Factors Associated With Retinal Vessel Traits in the Canadian Longitudinal Study on Aging

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Purpose. To determine the factors cross-sectionally and longitudinally associated with retinal vessel diameter, total area, and tortuosity in the Canadian Longitudinal Study on Aging (CLSA).

Methods. Of the 30,097 adults between ages 45 and 85 years old in the CLSA Comprehensive Cohort, 26,076 had at least one retinal image gradable by QUARTZ, a deep-learning algorithm that automatically assessed image quality, distinguished between arterioles and venules, and estimated retinal vessel traits over the entire retina. Questions were asked about demographic, lifestyle, and medical factors. Blood pressure, cholesterol, and C-reactive protein were measured. Participants returned for follow-up 3 years later. Multiple linear regression was used to provide adjusted estimates.

Results. Current smoking was strongly associated with wider arteriolar and venular diameters and their widening over 3 years ($P < 0.05$). Current smoking was also associated with a larger arteriolar and venular area and a 3-year increase in venular area ($P < 0.05$). Obesity was positively associated with venular diameter, total venular area, 3-year change in total venular area, and venular tortuosity ($P < 0.05$). Diastolic blood pressure was negatively associated with both arteriolar and venular diameter, area, and tortuosity, both cross-sectionally and longitudinally ($P < 0.05$). Diabetes was associated with wider arteriolar diameters cross-sectionally, and type 1 diabetes was associated with 3-year widening of arteriolar diameters ($P < 0.05$).

Conclusions. This work provides comprehensive information on the factors associated with retinal vessel traits and their change. Factors such as smoking, obesity, blood pressure, and diabetes were longitudinally related to retinal vessel traits, which play a role in the development of eye disease.

Keywords: CLSA, arteriole, venule, retinal vessel, longitudinal

Modern digital fundus photography and image analysis software provide a unique, non-invasive opportunity to visualize and obtain objective measurements of the retinal vasculature.[1–3] Retinal arterioles and venules are believed to reflect the health of the systemic microcirculation, which may play a key role in the development of many ocular and systemic diseases.[4,5] Therefore, the retinal vasculature may provide a valuable method for assessing the overall health of the microvascular system by enabling the detection of structural and pathological changes.

The retinal vasculature is thought to be affected by aging, hypertension, inflammation, arteriosclerosis, and endothelial dysfunction, although the full extent of factors is still under investigation.[6] Many prior epidemiological studies examining factors associated with retinal vessel traits in adults have been cross-sectional.[6–9] These studies have indicated that retinal arteriolar and venular diameter have different factors associated with them, indicating the importance of examining them separately.[6] For example, Tapp et al.[10] found that body mass index (BMI) and other measures of adiposity were associated with arteriolar and venular diameter in opposite directions. Racial and ethnic differences in vessel diameter have been identified.[6] However, most studies have only had a few racial and ethnic groups that could be examined at a time.

Although many studies have focused on retinal vessel diameter, other parameters such as tortuosity and area have been less frequently researched. Prior research has reported an association between systolic blood pressure and venular area.[11] Retinal vessel tortuosity, or curvature, can indicate the

health of the vasculature by providing insight into hemodynamics and perfusion. Its associated factors include age, sex, blood pressure, and BMI.[9,10]

The Canadian Longitudinal Study on Aging (CLSA) is a population-based study that collected comprehensive health-related data from a large cohort of Canadians and is comprised of many racial and ethnic groups.[12] Despite the abundance of retinal images collected by the study, these data have been underutilized by researchers. To address this, we examined the factors associated with retinal vessel diameter, total area, and tortuosity, as well as their changes over a 3-year period in a Canadian population.

Methods

Study Population and Design

We conducted both cross-sectional and longitudinal analyses using data from the CLSA Comprehensive Cohort.[12] This study includes 30,097 Canadian adults ages 45 to 85 years, recruited through random sampling of provincial healthcare databases and random digit dialing of landline phones. Baseline data were gathered between 2012 and 2015 through in-home interviews and physical assessments at CLSA Data Collection Sites (DCSs) 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 45 to 85 years old, lived in the community, spoke English or French, and resided within 25 to 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).

Data Collection

Retinal Images. Nonmydriatic retinal images were taken in each eye at both baseline and follow-up visits using a TRC-NW8 fundus camera (Topcon, Tokyo, Japan) with a D90 camera (Nikon, Tokyo, Japan) attached. Images were macular centered and had a 45° field of view. Most 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 were resized to a resolution of 4288 × 2848 pixels.

Retinal Vessel Traits. Retinal images were processed using a deep-learning algorithm referred to as Quantitative Analysis of Retinal Vessel Topology and Size (QUARTZ).[1,13] Within the QUARTZ vessel analysis module,[1] vessel width was measured using zero-crossings of the second derivative, and tortuosity was measured using a subdivided chord length method. The methods used within the vessel analysis module have been previously well documented and validated.[13] QUARTZ measures vessels across the inner retinal layer (supplied by the ophthalmic artery via the central retinal artery) contained in fundus images, including arterioles, pre- and post-capillaries, and venules. For the CLSA data, QUARTZ can determine inadequate image quality with a sensitivity of 91% and a specificity of 100%. QUARTZ can also distinguish between an arteriole and a venule with 88% accuracy, increasing to 96% using a probability cutoff of 0.8.[1] QUARTZ obtained thousands of measures of diameter and tortuosity from across the entire retinal image. The mean diameter, area, and tortuosity of each arteriole and venule were then summarized and weighted by the vessel segment length for each image. Area was calculated from the average vessel width multiplied by length, summed across vessel segments. Diameter and area are given in pixels and pixels^2, respectively, whereas tortuosity is a unitless measure.

