

Sex differences in quantitative fundus parameters measured by artificial intelligence: a cross-sectional community study

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Abstract

Background

Automated analysis of fundus photographs yields numerous quantitative measures, but sex differences in these measures and their modification by systemic conditions are not well characterized. We quantified these differences in a large community screening cohort.

Methods

This cross-sectional study included 21,844 participants contributing 32,576 eye-level records to a community health-screening program in Ganzhou, China. EVisionAI was used to quantify 49 vascular, optic disc and cup, peripapillary atrophy, and fundus tessellation density parameters from color fundus photographs. Generalized estimating equations clustered by participant estimated male-female differences in standardized parameters. Models were unadjusted, adjusted for age and age squared, and further adjusted for 20 binary systemic conditions. Sex-by-condition interactions were examined for 19 conditions; prostatic hyperplasia was assessed separately using a three-level variable. Benjamini–Hochberg correction was applied across all fundus parameters within each model for the primary comparisons and within each condition for the interaction analyses.

Results

Mean age was 63.6 ± 9.8 years in women and 63.9 ± 10.1 years in men. After full adjustment and FDR correction, sex differences were found in 41 of 49 parameters: 19 of 22 optic disc and cup, 8 of 11 vascular, 7 of 7 peripapillary atrophy, and 7 of 9 fundus tessellation density measures. The largest standardized differences in men were a lower disc vertical-to-horizontal ratio ($\beta = -0.170$; 95% confidence interval, -0.196 to -0.144) and a higher atrophy arc height-to-disc vertical diameter ratio ($\beta = 0.166$; 95% confidence interval, 0.141 to 0.192). The arteriole-to-venule ratio was also lower in men ($\beta = -0.113$; 95% confidence interval, -0.137 to -0.089). Estimates were generally stable across models. Twenty-three effect-modification findings remained significant after false discovery rate correction, predominantly involving prostatic hyperplasia.

Conclusions

Sex differences were present across most quantitative fundus parameters and changed little after adjustment for measured systemic conditions. Their relevance to screening requires validation in datasets with ocular biometry and clinical outcomes.

1 Background

Artificial intelligence systems applied to fundus photography can quantify numerous retinal features from a single image, including vascular caliber and complexity, optic disc and cup geometry, peripapillary atrophy (PPA) and fundus tessellation density.^{1–5} Many of these features are associated with cardiovascular risk, neurodegenerative disease and retinal age, supporting fundus imaging as a noninvasive window into systemic health.^{6–10} In line with this, population-scale oculomic studies have used retinal images to predict cardiovascular events and other systemic characteristics, while deep-learning models can classify sex, indicating that routine fundus photographs contain detectable sex-related information.^{11–15}

These signals may reflect established sex differences in ocular anatomy, driven by hormones that regulate ocular blood flow, intraocular pressure, and choroidal thickness.^{16–19} Ocular biometry, including axial length, shapes optic-disc and cup measurements, and men tend to have longer axial length in population samples.^{20–23} Accordingly, men have been reported to have larger optic discs, higher cup-to-disc ratios, lower arteriole-to-venule ratios, and a higher prevalence of beta-zone PPA.^{24,25} However, these observations come largely from manual measurements or focused on a limited set of ocular features.

Three key limitations recur in existing literature. Previous studies were often modest in size, adjusted incompletely for systemic conditions, or treated both eyes from the same participant as independent observations. Ignoring inter-eye correlation can underestimate standard errors and overstate statistical significance and precision.^{26,27} Systemic conditions also require consideration because hypertension, dyslipidemia, and metabolic abnormalities affect retinal structure, differ in prevalence by sex, and may confound or modify observed associations. Whether these conditions alter the magnitude or direction of sex-related differences remains uncertain.

To address these gaps, specifically the lack of adequately adjusted, clustering-aware estimates and the unknown role of systemic modification, a large community-based screening dataset from Ganzhou, China, was analyzed. Using generalized estimating equations (GEE) to account for the non-independence of bilateral eyes, the association between sex and AI-derived fundus parameters was estimated across three adjustment levels. The study aimed to characterize the pattern and magnitude of sex differences in these parameters and to determine the extent to which they are altered by systemic health.

