Retinal Vessel Caliber Is Associated with the 10-year Incidence of Glaucoma

The Blue Mountains Eye Study

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Purpose: To examine associations between quantitatively measured retinal vessel caliber and the 10-year incidence of primary open-angle glaucoma (OAG).

Design: Population-based cohort study.

Participants: The Blue Mountains Eye Study examined 3654 persons at baseline and 2461 persons at either 5 years, 10 years, or both times. After excluding 44 subjects with OAG at baseline, 2417 participants at risk of OAG at the 5- or 10-year examinations were included.

Methods: Retinal vessel calibers of baseline retinal photographs were measured using a computer-based program and summarized as central retinal artery and vein equivalents (CRAE, CRVE). Incident OAG was defined as the development of typical glaucomatous visual field loss combined with matching optic disc rim thinning and an enlarged cup-to-disc (C:D) ratio of >0.7 or C:D asymmetry between the 2 eyes (≥ 0.3) at either the 5- or 10-year examination. Generalized estimating equation models were used to account for correlation between eyes while adjusting for glaucoma risk characteristics including intraocular pressure (IOP) or ocular perfusion pressure (OPP).

Main Outcome Measures: We assessed the 10-year incidence of OAG.

Results: There were 82 persons (104 eyes) who developed incident OAG over the 10-year follow-up. After adjusting for age, sex, family history of glaucoma, smoking, diabetes, hypertension, hypercholesterolemia, body mass index, spherical equivalent refraction, and C:D ratio, narrower CRAE was associated with higher risk of incident OAG (adjusted odds ratio [OR], 1.77; 95% confidence interval [CI], 1.12–2.79, per standard deviation decrease in CRAE). This association persisted after further adjustment for IOP (adjusted OR, 1.87; 95% CI, 1.14–3.05) or OPP (adjusted OR, 1.76; 95% CI, 1.11–2.78), and remained significant when analyses were confined to eyes with IOP <20 mmHg and C:D ratio <0.6 at baseline. There were no independent associations between CRVE and incident OAG.

Conclusions: Retinal arteriolar narrowing, quantitatively measured from retinal photographs, was associated with long-term risk of OAG. These data support the concept that early vascular changes are involved in the pathogenesis of OAG and suggest that computer-based measurements of retinal vessel caliber may be useful to identify people with an increased risk of developing the clinical stage of glaucoma.

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Glaucoma is a leading cause of irreversible blindness worldwide. The prevalence of glaucoma is estimated to be 3% to 5% among general adult populations,[1] and because of population aging, the worldwide number of patients is estimated to double by 2030.[2] Patients with glaucoma are typically asymptomatic at the early stages, with typically half of glaucoma patients undiagnosed at the population level.[1]

Although elevated intraocular pressure (IOP) is well recognized as the main risk factor of primary open-angle glaucoma (OAG), not all people with elevated IOP develop OAG. It is now recognized that vascular risk factors (e.g., hypertension) may also have crucial roles in the pathogenesis of OAG[3–7] and its progression.[8] Variations in retinal vessel caliber might reflect either structural or functional alterations in the ocular circulation or both.[9] Retinal arteriolar narrowing has been linked to the thinning of the retinal nerve fiber layer in a number of studies, including patients with normal tension glaucoma,[10] and in general adult[11] and child populations.[12,13] We also previously reported baseline data from the Blue Mountains Eye Study (BMES) that eyes with OAG were 2.7 times more likely to have retinal arteriolar narrowing.[14] In the Singapore Malays Eye Study, both retinal arteriolar and venular narrowing were associated with the presence of glaucoma.[15]

The Beijing Eye Study also reported an association of narrower arteriolar caliber with the prevalence of glaucoma.[16] However, all these previous studies were cross-sectional in nature, and it is therefore impossible to determine cause and effect (e.g., whether retinal vessel narrowing reflects early

