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CLSA Webinar

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

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Image credit: eyerounds.org, University of Iowa

Retina and Retinal Vessels

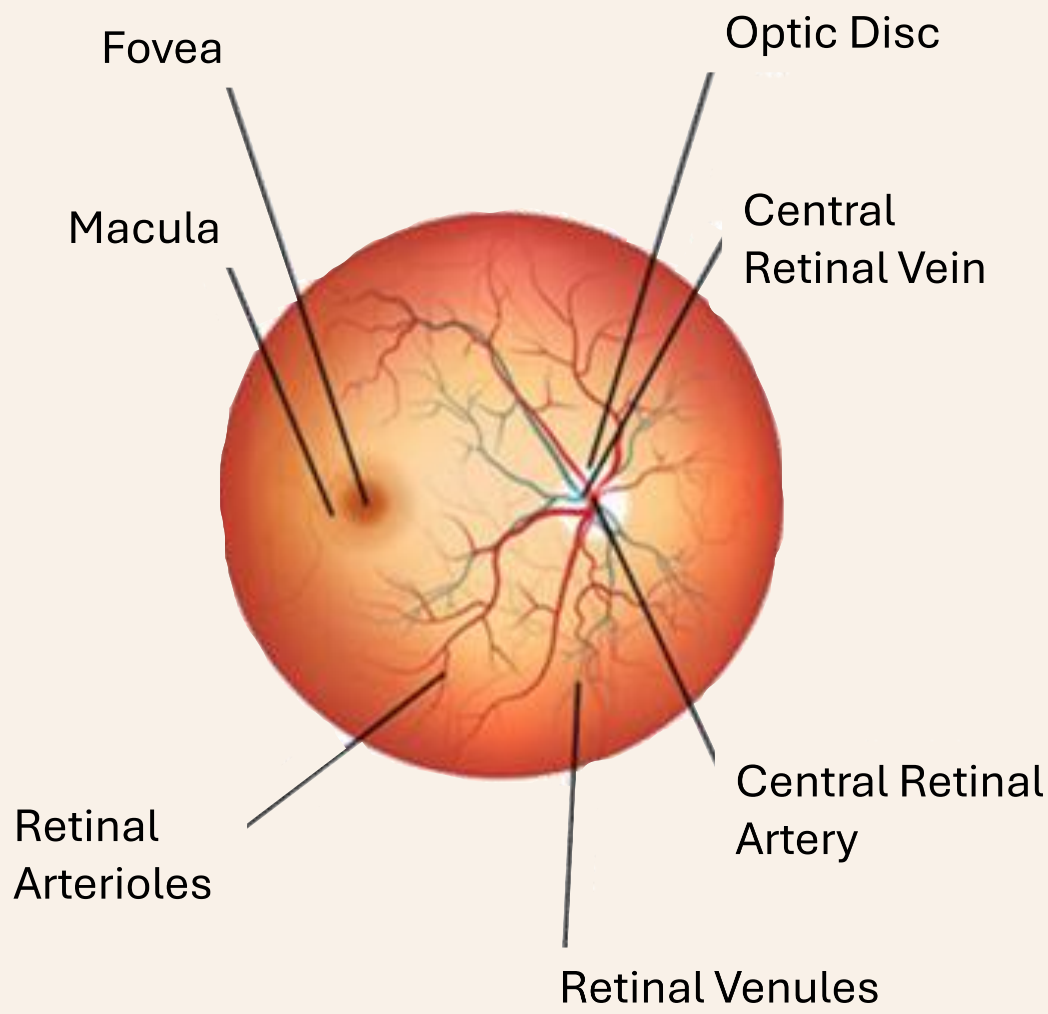
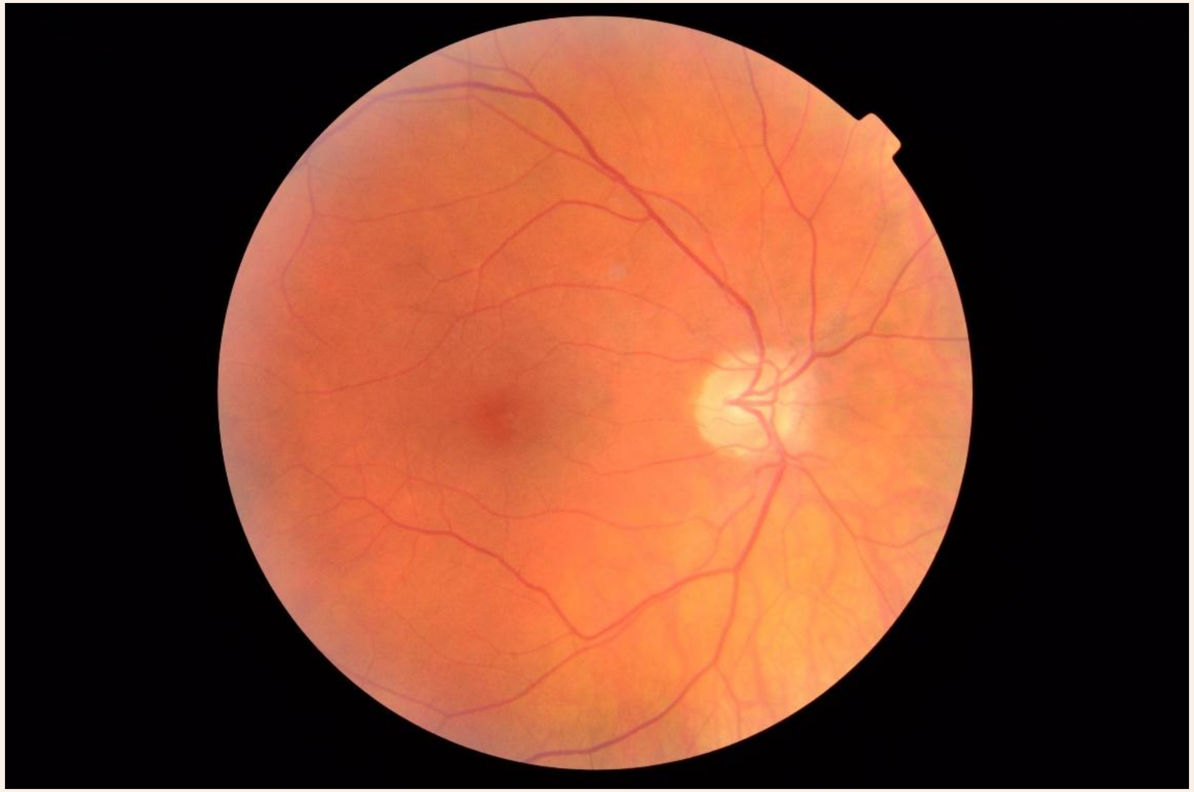