2 Methods

2.1 Study design and participants

This cross-sectional study used data from 10 branches of the Ganzhou Municipal Hospital Medical Group participating in a community health-screening program in Ganzhou, China: Dongwai, GanJiang, Liberation, Nanwai, Shahe, Shashi, Shuidong, Shuinan, Shuixi, and Zhangjiang. Participants underwent color fundus photography and systemic examination during the same screening visit between January 1 and December 31, 2023. A group-wide unique participant identifier allowed records from the same

participant to be linked across branches. Repeated records did not arise from attendance at different branches.

Among 37,007 participants with 72,775 eye-level records, exclusions were applied sequentially for image quality, positioning, and fundus pathology. The study aimed to characterize sex differences in fundus features among eyes without documented fundus pathology. Therefore, exclusions were applied at the eye level, and the unaffected fellow eye remained eligible when only one eye met an exclusion criterion. Three trained retina specialists, masked to participant sex and systemic-condition status, assessed image quality, eye positioning, and fundus pathology using predefined criteria. Disagreements were resolved by consensus.

First, 14,992 eyes with blur or exposure artifacts were excluded, leaving 30,983 participants with 57,783 eye-level records. Second, 846 eyes with incorrect positioning were excluded, leaving 30,737 participants with 56,937 eye-level records. Third, 24,361 eyes with fundus lesions were excluded. These lesions included myelinated nerve fibers, epiretinal membrane, diabetic or hypertensive retinopathy, retinal detachment, macular hole, retinal arterial or venous occlusion, optic disc edema or atrophy, age-related macular degeneration, and other retinal pathology.

The final dataset included 21,844 participants and 32,576 eye-level records. Of these participants, 12,066 contributed one record and 9,778 contributed two or more because of bilateral imaging, same-day repeat imaging, or both (Fig. 1). Repeated records from the same eye were acquired on the same day at the same branch. The Institutional Review Board of Ganzhou Municipal Hospital approved the study protocol (LW2024016H). All participants provided written informed consent, and the study was conducted in accordance with the Declaration of Helsinki.

2.2 Fundus imaging and parameters derived by AI

Fundus photography used an SW-8800 non-mydratic camera (45° field of view; SUOER Medical Equipment Co., Ltd.). Images were analyzed using EVisionAI (EVision Technology Co., Ltd., Beijing, China), an artificial intelligence platform for quantitative color fundus photograph analysis. Parameters were grouped into three domains. Vascular morphology domain comprised 11 parameters: vascular fractal dimension (VFD), vessel length (VL), average vessel diameter (AVD), average vascular curvature (AVC), vessel density (VD), average arterial diameter (AAD), average venous diameter (AVeD), arteriole-to-venule ratio (AVR), and the arcade-macula (VAM_Distance), arcade-1PD (VAPD1_Distance) and arcade-2PD (VAPD2_Distance) distances. Optic disc and cup geometry comprised 22 parameters: disc area (DA), disc horizontal and vertical diameters (HDD, VDD), disc roundness (DR), disc center-boundary distance (DCB), disc-macula distance (DDM), disc long-to-short axis ratio (LSR), macula center-boundary distance (MCB), cup area (CA), cup horizontal and vertical diameters (HCD, VCD), area cup-to-disc ratio (CDR), horizontal and vertical CDR (CDR_H, CDR_V), disc vertical-to-horizontal ratio (VHR_OD_VA), disc short-to-long axis ratio (SLR_OD), and maximum and minimum rim distances (MaxRD_OC, MinRD_OC) and the inferior, nasal, superior and temporal rim distances (RID, RND, RSD, RTD). The third domain