Demographic, Health, and Lifestyle Data. Demographic data including age, sex, income, and race/ethnicity were collected at baseline during the in-home visits 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: >$150K, $150 to $100K, $100 to $50K, $50K to $20K, and "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 the last 30 days), or not at all (not in the last 30 days)?" We defined current smokers as those who had smoked at least 100 cigarettes and currently smoked 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 categorized 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 DCS interviewer-led questionnaire, participants were asked to report doctor diagnoses of several health conditions, including heart disease (yes, no), stroke (yes, no), or diabetes (none, type 1, type 2, or neither). Height and weight were measured using standardized procedures during the DCS visit. 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; obese, ≥30.0 kg/m^2). Blood pressure was measured using a BpTRU monitor (VSM MedTech, Coquitlam, BC, Canada). Six blood pressure measurements were acquired, and an average of measurements two through six was used.

Blood Tests. Non-fasting venipuncture blood was collected from each participant during the DCS visit and analyzed at each DCS laboratory. Several soluble and cellular biomarkers were measured in serum including total cholesterol and the concentration of high-sensitivity C-reactive protein (hs-CRP) using a, cobas 8000 modular analyzer (Roche Diagnostics, Indianapolis, IN).

Statistical Analysis

The normality of the retinal vessel outcome measures was assessed using standardized normal probability plots. Diameter and area were normally distributed, but tortuosity measures were multiplied by 1000 and the natural log was taken to achieve normality. Multiple linear regression models

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were used to examine the associations with each retinal vessel trait. Both baseline and 3-year changes in retinal vessel traits were examined. Change models were adjusted for the baseline value of the retinal vessel trait. Regression models were run on right eyes because the sample sizes were slightly bigger for right eyes. The complex survey design (weights and strata) was accounted for in all analyses.

Results

Of the 30,097 CLSA participants, 26,076 (87%) had at least one acceptable QUARTZ image quality score and were therefore included in subsequent analyses. At round 2, 92% returned to follow-up. Those with an acceptable QUARTZ quality score are compared to those without acceptable scores in Table 1. Those with an acceptable score were substantially younger and less likely to have diabetes than those who were excluded. Also, shown in Table 1 are the descriptive statistics for the retinal vessel traits for right and left eyes to show their similarity. Values for right and left eyes were highly correlated ($r > 0.60$). Only right eyes were used in subsequent analyses.

Using linear regression, variables in cross-sectional analyses that showed statistically significant positive associations with arteriolar diameter (Table 2) included older age, female sex, and Black race, as well as Southeast Asian, South Asian, Arab and West Asian, Latin American, other, and mixed ethnicities (compared to White race), lower income, smoking, and diabetes ($P < 0.05$). For example, type 1 diabetes was associated with greater arteriolar diameter compared to people without diabetes ($\beta = 0.67$; 95% confidence interval [CI], 0.31–1.04) (Table 2, Fig. 1). Negative statistically significant associations were found with diastolic blood pressure ($P < 0.05$). For example, each 10-mm Hg increase in diastolic blood pressure was associated with a narrower arteriolar diameter ($\beta = -0.34$; 95% CI, −0.39 to −0.29). Weekly and daily drinkers of alcohol had thinner arterioles than never drinkers ($P < 0.05$). Similar but fewer positive statistically

Table 1. Selected Characteristics of Those With at Least One Image With an Acceptable QUARTZ Image Quality Score

	Acceptable Score ($n = 26,076$)	Unacceptable Score ($n = 4021$)	*P*
Age (y), mean ± SD	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/m^2), mean ± SD	28.4 ± 5.6	28.6 ± 5.5	0.005
SBP (mm Hg), mean ± SD	120.0 ± 16.3	124.3 ± 18.0	<0.001
DBP (mm Hg), mean ± SD	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	7.4	7.8	
Arteriolar diameter OD (pixels), mean ± SD	15.6 ± 1.6	—	—
Arteriolar diameter OS (pixels), mean ± SD	16.1 ± 1.8	—	—
Venular diameter OD (pixels), mean ± SD	17.4 ± 1.8	—	—
Venular diameter OS (pixels), mean ± SD	17.7 ± 1.9	—	—
Arteriolar area OD (kilopixel^2), mean ± SD	236.69 ± 44.76	—	—
Arteriolar area OS (kilopixel^2), mean ± SD	226.03 ± 48.35	—	—
Venular area OD (kilopixel^2), mean ± SD	263.43 ± 47.90	—	—
Venular area OS (kilopixel^2), mean ± SD	255.24 ± 49.30	—	—
Arteriolar tortuosity OD,* mean ± SD	1.2 ± 0.4	—	—
Arteriolar tortuosity OS,* mean ± SD	1.2 ± 0.4	—	—
Venular tortuosity OD,* mean ± SD	1.2 ± 0.2	—	—
Venular tortuosity OS,* mean ± SD	1.2 ± 0.2	—	—

DBP, diastolic blood pressure; OD, right eye; OS, left eye; SBP, systolic blood pressure.
* Tortuosity measures were multiplied by 1000 and the natural log was taken to achieve normality.