Image adapted from Retina Associates Kansas City

- Ocular blood vessels enter at the posterior pole of the eye
  - Classified as **arterioles** and **venules**
    - ~30-300 um in diameter
    - No autonomic nerve supply
  - Characteristics that we examined:
    - Diameter
    - Tortuosity

Determinants of Retinal Vessel Diameter

Fundus photo from a CLSA participant in the 99th percentile of arteriolar diameter.



Fundus photo from a CLSA participant in the 1st percentile of arteriolar diameter.

- Diameter can be impacted by the cumulative effects of aging, genetics, hypertension, atherosclerosis, inflammation, and endothelial dysfunction

Determinants of Retinal Vessel Tortuosity

Fundus photo from a CLSA participant in the 99th percentile of arteriolar tortuosity.

Fundus photo from a CLSA participant in the 1st percentile of arteriolar tortuosity.

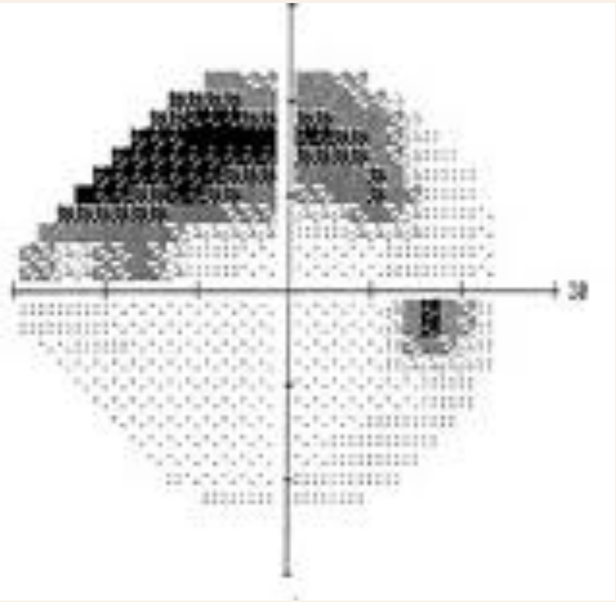
- Variation in tortuosity can occur in response to hypoxia, aging, hypertension, endothelial dysfunction, and atherosclerosis

Age-Related Eye Disease

Glaucoma and Age-related Macular Degeneration (AMD) are two of the leading causes of visual impairment and blindness in the world (Flaxman, 2017).

What is Glaucoma?

- Progressive degeneration of the optic nerve characterized by:
  - Thinning of Retinal Nerve Fiber Layer (RNFL)
  - Cupping of the optic disc (measured by the Cup-to-Disc Ratio(CDR))
- High Intraocular Pressure (IOP) is one of the biggest risk factors for developing glaucoma



Visual field image showing characteristic glaucomatous changes

Image adapted from "A view of glaucoma—are we seeing it clearly?" (Crabb 2016)

Age-Related Eye Disease

What is Age-Related Macular Degeneration (AMD)?

- AMD is a progressive degeneration of multiple retinal tissues due to various age-related changes.
- Choroidal neovascularization and geographic atrophy can occur in late-stage AMD, causing vision to deteriorate.

Normal Vision

Mild AMD

Severe AMD

Age-Related Eye Disease and Retinal Vessel Traits

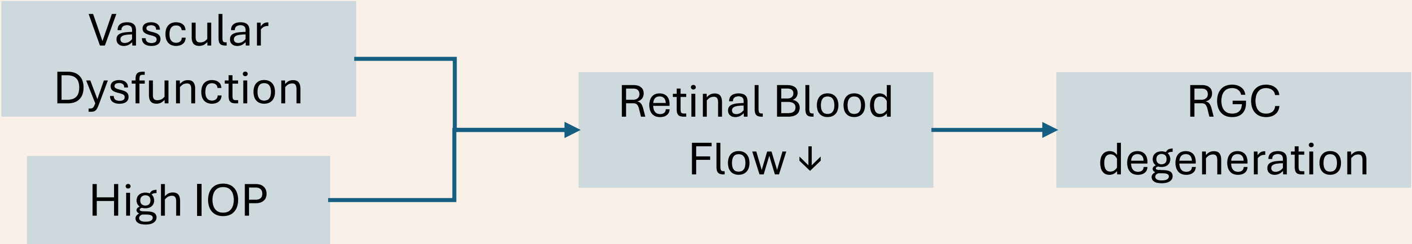
- Both glaucoma and AMD have been associated with disruptions of the retinal vasculature:
  - **Glaucoma** has generally been associated with arteriolar narrowing and decreased tortuosity (curvature) (Newman et al, 2017).
  - Associations between **AMD** and retinal vessel diameter are generally absent or inconsistent (Newman et al, 2017).