comprised 7 PPA parameters (atrophy arc area, height and width [AAA, AAH, AAW], atrophy arc-macula distance [AADM], atrophy arc-to-disc area ratio [AAR], arc width-to-disc-horizontal and arc height-to-disc-vertical ratios [AAW_DDH, AAH_DDV]) and 9 FTD parameters (global fundus [Fundus_FTD], the 4.5 mm optic disc-centered zone and its superior, inferior, nasal and temporal sectors [OD_4.5mm_FTD, OD_4.5mm_S_FTD, OD_4.5mm_I_FTD, OD_4.5mm_N_FTD, OD_4.5mm_T_FTD], and the 1, 3 and 6 mm macula-centered zones [M_1mm_FTD, M_3mm_FTD, M_6mm_FTD]). PPA and the retinal pigment epithelium were treated as distinct structures. Each parameter was standardized to zero mean and unit variance before modeling.

2.3 Systemic covariates

Twenty systemic conditions were extracted from each participant's medical record from the same visit and coded as binary (present or absent), spanning cardiovascular, metabolic and lipid, hepatobiliary and genitourinary domains. Cardiovascular conditions were elevated blood pressure (BP; systolic BP ≥ 140 or diastolic BP ≥ 90 mmHg), cardiac conduction block (CCB; bundle branch, atrioventricular, intra-atrial or sinoatrial block), premature contraction (atrial, ventricular, junctional or ectopic beats) and reduced hemoglobin (< 120 g/L in men, < 110 g/L in women). Metabolic and lipid conditions were elevated fasting glucose (≥ 7.0 mmol/L), elevated low-density lipoprotein (LDL-C; ≥ 3.4 mmol/L), reduced high-density lipoprotein (HDL-C; < 1.0 mmol/L in men, < 1.3 mmol/L in women), elevated triglycerides (TG; ≥ 1.7 mmol/L) and elevated total cholesterol (TC; ≥ 5.2 mmol/L). Hepatobiliary conditions were fatty liver, gallstone and hepatic cyst (all diagnosed on B-mode ultrasound), elevated total bilirubin (≥ 21 $\mu\text{mol/L}$) and abnormal liver function (aspartate aminotransferase [AST] > 40 U/L, alanine aminotransferase [ALT] > 40 U/L, or AST/ALT > 2). Genitourinary conditions were elevated creatinine (SCr; > 133 $\mu\text{mol/L}$ in men, > 106 $\mu\text{mol/L}$ in women), elevated blood urea nitrogen (BUN; > 8.2 mmol/L), hyperuricemia (UA; > 420 $\mu\text{mol/L}$ in men, > 360 $\mu\text{mol/L}$ in women), renal cyst, prostatic hyperplasia (PH) and urinary calculi; structural diagnoses (cysts, calculi, PH) relied on B-mode ultrasound. Although some systemic variables were originally available as ordered grades or continuous measurements, they were dichotomized according to predefined clinical or screening thresholds for the primary analysis. This strategy improved model parsimony, interpretability, and statistical stability across a large number of covariates and interaction tests, but may have reduced information on disease severity and dose–response patterns.

2.4 Statistical analysis

Generalized estimating equations (GEE) with an exchangeable working correlation matrix and robust sandwich standard errors were used, with participant-level clustering to account for bilateral eyes and repeated eye-level records. Repeated records from the same eye were retained within the participant-level cluster. A total of 1,254 participant-eye units had repeated records, all acquired on the same day; image acquisition order and the within-day interval were not included as covariates. Each fundus parameter was standardized to a mean of zero and a standard deviation of one.

For each parameter, three models estimated the association with male sex, with female sex as the reference. Model 1 was unadjusted, Model 2 included age and age², and Model 3 additionally included 20

binary systemic factors. For the primary sex comparisons, P values were adjusted using the Benjamini-Hochberg procedure across all 49 fundus parameters within each model. Complete-case analysis was performed separately for each model, with records excluded only when the outcome or required covariates were missing. Missingness was assessed at the eye-record level, with each row representing one eye at one visit. Among 32,576 eye-level records, 32,574 had complete covariate data for Model 3. Depending on outcome availability and adjustment set, individual models retained 21,305 to 32,574 records, resulting in the exclusion of 2 to 11,271 records. Participants and visits were not excluded as complete units, and no imputation was performed.

