

# Ethnic Variability in Retinal Vessel Caliber: A Potential Source of Measurement Error from Ocular Pigmentation?—The Sydney Childhood Eye Study

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**PURPOSE.** To describe the effects of ethnicity and iris color on measurement of retinal vascular caliber.

**METHODS.** The Sydney Childhood Eye Study (SCES) examined 1740 6-year-old children from 34 randomly selected Sydney schools during 2003 and 2004. Retinal arteriolar and venular calibers (central retinal arteriolar [CRAE] and central retinal venular [CRVE] equivalents) were measured from retinal photographs by a standardized computer-assisted method. Associations of retinal vascular caliber with ethnicity and iris color were analyzed.

**RESULTS.** Of the total participants, 1612 (92.6%) had gradable retinal photographs. CRAE and CRVE were normally distributed, with means (SD) of 163.2 (14.0) and 227.3 (18.3)  $\mu\text{m}$ , respectively. Both arteriolar and venular calibers were substantially wider in the East Asian than in the Caucasian children (CRAE, 171.5  $\mu\text{m}$  vs. 160.5  $\mu\text{m}$ ; and CRVE, 240.5  $\mu\text{m}$  vs. 222.4  $\mu\text{m}$ ;  $P < 0.0001$  for both comparisons). Among the Caucasian children, darker iris color was associated with wider arteriolar and venular caliber: CRAE increased from 157.5  $\mu\text{m}$  in blue eyes to 169.2  $\mu\text{m}$  in dark brown eyes ( $P$  for trend  $< 0.0001$ ), and CRVE increased from 218.4  $\mu\text{m}$  in blue eyes to 230.0  $\mu\text{m}$  in dark brown eyes ( $P$  for trend  $< 0.0001$ ). Among the children with dark brown eyes, there was no significant difference in CRAE between the Caucasian and the East Asian children, although mean CRVE was still approximately 10  $\mu\text{m}$  wider in the East Asian than in the Caucasian children.

**CONCLUSIONS.** Retinal vessel caliber was wider in the children of East Asian ethnicity. This difference was explained principally by darker iris color. Retinal pigmentation, as approximated by iris color, could be an important source of error in the measurement of retinal vessel caliber. If confirmed, this may affect comparisons of retinal vessel caliber between subjects with different ethnic backgrounds. (*Invest Ophthalmol Vis Sci*. 2008;49:1362–1366) DOI:10.1167/iovs.07-0150

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Retinal vessels provide clinicians and researchers with a unique opportunity to view and characterize the microvascular system noninvasively. Recently developed methods of measuring retinal vascular caliber from retinal photographs<sup>1–3</sup> have been used in several studies in adult populations,<sup>4,5</sup> showing that these measurements are predictive of various cardiovascular diseases.<sup>6–9</sup>

There is increasing evidence that retinal vascular caliber may vary between racial and ethnic groups. In the Multi-Ethnic Study of Atherosclerosis (MESA), the blacks and Hispanics had larger retinal arteriolar and venular caliber than the whites and Chinese, despite adjustment for cardiovascular risk factors.<sup>5</sup> The Singapore Cohort Study of Risk Factors for Myopia (SCORM) also found significant differences in retinal vascular caliber in Malay, Indian, and Chinese children.<sup>10</sup> The underlying reasons for these racial and ethnic differences are unclear and were thought possibly to reflect variations in levels and susceptibility to vascular risk factors (e.g., blood pressure), anthropometric and ocular biometry measures (e.g., axial length), and/or genetic factors.<sup>11,12</sup>