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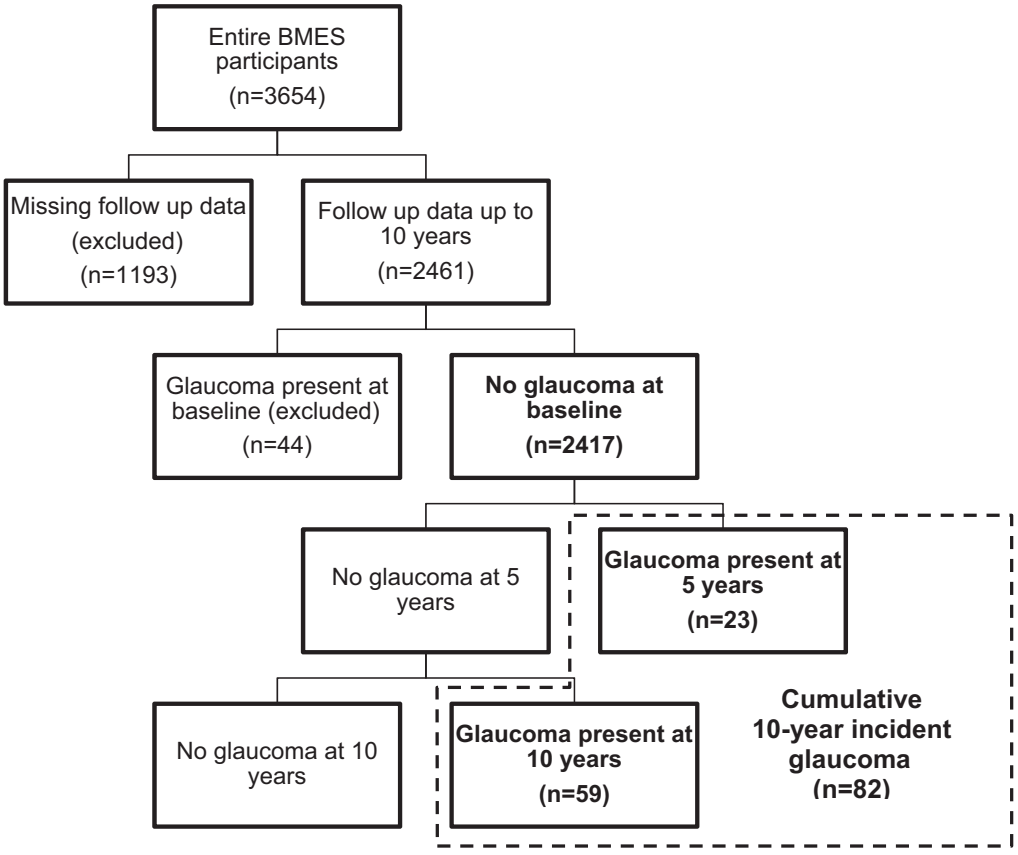

Figure 1. Flow chart of study participants' inclusion. BMES = Blue Mountains Eye Study.

vascular dysfunction before the development of glaucoma, or merely reflects progression of glaucomatous optic neuropathy). Only 1 study to date—the Rotterdam Eye Study—did not document a significant association between baseline retinal vessel caliber and the incidence of OAG over a period of 6.5 years after adjusting for confounding factors.[17]

In this analysis, we aimed to assess whether prospective associations existed between baseline retinal vessel caliber and the incidence of OAG over 10 years in the BMES cohort.

Methods

Study Population

The BMES is a population-based cohort study of eye diseases and other health outcomes in an urban Australian population ≥49 years of age. Details of the BMES have been described elsewhere.[1] Baseline participants (n = 3654) represented 82.4% of those eligible in 2 postcode areas of the Blue Mountains (New South Wales, Australia). This study was approved by the Western Sydney Area Health Service Human Research Ethics Committee; written, informed consent was obtained from all participants.

Of 3654 baseline participants, 340 were excluded at baseline because of missing or ungradable retinal images or because they had optic nerve diseases such as anterior ischemic optic neuropathy, optic disc drusen, or coloboma. Of the remaining 3314 persons, 2461 participants (67.4%) had follow-up data up to the 10-year follow-up examinations with information about both retinal vessel measurements and glaucoma diagnosis. Excluding 44 patients with glaucoma present at baseline, 2417 patients were included in the current analysis (Fig 1). Comparisons of the baseline characteristics of subjects included and excluded are shown in Table 1.