Table 2. Difference in Retinal Vessel Diameter by Sociodemographic Factors and Clinical Variables in Cross-Sectional and Longitudinal Analyses*

	Arteriolar Diameter (n = 21,754)		Venular Diameter (n = 21,754)		Arteriolar Diameter Change (n = 16,796)		Venular Diameter Change (n = 16,796)	
	β	95% CI	β	95% CI	β	95% CI	β	95% CI
Age, per 10 years	0.21	0.17, 0.25	0.38	0.34, 0.43	0.12	0.08, 0.15	0.27	0.23, 0.31
Female sex	0.12	0.06, 0.18	0.24	0.18, 0.31	0.07	0.01, 0.12	0.05	−0.01, 0.11
Ethnicity								
White	Ref.		Ref.		Ref.		Ref.	
Black	1.27	0.83, 1.71	0.37	0.07, 0.68	0.19	−0.29, 0.67	0.06	−0.24, 0.37
East Asian	0.11	−0.19, 0.41	−0.02	−0.34, 0.29	0.26	−0.10, 0.63	0.33	−0.15, 0.80
Southeast Asian	0.95	0.13, 1.77	0.28	−0.25, 0.81	0.42	−0.02, 0.86	0.67	−0.21, 1.55
South Asian	1.05	0.65, 1.46	0.22	−0.38, 0.81	0.23	−0.16, 0.62	0.14	−0.23, 0.50
Arab and West Asian	0.58	0.23, 0.93	−0.09	−0.46, 0.29	0.26	−0.02, 0.55	0.06	−0.23, 0.34
Latin American	0.60	0.24, 0.95	0.41	0.08, 0.74	0.21	−0.05, 0.47	−0.03	−0.47, 0.40
Other	0.81	0.29, 1.34	0.36	−0.02, 0.75	−0.11	−0.44, 0.22	−0.10	−0.46, 0.26
Mixed	0.40	0.18, 0.63	−0.02	−0.32, 0.27	0.15	−0.04, 0.33	0.02	−0.21, 0.24
Income								
High, 0	Ref.		Ref.		Ref.		Ref.	
1	0.04	−0.03, 0.11	0.05	−0.02, 0.12	0.04	−0.01, 0.10	0.03	−0.03, 0.09
2	0.14	0.06, 0.23	0.19	0.09, 0.29	−0.00	−0.08, 0.08	0.02	−0.08, 0.11
Low, 3	0.24	0.05, 0.44	0.24	0.05, 0.43	−0.05	−0.23, 0.13	0.05	−0.13, 0.23
Missing	0.12	−0.02, 0.26	0.01	−0.12, 0.15	−0.06	−0.18, 0.06	−0.09	−0.21, 0.03
BMI								
Underweight	−0.04	−0.41, 0.32	0.04	−0.45, 0.53	0.29	−0.21, 0.80	0.30	−0.22, 0.82
Normal	Ref.		Ref.		Ref.		Ref.	
Overweight	−0.04	−0.11, 0.03	0.06	−0.02, 0.14	−0.01	−0.07, 0.05	−0.01	−0.08, 0.06
Obese	0.07	−0.02, 0.15	0.16	0.07, 0.25	−0.01	−0.08, 0.06	0.06	−0.02, 0.14
SBP, per 10 mm Hg	−0.02	−0.05, 0.01	0.02	−0.01, 0.05	0.02	−0.01, 0.05	0.02	−0.01, 0.05
DBP, per 10 mm Hg	−0.34	−0.39, −0.29	−0.15	−0.20, −0.10	−0.05	−0.09, −0.01	−0.04	−0.09, 0.00
Smoking								
Never	Ref.		Ref.		Ref.		Ref.	
Former	0.10	0.04, 0.16	0.10	0.04, 0.17	0.02	−0.03, 0.07	0.06	0.01, 0.12
Current	0.72	0.60, 0.83	0.61	0.49, 0.73	0.28	0.18, 0.38	0.24	0.13, 0.34
Alcohol								
Never	Ref.		Ref.		Ref.		Ref.	
Occasional	−0.18	−0.47, 0.12	−0.09	−0.35, 0.17	0.04	−0.23, 0.30	−0.04	−0.33, 0.26
Weekly	−0.33	−0.62, −0.03	−0.20	−0.46, 0.06	0.03	−0.24, 0.29	−0.08	−0.37, 0.22
Daily	−0.38	−0.69, −0.08	−0.23	−0.50, 0.04	−0.02	−0.30, 0.25	−0.08	−0.39, 0.23
Diabetes								
None	Ref.		Ref.		Ref.		Ref.	
Type 1	0.67	0.31, 1.04	0.05	−0.53, 0.43	0.45	0.09, 0.81	0.29	−0.09, 0.68
Type 2	0.26	0.14, 0.37	0.01	−0.12, 0.13	0.10	−0.01, 0.21	−0.09	−0.21, 0.02
Neither	0.13	0.02, 0.24	0.03	−0.09, 0.15	0.07	−0.01, 0.16	0.08	−0.04, 0.20
Stroke	0.10	−0.22, 0.41	0.09	−0.20, 0.38	0.17	−0.02, 0.36	0.27	−0.07, 0.61
Heart disease	0.07	−0.04, 0.17	−0.03	−0.16, 0.09	0.05	−0.05, 0.14	0.01	−0.10, 0.13
hs-CRP	0.00	−0.00, 0.01	0.01	0.01, 0.02	0.00	−0.00, 0.01	−0.00	−0.01, 0.00
Cholesterol	−0.02	−0.05, 0.01	0.00	−0.03, 0.03	0.02	−0.01, 0.04	0.01	−0.01, 0.04