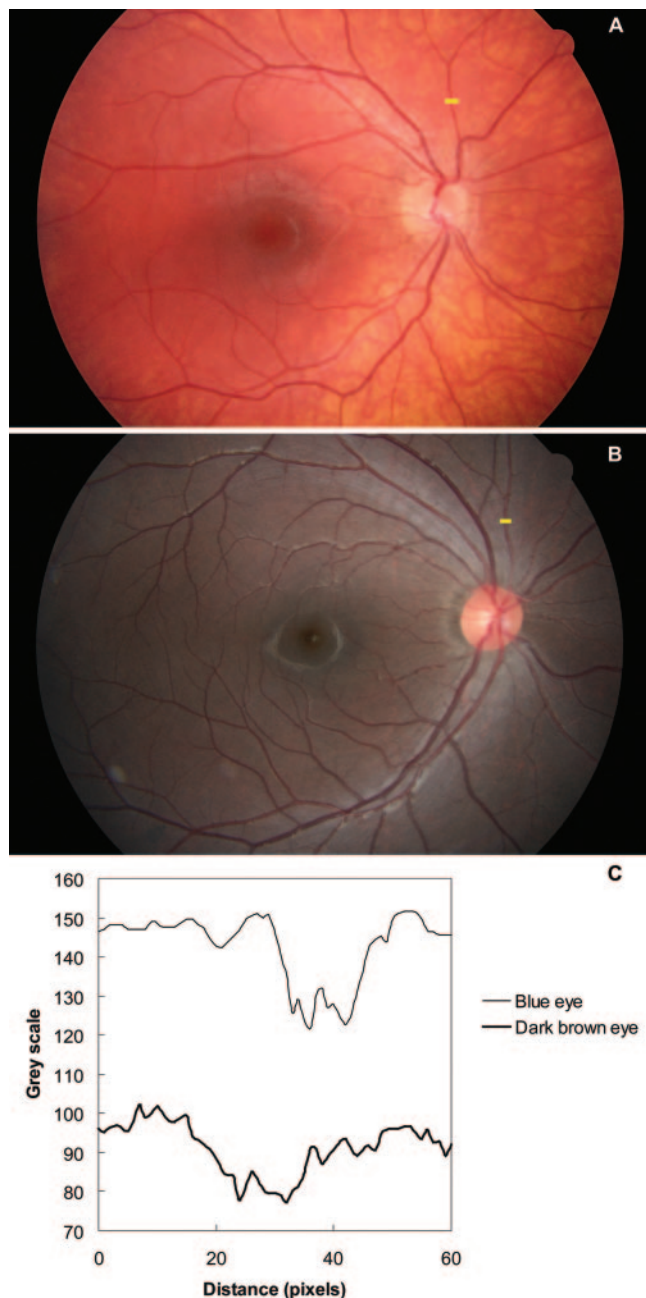
We now hypothesize that variations in contrast between retinal background color and the vessel edge affect retinal vessel caliber measurements from fundus photographs, and that variations in retinal pigmentation may explain some of the observed racial and ethnic differences. Figure 1 shows fundus photographs from two SCES children. The top photograph is from a blue-eyed Caucasian child and the middle photograph is from a dark brown-eyed East Asian child. The graph shows the pixel density curves over the marked arterioles. The contrast between the vessel edge and retinal background was greater in the blue eye than in the dark brown eye. The slope of the pixel density curve at the vessel edge in the blue eye was also steeper than that in the dark brown eye. As the measurement takes the mid-half value from the curve,<sup>13</sup> the gentler slope would give a wider absolute value for this measure.

In the present study, we used a semiautomated computer program to assess the variations in retinal vessel caliber, as measured from digital retinal images, by ethnicity and by iris color, a surrogate measure of retinal pigmentation, in a population-based sample of young, school-aged children. Children are the ideal population in which to test this hypothesis, as they are generally free from cardiovascular and ocular diseases.

## METHODS

### Study Population

The Sydney Childhood Eye Study is a population-based survey of eye health in school children residing in the metropolitan area of Sydney, Australia. This article describes data from the Sydney Myopia Study component, which examined grade one school children during 2003 and 2004. The study was approved by the Human Research Ethics Committee, University of Sydney and the Department of Education and Training, New South Wales, Australia, and adhered to the tenets of the Declaration of Helsinki. Informed written consent was obtained from



**FIGURE 1.** Fundus photographs from (A) a blue-eyed Caucasian child and (B) a dark-brown-eyed East Asian child. (C) Pixel density curves over the marked arterioles.

at least one parent, as well as verbal assent from each child. Detailed study methods have been described elsewhere.<sup>14,15</sup> In brief, 34 primary schools across the Sydney metropolitan region were selected through random cluster sampling, stratified on socioeconomic status. A proportionate mix of government-funded and private/religious schools was included.