Prostatic hyperplasia (PH) is male-specific; therefore, a conventional sex-by-PH interaction was not estimable because the female-with-PH stratum was absent and the design matrix was rank-deficient. PH was represented as a three-level factor comprising female participants, men without PH, and men with PH, with female participants as the reference. Modification by PH was estimated as the contrast between the two male strata relative to the female reference, using a linear combination of the corresponding coefficients.

Effect modification was assessed separately for each systemic factor. For the 19 standard binary factors, a sex-by-factor interaction term was added to the fully adjusted model containing age, age², and all 20 systemic factors. PH modification was assessed using the three-level factor described above. Benjamini-Hochberg false discovery rate correction was applied across fundus parameters within each systemic-factor family. A sensitivity analysis treated all interaction tests as a single FDR family (Supplemental Table 5).

Estimated marginal means by sex were calculated for each model in standardized and original measurement units (Supplemental Tables 1 and 2). Variance inflation factors were used to assess collinearity in the fully adjusted model (Supplemental Table 3). Analyses were conducted in R version 4.5.0 using the geepack package, with a two-sided significance threshold of $\alpha = 0.05$.

3 Results

3.1 Participants

The cohort comprised 32,576 eye-level fundus records from 21,844 participants (12,464 women, 9,380 men; 57.1% women at the person level). Women contributed 18,693 eye-level records and men contributed 13,883 records; 16,093 records were from right eyes and 16,483 from left eyes. Mean age was 63.6 ± 9.8 years in women and 63.9 ± 10.1 years in men ($P = 0.032$). Systemic-condition prevalence differed between the sexes for most conditions (Table 1): women had higher rates of elevated total cholesterol (35.4% versus 22.3%), elevated LDL-C and reduced HDL-C, while men had higher rates of hyperuricemia (33.9% versus 25.4%), renal cyst, hepatic cyst, elevated bilirubin and the cardiac-conduction variables. PH was present in 14.6% of men.

Table 1
Comparison of age and systemic conditions between men and women

Characteristic	Female (n = 12,464)	Male (n = 9,380)	P value
Age, years (mean $\pm$ SD)	63.6 $\pm$ 9.8	63.9 $\pm$ 10.1	0.032
Elevated blood pressure, n (%)	5039 (40.4)	3987 (42.5)	0.002
Elevated glucose, n (%)	3856 (30.9)	3228 (34.4)	< 0.001
Elevated LDL-C, n (%)	2184 (17.5)	1183 (12.6)	< 0.001
Reduced HDL-C, n (%)	1864 (15.0)	957 (10.2)	< 0.001
Elevated triglycerides, n (%)	3609 (29.0)	2528 (27.0)	0.001
Elevated total cholesterol, n (%)	4408 (35.4)	2095 (22.3)	< 0.001
Reduced hemoglobin, n (%)	844 (6.8)	547 (5.8)	0.005
Hyperuricemia, n (%)	3169 (25.4)	3177 (33.9)	< 0.001
Elevated creatinine, n (%)	1006 (8.1)	880 (9.4)	< 0.001
Elevated urea, n (%)	558 (4.5)	595 (6.3)	< 0.001
Fatty liver, n (%)	1778 (14.3)	1221 (13.0)	0.008
Abnormal liver function, n (%)	582 (4.7)	401 (4.3)	0.174
Elevated bilirubin, n (%)	351 (2.8)	604 (6.4)	< 0.001
Hepatic cyst, n (%)	964 (7.7)	1075 (11.5)	< 0.001
Gallstone, n (%)	1096 (8.8)	886 (9.4)	0.101
Renal cyst, n (%)	1083 (8.7)	1458 (15.5)	< 0.001
Urinary calculi, n (%)	1083 (8.7)	1221 (13.0)	< 0.001
Prostatic hyperplasia, n (%)	0 (0.0)	1366 (14.6)	< 0.001
Conduction block, n (%)	606 (4.9)	869 (9.3)	< 0.001
Premature contraction, n (%)	716 (5.7)	655 (7.0)	< 0.001