* Estimates were adjusted for each variable in the table and province; change models were also adjusted for baseline vessel trait.

significant associations were found with venular diameter (Table 2), including older age, female sex, Black race and Latin American ethnicity (compared to White race), lower income, obesity (Fig. 2), and smoking, whereas a negative statistically significant association was found with diastolic blood pressure ($P < 0.05$) (Fig. 3).

There were fewer associations when examining vessel diameter using the longitudinal data (Table 2). Older age, female sex, current smoking, and type 1 diabetes were positively statistically significantly associated with 3-year change in arteriolar diameter, whereas diastolic blood pressure was negatively associated ($P < 0.05$). For example, type 1 diabetes was associated with a 3-year increase in arteriolar diameter compared to people without diabetes ($\beta = 0.45$; 95% CI, 0.09–0.81). Similarly, older age and former and current smoking were positively statistically significantly associated with 3-year change in venular diameter, but diastolic blood pressure was negatively associated ($P < 0.05$).

There was a statistically significant positive association between arteriolar area and current smoking status, cholesterol, and hs-CRP ($P < 0.05$) (Table 3). For example, higher hs-CRP levels were associated with a greater arteriolar area ($\beta = 0.18$; 95% CI, 0.01–0.36). Older age; female sex; Black race; East Asian, Southeast Asian, and South Asian ethnicities (compared to White race); low and missing income (compared to high income); systolic blood pressure; diastolic blood pressure; and daily alcohol use (compared to never drinkers) were negatively associated with arteriolar

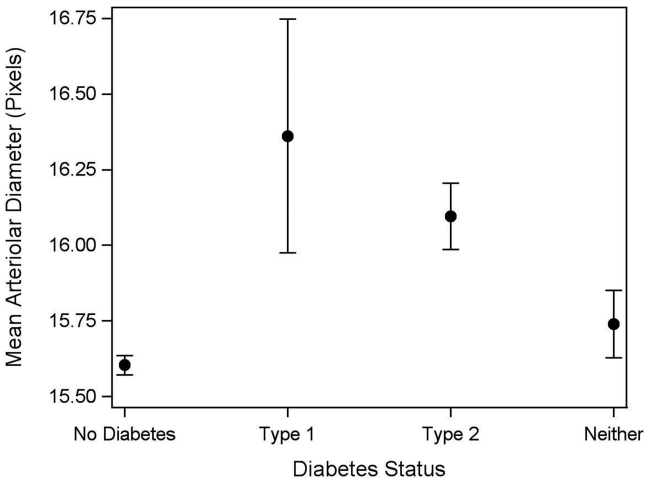

Figure 1. Mean arteriolar diameter by diabetes status using cross-sectional data.

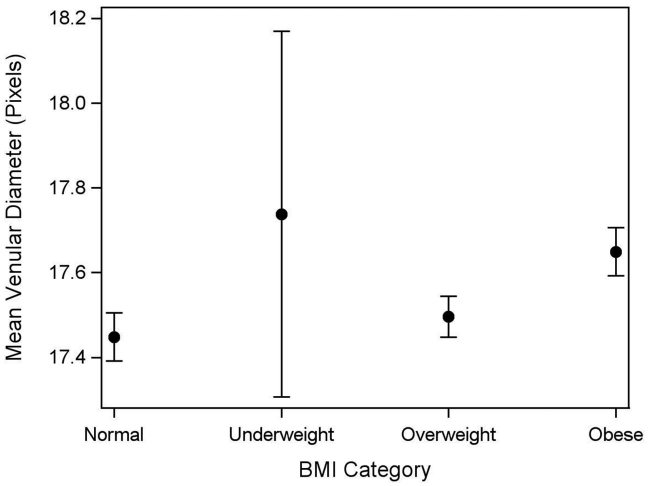

Figure 2. Mean venular diameter by BMI category using cross-sectional data.

