control for that may modify these associations.

In summary, an elevated level of CRP was associated with wider retinal venular caliber in this large multiethnic Asian population. The magnitudes of associations were similar in younger and older people and across the 3 major racial/ethnic groups (Chinese, Malays, and Indians). Diabetes significantly influenced the association between retinal venular caliber and CRP, such that the association was not present in persons with diabetes. The current analysis may improve our understanding of the association between inflammation and microvascular disease and supports the hypothesis that retinal venular caliber may be a marker for low-grade systemic inflammation.

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Author affiliations: Singapore Eye Research Institute, Singapore National Eye Centre, Singapore (Carol Yin-lui Cheung, Tien Yin Wong, Ecosse L. Lamoureux, Charumathi Sabanayagam); Centre for Eye Research Australia, University of Melbourne, Melbourne, Victoria, Australia (Tien Yin Wong, Ecosse L. Lamoureux); Department of Ophthalmology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore (Tien Yin Wong, Charumathi Sabanayagam); Department of Statistics and Applied Probability, Faculty of Science, National University of Singapore, Singapore (Jialiang Li); Department of Community, Occupational and Family Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore (Jeannette Lee, E. Shyong Tai); and Department of Endocrinology, Singapore General Hospital, Singapore (E. Shyong Tai).

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Conflict of interest: none declared.

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