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Retinal Vessel Traits and Age-Related Eye Disease in the Canadian Longitudinal Study on Aging

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ABSTRACT

Background: To cross-sectionally and longitudinally examine whether retinal vessel traits are associated with glaucoma-related outcomes (glaucoma, cup-to-disc ratio [CDR] and intraocular pressure [IOP]) and age-related macular degeneration (AMD).

Methods: Baseline and 3-year follow-up data from the 30 097 participants of the Canadian Longitudinal Study on Aging were used. The follow-up rate was 92%. QUARTZ, a deep learning algorithm, was used to extract data from retinal images including arteriolar and venular diameter, tortuosity and vertical CDR. Glaucoma and AMD were self-reported. IOP was measured. Multiple linear and logistic regression were used to adjust for demographic, lifestyle and clinical factors.

Results: Having wider arterioles was associated with a lower odds of glaucoma (OR = 0.36, 95% CI: 0.20, 0.65) at baseline but there was no association using longitudinal data. Instead, glaucoma at baseline was strongly associated with 3-year change in arteriolar diameter ($\beta = -0.21$, 95% CI: −0.37, −0.05) indicating that the cross-sectional association may have been due to reverse causality. Using longitudinal data, greater venular tortuosity was associated with a reduced 3-year development of glaucoma (OR = 0.52, 95% CI: 0.31, 0.87) and a 3-year reduction in the CDR ($\beta = -0.006$, 95% CI: −0.010, −0.002). Wider venular diameter was associated with a higher odds of AMD at baseline (OR = 2.77, 95% CI: 1.50, 5.15) and a higher odds of the 3-year development of AMD (OR = 4.15, 95% CI: 1.95, 8.82).

Conclusions: Understanding the temporal relationship of changes in the retinal microvasculature and the development of eye disease may lead to better treatment and prevention strategies.

1 | Introduction

Glaucoma and age-related macular degeneration (AMD) are two of the leading causes of visual impairment and blindness in the world [1]. Glaucoma is characterised by a progressive loss of retinal ganglion cells, which can be visualised on ophthalmic examination as optic disc cupping and measured by the cup-to-disc ratio (CDR) [2]. High intraocular pressure (IOP) is a major risk factor for the development of glaucoma and remains the only modifiable factor targeted by treatment. Meanwhile, AMD is a progressive degeneration of multiple retinal tissues including the photoreceptors, retinal pigment epithelium, Bruch's membrane, and the choriocapillaris due to various age-related changes [3]. Choroidal neovascularization

and geographic atrophy can occur in late-stage AMD, causing vision to deteriorate. Disruptions of the retinal vasculature have been found for both diseases [4, 5], as well as cardiovascular disease [6–8].

Because most prior research has been cross-sectional, the temporal relationship of the disease and the vascular disruptions is not entirely clear. For example, arteriolar narrowing has been found in glaucoma patients [4]. However, it is not clear if that narrowing leads to glaucoma or if the decreased metabolic needs of a glaucomatous retina lead to the narrowing. Since cross-sectional studies can suffer from reverse causality, longitudinal studies are critical to establish the temporality of retinal vessel diameter and age-related eye disease. This is important because if the vascular disruption precedes the development of eye disease, then treatments targeting this could potentially prevent the onset of eye disease. Two longitudinal studies examined the link between retinal vessel diameter and the incidence of glaucoma, with one of them finding a statistically significant association and one finding null results [9, 10]. Five longitudinal studies examined retinal vessel diameter and the incidence of AMD or its signs, with all but one finding null results [11–15]. However, longitudinal studies require much larger sample sizes than cross-sectional studies to be adequately powered. Using longitudinal data from the 30 097 participants of the Canadian Longitudinal Study on Aging (CLSA) [16], we examined the relationship between retinal vessel traits including diameter and tortuosity (i.e., curvature) and age-related eye diseases including glaucoma and AMD.

2 | Methods

2.1 | Study Population and Design

We conducted both cross-sectional and longitudinal analyses using data from the CLSA Comprehensive Cohort [16]. This study includes 30 097 Canadian adults aged 45–85 years, recruited through random sampling of provincial healthcare databases and random digit dialling of landline phones. Baseline data were gathered between 2012 and 2015 through in-home interviews and physical assessments at CLSA data collection sites in cities across Canada, including Victoria, Vancouver, Surrey, Calgary, Winnipeg, Hamilton, Ottawa, Montreal, Sherbrooke, Halifax and St. John's. Follow-up data were collected in the same manner 3 years later, between 2015 and 2018.

Participants were eligible if they were aged 45–85 years, lived in the community, spoke English or French, and resided within 25–50 km of a data collection site. Exclusion criteria included cognitive impairment, full-time membership in the Canadian Armed Forces, living on a federal First Nations reserve or settlement, residing in a long-term care facility, or not being a permanent resident or citizen. Written informed consent was obtained for all participants. Research Ethics Board approval was acquired for all CLSA sites in July 2010. The University of Ottawa Office of Research Ethics and Integrity gave approval for the present analysis in January 2023 (H-01-23-8331).

2.2 | Data Collection

2.2.1 | Retinal Images

Nonmydriatic retinal images were taken in each eye using a Topcon TRC-NW8 fundus camera. A Nikon D90 camera was attached. Images were centred on the macula and had a 45° field-of-view. The large majority of the images were saved in JPEG format with a resolution of 4288 × 2848 pixels. Images from one site were saved with a resolution of 4928 × 3264 pixels. These images were resized to 4288 × 2848 pixels to be consistent with the other images.