Diagnosis of Glaucoma

Details of the methods and definition of glaucoma have been reported previously.[1,14] In brief, a detailed eye examination was performed at each examination, including Goldmann applanation IOP measurements, Humphrey automated perimetery, optic disc

Table 1. Characteristics of Subjects Included and Excluded from the Analyses

	Included in Analysis (n = 2417)	Excluded from Analysis (n = 1237)	*P* Value
Age (yrs)	64.2 (8.6)	70.0 (10.8)	<0.001
Sex (% female)	680 (55.0%)	1392 (57.6%)	0.130
Hypertension (present/absent)	532 (43.1%)	946 (39.2%)	0.003
Diabetes (present/absent)	101 (8.2%)	117 (4.9%)	<0.001
Ever smoked	660 (56.9%)	1149 (48.9%)	<0.001
Intraocular pressure (mmHg)	16.0 (2.7)	16.3 (3.4)	0.001

Mean (standard deviation) or n (%).

photography and grading, and gonioscopy. At the baseline examination, a 30° suprathreshold, 76-point screening test was performed on both eyes (Humphrey Visual Field Analyzer 630 with Statpac 2, Humphrey Instruments, Inc., San Leandro, CA); 30° stereoscopic retinal photographs of the optic disc and other fields of both eyes were taken (Zeiss FF3 fundus camera; Carl Zeiss Meditec, Oberkochen, Germany). Participants with a history of glaucoma or ocular hypertension, or optic disc signs suggesting glaucoma, or a glaucomatous hemi-field difference of ≥5 points on the 76-point screening test were then asked to return for Humphrey 30-2 full-threshold visual field (VF) tests.

We diagnosed OAG when typical glaucomatous VF loss was present on the Humphrey 30-2 test, combined with matching optic disc rim thinning and an enlarged cup-to-disc (C:D) ratio of ≥0.7 or C:D asymmetry between the 2 eyes (≥0.3).[1] Gonioscopy was performed on all suspects to exclude angle closure, rubeosis, or secondary glaucoma (other than pseudoexfoliation). Ocular hypertension was diagnosed in participants with IOP in either eye of >21 mmHg but with no glaucomatous VF and no optic disc changes. The incidence of OAG was defined as eyes with no OAG at baseline but with OAG at either at 5 or 10 years. Persons with angle closure, rubeosis, or secondary glaucoma at baseline were excluded from the analysis. Persons who developed glaucoma other than OAG either after 5 or 10 years of follow-up were not included in the incident cases of OAG in this analysis.

Retinal Photography and Retinal Vessel Caliber Measurement

Details of the retinal photography and grading protocols have previously been described.[1,14,18–20] In brief, all vessels ≥25 μm passing completely through a circumferential zone 0.5 to 1 disc diameters from the optic disc margin were measured[14]; we excluded images as ungradable if there were undetected or missing vessels. Each vessel was identified as an arteriole or a venule by trained grader. The widest 6 arteriolar and venular calibers were then summarized as the central retinal artery equivalent (CRAE) or the central retinal vein equivalent (CRVE) using the revised Parr-Hubbard formulae[21] of Knudtson et al.[22] There were 4385 eyes and 4320 eyes with CRAE and CRVE data for analysis,[22] respectively.

Other Measurements

Blood pressure was measured once using a standardized mercury sphygmomanometer after participants had been comfortably seated for ≥5 minutes. Mean arterial blood pressure was calculated as 1/3 * systolic blood pressure + 2/3 * diastolic blood pressure. Body weight and height were measured and the body mass index was calculated as weight (in kg) divided by the square of height (in meters). Diabetes was diagnosed from either medical history or a fasting blood glucose level of ≥7.0 mg/l at the baseline examination. Hypertension was defined as present in persons currently using antihypertensive medications or with systolic blood pressure of ≥160 mmHg or diastolic blood pressure of ≥95 mmHg at the time of the examination. Spherical equivalent refraction (SER) was calculated as [SER (diopter)] = [spherical refractive power] + 1/2 * [cylinder refractive power]. Mean ocular perfusion pressure (OPP) was calculated as: [OPP (mmHg)] = [2/3 * diastolic blood pressure] + [1/3 * systolic blood pressure] – [IOP].

Statistical Methods

Stata 11.2 (StataCorp, College Station, TX) was used for data analysis. We used eye-specific data and generalized estimating equation models (with the logistic regression link function) controlling for correlation between the 2 eyes.[20] We estimated odds ratios (ORs) for the incidence of OAG in relation to baseline retinal vessel caliber, adjusting for potential confounding variables as follows: Model 1 was adjusted for age, sex, family history of glaucoma, smoking, diabetes, hypertension, hypercholesterolemia,[7] body mass index,[7,23,24] SER,[25] and C:D ratio; model 2 was adjusted for the same variables in model 1 plus IOP; and model 3 was adjusted for the same variables in model 1 plus OPP. We also repeated the analysis in the subgroup of persons with IOP <20 mmHg and C:D ratio < 0.6. $P<0.05$ was considered significant.