Key Knowledge Gap

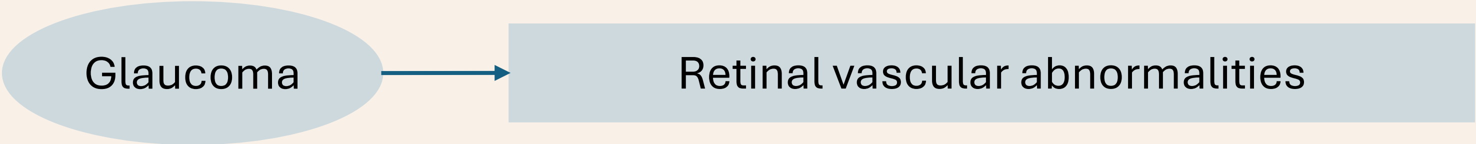
Most population-based studies have been cross sectional, limiting our understanding of the temporality between retinal vessel changes and the development of eye disease.

FOR EXAMPLE: Vascular hypotheses of glaucoma

1) RGC loss may occur due to impaired ocular blood flow from increased IOP or impaired autoregulation from vascular deregulatory factors.



2) Less blood flow is required to satisfy the metabolic needs of fewer cells

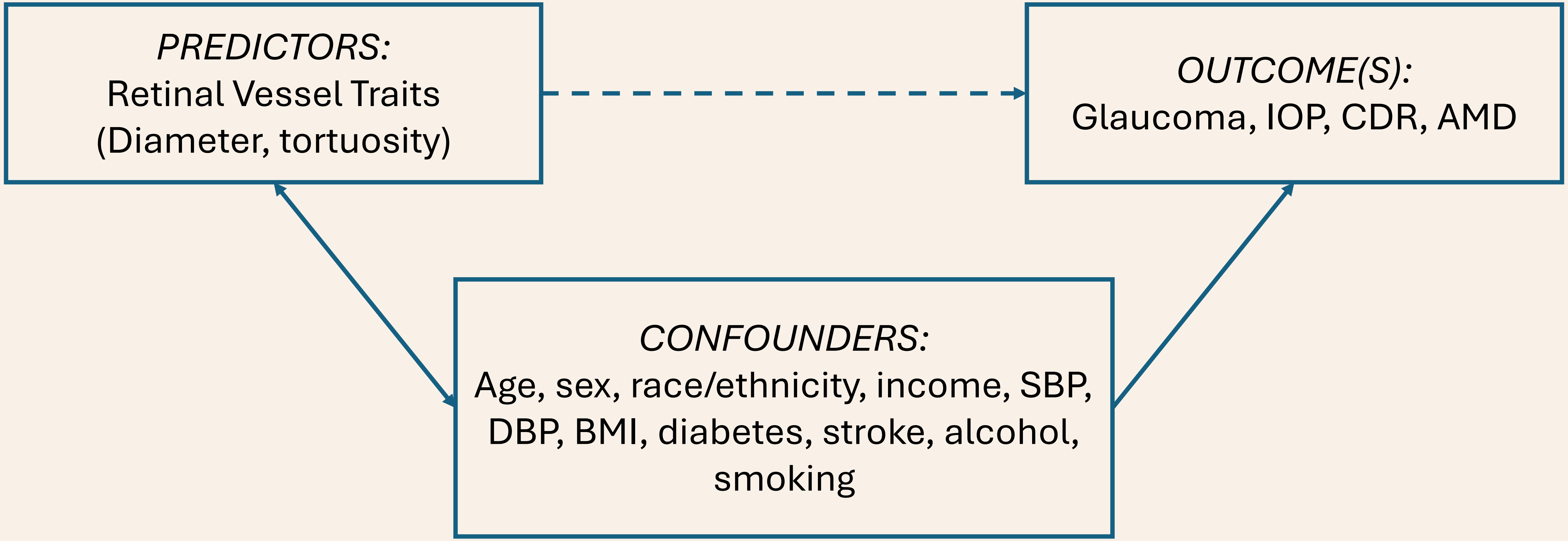


Objectives

- **Objective one**: Cross-sectionally and longitudinally investigate the relationship between retinal vessel characteristics and glaucomatous outcomes (intraocular pressure (IOP), cup-to-disc ratio (CDR), and glaucoma prevalence and incidence.

- **Objective two:** Examine the relationship between retinal vessel characteristics (width and tortuosity) and prevalence of AMD at baseline and its 3-year incidence.