2.2.2 | Retinal Vessel Traits

To process the retinal images, a deep learning algorithm called Quantitative Analysis of Retinal Vessel Topology and Size (QUARTZ) was used [17, 18]. QUARTZ takes measurements across the inner retinal layer, which includes arterioles, pre- and post-capillaries and venules. In the CLSA data, QUARTZ can evaluate inadequate image quality with a sensitivity of 91% and a specificity of 100% [17]. QUARTZ can also determine an arteriole from a venule with 88% accuracy, increasing to 96% using a probability cutoff of 0.8 [17]. QUARTZ produced thousands of measures of diameter and tortuosity from across the entire retinal image. The mean diameter and tortuosity of each arteriole and venule were then summarised, weighted by the vessel segment length for each image. The units for diameter are pixels while tortuosity is a unitless measure, with greater scores indicating curvier vessels. Measurements of the optic nerve vertical CDRs were also obtained from QUARTZ. In the CLSA data, the detection rate for optic disc localisation was very high at 99%, while the mean absolute error for vertical CDR was low at 0.0378 [17]. Larger CDRs may indicate glaucoma.

2.2.3 | Other Ocular Data

Participants were asked at baseline and follow-up: 'has a doctor ever told you that you have glaucoma [or macular degeneration]'. Corneal-compensated IOP was measured in each eye using the Reichart Ocular Response Analyzer (Reichart Technologies, Depew, NY, USA). Those participants who were taking medications with a Drug Identification Number indicating an IOP-lowering drug were noted. Pinhole-corrected visual acuity was measured in each eye using the illuminated Early Treatment of Diabetic Retinopathy Study chart with scores converted to logMAR for analysis.

2.2.4 | Demographic, Health, Lifestyle and Medication Data

Demographic data including age, sex, income and race/ethnicity were collected at baseline during the in-home visit using the interviewer administered questionnaire. Income was assessed by asking participants 'What is your best estimate of the total household income received by all household members, from all sources, before taxes and deductions, in the past

12 months?'. Participants were grouped into five categories: > $150 000, $150 000–$100 000, $100 000–$50 000, $50 000–$20 000, refused.

Smoking status was assessed by asking participants 'Have you smoked at least 100 cigarettes in your life?' and 'At the present time, do you smoke cigarettes daily, occasionally (at least once in last 30 days), or not at all (not in last 30 days)?'. We defined current smokers as those who had smoked at least 100 cigarettes and currently smokes daily or occasionally. Former smokers were those who reported smoking at least 100 cigarettes in life but had not smoked in the last 30 days. Frequency of alcohol consumption was similarly assessed by asking participants 'About how often during the past 12 months did you drink alcohol?'. We categorised responses into never, occasionally (zero to three times a month), weekly (between one and five times a week) or daily (six or more times a week).

During the interviewer-led questionnaire, participants were asked about diabetes using the following two questions: 'has a doctor ever told you that you have diabetes, borderline diabetes, or that your blood sugar is high'; if yes, then they were asked 'were you diagnosed with type 1, type 2, or neither'. Participants were also asked 'Has a doctor ever diagnosed you with stroke or cerebrovascular accident?'. At the data collection site, weight was measured using a 140-10 Healthweigh Digital Physician Scale while height was measured using a Seca 213 stadiometer. BMI was calculated using weight and height values each based on an average of two separate measurements. Body mass index (BMI) was calculated as weight (kg)/height squared (m^2) and classified according to the World Health Organization categories (underweight $<18.5\,kg/m^2$, normal weight 18.5–24.9 kg/m^2, overweight 25.0–29.9 kg/m^2, and obese $\geq 30.0\,kg/m^2$) [19]. Blood pressure was measured using the VSM BpTRU monitor (Medaval, Dublin, Ireland). Six blood pressure measurements were acquired, and an average of measurements two through six was used.

Questions were asked about certain medications. Participants were asked if they were currently taking any medications for high blood pressure or hypertension. They were also asked if they had ever taken systemic corticosteroids such as prednisone or cortisone by tablet.

2.3 | Statistical Analysis

Those with and without glaucoma/AMD were compared. Multiple linear regression models were used to examine the associations between each baseline retinal vessel trait and the IOP, CDR and the 3-year change values. Change values were calculated by taking the follow-up value minus the baseline value. Multiple logistic regression models were used to assess the associations between each baseline retinal vessel trait and baseline eye disease (glaucoma or AMD) or the 3-year development of eye disease. All models contained both the arteriolar and venular trait, as researchers have noted that they may confound each other [20, 21]. Models were adjusted initially for age, sex, race, income, BMI, systolic and diastolic blood pressure, stroke, diabetes, smoking, alcohol and province, according to prior research by our group that found associations between these variables and retinal vessel traits [22]. Models for the 3-year change outcomes were also adjusted for the baseline level of the outcome to account for floor/ceiling effects (i.e., those who already have narrow vessels may be less likely to become narrower over time). In an extended model, we additionally adjusted for IOP-lowering medications, medication for systemic hypertension, and systemic oral steroid use. Regression models for CDR and IOP were run for right eyes only since it is not possible to account for both the complex survey design (weight and strata) and the correlation between eyes. The complex survey design (weights and strata) was accounted for in all analyses. Stata/SE Version 16.1 for Windows was used.