Results

There were 82 persons (104 eyes) who developed incident OAG by the 10-year follow-up; 23 persons developed OAG by the time of the 5-year follow-up examinations, and a further 59 persons developed OAG by the time of 10-year follow-up examination.

Table 2. Characteristics of Study Subjects by Incidence of Open-Angle Glaucoma (OAG)

	Persons with Incident OAG (n = 82; 104 eyes)	Persons without Incident OAG (n = 2335; 4730 eyes)	*P* Value
Age (yrs)	68.2 (8.2)	64.1 (8.5)	<0.001
Sex (female %)	61 (74.4%)	1331 (57.0%)	0.002
Hypertension (%)	39 (47.6%)	907 (38.9%)	0.273
Systolic blood pressure (mmHg)	152.2 (21.8)	144.7 (20.3)	0.001
Diastolic blood pressure (mmHg)	85.8 (9.3)	83.4 (9.8)	0.030
Diabetes (%)	3 (3.7%)	114 (4.9%)	0.746
Body mass index (kg/m^2)	26.0 (5.0)	26.4 (4.4)	0.369
Hypercholesterolemia (%)	18 (17.3%)	1290 (27.3%)	0.027
Ever smoked (%)	39 (48.8%)	1110 (48.9%)	0.976
Spherical equivalent refraction (diopter)	+0.41 (+2.47)	+0.53 (+3.00)	0.611
Intraocular pressure (mmHg)	18.0 (3.3)	15.9 (2.6)	<0.001
Vertical cup-to-disc ratio	0.52 (0.12)	0.40 (0.13)	<0.001
Central retinal artery equivalent (μm)	156.1 (15.1)	160.6 (14.9)	0.003
Central retinal vein equivalent (μm)	233.4 (22.6)	240.3 (22.4)	0.003

Mean (SD) or n (%).

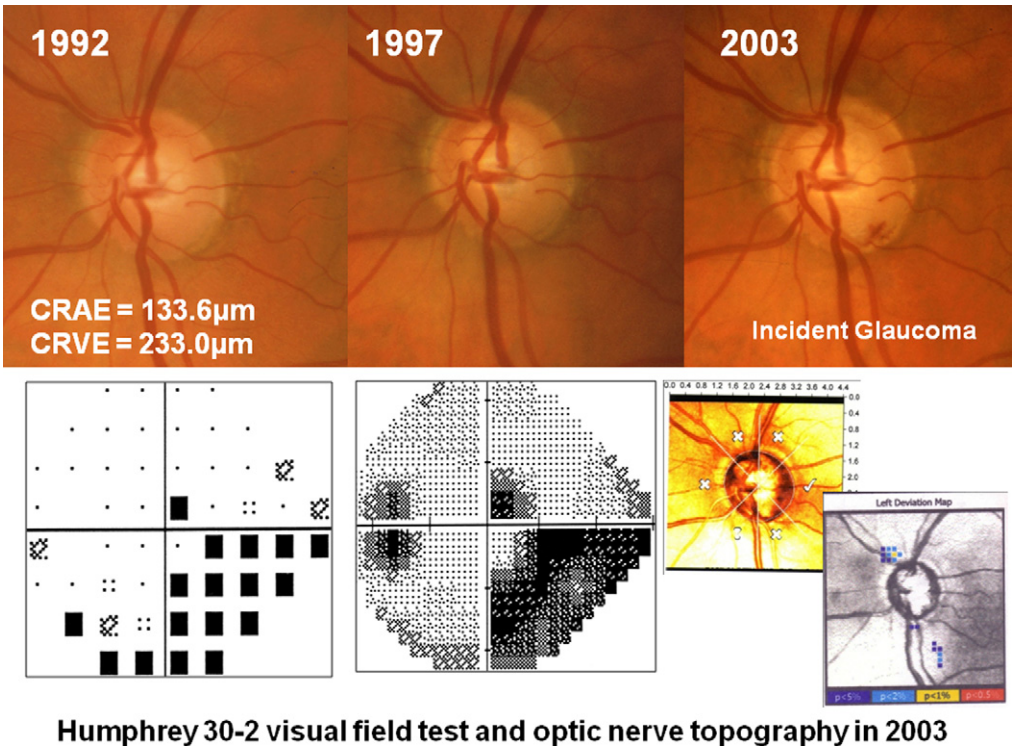

Figure 2. Case of generalized retinal arteriolar narrowing at baseline in the left eye; this patient developed incident glaucoma in this eye during the 10-year follow-up period. CRAE = central retinal artery equivalent; CRVE = central retinal vein equivalent.