Conceptual Framework



Others: systemic steroid use, use of systemic anti-hypertensive therapy, and use of ocular anti- hypertensive therapy

Methods

Data Source

- Baseline and 3-year follow-up data from the Canadian Longitudinal Study on Aging (CLSA) Comprehensive Cohort (n=30,097)

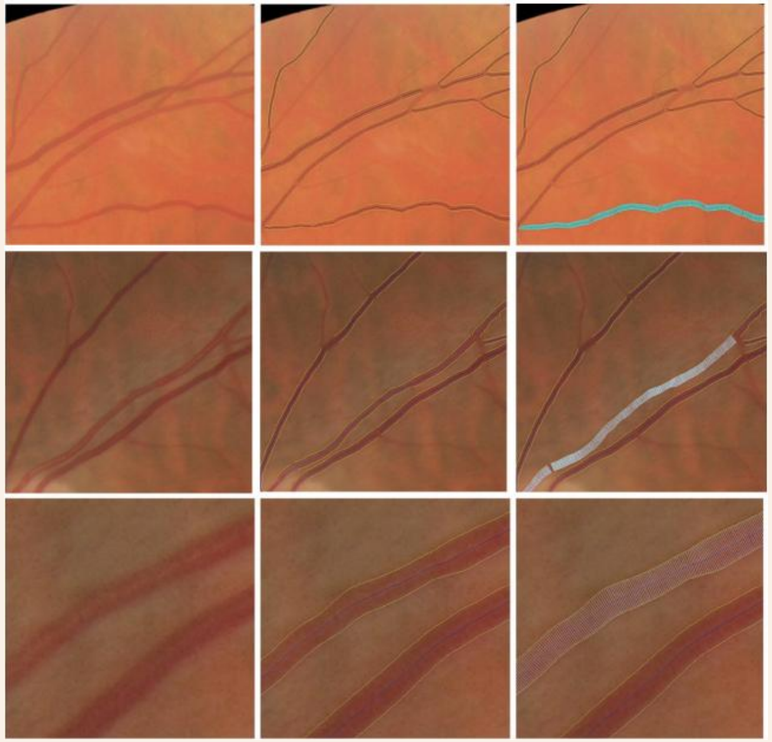
Data Collection

- Demographic, health, and lifestyle data were collected via physical assessment at a CLSA data collection site or interview questionnaire.
- Diagnoses of glaucoma or AMD were collected by self-report.
- Intraocular Pressure (IOP) was measured.

Methods

Retinal Images

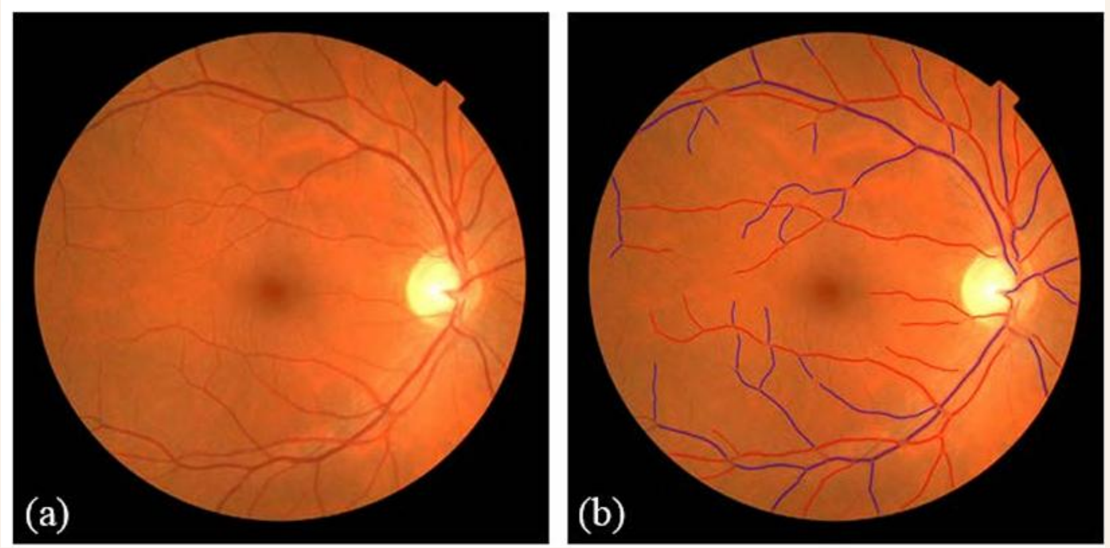
- Nonmydriatic macula-centred retinal images were taken of each eye using a fundus camera
- Retinal images were analyzed by Sarah Barman’s team using QUARTZ (Quantitative Analysis of Retinal Vessel Topology and Size), a deep learning algorithm, to extract data including arteriolar and venular diameter (in pixels), tortuosity, and Cup-to-Disc Ratio (CDR).
- The mean diameter and tortuosity of each arteriole and venule were summarized and weighted by the vessel segment length for each image.



Measuring vessel diameter using QUARTZ (Fraz, Welikala et al. 2015)

QUARTZ: Key Features

- Fully automated, uses a Deep Learning algorithm, processes an image in ~2 minutes
- Measures vessel characteristics over the entirety of the image.
- Can remove images of inadequate quality and non-retinal images.
  - While minimizing the number of wasted images.
- Differentiates between arterioles and venules
- Trained and validated on multiple datasets (UK Biobank, CLSA, EPIC-Norfolk, FOREVER).



Classification of arterioles and venules using QUARTZ (Welikala et al 2017)

QUARTZ: Vessel Diameter

- Vessel diameter was measured using zero-crossings of the second derivative.
- Method used to detect the edges of the blood vessels based on changes of brightness in the image.

