Evidence of Retinal Vascular Narrowing in Glaucomatous Eyes in an Asian Population

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Purpose. To examine the relationship between retinal vascular caliber and glaucoma in an Asian population.

Methods. A population-based, cross-sectional study of 3019 persons of Asian Malay ethnicity aged 40 to 80 years residing in Singapore. All participants had dilated digital retinal photographs taken of both eyes. From these, retinal vascular caliber was measured with a computer-based technique according to a standardized protocol. Glaucoma was diagnosed based on the International Society of Geographic and Epidemiologic Ophthalmology classification and included people with glaucomatous optic neuropathy and compatible visual field loss.

Results. There were 127 (4.2%) participants with glaucoma. Mean retinal arteriolar and venular calibers were significantly narrower in persons with than in those without glaucoma (136.4 μm vs. 139.7 μm, $P = 0.02$ and 209.2 μm vs. 219.7 μm, $P < 0.001$, respectively). After adjusting for age, sex, smoking, IOP, and other vascular risk factors, persons with narrower retinal arteriolar and venular caliber were more likely to have glaucoma (odds ratio [OR], 1.29; 95% confidence interval [CI], 1.07–1.56 and OR, 1.49; 95% CI, 1.24–1.79, for each SD reduction in arteriolar and venular caliber, respectively) and a vertical cup-to-disc ratio ≥ 0.7 (OR, 1.35; 95% CI, 1.12–1.63 and OR, 1.65; 95% CI, 1.38–1.98, respectively). Retinal vascular caliber was not associated with intraocular pressure.

Conclusions. These findings support an association of narrower retinal arteriolar and venular caliber changes with glaucomatous optic neuropathy, independent of intraocular pressure. (*Invest Ophthalmol Vis Sci.* 2008;49:5397–5402) DOI:10.1167/iovs.08-2142

There is increasing recognition that vascular risk factors and processes may have a role in the pathogenesis of glaucomatous optic neuropathy. Evidence for the "vascular theory" of glaucoma comes from studies that have shown associations of glaucoma with higher systemic blood pressure,[1] altered ocular hemodynamics,[1–4] vasospasm,[5–6] proliferative diabetic retinopathy,[7] and systemic vascular disease (e.g., migraine).[8] In the Early Manifest Glaucoma Trial and the Barbados Eye Study, lower systolic perfusion pressure, lower systolic blood pressure, and a history of cardiovascular disease were shown to be independent predictors of glaucoma progression,[9,10] lending further support to vascular disease processes in the evolution of glaucoma. Concomitantly, long-standing glaucoma itself may also lead to structural alterations in the retinal vasculature.[11–13]

However, previous research in this field has been limited in most studies by subjective methods used to ascertain changes in the retinal vasculature, such as the presence or absence of focal arteriolar narrowing,[11,12,14] or the measurement of retinal vascular caliber from projected slide transparencies.[15,16] Using new computer-based imaging techniques to quantitatively measure retinal vascular caliber, three studies have been conducted to examine the relationship between retinal vascular caliber and glaucoma in Caucasian populations, with one showing an association between narrower caliber and glaucoma but two others finding no association.[17–19] Additional studies are clearly indicated, particularly in Asians in whom the prevalence, subtypes, and risk factors for glaucoma may differ from Caucasians.[20,21] In fact, it has been hypothesized that intraocular pressure–independent vascular mechanisms could be more important in Asian glaucoma as demonstrated in Japanese populations.[22,23] In this study, we examined the relationship of quantitatively measured retinal vascular caliber and glaucoma in a population-based sample of Asian Malays in Singapore.

Methods

Study Population

The Singapore Malay Eye Study was a population-based, cross-sectional study of 3280 Malay men and women, aged 40 to 80 years, living in Singapore. The study design and details of sample recruitment have been described elsewhere.[24–27] In brief, an age-stratified random sampling of all Malay adults residing in the southwestern part of Singapore was performed, where 1400 names from each decade (40–49, 50–59, 60–69, and 70–79 years), or an initial 5600 names were selected. Of these, 4168 (74%) individuals were determined to be eligible to participate. A person was considered ineligible if he or she had moved from the residential address, had not lived there in the past 6 months, or was deceased or terminally ill. Of 4168 eligible individuals, 3280 participants took part in our study (78.7% participation rate). The study followed the principles of the Declaration of Helsinki, and ethics approval was granted from the Institutional Review Board of the Singapore Eye Research Institute. Written informed consent in either the Malay language or English was obtained from each participant.