P values from independent-samples t test (age) and chi-squared test (binary conditions). P values are two-sided; P < 0.05 was considered statistically significant. Prostatic hyperplasia was assessed only in male participants; female values were set to 0 by definition, and the P value should be interpreted descriptively. Abbreviation: LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

3.2 Retinal vascular morphology

Eight of the 11 vascular parameters differed by sex after full adjustment (Fig. 2; Model 3). Relative to women, men had a higher vascular fractal dimension ($\beta = 0.084$, 95% CI 0.059 to 0.109), higher vessel density ($\beta = 0.110$, 95% CI 0.085 to 0.135), longer vessels ($\beta = 0.104$, 95% CI 0.079 to 0.129) and a lower AVR ($\beta = -0.113$, 95% CI - 0.137 to - 0.089). The arcade-macula distance was greater in men ($\beta = 0.095$, 95% CI 0.070 to 0.120). Average arterial diameter was lower in men ($\beta = -0.057$, 95% CI - 0.081 to - 0.033). The remaining significant vascular differences were observed for VAPD1_Distance and VAPD2_Distance, whereas average vessel diameter, average vascular curvature and average venous diameter did not differ after full adjustment ($P = 0.861$, 0.538 and 0.634, respectively). Estimates for most parameters were similar across the three models, although average vessel diameter and average venous diameter attenuated to the null only after full adjustment.

3.3 Optic disc and cup geometry

Nineteen of the 22 optic disc and cup parameters differed by sex after full adjustment (Fig. 3). Most of these parameters also differed in the unadjusted and basic-adjusted models. Men had a lower disc vertical-to-horizontal ratio ($\beta = -0.170$, 95% CI - 0.196 to - 0.144) and a higher disc short-to-long axis ratio ($\beta = 0.161$, 95% CI 0.136 to 0.187), the two largest differences in this family, together with a lower disc long-to-short axis ratio ($\beta = -0.149$, 95% CI - 0.174 to - 0.124). Men also had higher disc roundness ($\beta = 0.142$, 95% CI 0.116 to 0.167), larger cup area ($\beta = 0.081$, 95% CI 0.055 to 0.106) and higher area, horizontal and vertical CDRs ($\beta = 0.077$, 0.043 and 0.088). Regarding the peripapillary rim, men had a greater RND ($\beta = 0.073$, 95% CI 0.049 to 0.097), whereas their RID and RSD were lower (RID, $\beta = -0.062$, 95% CI - 0.086 to - 0.037; RSD, $\beta = -0.064$, 95% CI - 0.089 to - 0.038). Disc vertical diameter and disc-macula distance and RTD did not differ after full adjustment ($P = 0.644$, 0.178, and 0.157, respectively). Estimates changed little between the unadjusted and fully adjusted models for most parameters.

3.4 Peripapillary atrophy and fundus tessellation density

All 7 PPA parameters and 7 of 9 FTD parameters differed by sex (Fig. 4; Model 3). Men had a higher atrophy arc height relative to disc vertical diameter ($\beta = 0.166$, 95% CI 0.141 to 0.192), greater atrophy arc height ($\beta = 0.150$, 95% CI 0.124 to 0.176) and greater atrophy arc width ($\beta = 0.106$, 95% CI 0.080 to 0.132). FTD was reported for the disc-centered 4.5 mm zone (OD_4.5mm_FTD and its sectors) and the macula-centered zones (M_1mm_FTD, M_3mm_FTD, M_6mm_FTD). FTD was higher in men in the disc-centered zone, including its inferior sector (OD_4.5mm_I_FTD, $\beta = 0.124$, 95% CI 0.097 to 0.151), whereas it was lower in men in the macula-centered zones (M_3mm_FTD $\beta = -0.107$, 95% CI - 0.132 to - 0.081; M_6mm_FTD $\beta = -0.096$, 95% CI - 0.122 to - 0.071; M_1mm_FTD $\beta = -0.084$, 95% CI - 0.110 to - 0.058). Fundus_FTD and the temporal sector of the disc-centered zone (OD_4.5mm_T_FTD) did not differ after full adjustment ($P = 0.543$ and 0.670, respectively).