3 | Results

Of the 30 097 CLSA participants, 26 076 (87%) had at least one acceptable QUARTZ image quality score. Those with unacceptable QUARTZ scores were older, had higher systolic blood pressure, were more likely to smoke, and to have diabetes ($p<0.05$) (data not shown). Of those with acceptable QUARTZ image quality scores who answered the question on glaucoma ($n=25\,942$), those with and without a report of glaucoma are compared in Table 1. Those who reported a diagnosis of glaucoma were older, more likely to be female, had higher systolic blood pressure, more likely to drink alcohol every day and to have diabetes, to have higher IOP, and worse CDR ($p<0.05$). They also had wider arteriolar and venular diameter ($p<0.05$). Those who reported a diagnosis of AMD (Table 2) had worse visual acuity, were older, more likely to be female, to have higher systolic blood pressure, to drink alcohol daily, to have diabetes and had wider venular diameter and reduced venular tortuosity ($p<0.05$). A high percentage of CLSA participants returned to follow-up (92%). Of those with retinal images, there were 464 people (2.1%) with incident glaucoma and 415 with incident AMD (1.9%). Images reflecting the 1st and 99th percentile values of arteriolar diameter and tortuosity are shown in Figures S1–S4.

The cross-sectional adjusted associations between retinal vessel traits and glaucoma-related outcomes are shown in Table 3. After adjustment for demographic, lifestyle and medical variables (Model 1a), having wider arterioles (per 10-pixel increase) was associated with a lower odds of glaucoma (OR = 0.36, 95% CI: 0.20, 0.65) while having wider venules was associated with a higher odds of glaucoma (OR = 2.39, 95% CI: 1.41, 4.05). However, the association between arteriolar diameter and glaucoma was no longer statistically significant after adjustment for additional variables like IOP-lowering treatment (Model 1b) (OR = 0.77, 95% CI: 0.38, 1.54). Neither arteriolar nor venular tortuosity were associated with glaucoma in either model ($p>0.05$). Both wider arterioles and wider venules were associated with a smaller CDR in both models ($\beta=-0.021$, 95% CI: −0.033, −0.009 and $\beta=-0.012$, 95% CI: −0.022, −0.001, respectively, in Model 1b). Arteriolar and venular tortuosity were associated with CDR but in opposite directions in both models ($\beta=0.010$, 95% CI: 0.005, 0.014 and $\beta=-0.034$, 95% CI: −0.041, −0.27, respectively, in Model 2b). Wider venules were inversely associated with IOP ($\beta=-1.93$, 95% CI: −2.35, −1.52) while arterioles were not associated with IOP in Model 1a, but they had borderline statistical significance in Model 1b ($\beta=0.50$, 95% CI:

TABLE 1 | Selected characteristics of those with and without a report of glaucoma at baseline.

	Glaucoma ($n=1169$), mean (SD) or %	No glaucoma ($n=24\,773$), mean (SD) or %	p
Age, years	66.89 (10.50)	58.50 (9.58)	<0.001
Female sex	58.17%	52.46%	0.007
Race/ethnicity			
White	93.53%	93.82%	0.811
Non-White	6.47%	6.18%	
BMI, kg/m^2	28.62 (6.11)	28.43 (5.69)	0.463
SBP, mmHg	123.09 (18.08)	119.84 (16.22)	<0.001
DBP, mmHg	72.32 (10.75)	74.75 (9.90)	<0.001
Smoking			
Never	41.24%	44.50%	0.110
Former	48.69%	44.06%	
Current	10.06%	11.43%	
Alcohol			
Never	2.40%	2.37%	<0.001
Occasional	49.24%	42.37%	
Weekly	32.42%	41.94%	
Daily	15.95%	13.31%	
Diabetes			
None	73.30%	83.69%	<0.001
Type 1	1.51%	0.56%	
Type 2	17.10%	8.37%	
Neither	8.09%	7.38%	
IOP, mmHg OD	17.38 (4.91)	15.61 (3.94)	<0.001
IOP, mmHg OS	17.71 (5.43)	16.03 (3.94)	<0.001
CDR OD	0.50 (0.12)	0.44 (0.09)	<0.001
CDR OS	0.50 (0.12)	0.44 (0.09)	<0.001
Arteriolar diameter OD, pixels	15.88 (1.99)	15.65 (1.64)	0.004
Arteriolar diameter OS, pixels	16.27 (2.16)	16.10 (1.78)	0.046
Venular diameter OD, pixels	18.10 (2.33)	17.51 (1.81)	<0.001
Venular diameter OS, pixels	18.38 (2.64)	17.75 (1.91)	<0.001
Arteriolar tortuosity[a] OD	1.24 (0.45)	1.23 (0.39)	0.376
Arteriolar tortuosity[a] OS	1.26 (0.46)	1.23 (0.39)	0.170
Venular tortuosity[a] OD	1.19 (0.32)	1.18 (0.24)	0.383
Venular tortuosity[a] OS	1.20 (0.29)	1.20 (0.25)	0.896

Abbreviations: BMI, body mass index; CDR, cup-to-disc ratio; DBP, diastolic blood pressure; IOP, intraocular pressure; OD, right eye; OS, left eye; SBP, systolic blood pressure.
[a]Tortuosity measures were multiplied by 1000 and the natural log taken to achieve normality.

0.00, 1.00). Both arteriolar and venular tortuosity were associated with IOP ($\beta=-0.24$, 95% CI: −0.42, −0.05 and $\beta=-0.37$, 95% CI: −0.66, −0.09, respectively, in Model 2b).

The longitudinal adjusted associations between retinal vessel traits and glaucoma-related outcomes are shown in Table 4. Unlike our cross-sectional associations between vessel diameter and glaucoma

TABLE 2 | Selected characteristics of those with and without a report of AMD at baseline.