Retinal Photography and Quantitative Assessment of Retinal Vascular Caliber

Participants had a comprehensive interview and ocular examination using a standardized protocol based on that from the Tanjong Pagar

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Survey and the Blue Mountains Eye Study.[25] Relevant parts of the examination are included here.

Digital fundus photography (Canon CR-DGi with a 10D SLR back; Canon, Tokyo Japan) was performed after pupil dilation with tropicamide 1% and phenylephrine hydrochloride 2.5%, except for a few participants with history of allergy to mydriatic eye drops and those with closed anterior chamber angles and IOP > 21 mm Hg, in whom undilated photographs were taken. Two retinal images, Early Treatment for Diabetic Retinopathy Study (ETDRS) standard field 1 (centered on the optic disc) and ETDRS standard field 2 (centered on the fovea), were obtained.[28] Images were sent to the Retinal Vascular Imaging Grading Centre (Centre for Eye Research Australia, University of Melbourne) for retinal vessel measurement.

Retinal vascular caliber was measured by computer-assisted software (IVAN, University of Wisconsin, Madison, WI), according to a standardized protocol as used in other population-based studies.[29–32] A trained grader, masked to participant characteristics, performed all the vessel measurements using the optic disc-centered image of the right eye for each participant. If the right eye image was not available or ungradable due to poor quality or ocular disease or the grader could not measure the six widest arterioles or venules from the right eye image, the left eye image was then graded.[32] All arterioles and venules coursing through a specified zone 0.5 to 1 disc diameter away from the optic disc margin were measured in micrometers and combined into summary measures (referred to as central retinal arteriolar equivalent or CRAE and central retinal venular equivalent or CRVE) using the improved Parr and Hubbard formulas[33] as described by Knudtson et al.[34]

Quality control procedures were implemented during the retinal grading.[32] We randomly selected 200 retinal photographs to assess intragrader reliability and found intragrader intraclass correlation coefficients (95% confidence interval [CI]) to be 0.99 (0.98–0.99) for CRAE and 0.94 (0.92–0.96) for CRVE. Bland-Altman plots were performed to confirm the CRAE and CRVE reliability over the range of CRAE/CRVE values; these showed that the mean difference between measurements was close to zero, with no change in magnitude of difference as CRAE and CRVE increased (data not shown).

Glaucoma Assessment

Glaucoma was diagnosed according to the International Society of Geographic and Epidemiologic Ophthalmology (ISGEO) classification.[35] Definitive information on the presence of glaucomatous optic disc damage and visual field loss was not always available (e.g., due to media opacity or poor vision), and in such cases, glaucoma was diagnosed based on three levels of evidence. The highest level of evidence (category 1) required an optic disc abnormality (vertical cup-to-disc ratio [CDR] or vertical CDR asymmetry ≥97.5th percentile or neuroretinal width between 11 and 1 or 5 and 7 o'clock <0.1 vertical CDR) and a corresponding glaucomatous visual field defect. In the second (category 2), if a visual field test could not be performed satisfactorily, a severely damaged optic disc (vertical CDR or vertical CDR asymmetry ≥99.5th percentile) would be sufficient to make the diagnosis. A diagnosis of category 1 or 2 glaucoma required that there be no other explanation for the vertical CDR finding (dysplastic disc or marked anisometropia) or visual field defect (due to retinal vascular disease, macular degeneration or cerebrovascular diseases). Glaucoma was diagnosed in category 3 cases if the optic disc could not be examined due to media opacity or if subject was blind (corrected visual acuity, <3/60), had undergone glaucoma surgery, or had intraocular pressure (IOP) > 99.5th percentile.[35]