As shown in Table 2, persons who developed OAG over this period were older and had higher systolic and diastolic blood pressures or higher IOP at baseline; persons who developed OAG were also more likely to be female. The vertical C:D ratio at baseline for persons who developed OAG was 0.52 (standard deviation [SD] 0.12), which was significantly greater than that in persons who did not develop OAG (0.40; SD, 0.13; $P<0.001$). The mean baseline CRAE and CRVE in persons who developed OAG were 156.1 μm (SD, 15.1) and 233.4 μm (SD, 22.6), respectively; and were 160.6 μm (SD, 14.9) and 240.3 μm (SD, 22.4), respectively, among those who did not develop OAG. Retinal photographs, Humphrey VF, and optic nerve topography (Heidelberg Retina Tomograph II; Heidelberg Instruments, Heidelberg, Germany) of a selected case that developed OAG with retinal arteriolar narrowing are shown in Figure 2.

Eyes with narrower retinal arteriolar and venular caliber at baseline were more likely to develop OAG. Each SD decrease in arteriolar caliber was associated with a 77% greater risk of incident OAG (adjusted OR, 1.77; 95% confidence interval [CI], 1.12–2.79; $P = 0.014$) after adjusting for age, sex, body mass index, glaucoma family history, smoking, diabetes, hypertension, hypercholesterolemia, SER, and C:D ratio (model 1, Table 3). Narrower retinal arteriolar caliber was consistently associated with increased incident OAG. This association persisted after further adjustment for IOP (adjusted OR, 1.87; 95% CI, 1.14–3.05; $P = 0.013$ [model 2]) or OPP (adjusted OR, 1.76; 95% CI, 1.11–2.78; $P = 0.016$ [model 3]; Table 3). Eyes in the lowest quartile of arteriolar caliber had around a 4-fold greater risk of developing OAG compared with eyes in the highest quartile of arteriolar caliber, after full adjustment for potential glaucoma risk characteristics including IOP or OPP (adjusted OR, 4.34; 95% CI, 1.13–16.7 [$P = 0.033$, model 2] and 3.94; 95% CI, 1.14–13.6 [$P = 0.030$, model 3], respectively [Table 3]).

We then repeated the analyses in the subgroup of eyes with relatively low OAG risk, that is, IOP <20 mmHg or C:D ratio <0.6. Even among this subgroup, there was a consistent and significant association between narrower retinal arteriolar caliber and incident OAG after adjusting for potential glaucoma risk characteristics including IOP (adjusted OR per SD decrease in CRAE, 2.05; 95% CI, 1.11–3.80 [$P = 0.022$] and adjusted OR for narrowest quartile versus largest quartile 7.46; 95% CI, 1.19–46.9 [$P = 0.032$]) or OPP (adjusted OR per SD decrease in CRAE 2.04; 95% CI, 1.09–3.79 [$P = 0.025$] and adjusted OR for narrowest quartile versus largest quartile 7.25; 95% CI, 1.09–48.3 [$P = 0.041$]).

There was no significant interaction with hypertension (P for interaction between hypertension and the narrowest vs highest quartile of CRAE = 0.662). However, when we stratified the analyses by the presence of hypertension, the association between narrower retinal arteriolar caliber and incident OAG was significant only in persons without hypertension (OR per SD decrease in CRAE, 2.76; 95% CI, 1.07–7.15; $P = 0.037$, adjusting for potential glaucoma risk characteristics including IOP). There was no association in persons with hypertension, either for those who were taking or not taking medication for hypertension.

There were no associations between narrower venular caliber and incident OAG after adjusting for potential risk characteristics.