	AMD ($n=979$), mean (SD) or %	No AMD ($n=24\,952$), mean (SD) or %	p
OD pinhole visual acuity, logMAR	0.21 (0.25)	0.08 (0.15)	<0.001
Age, years	68.39 (11.95)	58.54 (9.54)	<0.001
Female sex	59.22%	52.47%	0.004
Race/ethnicity			
White	94.55%	93.78%	0.645
Non-White	5.45%	6.22%	
BMI, kg/m^2	28.61 (6.45)	28.44 (5.68)	0.535
SBP, mmHg	124.92 (20.28)	119.84 (16.19)	<0.001
DBP, mmHg	72.79 (10.95)	74.72 (9.92)	<0.001
Smoking			
Never	41.78%	44.40%	0.058
Former	49.25%	44.11%	
Current	8.98%	11.48%	
Alcohol			
Never	2.93%	2.36%	0.001
Occasional	46.84%	42.52%	
Weekly	33.12%	41.79%	
Daily	17.11%	13.34%	
Diabetes			
None	76.20%	83.56%	<0.001
Type 1	0.29%	0.59%	
Type 2	14.19%	8.53%	
Neither	9.32%	7.32%	
Arteriolar diameter OD, pixels	15.70 (1.96)	15.66 (1.64)	0.651
Arteriolar diameter OS, pixels	16.14 (2.27)	16.10 (1.79)	0.725
Venular diameter OD, pixels	18.15 (2.41)	17.52 (1.82)	<0.001
Venular diameter OS, pixels	18.52 (2.67)	17.76 (1.92)	<0.001
Arteriolar tortuosity[a] OD	1.22 (0.43)	1.23 (0.39)	0.703
Arteriolar tortuosity[a] OS	1.23 (0.44)	1.24 (0.39)	0.597
Venular tortuosity[a] OD	1.14 (0.30)	1.18 (0.24)	0.008
Venular tortuosity[a] OS	1.16 (0.31)	1.20 (0.25)	0.015

Abbreviations: AMD, age-related macular degeneration; BMI, body mass index; DBP, diastolic blood pressure; OD, right eye; OS, left eye; SBP, systolic blood pressure.
[a]Tortuosity measures were multiplied by 1000 and the natural log taken to achieve normality.

(Table 3, Model 1a), there were no statistically significant associations between retinal vessel diameter and the 3-year development of glaucoma. To determine whether the cross-sectional association between arteriolar diameter and glaucoma at baseline was due to reverse causality, we examined whether glaucoma at baseline was associated with the 3-year change in arteriolar diameter. In fact, it was strongly associated ($\beta=-0.21$, 95% CI: −0.37, −0.05) indicating that the cross-sectional association may have been due at least in part to reverse causality. Venular tortuosity was strongly inversely associated with the 3-year development of glaucoma in both models (OR = 0.52, 95% CI: 0.31, 0.87 in Model 2a). Also, venular tortuosity was inversely associated with the 3-year change in CDR in both models ($\beta=-0.006$, 95% CI: −0.010, −0.002 in Model 2a). Venular diameter and arteriolar tortuosity were inversely

TABLE 3 | Cross-sectional associations between retinal vessel traits and glaucoma outcomes adjusted for two sets of variables.

		Glaucoma ($n=23\,993$)[b]		CDR ($n=23\,824$)		IOP ($n=23\,279$)	
Model	**Vessel trait**[a]	**OR**	**95% CI**	**β**	**95% CI**	**β**	**95% CI**
1a[c]	Arteriolar diameter	**0.36**	**0.20, 0.65**	**−0.023**	**−0.035, −0.011**	0.40	−0.09, 0.90
	Venular diameter	**2.39**	**1.41, 4.05**	**−0.012**	**−0.023, −0.001**	**−1.93**	**−2.35, −1.52**
1b[d]	Arteriolar diameter	0.77	0.38, 1.54	**−0.021**	**−0.033, −0.009**	**0.50**	**0.00, 1.00**
	Venular diameter	**2.06**	**1.11, 3.82**	**−0.012**	**−0.022, −0.001**	**−1.99**	**−2.41, −1.57**
2a[c]	Arteriolar tortuosity	1.08	0.85, 1.36	**0.009**	**0.005, 0.013**	**−0.26**	**−0.44, −0.08**
	Venular tortuosity	0.92	0.56, 1.50	**−0.034**	**−0.041, −0.027**	**−0.39**	**−0.67, −0.10**
2b[d]	Arteriolar tortuosity	1.13	0.85, 1.51	**0.010**	**0.005, 0.014**	**−0.24**	**−0.42, −0.05**
	Venular tortuosity	1.02	0.66, 1.58	**−0.034**	**−0.041, −0.027**	**−0.37**	**−0.66, −0.09**

Abbreviations: CDR, cup-to-disc ratio; CI, confidence interval; IOP, intraocular pressure; OR, odds ratio.
[a]Per 10-pixel increase in diameter or 1-unit increase in tortuosity.
[b]Sample size is for Model 1a.
[c]Each model run separately containing both the arteriolar and venular trait; models also adjusted for age, sex, race, income, BMI, systolic and diastolic blood pressure, stroke, diabetes, smoking, alcohol and province; statistically significant results shown in bold.
[d]Each model run separately containing both the arteriolar and venular trait; models also adjusted for age, sex, race, income, BMI, systolic and diastolic blood pressure, stroke, diabetes, smoking, alcohol, province, systemic steroid use, use of systemic anti-hypertensive therapy and use of ocular anti-hypertensive therapy.

TABLE 4 | Longitudinal associations between baseline retinal vessel traits and glaucoma outcomes adjusted for two sets of variables.