Primary angle-closure glaucoma (PACG) was defined as an eye with an occludable anterior chamber angle,[36] features of trabecular obstruction by peripheral iris (peripheral anterior synechiae, elevated IOP, iris whirling, "glaukomflecken" lens opacities, or excessive pigment deposition on the trabecular surface) and evidence of glaucoma as just defined. Primary open-angle glaucoma (POAG) was defined as an eye with an open anterior chamber angle, without features of trabecular obstruction by peripheral iris, evidence of glaucoma as just defined and an IOP > 21.0 mm Hg. A diagnosis of normal-tension glaucoma (NTG) was made if IOP ≤ 21 mm Hg and the previously described features of POAG were present. Secondary glaucoma was defined as evidence of glaucoma due to a secondary cause, such as pseudophakic glaucoma, pseudoexfoliative glaucoma, developmental glaucoma, and neovascular glaucoma. Final definition and classification of glaucoma cases were reviewed by a senior glaucoma specialist (TA).

Assessment of IOP and Vertical CDR

Participants had a standardized examination procedure at a centralized clinic. Slit lamp examination (BQ-900; Haag-Streit, Köniz, Switzerland) was performed before and after pupil dilation. IOP was measured with Goldmann applanation tonometry (Haag-Streit), in a standardized protocol. One reading was taken from each eye. If the IOP reading was >21 mm Hg, another reading was taken.[24] The optic disc was examined through a 78-D lens at ×10 magnification using the same technique as was used in a population-based study of Chinese people in Singapore (the Tanjong Pagar Survey).[26,37] Vertical dimensions of the disc and cup were measured with an eyepiece graticule, etched in 0.1 units. For analysis, we defined a large vertical CDR as ≥0.7 and ocular hypertension as IOP > 21 mm Hg in persons without glaucoma. We also analyzed associations using definitions of CDR ≥0.5 and ≥0.6.

Assessment of Covariates

Participants underwent a standardized interview, examination, and collection of nonfasting venous blood samples. Height was measured in centimeters with a wall-mounted measuring tape. Weight was measured in kilograms using a digital scale (SECA, model 782-2321009; Vogel & Halke, Hamburg, Germany). Body mass index (BMI) was calculated as kg/m^2. Systolic and diastolic blood pressures and pulse rate were measured with a digital automatic blood pressure monitor (Dinamap model Pro Series DP110X-RW, 100V2; GE Medical Systems, Inc., Milwaukee, WI). The mean arterial blood pressure was calculated as ⅔ of the diastolic blood pressure + ⅓ of the systolic value. Hypertension was defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or physician diagnosis. Diabetes mellitus was defined as random glucose ≥ 11.1 mM; use of diabetic medication or physician diagnosed diabetes. Nonfasting venous blood samples were analyzed for serum lipids, glycosylated hemoglobin $HbA1_C$, and glucose on the same day. A detailed interviewer-administered questionnaire was used to collect information about medical history, cigarette smoking, alcohol consumption, current medication use, and socioeconomic status.[25]

Statistical Analysis

Statistical analysis was performed with commercial software (SPSS, ver. 15.0; SPSS Inc., Chicago, IL). Results were reported as means or proportions, with differences tested with analysis of variance or χ^2 tests. The differences in mean CRAE and CRVE between groups for glaucoma, subtypes of glaucoma, IOP, and vertical CDR were also tested using analysis of variance. To study the hypothesis that narrower retinal vascular caliber is associated with different outcomes (presence of glaucoma, larger vertical CDR, POAG, and NTG), logistic regression models were constructed to determine the odds ratio (OR) and its 95% CI of these outcomes, per standard decrease in CRAE and CRVE. We initially adjusted for age and sex (model 1) and further adjusted for smoking status, axial length, BMI, serum glucose, systolic blood pressure, and hypertension status (model 2).

Analysis was performed on retinal vascular caliber data from the right eye; if right eye data were not available, left eye data were used. Therefore, if a subject had both eyes diagnosed with glaucoma, the right eye data were used. If the subject's right eye only had glaucoma, then right eye data were used, and if the left eye only had glaucoma, the left eye data were used. If the subject had glaucoma in one eye but the only available retinal caliber data were from the other eye, this data

were treated as missing. Finally, we performed stratified analyses by hypertension status.