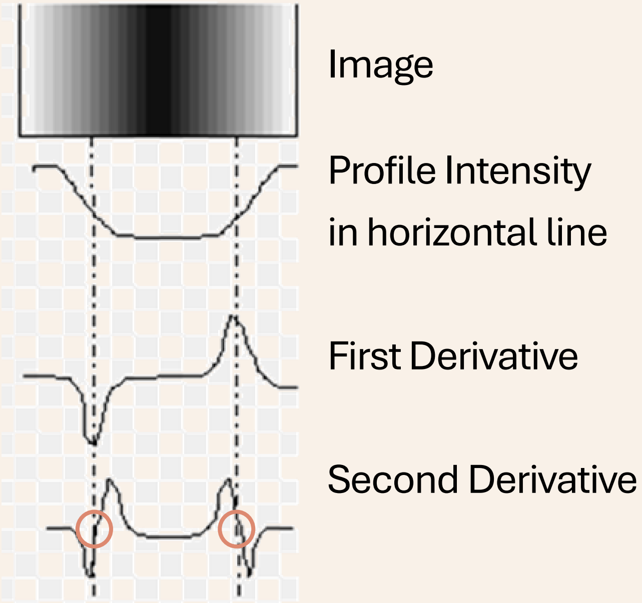
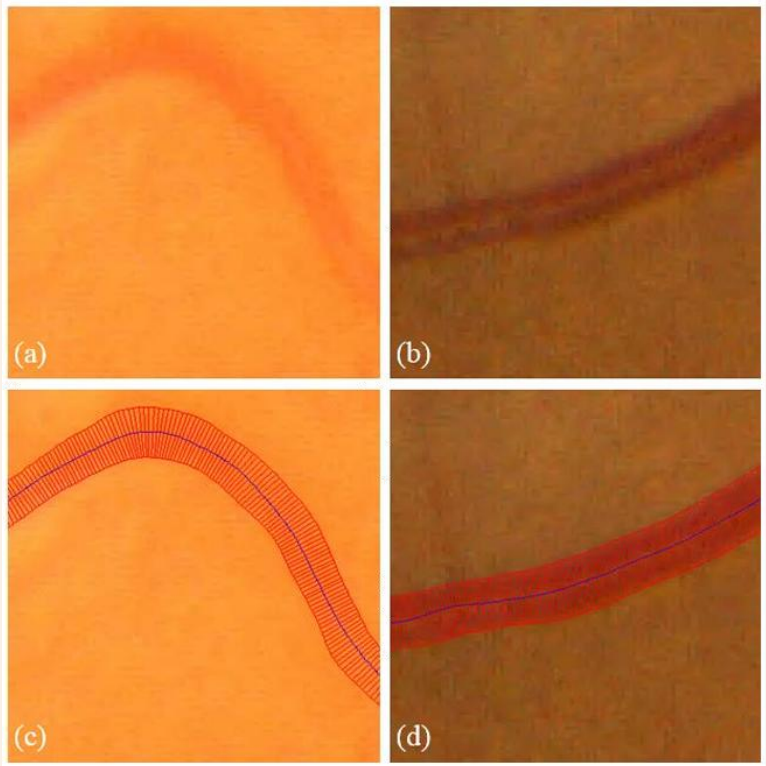


Illustration of zero-crossings of the second derivative method



Measurement of vessel diameter using QUARTZ (Welikala et al 2017)

QUARTZ : Vessel Tortuosity

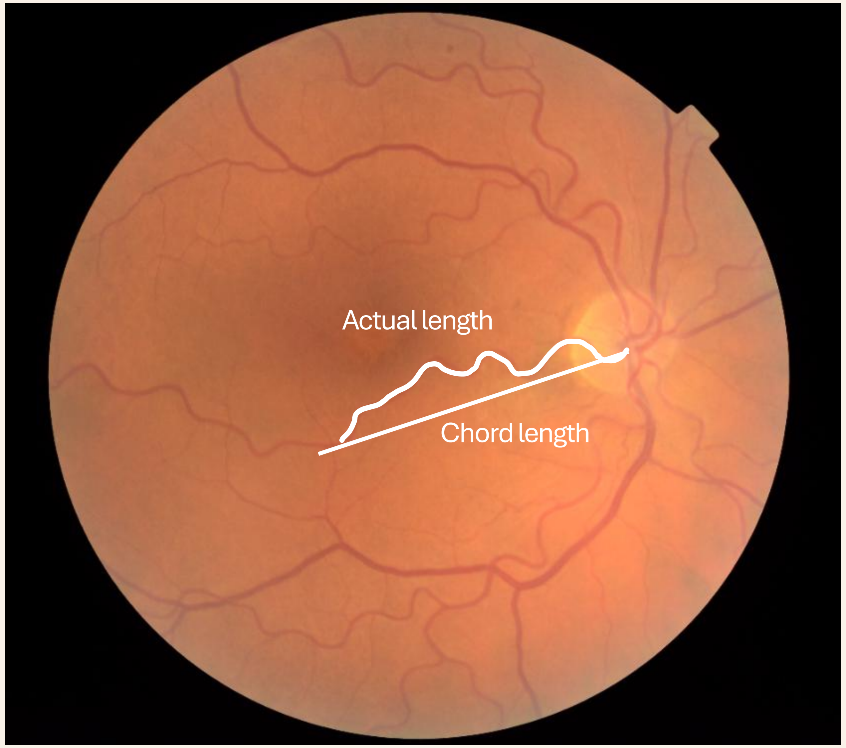


Illustration of tortuosity measurement on an image from the 99th percentile of retinal vessel tortuosity from the CLSA

- Tortuosity was measured using a subdivided chord length method.
  - Tortuosity = actual length / chord length

- A higher tortuosity value means a more curved/twisted vessel

Data Analysis

- Normality of continuous outcomes was assessed (Vessel traits, IOP, CDR).
- Complete case analysis using right eye data only.
- Models adjusted for the complex survey design (weight and strata).