		Development of glaucoma ($n=20\,994$)[c]		CDR change ($n=18\,108$)		IOP change ($n=19\,386$)	
Model[a]	**Vessel trait**[b]	**OR**	**95% CI**	**β**	**95% CI**	**β**	**95% CI**
1a[a]	Arteriolar diameter	1.74	0.56, 5.41	−0.002	−0.009, 0.005	−0.20	−0.64, 0.24
	Venular diameter	1.12	0.46, 2.71	−0.005	−0.011, 0.001	**−0.71**	**−1.12, −0.31**
1b[b]	Arteriolar diameter	1.87	0.59, 5.94	−0.002	−0.009, 0.005	−0.15	−0.60, 0.30
	Venular diameter	1.25	0.50, 3.10	−0.005	−0.011, 0.001	**−0.73**	**−1.15, −0.32**
2a[a]	Arteriolar tortuosity	1.12	0.79, 1.58	0.001	−0.001, 0.003	**−0.181**	**−0.36, −0.0**
	Venular tortuosity	**0.52**	**0.31, 0.87**	**−0.006**	**−0.010, −0.002**	−0.24	−0.50, 0.01
2b[b]	Arteriolar tortuosity	1.21	0.85, 1.72	0.001	−0.001, 0.003	−0.18	−0.35, 0.01
	Venular tortuosity	**0.53**	**0.31, 0.91**	**−0.006**	**−0.011, −0.002**	−0.25	−0.51, 0.02

Abbreviations: CDR, cup-to-disc ratio; CI, confidence interval; IOP, intraocular pressure; OR, odds ratio.
[a]Each model runs separately containing both the arteriolar and venular trait; models also adjusted for age, sex, race, income, BMI, systolic and diastolic blood pressure, stroke, diabetes, smoking, alcohol and province; change models also adjusted for baseline level of outcome; statistically significant results shown in bold.
[b]Each model ran separately containing both the arteriolar and venular trait; models also adjusted for age, sex, race, income, BMI, systolic and diastolic blood pressure, stroke, diabetes, smoking, alcohol, province, systemic steroid use, use of systemic anti-hypertensive therapy, and use of ocular anti-hypertensive therapy. Per 10-pixel increase in diameter or 1-unit increase in tortuosity.
[c]Sample size is for Model 1a.

associated with the 3-year change in IOP ($\beta=-0.71$, 95% CI: −1.12, −0.31 and $\beta=-0.18$, 95% CI: −0.36, −0.01 in Models 1a and 2a, respectively).

The cross-sectional and longitudinal adjusted associations between AMD and retinal vascular diameter and tortuosity are shown in Table 5. Having wider arterioles was associated with a lower odds of AMD at baseline (OR = 0.19, 95% CI: 0.10, 0.37). By contrast, wider venular diameter was associated with a higher odds of both baseline AMD and the 3-year development of AMD (OR = 2.77, 95% CI: 1.50, 5.15 and OR = 4.15, 95% CI: 1.95, 8.82, respectively). Arteriolar tortuosity was not associated with AMD, while more tortuous retinal venules were strongly associated with a lower odds of having AMD at baseline (OR = 0.45, 95% CI: 0.29, 0.69) but not with the 3-year development of AMD (OR = 0.64, 95% CI: 0.37, 1.10).

4 | Discussion

We have identified many cross-sectional and some longitudinal associations between retinal vessel traits and age-related eye

TABLE 5 | Cross-sectional and 3-year longitudinal associations between baseline retinal vessel traits and baseline AMD and the 3-year development of AMD.

Model[a]	Vessel trait[b]	AMD at baseline ($n = 24000$)		Development of AMD ($n = 20854$)	
		OR	95% CI	OR	95% CI
1	Arteriolar diameter	**0.19**	**0.10, 0.37**	0.82	0.33, 2.05
	Venular diameter	**2.77**	**1.50, 5.15**	**4.15**	**1.95, 8.82**
2	Arteriolar tortuosity	0.96	0.75, 1.22	1.23	0.85, 1.78
	Venular tortuosity	**0.45**	**0.29, 0.69**	0.64	0.37, 1.10

Abbreviations: AMD, age-related macular degeneration; CI, confidence interval; OR, odds ratio.
[a]Each model runs separately containing both the arteriolar and venular traits; models also adjusted for age, sex, race, income, BMI, systolic and diastolic blood pressure, stroke, diabetes, smoking, alcohol, and province; statistically significant results shown in bold.
[b]Per 10 pixel increase in diameter or 1 unit increase in tortuosity.

disease. Sometimes, the cross-sectional and longitudinal associations were consistent, and other times they were not.

First, using cross-sectional data, arteriolar diameter was inversely associated with glaucoma and CDR. This is consistent with most prior literature included in a systematic review and a more recent study by Rudnicka et al. that reported that narrower arterioles were associated with glaucoma [4, 23]. However, in our study, the additional adjustment for IOP-lowering medication eliminated the cross-sectional association between arteriolar diameter and glaucoma. Furthermore, arteriolar diameter was not associated with the 3-year development of glaucoma or the 3-year change in CDR. To check if reverse causality was in part causing the cross-sectional association, we examined whether glaucoma at baseline was associated with the 3-year narrowing of retinal arterioles, and indeed it was. Therefore, the cross-sectional association that we found between arteriolar diameter and glaucoma may have only been due to reverse causality. In other words, our data indicate that glaucoma (or glaucoma treatment) causes arteriolar narrowing rather than the other way around. The temporality of this is critical because if vascular disruptions precede the development of eye disease, treatments could target this to prevent the onset of eye disease. To date, to our knowledge, only one longitudinal study has established a statistically significant association between arteriolar diameter (central retinal arteriolar equivalent [CRAE]) and the incidence of glaucoma [9]. This study did not adjust for IOP-lowering medication. More longitudinal studies are needed to disentangle the temporality of retinal vessel changes and the onset of eye disease.