Results

Fundus photography was performed for 3264 participants (99.5% of the total study population). Of these, 3193 people had suitable retinal photographs for measurement of retinal vascular caliber. We further excluded 174 participants who had ungradable images or had fewer than six large, gradable arterioles or venules (preventing calculation of CRAE/CRVE), leaving 3019 participants who were considered eligible for the analysis (92.0% of the total 3280 participants).

The characteristics of participants with and without gradable photographs are summarized in Table 1. Compared with excluded participants, those included were more likely to be nonmyopic, younger, and have hypertension, higher BMI, and lower systolic blood pressure.

Table 2 shows that there were 127 (4.2%) cases of glaucoma in our study population. Of these 127 cases, 97 were diagnosed as category 1, and 30 cases were diagnosed as category 2, no patients were diagnosed as category 3 of the ISGEO classification.[35] Compared with those in persons without glaucoma, retinal arteriolar ($P = 0.022$) and venular ($P < 0.001$) calibers were narrower in eyes of persons with glaucoma. These differences were also seen in different glaucoma subtypes. In addition, retinal vascular calibers were narrower in eyes with larger vertical CDR (P for trend $= 0.005$ for CRAE and P for trend < 0.001 for CRVE).

There was no difference in mean retinal arteriolar or venular caliber by IOP categories or between the NTG and high-pressure POAG subgroups (data not shown, $P = 0.789$ and $P = 0.619$, respectively)

Table 3 shows the odds of glaucoma, vertical CDR ≥ 0.7, POAG, and NTG in relationship to narrower retinal vascular caliber (per SD decrease in CRAE and CRVE). After adjustment for age, sex, smoking, BMI, blood pressure, IOP, and other potential confounders, narrower retinal arteriolar and venular calibers were associated with increased odds of glaucoma (OR 1.29 for CRAE and 1.49 for CRVE) and with vertical CDR ≥ 0.7 (OR 1.35 for CRAE and 1.65 for CRVE).

In a separate analysis using diabetes (instead of serum glucose) and excluding axial length in the models, results were similar (data not shown).

In supplementary analyses, this pattern of association was statistically significant for alternative cutoffs (0.5 and 0.6) for large vertical CDR. Using a vertical CDR ≥ 0.5, the OR was 1.14 (95% CI, 1.05–1.25; $P = 0.003$) per SD decrease in CRAE, and 1.25 (95% CI, 1.15–1.36; $P < 0.001$) per SD decrease in CRVE. With a vertical CDR ≥ 0.6, the respective OR was 1.26 (95% CI, 1.12–1.42; $P < 0.001$) for CRAE and 1.36 (95% CI, 1.20–1.53; $P < 0.001$) for CRVE. Associations were largely similar in people with and without hypertension (data not shown). Supplementary analyses were also conducted to exclude the potential effects of topical antiglaucoma medications and systemic antihypertensives on retinal vessel caliber. After excluding patients on topical antiglaucoma medications ($n = 4$) and adjusting for the use of hypertensive medications the results remained similar and significant (data not shown). Analysis was also performed to study the association of retinal vascular caliber with ocular hypertension, this showed that a narrower retinal venular caliber (OR 1.28 for CRVE), but not arteriolar caliber, was associated with ocular hypertension (data not shown).

Discussion

The measurement of retinal vessel caliber from fundus photographs is a new, noninvasive technique to quantify retinal vascular changes and allows further exploration of the vascular etiology of glaucoma. This parameter is easier to measure than ocular blood flow and can be measured in large epidemiologic studies and clinical trials. However, existing population data regarding an association between retinal caliber and glaucoma remain limited, and the results are variable across different studies.[15,17–19] Consistency in findings across multiple studies of different populations is needed to reveal true associations and exclude associations that may be due to chance or confounding factors. For this reason, confirmation studies enhance the quality of evidence in the literature.