### Demographic Data

Demographic data were obtained from a comprehensive 193-item questionnaire sent to parents. Questions covered topics including socioeconomic status, medical and ocular history, and birth history (including birth weight and gestational age). Each child's ethnicity was determined from the ethnicity of both parents. Ethnic groups repre-

sented were European Caucasian, East Asian, South Asian (Indian/Pakistani/Sri Lankan), African, Melanesian/Polynesian, Middle Eastern, Indigenous Australian, and South American.

### Ocular Examination and Retinal Photography

Iris color was assessed from the undilated pupil of each eye and graded by the observer as blue, hazel-green, tan-brown, or dark brown.

Axial length was measured before cycloplegia with an optical biometer (IOLMaster; Carl Zeiss Meditec, Oberkochen, Germany), using dual-beam partial-coherence interferometry (PCI).<sup>16</sup> The average of five measurements was used for analysis.

Cycloplegia was induced by instilling cyclopentolate 1% and tropicamide 1%, 2 drops each, separated by 5 minutes. Phenylephrine 2.5% was also instilled in a small proportion of children, to achieve adequate mydriasis ( $\geq 6$  mm). Autorefractometry (RK-F1 autorefractor/keratometer, Canon, Tokyo, Japan) was performed 25 to 30 minutes after the last drop. Five autorefractometry measurements were performed automatically. The median measurement obtained by the instrument was used for analyses.

Mydriatic 60° digital photographs of the optic disc and macula of both eyes were taken with a fundus camera (model 60UVI-D10; Canon). Methods used to measure and summarize retinal vascular caliber from the digital retinal photographs have been described elsewhere.<sup>1,17,18</sup> Briefly, a computer imaging program (IVAN; University of Wisconsin, Madison, WI) was used to measure the caliber of all retinal vessels located one half to one disc diameter from the optic disc margin in the digital retinal photograph. Using the Knudtson-Hubbard formula,<sup>3</sup> we summarized these measurements as central retinal arteriolar (CRAE) and central retinal venular equivalents (CRVE), representing the average arteriolar and venular calibers in the examined eye, respectively. A single grader (BT), masked to participant characteristics, performed all retinal measurements.<sup>18</sup> High correlation between the right and left eyes in retinal vascular caliber measurements has been reported.<sup>19</sup> Data from the right eyes were used. High intra- and intergrader reproducibility of the retinal vascular measurements obtained with a computer-based program has been reported.<sup>1,2</sup>

### Anthropometric and Blood Pressure Measurements

Anthropometric measurements including height, weight, and waist circumference, were collected for each child.<sup>18</sup> Height without shoes was measured with a freestanding height rod (model 220; Seca, North Rocks, NSW, Australia). Weight was measured with an electronic scale (model TBF-300; Tanita, Tokyo, Japan). Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared.

Sitting blood pressure and heart rate were measured in the right arm with an oscillometric blood pressure recorder (HEM-907; Omron, Sydney, NSW, Australia).<sup>18</sup> After the child had 10 minutes of quiet rest, a single measure of blood pressure was taken using an appropriately sized cuff. Mean arterial blood pressure (MABP) was calculated as one third of the systolic (SBP) plus two thirds of the diastolic blood pressure (DBP).

### Statistical Analysis

Analyses were performed for the right eye data (SAS ver. 9.1; SAS Institute, Cary, NC).  $\chi^2$  and *t*-tests were used to compare selected characteristics between subgroups. Multivariate adjusted means for retinal vascular caliber in subgroups were calculated using analysis of covariance. Mixed models were used for additional adjustment for cluster-sampling effects.