Evidence supporting a vascular pathogenesis of glaucoma and also the potential for vascular changes to develop secondary to glaucoma is discussed in a review [24]. In short, the vascular theory of glaucoma proposes that low perfusion pressure, impaired vascular autoregulation, and faulty neurovascular coupling may cause glaucoma [24]. However, there is also evidence in humans and animal models that the opposite is true: that glaucoma could cause vascular abnormalities perhaps in part because glaucomatous retinal ganglion cells may need reduced blood supply [24]. More longitudinal studies are necessary to disentangle the temporal relationship between vessel abnormalities and glaucoma.

Venular diameter was positively associated with both baseline AMD and the 3-year development of AMD. Most prior studies in a recent systematic review have not found a statistically significant association between vessel width and signs of AMD, although three studies are consistent with our findings [25]. For example, Jeganathan et al. found in a cross-sectional study that widened venular diameter was associated with early AMD (OR = 1.52, 95% CI: 1.11, 2.09) [26]. Liew et al. found in a longitudinal study that wider venules were associated with the 10-year development of RPE abnormalities (RR = 1.1, 95% CI: 1.0, 1.3) [13]. Also, Wickremasinghe et al. found that wider venular diameter was associated with worse response to bevacizumab in patients with neovascular AMD [27]. By contrast, we found that arteriolar diameter was negatively associated with baseline AMD. This is consistent with findings from a systematic review by Toulouie et al., where narrower CRAE was associated with central geographic atrophy in eyes with AMD [28]. In addition, several studies using optical coherence tomography angiography have demonstrated an association between AMD and reduced vascular density [5]. Trinh et al. proposed that reduced vascular density might be due in part to vessel thinning or constriction [29].

In addition to vessel diameter, we also examined tortuosity. We found that venular tortuosity was negatively associated with the 3-year development of glaucoma and change in CDR. This is consistent with Wu et al. [30] and Koh et al. [31] who found that less tortuosity (straighter vessels) was associated with glaucoma and a thinner neuroretinal rim, respectively. We found that increased venular tortuosity was also inversely associated with baseline AMD. We are not aware of any prior studies that examined tortuosity and AMD. Ischemic heart disease death is also associated with straighter retinal vessels [32]. Witt et al. proposed that reduced tortuosity may cause endothelial dysfunction and impairments in oxygenation in the microvasculature [32].

Finally, we also examined the association between retinal vessel traits and IOP and the 3-year change in IOP. There is evidence to suggest that some topical hypotensive medications for glaucoma treatment, particularly beta-blockers and marginally prostaglandin analogues, are associated with narrowing of the retinal vessels [33, 34]. However, regarding the reverse direction, only one previous study, to our knowledge, has assessed retinal vessel traits and their longitudinal relation to change in IOP [35]. That study found no longitudinal associations between retinal vessel diameter and IOP change. However, it did show that increased IOP at follow-up was associated with increased arteriolar tortuosity, while higher IOP at baseline was associated with more tortuous venules at follow-up. We were unable to replicate these findings in our study and instead found that arteriolar tortuosity was inversely associated with IOP and its 3-year change. This is consistent with findings from a cross-sectional study conducted

by Wu et al., who found that arteriolar tortuosity was lower in eyes with higher IOP [30].

Strengths of this research include the use of a large, national, longitudinal dataset with comprehensive physical exam and questionnaire data, the use of a deep learning approach called QUARTZ to provide retinal vessel data on the entire retina rather than only the area around the optic disc, and the assessment of multiple ocular outcomes. A limitation of this work is that glaucoma and AMD were assessed by self-report of a doctor's diagnosis, which is less valid than an eye exam or a medical record. However, for glaucoma, we had supplementary data from the retinal image and the physical exam such as CDR and IOP. Our incidence rate of glaucoma is similar to what other studies have found. The 3-year incidence of glaucoma in the CLSA was 2.1% (1.9% after complex survey design adjustment), which is similar to what was reported in other studies with similar age groups [36, 37]. The prevalence of AMD in the CLSA was 4.3% (3.4% after complex survey design adjustment), which is a bit higher than what participants of the Beaver Dam Eye Study self-reported in 1991 (2.1%) [38]. With the self-report of AMD, it is difficult to know if people are referring to a diagnosis of late-stage AMD, intermediate AMD, or a mix of both, so comparing to prevalence rates using a clinical exam is difficult. Furthermore, both glaucoma and AMD differ by race/ethnicity. Our population is largely of a White, European ancestry background. Our results may differ in populations with different ethnic backgrounds. Another limitation is that we do not know in which eye the person had glaucoma or AMD. Other analyses for CDR and IOP were limited to right eye data only to match the eye used for the retinal vessel traits. Furthermore, we lacked data on axial length, so we were unable to convert pixels to microns. However, we can provide a rough estimate of how many microns a pixel equals in the CLSA. The average vertical optic disc diameter in the CLSA was 418 pixels, while the average vertical optic disc diameter in White people in Quigley et al. was 1820 μm [39]. Therefore, 1 pixel equals approximately 4.35 μm. Finally, statistical power was reduced for our longitudinal analyses due to losses to follow-up and a smaller number of incident versus prevalent cases of glaucoma and AMD. Some people (15%) had unacceptable QUARTZ image quality scores and therefore were missing from our analyses. This could have caused selection bias.