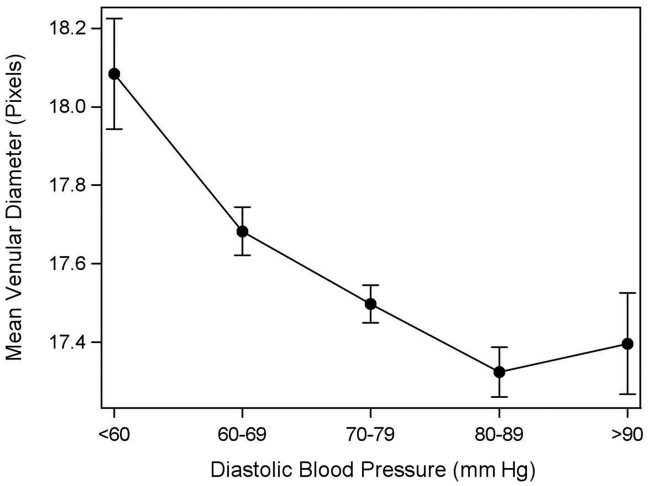

Figure 3. Mean venular diameter by diastolic blood pressure using cross-sectional data.

area ($P < 0.05$). As for arteriolar area, venular area was negatively associated with older age, female sex, South Asian ethnicity, and systolic blood pressure ($P < 0.05$). In contrast, venular area was positively statistically significantly associated with the following variables: Arab and West Asian and Latin American ethnicities (compared to White race), overweight and obesity, former and current smoking, hs-CRP, and cholesterol ($P < 0.05$).

Using longitudinal data, arteriolar area had very few statistically significant associations (Table 3). The 3-year change in arteriolar area was negatively associated with older age and higher diastolic blood pressure ($P < 0.05$). Meanwhile, the 3-year change in venular area was positively statistically significantly associated with lower income, overweight and obesity, and former and current smoking ($P < 0.05$). For example, obesity was associated with a 3-year increase in venular area compared to people with normal BMI ($\beta = 3.52$; 95% CI, 1.51–5.51). The 3-year change in venular area was also negatively associated with older age, female sex, East Asian ethnicity (compared to White race), underweight BMI (compared to normal), diastolic blood pressure, type 1 diabetes, and hs-CRP concentration ($P < 0.05$).

In Table 4, we present associations for vascular tortuosity using both cross-sectional and longitudinal data. Arteriolar tortuosity was statistically significantly negatively associated with diastolic blood pressure, and East Asian, Southeast Asian, South Asian, Arab and West Asian, and mixed ethnicities (compared to White race), whereas systolic blood pressure, stroke, and cholesterol were positively associated ($P < 0.05$). Venular tortuosity was positively associated with older age, overweight and obesity, systolic blood pressure, current smoking status, and hs-CRP ($P < 0.05$). For example, current smokers had more venular tortuosity than never smokers ($\beta = 0.04$; 95% CI, 0.02–0.06). East Asian and Arab/West Asian ethnicities and diastolic blood pressure were negatively associated with venular tortuosity ($P < 0.05$).

Longitudinally, arteriolar tortuosity was positively associated with female sex, other ethnicity (compared to White race), and heart disease and was negatively associated with mixed ethnicity and missing income data (compared to high income) ($P < 0.05$) (Table 4). The 3-year change in venular tortuosity was positively associated with lower income and systolic blood pressure but was negatively associated with older age, East Asian ethnicity, and diastolic blood pressure ($P < 0.05$). No statistically significant interactions by age (<65 or ≥65 years) or sex were detected.

Discussion

This work is one of the few very large studies to comprehensively examine risk factors for retinal vessel traits in adults using both cross-sectional and longitudinal data. We have both identified new associations and confirmed previously reported associations. Several demographic variables were associated with the retinal vessel traits and their changes. We found that older age was associated with wider arteriolar and venular diameter and widening over the 3 years, whereas other studies have found a narrowing with age.[6] These differences may be due to the way the retinal vessels were measured. We used QUARTZ, which obtains thousands of measures of diameter from across the entire retinal image, but other studies measured only vessels near the optic disk and then used models to project the diameter of the central

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Table 3. Difference in Retinal Vessel Area (Kilopixels) by Sociodemographic Factors and Clinical Variables in Cross-Sectional and Longitudinal Analyses*