### RESULTS

Of the 1740 examined children, 1612 (92.6%) had gradable retinal photographs, including 795 (49.3%) girls and 817

TABLE 1. Characteristics of the Study Participants

|                          | All<br>( <i>n</i> = 1612) | European<br>Caucasian<br>( <i>n</i> = 1023) | East Asian<br>( <i>n</i> = 272) | <i>P</i> |
|--------------------------|---------------------------|---|---------------------------------|----------|
| Age (y)                  | 6.7 (0.4)                 | 6.8 (0.4)                                   | 6.5 (0.4)                       | 0.0001   |
| Height (cm)              | 120.6 (5.7)               | 121.6 (5.7)                                 | 119.0 (5.1)                     | 0.0001   |
| BMI (kg/m <sup>2</sup> ) | 16.2 (2.1)                | 16.2 (2.0)                                  | 15.7 (2.0)                      | 0.0004   |
| SBP (mm Hg)              | 99.8 (10.5)               | 99.5 (10.2)                                 | 98.4 (9.4)                      | 0.11     |
| DBP (mm Hg)              | 60.3 (10.1)               | 59.6 (9.6)                                  | 60.6 (9.1)                      | 0.13     |
| Birth weight (g)         | 3382 (569)                | 3434 (576)                                  | 3231 (559)                      | 0.0001   |
| Spherical equivalent (D) | 1.28 (0.87)               | 1.41 (0.82)                                 | 0.90 (0.76)                     | 0.0001   |
| Axial length (mm)        | 22.6 (0.69)               | 22.5 (0.70)                                 | 22.6 (0.65)                     | 0.16     |
| Iris color               |                           |   |                                 |          |
| Blue                     | 29.2                      | 43.1  | 0.0                             |          |
| Hazel-green              | 20.1                      | 28.2  | 0.0                             |          |
| Tan-brown                | 20.5                      | 23.2  | 0.7                             |          |
| Dark brown               | 30.2                      | 5.5   | 99.3                            | 0.0001   |

Data are the means (SD) and percentages (%).

(50.7%) boys. The mean age of participants was 6.7 years. The ethnic composition of children was predominantly European Caucasian (*n* = 1023, 63.5%) and East Asian (*n* = 272, 16.9%). There were also 78 (4.8%) Middle Eastern and 38 (2.4%) South Asian children. The remaining 201 (12.5%) children belonged to five other ethnic categories too low in number for their data to be reported separately.

Table 1 presents selected characteristics of the study population stratified by the two main ethnic groups. The East Asian children were younger and shorter and had lower BMI, lower birthweight, and more myopic refraction than did the European Caucasian children. Almost all (99.3%) of the East Asian children and only 5.5% of the Caucasian children had dark brown iris color. There was no difference in SBP, DBP, and axial length between these two ethnic groups.

The mean retinal arteriolar caliber (CRAE) was normally distributed (mean  $\pm$  SD of  $163.2 \pm 14.0 \mu\text{m}$ ; range, 124.5–207.3). The mean retinal venular caliber (CRVE) was also normally distributed (mean  $\pm$  SD of  $227.3 \pm 18.3 \mu\text{m}$ ; range, 175.3–288.6  $\mu\text{m}$ ). Figure 2 shows the distribution of CRAE and CRVE in both the Caucasian and East Asian children.

Table 2 shows the mean retinal arteriolar and venular caliber by age, gender, and ethnic group. There was no difference in retinal vascular caliber between the 6- and 7-year-old children. Boys had slightly narrower retinal vascular caliber than did the girls ( $P < 0.0001$  for both calibers), but this difference became nonsignificant after adjustment for other confounding factors, including age, ethnicity, birthweight, height, BMI, MABP, and axial length.

The East Asian, South Asian, and Middle Eastern children all had significantly wider measured retinal arteriolar and venular caliber than did the European Caucasian children, with the greatest difference ( $\sim 10 \mu\text{m}$  CRAE,  $20 \mu\text{m}$  CRVE) observed between the East Asian (mean CRAE,  $171.5 \mu\text{m}$ ; mean CRVE,  $240.5 \mu\text{m}$ ) and Caucasian children (mean CRAE,  $160.5 \mu\text{m}$ ; mean CRVE,  $222.4 \mu\text{m}$ ),  $P < 0.0001$  for both calibers, after multivariate adjustment.