This work provides additional longitudinal analysis of the relationship between retinal vessel traits and age-related eye disease. Our strongest and most consistent evidence is that wider retinal venules are associated with AMD and that venular tortuosity is associated with glaucoma and glaucoma-related traits. Understanding how changes in the retinal microvasculature affect the development of eye disease is crucial to improving treatments and prevention strategies.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data are available from the Canadian Longitudinal Study on Aging (www.clsa-elcv.ca) for researchers who meet the criteria for access to de-identified CLSA data.

References

1. S. R. Flaxman, R. R. A. Bourne, S. Resnikoff, et al., "Global Causes of Blindness and Distance Vision Impairment 1990-2020: A Systematic Review and Meta-Analysis," *Lancet Global Health* 5, no. 12 (2017): e1221–e1234.

2. R. N. Weinreb, T. Aung, and F. A. Medeiros, "The Pathophysiology and Treatment of Glaucoma: A Review," *Journal of the American Medical Association* 311 (2014): 1901–1911.

3. M. Fleckenstein, S. Schmitz-Valckenberg, and U. Chakravarthy, "Age-Related Macular Degeneration: A Review," *JAMA* 331, no. 2 (2024): 147–157.

4. K. K. W. Chan, F. Tang, C. C. Y. Tham, A. L. Young, and C. Y. Cheung, "Retinal Vasculature in Glaucoma: A Review," *BMJ Open Ophthalmology* 1, no. 1 (2017): e000032.

5. T. R. P. Taylor, M. J. Menten, D. Rueckert, S. Sivaprasad, and A. J. Lotery, "The Role of the Retinal Vasculature in Age-Related Macular Degeneration: A Spotlight on OCTA," *Eye* 38, no. 3 (2024): 442–449.

6. T. Y. Wong, A. Kamineni, R. Klein, et al., "Quantitative Retinal Venular Caliber and Risk of Cardiovascular Disease in Older Persons: The Cardiovascular Health Study," *Archives of Internal Medicine* 166, no. 21 (2006): 2388–2394.

7. T. H. Rim, A. W. J. Teo, H. H. S. Yang, C. Y. Cheung, and T. Y. Wong, "Retinal Vascular Signs and Cerebrovascular Diseases," *Journal of Neuro-Ophthalmology* 40, no. 1 (2020): 44–59.

8. O. M. Dumitrascu, B. M. Demaerschalk, C. Valencia Sanchez, et al., "Retinal Microvascular Abnormalities as Surrogate Markers of Cerebrovascular Ischemic Disease: A Meta-Analysis," *Journal of Stroke and Cerebrovascular Diseases* 27, no. 7 (2018): 1960–1968.

9. R. Kawasaki, J. J. Wang, E. Rochtchina, A. J. Lee, T. Y. Wong, and P. Mitchell, "Retinal Vessel Caliber Is Associated With the 10-Year Incidence of Glaucoma: The Blue Mountains Eye Study," *Ophthalmology* 120, no. 1 (2013): 84–90.

10. M. K. Ikram, S. de Voogd, R. C. Wolfs, et al., "Retinal Vessel Diameters and Incident Open-Angle Glaucoma and Optic Disc Changes: The Rotterdam Study," *Investigative Ophthalmology & Visual Science* 46, no. 4 (2005): 1182–1187.

11. R. Klein, B. E. Klein, S. C. Tomany, and T. Y. Wong, "The Relation of Retinal Microvascular Characteristics to Age-Related Eye Disease: The Beaver Dam Eye Study," *American Journal of Ophthalmology* 137, no. 3 (2004): 435–444.

12. J. J. Wang, P. Mitchell, E. Rochtchina, A. G. Tan, T. Y. Wong, and R. Klein, "Retinal Vessel Wall Signs and the 5 Year Incidence of Age Related Maculopathy: The Blue Mountains Eye Study," *British Journal of Ophthalmology* 88, no. 1 (2004): 104–109.

13. G. Liew, S. Kaushik, E. Rochtchina, A. G. Tan, P. Mitchell, and J. J. Wang, "Retinal Vessel Signs and 10-Year Incident Age-Related Maculopathy: The Blue Mountains Eye Study," *Ophthalmology* 113, no. 9 (2006): 1481–1487.

14. M. K. Ikram, R. van Leeuwen, J. R. Vingerling, A. Hofman, and P. T. de Jong, "Retinal Vessel Diameters and the Risk of Incident Age-Related Macular Disease: The Rotterdam Study," *Ophthalmology* 112, no. 4 (2005): 548–552.

15. Q. S. You, L. Xu, H. Yang, et al., "Five-Year Incidence of Age-Related Macular Degeneration: The Beijing Eye Study," *Ophthalmology* 119, no. 12 (2012): 2519–2525.

16. P. Raina, C. Wolfson, S. Kirkland, et al., "Cohort Profile: The Canadian Longitudinal Study on Aging (CLSA)," *International Journal of Epidemiology* 48, no. 6 (2019): 1752–1753j.

17. R. A. Welikala, J. Fajtl, G. Johnson, et al., "Artificial Intelligence-Enabled Retinal Vasculometry at Scale Utilizing the UK Biobank, CLSA, and NEL DESP Datasets," paper presented at IEEE-EMBS International Conference on Biomedical and Health Informatics, Houston, TX, November 10–13, 2024.

18. R. A. Welikala, M. M. Fraz, M. M. Habib, et al., "Automated Quantification of Retinal Vessel Morphometry in the UK Biobank Cohort," paper presented at Seventh International Conference on Image Processing Theory, Tools and Applications, Montreal, QC, Canada, November 28–December 1, 2017.