Discussion

It is well recognized that vascular risk factors have a potentially important role in the pathogenesis of OAG,[3,4] with many studies showing associations of glaucoma with hypertension, altered ocular hemodynamics (e.g., reduced blood flow), va-

Table 3. Odds Ratios (OR) for Cumulative 10-Year Incident Glaucoma by Retinal Vessel Caliber Size: The Blue Mountains Eye Study

	No. of Eyes	No. of Eyes with Incident OAG (%)	Model 1		Model 2		Model 3	
			OR (95% CI)	*P Value*	*OR (95% CI)*	*P Value*	*OR (95% CI)*	*P Value*
Central retinal artery equivalent (μm)								
Q1: 93.4–150.9	1086	36 (3.3)	4.02 (1.17–13.9)	0.028	4.34 (1.13–16.7)	0.033	3.94 (1.14–13.6)	0.030
Q2: 151.0–160.5	1098	29 (2.6)	3.13 (0.93–10.5)	0.065	3.71 (0.98–14.0)	0.053	3.08 (0.92–10.3)	0.068
Q3: 160.6–170.6	1104	18 (1.6)	0.93 (0.26–3.35)	0.916	0.90 (0.23–3.56)	0.885	0.92 (0.26–3.31)	0.903
Q4: 170.7–215.0	1097	16 (1.5)	1 (Reference)	—	1 (Reference)	—	1 (Reference)	—
Per SD decrease (per −14.9 μm)			1.77 (1.12–2.79)	0.014	1.87 (1.14–3.05)	0.013	1.76 (1.11–2.78)	0.016
Central retinal vein equivalent (μm)								
Q1: 167.6–225.3	1073	32 (3.0)	2.27 (0.65–7.90)	0.199	2.61 (0.64–10.6)	0.180	2.25 (0.65–7.83)	0.200
Q2: 225.4–239.5	1085	29 (2.7)	2.51 (0.75–8.35)	0.134	2.70 (0.69–10.5)	0.152	2.50 (0.75–8.28)	0.134
Q3: 239.6–254.8	1082	17 (1.6)	1.55 (0.46–5.26)	0.481	1.82 (0.47–7.11)	0.389	1.55 (0.46–5.24)	0.480
Q4: 254.9–331.1	1080	18 (1.7)	1 (Reference)	—	1 (Reference)	—	1 (Reference)	—
Per SD decrease (per −22.4 μm)			1.33 (0.86–2.06)	0.196	1.42 (0.88–2.29)	0.150	1.33 (0.86–2.05)	0.199

CI = confidence interval; OAG = open-angle glaucoma; Model 1 = Logistic generalized estimating equations model adjusting for age, sex, family history of glaucoma, smoking, diabetes, hypertension, hypercholesterolemia, body mass index, spherical equivalent refraction, and cup-to-disc ratio; Model 2 = model adjusting for the same variables in model 1 plus intraocular pressure; model 3 = model adjusting for the same variables in model 1 plus mean perfusion pressure; Q1–Q4 = narrowest quartile (Q1) to widest quartile (Q4) of retinal vessel caliber; SD = standard deviation.

sospasm, and systemic vascular diseases (e.g., migraine).[3,4] In this study, we showed that narrowed retinal arteriolar caliber, measured quantitatively from baseline photographs, is associated with a greater long-term risk of developing OAG in an older Australian cohort over a 10-year follow-up period. This adds further support to previous cross-sectional findings from multiple, population-based studies, including the BMES,[14] the Singapore Malays Eye Study,[15] and the Beijing Eye Study,[16] and supports the "vascular theory" of OAG that vascular dysfunction may be among the pathogenic factors in the development of OAG.[3–5]

We found that persons in the lowest quartile of retinal arteriolar caliber at baseline had around a 4-fold higher risk of developing OAG compared with those in the highest quartile of arteriolar caliber, independent of other systemic and ocular OAG risk factors, including IOP or OPP. For each SD decrease in CRAE, there was an approximate 80% increased risk of OAG. The vertical C:D ratio for persons who developed OAG was significantly greater than that in persons who did not develop OAG at baseline. Therefore, we further examined whether this association was present in persons with a relatively low risk of OAG; we confirmed that this association was also seen in eyes with IOP <20 mmHg and C:D ratio <0.6. Although we did not find effect modification by hypertension status, the overall association was mainly driven in persons without hypertension. This is because hypertension has been shown to decrease retinal arteriolar caliber[26–29]; therefore, persons with hypertension might already have narrower retinal arteriolar caliber, irrespective of the presence of OAG.