- Logistic regression was used to determine the association between each retinal vessel trait and glaucoma, AMD, and their development over three years.
- Linear regression was used for IOP, CDR, and their 3-year change.
- Each model was adjusted for potential confounders:
  - Age, sex, race, income, BMI, diabetes, systolic and diastolic blood pressure, stroke, smoking, alcohol, and province
  - And additionally adjusted for systemic steroid use, use of systemic anti-hypertensive therapy, and use of ocular anti- hypertensive therapy.

Special Analytical Considerations

- Models included both the arteriolar and venular trait.
- Models for the 3-year change outcomes were *adjusted for the baseline level* to account for floor/ceiling effects.

Results

- 87% of CLSA participants had acceptable images in at least one eye.
- Those with unacceptable image scores were:
  - Older
  - More likely to have diabetes
- Values for vessel traits between right and left eyes were highly correlated (r>0.60).

	Acceptable Score (n=26,076)	Unacceptable Score (n=4,021)	P-value
Age, Years	58.8 (9.7)	67.4 (10.8)	<0.001
Female sex	52.6%	51.2%	0.261
Race/ethnicity			0.712
White	93.8	93.3	
Black	0.8	1.2	
East Asian	0.8	0.8	
Southeast Asian	0.4	0.3	
South Asian	0.9	0.9	
Arab and West Asian	0.5	0.4	
Latin American	0.4	0.3	
Other	0.8	0.9	
Mixed	1.8	1.9	
BMI, kg/m2	28.4 (5.6)	28.6 (5.5)	0.005
SBP, mmHg	120.0 (16.3)	124.3 (18.0)	<0.001
DBP, mmHg	74.7 (10.0)	72.9 (10.4)	<0.001
Smoking			<0.001
Never	44.3%	39.3%	
Former	44.3%	47.5%	
Current	11.4%	13.2%	
Alcohol			<0.001
Never	2.4%	4.2%	
Occasional	42.7%	46.4%	
Weekly	41.5%	33.0%	
Daily	13.4%	16.4%	
Diabetes			<0.001
None	83.2%	76.7%	
Type 1	0.6%	1.2%	
Type 2	8.8%	14.3%	
Neither Type	7.4%	7.8%	
Arteriolar diameter OD, pixels	15.6 (1.6)		
Arteriolar diameter OS, pixels	16.1 (1.8)		
Venular diameter OD, pixels	17.4 (1.8)		
Venular diameter OS, pixels	17.7 (1.9)		
Arteriolar area OD, kilopixel^2	236.69 (44.76)		
Arteriolar area OS, kilopixel^2	226.03 (48.35)		
Venular area OD, kilopixel^2	263.43 (47.90)		
Venular area OS, kilopixel^2	255.24 (49.30)		
Arteriolar tortuosity* OD	1.2 (0.4)		
Arteriolar tortuosity* OS	1.2 (0.4)		
Venular tortuosity* OD	1.2 (0.2)		
Venular tortuosity* OS	1.2 (0.2)		

O'Neil A, Welikala RA, Barman S, Owen CG, Rudnicka AR, Rakesh M, et al. Factors Associated With Retinal Vessel Traits in the Canadian Longitudinal Study on Aging. Invest Ophthalmol Vis Sci. 2025;66(3):13.

Results

Key Characteristics of those with Glaucoma

- 4.5% reported a diagnosis of glaucoma
- They were older, more likely to be female, had higher systolic blood pressure, more likely to drink alcohol every day and to have diabetes ($p < 0.05$).
- They had higher IOP, and worse CDR ($p < 0.05$).
- ***They had wider arteriolar and venular diameter ($p < 0.05$).***

Key Characteristics of those with AMD

- 3.8% reported a diagnosis of AMD
- They had worse visual acuity, were older, more likely to be female, to have higher systolic blood pressure, to drink alcohol daily, to have diabetes ($p < 0.05$).
- ***They had wider venular diameter and reduced venular tortuosity ($p < 0.05$).***

Results

Cross-sectional associations between retinal vessel traits and glaucoma outcomes

Model*	Vessel Trait †	Glaucoma n=23,993 OR	95% CI	CDR n=23,824 β	95% CI	IOP n=23,279 β	95% CI
1	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**	**-2.23, -1.52**
2	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**

*Models adjusted for age, sex, race, income, BMI, systolic and diastolic blood pressure, diabetes, stroke, smoking, alcohol, and province

† Per 10 pixel increase in diameter or 1 unit increase in tortuosity

A O'Neil, R Welikala, S Barman, CG Owen, A Rudnicka, M Rakesh, MH Roy-Gagnon, D Maberley, EE. Freeman. Retinal vessel traits and age-related eye disease in the Canadian Longitudinal Study on Aging. *Clinical and Experimental Ophthalmology*, 2025