19. WHO, "A Healthy Lifestyle—WHO Recommendations 2021," https://www.euro.who.int/en/health-topics/disease-prevention/nutrition/a-healthy-lifestyle/body-mass-index-bmi.

20. G. Liew, T. Y. Wong, P. Mitchell, and J. J. Wang, "Are Narrower or Wider Retinal Venules Associated With Incident Hypertension?," *Hypertension* 48, no. 2 (2006): e10.

21. C. Sun, J. J. Wang, D. A. Mackey, and T. Y. Wong, "Retinal Vascular Caliber: Systemic, Environmental, and Genetic Associations," *Survey of Ophthalmology* 54, no. 1 (2009): 74–95.

22. A. O'Neil, R. A. Welikala, S. Barman, et al., "Factors Associated With Retinal Vessel Traits in the Canadian Longitudinal Study on Aging," *Investigative Ophthalmology & Visual Science* 66, no. 3 (2025): 13.

23. A. R. Rudnicka, C. G. Owen, R. A. Welikala, et al., "Retinal Vasculometry Associations With Glaucoma: Findings From the European Prospective Investigation of Cancer-Norfolk Eye Study," *American Journal of Ophthalmology* 220 (2020): 140–151.

24. X. Wang, M. Wang, H. Liu, et al., "The Association Between Vascular Abnormalities and Glaucoma-What Comes First?," *International Journal of Molecular Sciences* 24, no. 17 (2023): 13211.

25. A. Newman, N. Andrew, and R. Casson, "Review of the Association Between Retinal Microvascular Characteristics and Eye Disease," *Clinical & Experimental Ophthalmology* 46, no. 5 (2018): 531–552.

26. V. S. Jeganathan, R. Kawasaki, J. J. Wang, et al., "Retinal Vascular Caliber and Age-Related Macular Degeneration: The Singapore Malay Eye Study," *American Journal of Ophthalmology* 146, no. 6 (2008): 954–959.e1.

27. S. S. Wickremasinghe, L. Busija, R. H. Guymer, T. Y. Wong, and S. Qureshi, "Retinal Venular Caliber Predicts Visual Outcome After Intravitreal Ranibizumab Injection Treatments for Neovascular AMD," *Investigative Ophthalmology & Visual Science* 53, no. 1 (2012): 37–41.

28. S. Toulouie, S. Chang, J. Pan, K. Snyder, and G. Yiu, "Relationship of Retinal Vessel Caliber With Age-Related Macular Degeneration," *Journal of Ophthalmology* 2022 (2022): 8210599.

29. M. Trinh, M. Kalloniatis, and L. Nivison-Smith, "Vascular Changes in Intermediate Age-Related Macular Degeneration Quantified Using Optical Coherence Tomography Angiography," *Translational Vision Science & Technology* 8, no. 4 (2019): 20.

30. R. Wu, C. Y. Cheung, S. M. Saw, P. Mitchell, T. Aung, and T. Y. Wong, "Retinal Vascular Geometry and Glaucoma: The Singapore Malay Eye Study," *Ophthalmology* 120, no. 1 (2013): 77–83.

31. V. Koh, C. Y. Cheung, Y. Zheng, T. Y. Wong, W. Wong, and T. Aung, "Relationship of Retinal Vascular Tortuosity With the Neuroretinal Rim: The Singapore Malay Eye Study," *Investigative Ophthalmology & Visual Science* 51, no. 7 (2010): 3736–3741.

32. N. Witt, T. Y. Wong, A. D. Hughes, et al., "Abnormalities of Retinal Microvascular Structure and Risk of Mortality From Ischemic Heart Disease and Stroke," *Hypertension* 47, no. 5 (2006): 975–981.

33. T. Y. Wong, M. D. Knudtson, B. E. Klein, R. Klein, and L. D. Hubbard, "Medication Use and Retinal Vessel Diameters," *American Journal of Ophthalmology* 139, no. 2 (2005): 373–375.

34. K. P. Howard, B. E. Klein, J. O. Dreyer, L. G. Danforth, and R. Klein, "Cross-Sectional Associations of Medication and Supplement Use With Retinal Vascular Diameter in the Beaver Dam Eye Study," *JAMA Ophthalmology* 132, no. 1 (2014): 23–31.

35. J. Freiberg, R. Welikala, J. Rovelt, et al., "Longitudinal Associations of Retinal Vessel Morphology With Intraocular Pressure and Blood Pressure at Follow-Up Visit-Findings From a Danish Eye and Vision Cohort, Project FOREVER," *Acta Ophthalmologica* 103 (2025): 33–42.

36. R. Varma, D. Wang, C. Wu, et al., "Four-Year Incidence of Open-Angle Glaucoma and Ocular Hypertension: The Los Angeles Latino Eye Study," *American Journal of Ophthalmology* 154, no. 2 (2012): 315–325.e1.

37. B. N. Mukesh, C. A. McCarty, J. L. Rait, and H. R. Taylor, "Five-Year Incidence of Open-Angle Glaucoma: The Visual Impairment Project," *Ophthalmology* 109, no. 6 (2002): 1047–1051.

38. K. L. Linton, B. E. Klein, and R. Klein, "The Validity of Self-Reported and Surrogate-Reported Cataract and Age-Related Macular Degeneration in the Beaver Dam Eye Study," *American Journal of Epidemiology* 134, no. 12 (1991): 1438–1446.

39. H. A. Quigley, A. E. Brown, J. D. Morrison, and S. M. Drance, "The Size and Shape of the Optic Disc in Normal Human Eyes," *Archives of Ophthalmology* 108, no. 1 (1990): 51–57.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.