3.5 Modification of sex differences by systemic factors

Twenty-three sex-by-systemic-factor interactions were significant after FDR correction within each systemic factor (Fig. 5; Supplemental Table 4). Seventeen significant PH-related differences were observed; because PH occurred only in men, these estimates reflect differences between men with and without PH. Compared with men without PH, men with PH had a smaller disc center-boundary distance ($\beta = -0.247$, 95% CI -0.290 to -0.204), lower FTD in the inferior and nasal sectors of the disc-centered zone (OD_4.5mm_I_FTD and OD_4.5mm_N_FTD; $\beta = -0.214$ and -0.182), higher average vessel and venous diameters ($\beta = 0.190$ and 0.148), and lower vessel density and vessel length ($\beta = -0.141$ and -0.104). Hyperuricemia modified the sex difference in disc center-boundary distance ($\beta = 0.104$, FDR = 0.002). Hepatic cyst modified four vascular parameters, including average vessel diameter ($\beta = -0.152$, FDR = 0.005) and vessel density ($\beta = 0.126$, FDR = 0.019). Elevated glucose also modified the sex difference in average vascular curvature ($\beta = -0.084$, FDR = 0.0497). In the sensitivity analysis using FDR correction across the full interaction family, 15 interactions remained significant, mainly involving PH, hyperuricemia-related DCB, and hepatic cyst-related vessel diameter measures.

4 Discussion

In this large community-based screening study of 32,576 fundus observations, sex-associated differences were identified across most quantitative fundus parameters. Effect sizes were small to moderate and changed little after adjustment for age and systemic conditions. Differences were most consistent in the optic disc and cup, where 19 of 22 parameters differed between men and women, while fundus tessellation showed region-specific patterns.

Among the vascular parameters, men had a lower AVR, primarily reflecting a lower average arterial diameter because average venous diameter did not differ after adjustment. This vascular pattern is consistent with previous population studies reporting lower arteriole-to-venule ratios in men and sex differences in hypertensive retinopathy risk.^{25,28} Such sex differences in vascular caliber are clinically relevant because AI-quantified retinal-vessel caliber has itself been shown to stratify cardiovascular disease risk, so a model that does not account for sex may misattribute caliber-based risk.² One proposed mechanism is the vasodilatory effect of estrogen through endothelial nitric oxide synthase, which may preserve arterial tone in women;²⁹ although this mechanism could not be evaluated in the present cross-sectional study.

Men had larger optic discs and cups, higher CDRs, and a rounder, more horizontally elongated optic disc, consistent with findings from Asian population cohorts.²¹ Ocular biometry may partly explain these differences because men tend to have longer axial length.^{22,23,30} The fully adjusted difference in cup-to-disc ratio was 0.077 standard deviations, corresponding to approximately 0.005 in the original measurement scale (Supplemental Table 2). Although small at the individual level, such a difference may affect referral performance when a single glaucoma-screening threshold is applied across a population. Evaluation of sex-specific thresholds requires datasets containing axial length and clinical outcomes.

PPA showed consistent sex differences, with greater atrophy arc height, width and area in men. PPA is associated with axial elongation and has been linked to glaucoma progression.^{31,32} FTD showed opposite regional patterns, with higher density in men in the peripapillary zone but lower density in the macula-centered zones with no difference in the global measure. Previous population studies have reported higher overall tessellation in men and an inverse association with choroidal thickness.^{1,33} The absence of a global sex difference here is consistent with the opposing regional effects offsetting one another, so a single global index may not capture regional sex differences. A longitudinal population study similarly found that macular and peripapillary tessellation reflected choroidal thickness within their respective regions.³⁴ Regional variation in choroidal thickness may therefore contribute to the observed pattern, but confirmation requires region-resolved choroidal imaging.