Malays comprise the third largest ethnic/racial group in Asia, accounting for 5% of the world's population.[38] There are approximately 300 to 400 million Malays living in Southeast Asia. Similar to other ethnic populations, glaucoma is an important sight-threatening eye disease in Malay adults.[39] In this study, we demonstrate an association of quantitatively measured retinal vascular caliber and glaucoma. Persons with narrower retinal vessels were more likely to have glaucoma and larger vertical CDR, even after factoring the effects of blood pressure, smoking, age, IOP and other risk factors. Of note, retinal vascular caliber was not associated with IOP. These findings support the vascular theory in the pathogenesis of glaucomatous optic neuropathy that is independent of IOP.[40–42]

Table 1. Characteristics of Participants with and without Gradable Photographs

Characteristic	Nongradable Photographs ($n = 174$)	Gradable Photographs ($n = 3019$)	*P*
Sex (% men)	84 (48.3)	1455 (48.2)	0.983
Hypertension (%)	150 (86.2)	2024 (67.1)	<0.001
Diabetes (%)	49 (28.3)	690 (22.9)	0.097
Myopia (%)	95 (57.9)	700 (23.5)	<0.001
Smoking, *n* (%)			
Current	27 (15.5)	624 (20.7)	
Past	39 (22.4)	533 (17.7)	
Never	108 (62.1)	1862 (61.7)	0.121
Age (y)	70.94 (7.15)	57.69 (10.64)	<0.001
Body mass index (kg/m^2)	25.25 (4.64)	26.44 (5.12)	0.003
Serum glucose (mmol/L)	7.07 (3.91)	6.76 (3.67)	0.298
Systolic blood pressure (mm Hg)	159.58 (25.51)	145.92 (23.14)	<0.001
Diastolic blood pressure (mm Hg)	80.80 (12.65)	79.59 (11.09)	0.166

Data are presented as either number (%) or mean (SD).

Table 2. Relationship of Glaucoma and Its Related Ocular Parameters with Retinal Vascular Caliber

Ocular Parameters/ Outcomes	*n*	Retinal Arteriolar Caliber (CRAE)	*P*	Retinal Venular Caliber (CRVE)	*P*
Total population	3019	139.54 (15.71)	—	219.26 (22.20)	—
Any glaucoma					
Absent	2892	139.68 (15.70)		219.71 (23.12)	
Present	127	136.42 (15.71)	0.022	209.19 (21.64)	<0.001
POAG					
Absent	2931	139.63 (15.73)		219.58 (22.13)	
Present	88	136.55 (14.77)	0.070	208.80 (22.17)	<0.001
PACG					
Absent	3014	139.55 (15.70)		219.27 (22.04)	
Present	5	130.61 (21.96)	0.204	217.95 (21.64)	0.895
Secondary glaucoma					
Absent	2985	139.57 (15.69)		219.38 (22.19)	
Present	34	136.93 (17.45)	0.330	208.90 (20.57)	0.006
NTG					
Absent	2945	139.61 (15.77)		219.51 (22.19)	
Present	74	136.81 (13.23)	0.130	209.49 (20.41)	<0.001
Vertical CDR					
1st quartile	935	140.07 (16.14)		220.68 (22.71)	
2nd quartile	631	139.97 (15.59)		221.06 (20.92)	
3rd quartile	872	140.08 (15.75)		219.41 (22.38)	
4th quartile	579	137.45 (14.92)	0.005	214.82 (21.90)	<0.001
IOP					
1st quartile	878	139.45 (16.19)		218.90 (21.90)	
2nd quartile	746	139.73 (15.11)		219.84 (21.48)	
3rd quartile	836	139.49 (15.68)		218.84 (22.27)	
4th quartile	555	139.54 (15.79)	0.986	219.69 (23.46)	0.715

Data are expressed as mean micrometers (SD).