Results from Supplemental Analyses

Cross-sectional associations between retinal vessel traits and glaucoma outcomes

Model	Vessel Trait‡	Glaucoma n=23,993 ¶		CDR n=23,824		IOP n=23,279	
		OR	95% CI	β	95% CI	β	95% CI
1a*	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†	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*	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†	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**

*Models adjusted for (a) age, sex, race, income, BMI, systolic and diastolic blood pressure, diabetes, stroke, smoking, alcohol, and province (b) Additionally adjusted for 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

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Results

Longitudinal associations between retinal vessel traits and glaucoma outcomes

Model*	Vessel Trait †	Development of Glaucoma n=20,994 OR	95% CI	CDR Change n=18,108 β	95% CI	IOP Change n=19,386 β	95% CI
1	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**
2	Arteriolar tortuosity	1.12	0.79, 1.58	0.001	-0.001, 0.003	**-0.18**	**-0.36, -0.01**
	Venular tortuosity	**0.52**	**0.31, 0.87**	**-0.006**	**-0.010, -0.002**	-0.24	-0.50, 0.01

*Models adjusted for age, sex, race, income, BMI, systolic and diastolic blood pressure, diabetes, stroke, smoking, alcohol, province, and baseline CDR or IOP (as relevant)

† Per 10 pixel increase in diameter or 1 unit increase in tortuosity

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Results

Cross-Sectional Association

Retinal vessel diameter at baseline ↔ Having glaucoma at baseline

OR=0.36
95% CI:0.20, 0.65

Longitudinal Association

Retinal vessel diameter at baseline → Developing glaucoma at year 3

OR=1.74
95% CI:0.56, 5.41

Reverse Longitudinal Association

Having glaucoma at baseline → 3-year change (narrowing) in arteriolar diameter

β=-0.21
95% CI:-0.37, -0.05

Results

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

Model*	Vessel Trait †	AMD at Baseline n=24,000 OR	95% CI	Development of AMD n=20,854 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

*Models adjusted for age, sex, race, income, BMI, systolic and diastolic blood pressure, diabetes, stroke, smoking, alcohol, and province

† Per 10 pixel increase in diameter or 1 unit increase in tortuosity

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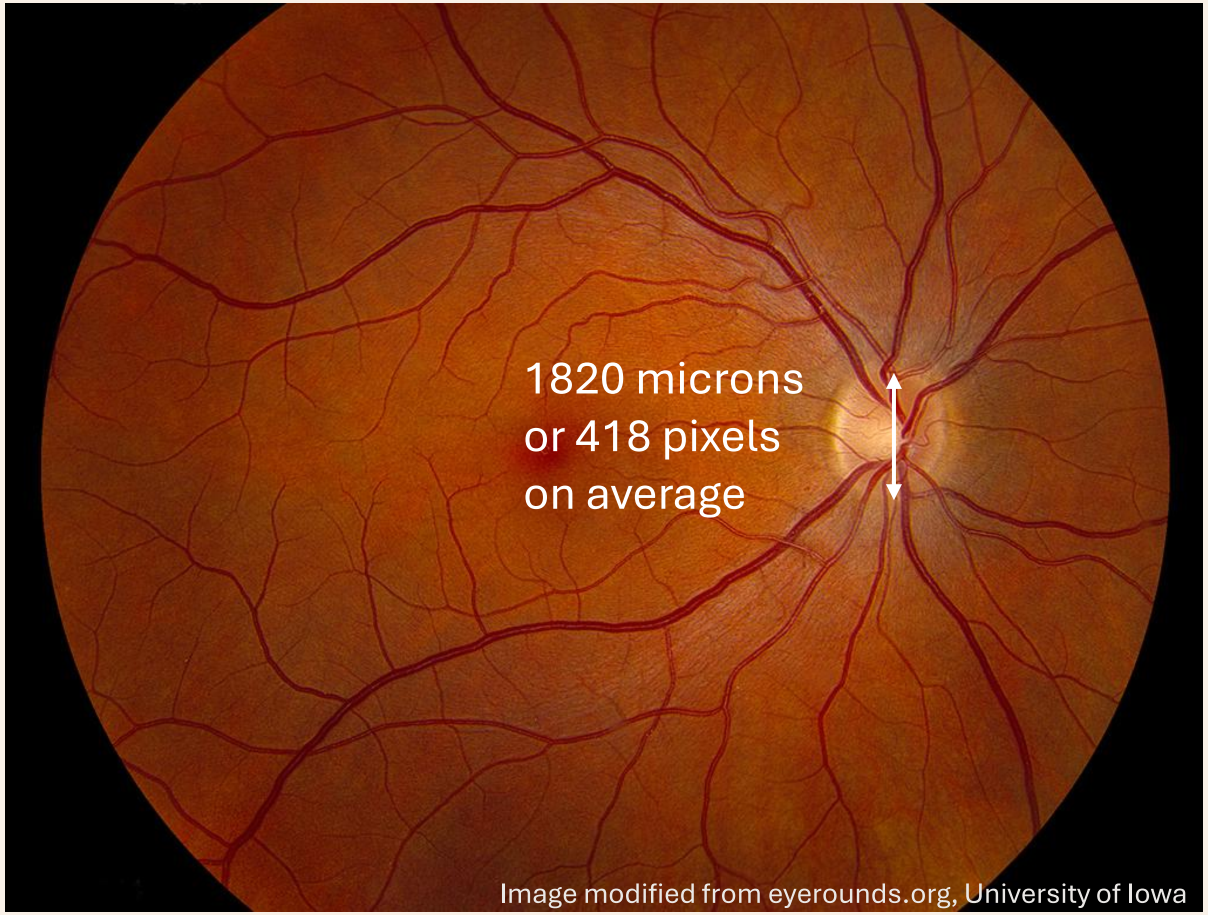
Pixel/Micron Conversion



Putting our results into perspective:

- The average vertical optic disc diameter in the CLSA was 418 pixels
- The average vertical optic disc diameter in a similarly predominantly white population was 1820 microns (Quigley et al)

1820 microns / 418 pixels = **4.35 microns/pixel**

- Therefore, 1 pixel equals approximately 4.35 microns.