	Arteriolar Area (n = 21,754)		Venular Area (n = 21,754)		Arteriolar Area Change (n = 16,796)		Venular Area Change (n = 16,796)	
	β	95% CI	β	95% CI	β	95% CI	β	95% CI
Age, per 1 year	−1.72	−1.84, −1.61	−1.49	−1.61, −1.37	−0.66	−0.76, −0.55	−0.96	−1.07, −0.86
Female sex	−3.01	−4.86, −1.30	−10.80	−12.73, −8.87	−1.07	−2.42, 0.33	−3.31	−4.90, −1.72
Ethnicity								
White	Ref.		Ref.		Ref.		Ref.	
Black	−17.20	−28.48, −5.82	7.58	−6.72, 21.89	1.13	−7.52, 9.79	−5.73	−17.89, 6.44
East Asian	−23.43	−30.88, −15.99	3.37	−4.72, 11.47	−4.15	−11.89, 3.58	−16.99	−28.82, −5.16
Southeast Asian	−12.01	−23.40, −0.62	−32.33	−74.29, 9.62	0.85	−12.36, 14.08	−3.15	−23.31, 17.01
South Asian	−28.48	−38.82, −18.14	−17.43	−32.37, −2.48	−7.03	−16.43, 2.37	−12.53	−25.76, 0.70
Arab and West Asian	−4.97	−18.89, 8.95	17.21	4.46, 29.95	4.46	−5.23, 14.15	9.23	−4.38, 22.86
Latin American	9.37	−1.50, 20.24	11.61	0.31, 22.91	4.79	−2.80, 12.39	6.85	−5.86, 19.55
Other	−4.43	−15.65, 6.78	−2.98	−16.19, 10.23	−0.25	−11.25, 10.75	0.55	−6.87, 7.98
Mixed	−0.67	−8.46, 7.11	6.56	−0.18, 13.30	−1.07	−6.05, 3.91	−4.25	−10.70, 2.01
Income								
0, high	Ref.		Ref.		Ref.		Ref.	
1	−0.64	−2.61, 1.33	−0.57	−2.61, 1.48	−1.35	−2.92, 0.21	0.23	−1.49, 1.96
2	0.62	−1.92, 3.16	1.06	−1.82, 3.93	−0.92	−2.94, 1.09	1.50	−0.82, 3.81
3, low	−5.99	−10.58, −1.39	−2.40	−7.61, 2.82	2.07	−2.07, 6.22	4.91	1.11, 8.70
Missing	−4.04	−7.57, −0.53	0.82	−2.83, 4.47	−0.87	−3.91, 2.17	0.13	−3.01, 3.32
BMI								
Underweight	−1.66	−11.58, 8.27	−1.16	−9.83, 7.51	−2.20	−10.89, 6.48	−10.21	−18.70, −1.72
Normal	Ref.		Ref.		Ref.		Ref.	
Overweight	−0.42	−2.41, 1.57	3.16	1.11, 5.21	0.17	−1.43, 1.76	2.59	0.84, 4.34
Obese	−1.87	−4.23, 0.48	6.76	4.16, 9.35	−0.57	−2.32, 1.19	3.52	1.51, 5.51
SBP, per 1 mm Hg	−0.20	−0.28, −0.12	−0.23	−0.32, −0.15	0.05	−0.02, 0.13	0.01	−0.07, 0.09
DBP, per 1 mm Hg	−0.70	−0.83, −0.57	0.09	−0.05, 0.22	−0.30	−0.41, −0.20	−0.16	−0.28, −0.04
Smoking								
Never	Ref.		Ref.		Ref.		Ref.	
Former	1.37	−0.31, 3.05	2.21	0.46, 3.96	1.06	−0.32, 2.44	1.60	0.13, 3.07
Current	11.90	8.69, 15.11	20.03	16.60, 23.47	−0.54	−3.13, 2.06	3.48	0.28, 6.68
Alcohol								
Never	Ref.		Ref.		Ref.		Ref.	
Occasional	−1.42	−7.61, 4.76	3.58	−2.74, 9.89	−3.75	−8.79, 1.28	0.94	−5.99, 7.88
Weekly	−3.97	−10.21, 2.26	3.11	−3.22, 9.43	−4.21	−9.28, 0.86	1.96	−4.99, 8.91
Daily	−8.10	−14.64, −1.57	1.28	−5.27, 7.82	−5.20	−10.58, 0.18	1.45	−5.73, 8.64
Diabetes								
None	Ref.		Ref.		Ref.		Ref.	
Type 1	−1.54	−14.76, 11.69	−14.72	−31.67, 2.24	−2.88	−12.21, 6.45	−14.86	−24.19, −5.53
Type 2	−2.21	−5.39, 0.95	1.02	−2.24, 4.28	−2.40	−5.02, 0.22	−1.02	−4.27, 2.23
Neither	−1.68	−5.00, 1.65	0.65	−2.76, 4.06	1.61	−0.94, 4.14	1.19	−1.51, 3.90
Stroke	−7.93	−14.99, −0.87	−2.00	−11.73, 7.71	0.84	−7.48, 9.16	3.14	−4.40, 10.69
Heart disease	0.62	−2.43, 3.68	−1.37	−4.95, 2.20	−1.19	−3.63, 1.24	−1.58	−4.40, 1.23
hs-CRP	0.18	0.01, 0.36	0.30	0.13, 0.47	−0.10	−0.21, 0.02	−0.26	−0.43, −0.09
Cholesterol	1.51	0.72, 2.30	1.92	1.08, 2.75	0.14	−0.51, 0.79	−0.44	−1.14, 0.26

* Estimates were adjusted for each variable in the table and province; change models were also adjusted for baseline vessel trait.

retinal arteriolar equivalent (CRAE) or central retinal venular equivalent (CRVE). It is possible that the CRAE and CRVE do narrow with age but that there is a widening of the arterioles and venules more broadly across the retina. Our results are partially supported by findings from the UK Biobank using QUARTZ, which also showed that venular diameter widened with age.[9] We found that older age was associated with a reduction in retinal arteriolar and venular area, both cross-sectionally and over a 3-year period, which is consistent with other research.[11,14,15]

We also saw several associations with race/ethnicity and arteriolar traits such that people from almost every other racial/ethnic group had wider, less tortuous arterioles than White people. No prior study has included as many racial and ethnic groups as the CLSA, but this finding is consistent with prior research.[6,7,16] These associations persisted after adjustment for cardiovascular risk factors such as smoking, obesity, blood pressure, and diabetes. Some have proposed that racial and ethnic differences in vessel diameter could be due to measurement error due to ocular pigmentation[17]; however, differences in vessel geometry could also be due to genetic differences.[18–20] Lower incomes were also associated with wider vessels, although not in longitudinal analyses. Lower income may be a marker for a less healthy lifestyle, more medical comorbidity, or living in a less healthy environment.