Glaucomatous optic neuropathy has long been linked with alterations in blood flow,[41] with studies demonstrating reductions in ocular blood flow in glaucomatous eyes.[40] It is also known that as neuronal tissue atrophies, secondary blood vessels changes occur.[41] Changes in ocular blood flow have been further associated with structural vascular changes, since ocular blood flow is regulated by the relative resistance to flow (i.e., by the regulation of the size of the vessels).[41] It is important to note that retinal vessels have no autonomic innervation and are regulated by endothelial cells that respond to variation in perfusion pressure and by the neural retinal tissue in response to changes in retinal activity. In the vascular theory of glaucoma, it has been hypothesized that blood vessel disease caused by inflammation, arteriosclerosis, or thrombosis leads to vascular dysregulation,[41] and defective auto regulation of ocular blood flow, resulting in ischemic optic nerve damage and glaucomatous optic neuropathy. This is supported by population data showing that low diastolic ocular perfusion pressure,[9,42,43] and reduced ocular perfusion pressure[44,45] are risk factors for glaucoma. Our study provides further evidence to support the theory that vascular dysregulation, changes in ocular perfusion pressure and altered blood flow, reflected by narrowed retinal vascular caliber, are closely associated with glaucomatous optic neuropathy. Whether these changes result in or are a consequence of altered blood flow cannot be determined by this cross-sectional study and would require longitudinal data.

Our findings in Asian people are consistent with cross-sectional data from two other population-based studies. In the Blue Mountains Eye Study, participants with POAG were shown to have narrower retinal arterioles and venules than those without POAG.[17] More recently, the Beijing Eye Study, using subjective methods to measure retinal caliber from projected slide transparencies, found that retinal arterioles but not venules were significantly narrower in people with glaucoma.[15] However, two other studies, the Beaver Dam Eye Study (cross-sectional data) and the Rotterdam Study (prospective data), did not find significant associations of retinal vascu-

Table 3. Relationships of Retinal Vascular Caliber Changes with Glaucoma, Large Vertical CDR, POAG, and NTG

Retinal Caliber (per SD Decrease)	Any Glaucoma OR (95% CI)	*P*	Vertical CDR ≥ 0.7 OR (95% CI)	*P*	POAG OR (95% CI)	*P*	NTG OR (95% CI)	*P*
Retinal arteriolar caliber, CRAE								
Model 1	1.17 (0.99–1.40)	0.073	1.28 (1.08–1.51)	0.004	1.23 (0.75–2.03)	0.414	1.15 (0.92–1.45)	0.225
Model 2	1.22 (1.02–1.46)	0.037	1.28 (1.07–1.54)	0.007	1.54 (0.91–2.62)	0.109	1.16 (0.91–1.48)	0.241
Model 3	1.29 (1.07–1.56)	0.009	1.35 (1.12–1.63)	0.001	2.29 (1.27–4.12)	0.006	1.17 (0.92–1.49)	0.205
Retinal venular caliber, CRVE								
Model 1	1.46 (1.23–1.74)	<0.001	1.64 (1.39–1.94)	<0.001	1.59 (0.98–2.56)	0.059	1.48 (1.18–1.85)	0.001
Model 2	1.49 (1.24–1.78)	<0.001	1.65 (1.38–1.97)	<0.001	2.03 (1.22–3.39)	0.007	1.45 (1.14–1.84)	0.002
Model 3	1.49 (1.24–1.79)	<0.001	1.65 (1.38–1.98)	<0.001	2.16 (1.22–3.82)	0.008	1.45 (1.14–1.84)	0.002

Model 1: adjusted for age and sex; model 2: adjusted for age, sex, smoking status, axial length, BMI, serum glucose, systolic blood pressure, and hypertension status; model 3: adjusted for age, sex, smoking status, axial length, BMI, serum glucose, systolic blood pressure, hypertension status, and IOP.

lar caliber and POAG.[18,19] The reasons for these disparities are not apparent. Since retinal vascular caliber was measured in the Beaver Dam and Rotterdam studies using similar computer software and protocols, these differences may relate to study sample (e.g., Rotterdam examined older people) and glaucoma definitions (e.g., Beaver Dam defined glaucoma with IOP criteria). The Beaver Dam, Rotterdam, and Blue Mountains studies all involved white populations and had somewhat conflicting results.[17–19] Our study, however agrees with both the Blue Mountains Eye Study and the Beijing Eye Study, which was conducted in Chinese Asians.[15] Thus, there is evidence in three of the five studies that suggests an association between retinal vessel caliber and glaucoma.[15,16–19] Given the re-emergence of vascular disease as an important risk factor for glaucoma,[10,46] studies are clearly warranted to investigate this further.