Our study does not provide information about the potential mechanisms underlying the relationship of retinal arteriolar narrowing and OAG. We hypothesize that retinal arteriolar narrowing could be a result of decreased oxygen demand after loss of retinal ganglion cells, which is recognized as an early pathologic change of OAG.[30–32] The inner retina (including the retinal ganglion cell layer) and the optic nerve head have 2 sources of blood supply,[33] namely, the central retinal artery and retinal arterioles supplying the inner retina and short posterior ciliary arteries supplying the pre- to retrolaminar cribrosa region of the optic disc. Measurement of CRAE, an estimated caliber of the central retinal artery and retinal arterioles, reflects blood supply to the inner retina including the retinal nerve fiber layer, which is primarily affected by glaucomatous optic neuropathy.[30–32] Studies have shown a link between OAG and the retinal blood flow of the peripapillay area,[34] retinal arteriovenous passage time[35] and focal retinal arteriolar narrowing.[36,37] Recently, a link between retinal vessel caliber and retinal nerve fiber layer thickness was confirmed by optical coherence tomography among patients with normal tension glaucoma[10] and in general adult and pediatric population-based samples.[11–13]

Our findings lend support to the involvement of retinal microvascular changes in the early course or pathogenesis of OAG. Because we did not have retinal nerve fiber layer measurements at the baseline examination, we could not confirm whether retinal vessel caliber changes anteceded subtle nerve fiber layer defects (hypothesized in the vascular theory of glaucoma) or were a subsequent change secondary to the thinning of retinal nerve fiber layer.

Our study can be compared with the Rotterdam Study, which found no significant associations between baseline retinal vessel caliber and incident OAG over 6.5 years. Potential explanations for the discrepancy between our study and the Rotterdam Eye Study may include differences in follow-up duration of the study samples, sample characteristics, and analysis. Our study had a 10-year follow-up period compared with the 6.5-year follow-up period in Rotterdam Eye Study when their study report was based. As

a result, the BMES has a higher cumulative incidence of OAG than in the Rotterdam Study (82 cases/2417 subjects over 10 years vs 74 cases/3469 subjects over 6.5 years, respectively). In relation to the analysis, our adjusted models overlapped with most of the variables used in the Rotterdam Study[17]; however, intima media thickness was not available in the BMES. Whether this variable had a critical confounding effect between retinal arteriolar narrowing and incident OAG is not known. Clearly, further studies are warranted to confirm our findings.

A strength of the retinal vessel caliber measurements used in our study is that these were based on multiple arterioles or venules within the area 0.5 to 1 disc-diameter from the edge of the optic disc. These measurements are considered to reflect the caliber of the central retinal artery or vein (as the CRAE or CRVE, respectively), rather than isolated sectors of focal arteriolar narrowing. A limitation is that the systemic and ocular risk factors of participants in our study were determined only at a single examination (baseline). These baseline characteristics could have changed over time, and incorporating the changes over time might provide more precise assessment for the associations. However, because OAG is likely to develop many years before its clinical manifestations, it is difficult to establish whether the retinal microvascular signs are associated with the course of OAG or represent a factor that contributes to the initiation of OAG.

Other limitations include the failure to include other potential confounders not documented in our study such as the measurement of central corneal thickness or of optical coherence tomography parameters (retinal nerve fiber or retinal ganglion cell layer thickness). Although central corneal thickness might not be directly associated with retinal vessel caliber, retinal vessel caliber and retinal nerve fiber thickness have been consistently associated.[10–13] Retinal arteriolar narrowing could thus be a manifestation secondary to the reduction in retinal nerve fiber thickness that occurs before clinical stages of OAG. A further limitation is that subjects included in this analysis were significantly older, more likely to have hypertension and diabetes, and more likely to smoke compared with those excluded from the analysis (Table 1). These differences could also have influenced the results of our study by either over- or underestimating the strength of association.

In conclusion, we describe a prospective association between baseline retinal arteriolar caliber narrowing and an increased long-term risk of OAG in an older, Australian, population-based cohort over a 10-year period. Our findings suggest involvement of retinal microvascular changes in the early course or pathogenesis of OAG. However, we cannot differentiate whether this observation is an early sign of vascular change antecedent to the clinical manifestation of OAG or concurrent or a secondary change due to progressive retinal nerve fiber layer loss. Further studies with detailed assessment of risk characteristics (e.g., central corneal thickness) and much earlier OAG changes (e.g., retinal ganglion cell layer thickness assessed using spectral-domain optical coherence tomography) or for different subtypes of OAG (e.g., normal tension glaucoma or pseudoexfoliation glaucoma) are now warranted to fully understand the exact role of microvascular alterations in the course and pathogenesis of glaucoma. Our study also raises the possibility that computer-based methods (particularly if relatively automated) of measuring retinal vessel caliber may be useful to identify people with an increased risk of glaucoma.

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