Lifestyle factors were also associated with retinal vessel traits. Current smoking was strongly associated with wider

Table 4. Difference in Retinal Vessel Tortuosity by Sociodemographic Factors and Clinical Variables in Cross-Sectional and Longitudinal Analyses*

	Arteriolar Tortuosity (n = 21,698)		Venular Tortuosity (n = 21,672)		Arteriolar Tortuosity Change| (n = 16,704)		Venular Tortuosity Change (n = 16,670)	
	β	95% CI	B	95% CI	β	95% CI	B	95% CI
Age, per 10 years	−0.00	−0.01, 0.01	0.01	0.00, 0.02	−0.00	−0.00, 0.00	−0.01	−0.01, −0.01
Female sex	0.02	−0.00, 0.03	0.00	−0.01, 0.01	0.01	0.00, 0.02	−0.00	−0.01, 0.00
Ethnicity								
White	Ref.		Ref.		Ref.		Ref.	
Black	0.00	−0.09, 0.09	0.00	−0.05, 0.05	0.01	−0.03, 0.06	0.01	−0.01, 0.04
East Asian	−0.39	−0.45, −0.33	−0.05	−0.10, −0.01	−0.01	−0.05, 0.03	−0.03	−0.06, −0.01
Southeast Asian	−0.24	−0.37, −0.12	0.06	−0.15, 0.27	−0.02	−0.07, 0.03	−0.02	−0.08, 0.05
South Asian	−0.18	−0.24, −0.11	−0.01	−0.08, 0.05	−0.03	−0.06, 0.01	0.00	−0.03, 0.04
Arab and West Asian	−0.21	−0.32, −0.11	−0.06	−0.10, −0.01	0.01	−0.03, 0.05	−0.00	−0.04, 0.03
Latin American	−0.06	−0.14, 0.02	−0.01	−0.06, 0.04	0.01	−0.02, 0.04	−0.04	−0.08, −0.01
Other	−0.10	−0.20, 0.00	−0.04	−0.08, −0.00	0.05	0.01, 0.09	0.01	−0.02, 0.04
Mixed	−0.06	−0.13, −0.00	0.02	−0.03, 0.07	−0.02	−0.04, −0.00	0.01	−0.01, 0.03
Income								
0, high	Ref.		Ref.		Ref.		Ref.	
1	−0.00	−0.02, 0.01	−0.00	−0.01, 0.01	−0.00	−0.01. 0.00	−0.00	−0.01, 0.00
2	−0.01	−0.03, 0.01	0.00	−0.01, 0.02	−0.00	−0.01, 0.01	0.01	−0.00, 0.02
3, low	0.01	−0.03, 0.05	0.02	−0.01, 0.05	−0.01	−0.04, 0.01	0.02	0.00, 0.04
Missing	0.01	−0.02, 0.04	0.02	−0.01, 0.04	−0.02	−0.04, −0.01	−0.00	−0.02, 0.01
BMI								
Underweight	0.00	−0.07, 0.07	0.04	−0.02, 0.11	0.00	−0.05, 0.05	0.00	−0.03, 0.04
Normal	Ref.		Ref.		Ref.		Ref.	
Overweight	−0.02	−0.03, 0.00	0.02	0.01, 0.03	0.00	−0.00, 0.01	0.00	−0.00, 0.01
Obese	−0.02	−0.04, 0.00	0.04	0.03, 0.05	−0.00	−0.01, 0.01	−0.00	−0.01, 0.01
SBP, per 10 mm Hg	0.01	0.01, 0.02	0.01	0.01, 0.02	0.00	−0.00, 0.00	0.01	0.00, 0.01
DBP, per 10 mm Hg	−0.02	−0.04, −0.01	−0.03	−0.03, −0.02	−0.00	−0.01, 0.00	−0.01	−0.01, −0.00
Smoking								
Never	Ref.		Ref.		Ref.		Ref.	
Former	−0.00	−0.02, 0.01	0.00	−0.01, 0.01	−0.00	−0.01, 0.01	0.00	−0.00, 0.01
Current	0.01	−0.01, 0.04	0.04	0.02, 0.06	0.01	−0.01, 0.02	0.00	−0.01, 0.02
Alcohol								
Never	Ref.		Ref.		Ref.		Ref.	
Occasional	0.00	−0.05, 0.05	0.00	−0.03, 0.04	0.00	−0.02, 0.02	−0.01	−0.03, 0.01
Weekly	0.01	−0.04, 0.06	0.00	−0.03, 0.04	0.01	−0.02, 0.03	−0.00	−0.02, 0.02
Daily	−0.01	−0.07, 0.04	0.00	−0.04, 0.04	0.02	−0.01, 0.04	−0.00	−0.02, 0.02
Diabetes								
None	Ref.		Ref.		Ref.		Ref.	
Type 1	0.07	−0.04, 0.17	0.03	−0.03, 0.08	0.04	−0.01, 0.09	0.01	−0.03, 0.05
Type 2	−0.02	−0.05, 0.01	0.00	−0.01, 0.02	0.01	−0.00, 0.02	0.01	−0.01, 0.02
Neither	−0.01	−0.03, 0.02	−0.00	−0.02, 0.01	0.01	−0.00, 0.02	−0.00	−0.01, 0.01
Stroke	0.07	0.00, 0.14	0.01	−0.04, 0.06	−0.00	−0.05, 0.04	−0.01	−0.03, 0.02
Heart disease	−0.01	−0.03, 0.02	−0.00	−0.02, 0.02	0.01	0.00, 0.03	−0.00	−0.01, 0.01
hs-CRP, per 10 units	0.01	−0.00, 0.03	0.02	0.01, 0.03	−0.00	−0.01, 0.00	−0.00	−0.01, 0.01
Cholesterol	0.01	0.00, 0.01	−0.00	−0.01, 0.00	0.00	−0.00, 0.01	−0.00	−0.00, 0.00