As an example with the AMD results, we can say that for every 10 pixel (or 43.5 micron) increase in venular diameter, the odds of having AMD at baseline were 2.77 times higher

Discussion

Objective 1 – Glaucoma

Main Finding 1: Narrower arterioles were only *cross-sectionally* associated with glaucoma.

- Additional adjustment for IOP- lowering medication eliminated this association.
- Not associated with 3-year development of glaucoma.
  - Reverse longitudinal association was statistically significant (β=-0.21, 95% CI -0.37, -0.05)
  - Suggests reverse causality as reason for cross-sectional association
- Previous longitudinal studies:
  - Consistent with Ikram *et al* (2005) - Rotterdam Study
  - Inconsistent with Kawasaki *et al* (2013) - Blue Mountains Eye Study

Discussion

Main Finding 2: More tortuous (curvy) venules were associated with lower odds of developing glaucoma.

- Previous cross-sectional findings showed that straighter vessels were associated with glaucoma (Wu *et al*, 2013) and a thinner neuro-retinal rim (Koh *et al*, 2010)
- Suggests that straighter venules may precede development of glaucoma

Objective 2 – AMD

Discussion

Main Finding 3: Venular diameter was positively associated with baseline AMD and 3-year development of AMD

- Not consistent with previous longitudinal studies:
  - Liew *et al* (2006)
  - Ikram *et al* (2005)
  - You *et al* (2012)
- Consistent with studies showing wider venular diameter was associated with:
  - Early AMD (Jeganathan *et al*, 2008) (SiMES)
  - 10-year development of RPE abnormalities (Liew *et al*, 2006) (BMES)
  - Worse response to treatment in patients with neovascular AMD (Wickremasinghe *et al*, 2012)

Discussion

Main Finding 4: Increased venular tortuosity was associated with lower odds of AMD at baseline

- We are not aware of any prior studies that examined tortuosity and AMD.

Discrepancies in the Literature

1) **Differences in which confounding factors are accounted for**

2) **Fundus Image Analysis Software**
   - Agreement between software is generally poor
   - Differences in vessel identification, segmentation, and area assessed

3) **Ethnicity**
   - Confounding effects from differences in diet or genetic factors

Clinical Implications

1) Screening

- Can we screen for glaucoma or AMD using fundus images?
- Fundus images are a quick diagnostic test, can using retinal vessels captured in these images help flag patients with these vision threatening conditions?

2) Prediction

- Can retinal vessel characteristics help predict who will develop glaucoma/progressive glaucoma or AMD?
- Does including retinal vessel characteristics into predictive models better predict the development of eye disease?

3) Treatment

- If retinal vessel changes increase the risk of disease, is this something that can be targeted for treatment?
- Can vessels be used as a marker of treatment efficacy?

Strengths

- **Leveraging data from the CLSA**
  - Large, population-based sample
  - Access to longitudinal data, 92% retention rate
  - Comprehensive physical assessment and questionnaire data
- **QUARTZ provides data over entire retina**
  - Traditional methods focus on a specific area around the optic nerve and rely on the 6 largest vessels
- **Relying on diameter only offers a simplified view of retinal vessel anatomy**
  - We used two different characteristics to gain a better understanding
- **Prior research has focused on arteriolar diameter only**
  - We assessed arteriolar and venular characteristics separately
  - We adjusted for the fellow vessel to see their associations independent from each other

Limitations

- Some participants were excluded due to inadequate image quality
- We did not have information on axial length/refractive error
- Reliance on self-reported diagnoses of systemic and ocular disease
- Reports of glaucoma/AMD were not assessed at the eye-level
- No data on type or severity of glaucoma and AMD

Conclusion

- First to investigate retinal vessel characteristics in relation to age-related eye disease in a Canadian population
- In leveraging underutilized retinal images from the CLSA alongside its longitudinal data, this research:
  - Advances the understanding of the vascular mechanisms underlying glaucoma and AMD
- Translation to clinical applications

Acknowledgements

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- Co-Authors: Marie-Hélène Roy-Gagnon, David Maberley, Roshan A. Welikala, Sarah Barman, Christopher G. Owen, Alicja R. Rudnicka, Mohan Rakesh
- This research has been conducted using the CLSA Baseline Comprehensive Dataset version 7.0 , Follow-up 1 Comprehensive Dataset version 4.0, and Baseline Retinal Scans under Application Number 2209017.
    - The CLSA is led by primary investigators: Drs. Parminder Raina, Christina Wolfson and Susan Kirkland
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Clinical & Experimental Ophthalmology

ORIGINAL ARTICLE-CLINICAL SCIENCE OPEN ACCESS

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

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Thank you to the CLSA for inviting us to share our work!

Thank you for listening

Questions?

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