Among the European Caucasian children, darker iris color was associated with wider arteriolar and venular caliber (Table 3). Multivariate adjusted mean CRAE increased from  $157.5 \mu\text{m}$  in blue eyes to  $169.2 \mu\text{m}$  in dark brown eyes ( $P$  for trend  $< 0.0001$ ). Multivariate adjusted mean CRVE increased from  $218.4 \mu\text{m}$  in blue eyes to  $230.0 \mu\text{m}$  in dark brown eyes ( $P$  for trend  $< 0.0001$ ). The findings were similar when children from all ethnic groups were included (Table 3).

We assessed the ethnic differences in retinal vascular caliber only in the children with dark brown eyes, as this was the

only iris color group that included all ethnicities (Table 4). In this comparison, there was no significant difference in CRAE between European Caucasian and East Asian children ( $P = 0.24$ ), but the mean CRVE was still approximately  $10 \mu\text{m}$  wider in the East Asian than in the Caucasian children ( $P = 0.0004$ ). Both caliber measures were not significantly different in the South Asian and Middle Eastern children, when compared with the Caucasian children.

## DISCUSSION

In this study, we found significant differences in retinal vascular caliber, as measured using a semiautomated computer pro-

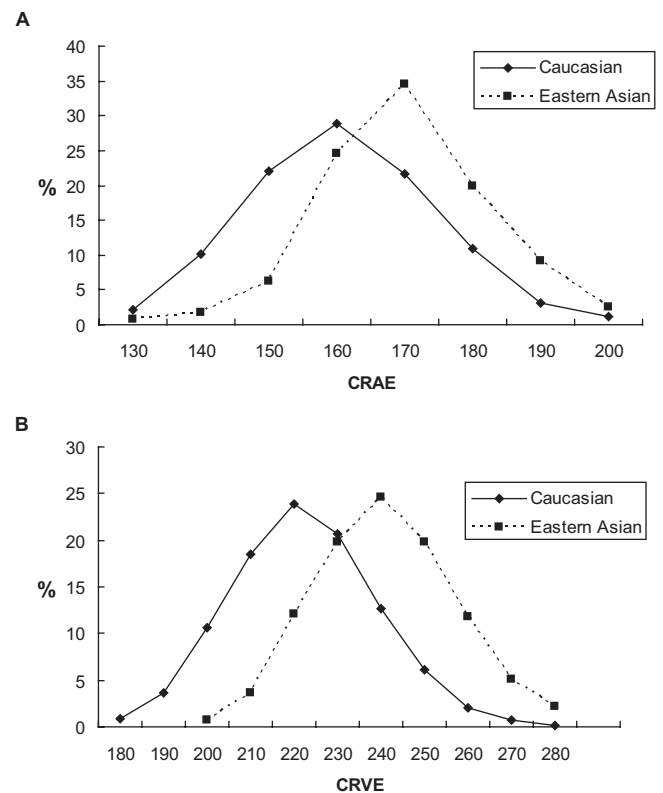


FIGURE 2. Distribution of (A) retinal arteriolar caliber (CRAE) and (B) retinal venular caliber (CRVE) in European Caucasian and East Asian children in the Sydney Childhood Eye Study (*n* = 1612).

TABLE 2. Mean Retinal Arteriolar and Venular Calibers by Age, Gender, and Ethnicity