* Estimates were adjusted for each variable in the table and province; change models were also adjusted for baseline vessel trait.

arteriolar and venular diameters and their widening over 3 years. Current smoking was also associated with a larger arteriolar and venular area and a 3-year widening of venular area. This is consistent with prior research.[6,21–23] Proposed biological mechanisms include impaired autoregulation of retinal vessel diameter,[24] response to nicotine-induced tissue hypoxia,[25] and inflammation.[26,27] For example, smoking is thought to cause vascular injury that elevates inflammatory markers.[28] A systematic review found that inflammatory markers such as CRP are associated with wider retinal vessels.[29] By contrast, weekly and daily alcohol use were associated with narrower arteriolar diameters cross-sectionally but not longitudinally. The Multi-Ethnic Study of Atherosclerosis (MESA) also showed a negative association between alcohol and arteriolar diameter.[7] Excessive alcohol consumption has been shown to constrict retinal vessels in healthy volunteers.[30] The mechanism of this constriction may be through activation of the sympathetic nervous system and its effect on vascular smooth muscle cells.[31] Obesity was positively associated with venular diameter, total venular area, 3-year change in total venular area, and venular tortuosity. Tapp et al.[10] also found a positive association between BMI and venular diameter in the UK Biobank. Several studies have found a positive association between obesity and CRVE in children, adolescents, and adults.[6,32] The

effect of obesity on the eye has been described in a review.[33]

Medical factors were also associated with retinal vessel traits. Diastolic blood pressure was fairly consistently negatively associated with diameter, area, and tortuosity, both cross-sectionally and longitudinally. These results are consistent with prior literature.[6] Systolic blood pressure was associated with area and tortuosity but only cross-sectionally. The effect of hypertension on the eye has been described.[34,35] Diabetes was associated with wider arteriolar diameters cross-sectionally, and type 1 diabetes was specifically associated with 3-year widening of arteriolar diameters. This dilatation of retinal arterioles has been observed in previous studies[6] and in people with early-stage diabetic retinopathy.[36] The widening is thought to be due to changes in retinal metabolism and can lead to hyperperfusion and tissue damage.[36] The concentration of CRP was consistently positively associated with retinal venular traits in our cross-sectional analyses but was negatively associated with venular area in longitudinal analyses. Previous studies have also found stronger associations between inflammatory biomarkers and venular traits compared to arterial traits.[29] Widening of venules is thought to be caused by endothelial dysfunction leading to vessel remodeling; increased nitric oxide production may also be involved.[29,37]

Strengths of this research include the use of a large, national, longitudinal dataset with extensive questionnaire, physical exam, and blood data. We used a deep-learning approach known as QUARTZ to provide retinal vessel data on the entire retina rather than only the area around the optic disk. We had data on nine different racial and ethnic groups, more than any other study has presented, to the best of our knowledge. A limitation of this work is that some people did not have an image that could be evaluated by QUARTZ. They tended to be older and more likely to have diabetes than those who did have a gradable image. Some people did not return for the follow-up or did not have a retinal image taken at the follow-up, so our sample size was reduced for the longitudinal analyses. The majority of the sample was White so our sample sizes for the other racial/ethnic groups were small. Some exposure or confounder data were collected by self-report (smoking, alcohol, stroke, diabetes), which could lead to misclassification. However, any misclassification would be unlikely to differ by the value of the retinal vessel trait. This would lead to bias toward the null, meaning our measures of association are conservative. Finally, without data on refractive error or axial length, we were unable to convert from pixels to micrometers.

In conclusion, this work provides comprehensive information on the factors associated with retinal vessel traits. Factors such as smoking, alcohol, blood pressure, obesity, and diabetes were found to be related to retinal vessel traits, which may increase the risk of subsequent eye disease.[4]

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