Our study also provides new data on the association between retinal vascular caliber and different glaucoma subtypes. We confirm the same pattern of associations (both narrower arteriolar and venular caliber) for all glaucoma subtypes, although the association with PACG was not statistically significant, due to the small number of cases in this subgroup. The magnitude of this difference is greater than that in the PACG group compared with the other glaucoma subtypes, perhaps due to the PACG group's being older. However, it is difficult to draw conclusions from this finding, as the number of cases was so small. It should be noted, however, that although the differences in retinal caliber between eyes with and without glaucoma were statistically significant, the actual magnitude of these differences, particularly for arteriolar caliber, was very small. The magnitude of the difference in arteriolar caliber between eyes with and without glaucoma (3 μm) was about half the difference between eyes in persons with and without hypertension (7.2 μm), but more than the difference between persons with and without diabetes (2 μm).[32] Thus, small differences in vessel caliber may be detectable in persons with different pathologic conditions (i.e., glaucoma, hypertension, diabetes) and may provide some insights into the microvascular contribution to different vascular/metabolic diseases. However, further studies are needed to evaluate retinal vessel diameter measurement as a clinical assessment tool for glaucoma.

Furthermore, our study also showed a significant association between narrower retinal vascular caliber and larger vertical CDR, irrespective of definition (i.e., $\geq$0.7, $\geq$0.6, or $\geq$0.5). In keeping with this finding, researchers have reported a correlation of narrower retinal arterioles with loss of neuroretinal rim in patients with glaucoma.[11,14] Nevertheless, a recent study in children without glaucoma did not find an association between retinal vessels and CDR,[47] suggesting that this association is predominantly driven by the development of glaucomatous damage with age. An equally important observation is the lack of association between retinal vascular caliber and IOP, which is consistent with previous studies in adults and children[19,48] and supports IOP-independent vascular mechanisms linking retinal caliber with glaucoma.

Of interest, we could not demonstrate differences in retinal vascular caliber between eyes with NTG and the high-pressure POAG subgroup. If vascular mechanisms were of even more importance in NTG, it would be expected that there would be greater narrowing of retinal vascular caliber in NTG than in POAG. Nevertheless, our findings are in keeping with the Blue Mountains Eye Study, which also found no significant difference in mean arteriolar diameter between these two subgroups.[17] Thus, it is possible that the vascular processes associated with POAG and NTG are not substantially different.

The strengths of our study include its population-based sample, quantitative assessments of retinal vascular caliber with high precision (intragrader intraclass correlation coefficients, 0.94–0.99), standardized assessment of glaucoma, and adjustments for potential confounders, including ocular biometric factors. Limitations should also be noted. As noted, the cross-sectional nature of our data does not provide temporal information of these associations to determine whether narrowing of retinal vessels is antecedent or consequent to glaucomatous optic neuropathy. Because only one longitudinal study (Rotterdam) has examined this question, further studies are clearly needed. Second, caution should be exercised in interpreting the results regarding glaucoma subtypes, as these analyses were limited by study power. Finally, magnification effects on retinal vascular caliber measurements could have distorted some of the associations.[49] To account for ocular magnification, we adjusted for ocular biometry (e.g., axial length) in our analytical models.[49,50] It is important to note, however, that random errors in retinal vascular caliber measurements caused by ocular magnification are likely to bias our results to null.

In summary, we demonstrated in an Asian population that narrower retinal vessels are associated both with the presence of glaucoma and larger vertical CDR, but not with IOP. These findings further support the concept that vascular processes and mechanisms that are pressure independent are associated with glaucomatous optic neuropathy. Prospective studies will provide a clearer answer to the key question of whether quantitative measurement of retinal vascular caliber may be used to predict the development of glaucoma in the community.

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