| Subgroup            | n    | Retinal Arteriolar Caliber |                     |        | Retinal Venular Caliber |                     |        |
|---------------------|------|----------------------------|---------------------|--------|-------------------------|---------------------|--------|
|                     |      | Unadjusted                 | Adjusted*           | P†     | Unadjusted              | Adjusted*           | P†     |
| 6-Year-olds         | 1198 | 163.5 (162.7–164.3)        | 165.4 (163.9–166.9) |        | 228.0 (227.0–229.0)     | 232.1 (230.2–234.1) |        |
| 7-Year-olds         | 414  | 162.4 (161.0–163.7)        | 165.7 (163.4–167.9) | 0.78   | 225.3 (223.6–227.1)     | 232.4 (230.1–234.6) | 0.81   |
| Girls               | 795  | 164.9 (163.9–165.9)        | 165.9 (163.9–167.9) |        | 229.5 (228.2–230.7)     | 232.5 (230.3–234.6) |        |
| Boys                | 817  | 161.5 (160.6–162.5)        | 165.1 (163.8–166.5) | 0.23   | 225.2 (224.0–226.5)     | 232.1 (230.1–234.0) | 0.65   |
| European Caucasian‡ | 1023 | 160.8 (160.0–161.7)        | 160.5 (159.4–161.6) |        | 222.3 (221.3–223.3)     | 222.5 (221.1–223.9) |        |
| Eastern Asian       | 272  | 170.4 (168.9–171.9)        | 171.5 (169.5–173.6) | 0.0001 | 240.5 (238.6–242.4)     | 240.6 (237.8–243.3) | 0.0001 |
| South Asian         | 38   | 166.3 (161.2–171.3)        | 165.9 (163.2–168.5) | 0.002  | 233.9 (227.7–240.0)     | 233.2 (227.6–238.9) | 0.002  |
| Middle Eastern      | 78   | 166.4 (163.2–169.6)        | 165.8 (161.2–170.5) | 0.13   | 232.9 (229.4–236.4)     | 233.6 (230.1–237.2) | 0.0001 |
| Other               | 201  | 163.6 (161.7–165.5)        | 163.9 (161.6–166.1) | 0.05   | 231.6 (229.1–234.0)     | 231.4 (228.2–234.6) | 0.0001 |

Data are mean micrometers (95% CI).

\* Adjusted for age, gender, ethnicity, birthweight, height, BMI, MABP, and axial length.

† Probability for adjusted means comparison, Bonferroni adjustment for multiple group comparison was applied.

‡ Probability provided for comparison between European Caucasian children and those of other ethnic groups.

gram, in children of different racial and ethnic groups and in eyes of different iris colors. The East Asian children and those European Caucasian children with darker iris color had wider retinal arteriolar and venular caliber. To elucidate the reasons behind the ethnic differences in retinal vessel caliber and to differentiate “ethnicity” from “iris color,” we examine this association in the subgroup of Caucasian children with different iris color. The magnitude of the association with iris color among European Caucasian children remained very strong (~10  $\mu\text{m}$  difference in the mean arteriolar and venular caliber between blue eyes and dark brown eyes). Thus, we suggest that the racial-ethnic variation in retinal vessel caliber is principally explained by darker iris color, a proxy for retinal pigmentation.

We further tested our hypothesis using data from the Blue Mountains Eye Study (a population that included 98% European Caucasian adults aged 49+ years) and found similar association between iris color and retinal vascular caliber, although a different computer program, Retinal Analysis,<sup>13</sup> was used for the measurements. Both retinal arteriolar and venular calibers were significantly wider (~5  $\mu\text{m}$  difference for both) in persons with dark brown irises than in those with blue irises ( $P < 0.0001$  after controlling for age, gender, BMI, smoking and MABP; Rochtchina E, unpublished data, 2007).

Our study is consistent with and provides a new explanation for the findings in two other studies that examined racial and ethnic differences in retinal vascular caliber. In the MESA

study population, the African-Americans and Hispanics, who have darker fundus pigmentation, were reported to have wider mean arteriolar and venular calibers compared with that of the whites and Chinese. Also, the Chinese had wider mean venular caliber than did the whites.<sup>5</sup> The SCORM data showed that both retinal arterioles and venules were wider in the Malay or Indian children (who have somewhat darker retinal pigmentation) than in the Chinese children, even after adjustment for age, gender, refraction, and other factors.<sup>10</sup> Darker iris color correlates highly with non-Caucasian ethnicity. In our sample, among children with dark brown eyes, only 11% were of European Caucasian ethnicity. We therefore propose that the observed ethnic differences in retinal caliber are likely to be at least partly explained by the different retinal pigment background indicated by various iris colors. Our findings from subgroup analyses of children with dark brown iris color support this hypothesis. Among children with dark brown eyes, we found no difference in the mean arteriolar caliber between European Caucasian and East Asian children. The difference in the mean venular caliber remained significant, with a reduced magnitude (Table 4).

Our study suggests that a higher level of retinal pigmentation (represented by darker iris color) may reduce the contrast between the background and retinal vessels, making the vessel edge harder to detect with the semiautomatic computer program. This seems likely to result in measurements that exceed the true boundary of the vessel. We are currently planning a

TABLE 3. Mean Retinal Arteriolar and Venular Caliber by Iris Color

| Iris Color         | n (%)      | Retinal Arteriolar Caliber | Retinal Venular Caliber |
|--------------------|------------|----------------------------|-------------------------|
| All children       |            |                            |                         |
| Blue               | 470 (29.2) | 157.1 (155.7–158.4)        | 218.4 (216.6–220.1)     |
| Hazel-green        | 324 (20.1) | 161.0 (159.3–162.7)        | 223.6 (221.5–225.8)     |
| Tan-brown          | 329 (20.5) | 164.1 (162.8–165.4)        | 228.9 (227.0–230.7)     |
| Dark brown         | 486 (30.2) | 169.8 (168.4–171.3)        | 237.7 (235.9–239.5)     |
| P for trend        |            | <0.0001                    | <0.0001                 |
| European Caucasian |            |                            |                         |
| Blue               | 440 (43.1) | 157.5 (156.2–158.9)        | 218.4 (216.5–220.4)     |
| Hazel-green        | 287 (28.2) | 161.7 (160.0–163.3)        | 223.4 (221.2–225.6)     |
| Tan-brown          | 237 (23.2) | 163.9 (162.3–165.4)        | 228.1 (226.1–230.0)     |
| Dark brown         | 56 (5.5)   | 169.2 (165.5–173.0)        | 230.0 (225.7–234.2)     |
| P for trend        |            | <0.0001                    | <0.0001                 |

Data are mean micrometers (95% CI) adjusted for age, gender, height, BMI, birthweight, axial length, and MABP.

TABLE 4. Mean Retinal Arteriolar and Venular Caliber in Children with Dark Brown Iris Color, by Ethnicity

| Ethnicity          | n (%)       | Retinal Arteriolar Caliber | Retinal Venular Caliber |
|--------------------|-------------|----------------------------|-------------------------|
| European Caucasian | 56 (11.5%)  | 168.3 (164.5–172.2)        | 228.9 (224.6–233.2)     |
| East Asian         | 270 (55.6%) | 170.8 (169.0–172.6)        | 240.0 (238.0–242.0)*    |
| South Asian        | 36 (7.4%)   | 164.7 (162.0–167.4)        | 231.4 (225.0–237.8)     |
| Middle Eastern     | 34 (7.0%)   | 166.7 (159.5–173.9)        | 234.7 (229.6–239.8)     |
| Other/mixed        | 90 (18.5%)  | 166.7 (163.9–169.5)        | 237.3 (232.9–241.8)*    |

Data are mean micrometers (95% CI) adjusted for age, gender, height, BMI, birthweight, axial length, and MABP.

\* Significantly different from the European Caucasian children ( $P < 0.001$ ).

fluorescein angiographic comparison study for investigation of this hypothesis.

We should consider alternative hypotheses. It is possible, for example, that the observed relationship between retinal vessel caliber with iris color is in part attributable to genetic differences.<sup>20</sup> However, we have no means to determine whether there is a genetic influence.

In summary, darker iris color was found to be associated with wider retinal vascular caliber, as measured with a standardized semiautomated computer program from digital retinal images. Retinal pigmentation, as approximated by iris color, could be an important source of error in the measurement of retinal vessel caliber, and this measurement error may largely explain the observed ethnic differences in retinal vessel caliber. If this measurement error is confirmed by other studies, the effect of contrast may have to be taken into account when comparing retinal vessel caliber among subjects with different ethnic backgrounds.

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