Systemic conditions modified the sex differences in 23 instances after correction, but these effects were concentrated rather than diffuse. Most involved PH, which was associated with lower VD and FTD and a smaller disc center-boundary distance in men. Because PH occurs only in men, these interactions compare men with and without PH rather than men with women. PH may mark vascular, metabolic or inflammatory heterogeneity within men, but the present cross-sectional data cannot separate these pathways.^{35,36} The remaining significant interactions involved hyperuricemia, hepatic cyst, and elevated glucose, primarily in vascular and optic disc parameters. Although hyperuricemia is associated with hypertension, renal disease, and cardiovascular disease, its independent causal role remains uncertain.³⁷ The absence of significant modification for most systemic conditions suggests that differences in systemic-condition prevalence were not the main explanation for the observed sex-associated patterns.

These findings suggest that sex should be considered when reference ranges or AI-based screening models are built on fundus parameters. A model that ignores sex could misestimate structure-based risk where the sexes differ, particularly for the disc, the region most relevant to glaucoma screening.

Several limitations should be considered. Axial length, refraction, and intraocular pressure were unavailable. Axial length is an established determinant of optic disc size and shape and of fundus tessellation, and men have, on average, longer eyes than women in population samples. In the EPIC-Norfolk Eye Study, mean axial length was 23.80 ± 1.16 mm in men and 23.29 ± 1.15 mm in women; therefore, an unknown fraction of the disc-shape and tessellation differences reported here may be mediated by sex differences in axial length rather than by sex itself.^{22,23,30} Our disc and tessellation findings should therefore be read as the observed sex difference in this cohort rather than as a sex effect independent of ocular biometry. The cross-sectional design precludes causal inference. Systemic conditions were represented as binary screening indicators, limiting assessment of severity and dose-response relationships. Reduced hemoglobin was also defined by a screening threshold without information on cause, despite the heterogeneous causes of anemia in older adults.^{38,39} The cohort came from a single regional screening setting and was ethnically homogeneous, which limits generalizability. All photographs were acquired with a single non-mydratic fundus camera and analyzed using a single AI

platform. Previous studies evaluated related methods for FTD segmentation and severe-tessellation screening and for automated pixel-pitch calibration of 45° fundus photographs.^{40–42} However, these studies did not externally validate all 49 vascular, optic disc and cup, PPA, and FTD outputs generated from SW-8800 images in an older community population. The reproducibility and transportability of these measurements across camera models, analytical platforms, and populations therefore remain uncertain.

5 Conclusion

This study provides a large-scale descriptive atlas of sex differences across AI-derived fundus parameters and demonstrates a reusable analytical framework, combining generalized estimating equations with clustering-aware inference and a three-level reparameterization for the male-specific factor. Male sex was associated with most parameters, with small-to-moderate effect sizes, most consistently for the optic disc. Because ocular biometry was not available, these estimates describe the observed sex differences in this cohort rather than sex effects independent of axial length, and should be interpreted as a reference map rather than as evidence for any specific screening threshold. Whether sex-specific reference values improve AI-based fundus screening will require confirmation in studies that incorporate axial length and longitudinal outcomes.

Abbreviations

6.1 General and statistical terms

AI: artificial intelligence; AMD: age-related macular degeneration; CI: confidence interval; FDR: false discovery rate; FTD: fundus tessellation density; GEE: generalized estimating equations; PPA: peripapillary atrophy; SD: standard deviation.

6.2 Systemic variables

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BP: blood pressure; BUN: blood urea nitrogen; CCB: cardiac conduction block; HDL-C: high-density lipoprotein cholesterol; HGB: hemoglobin; LDL-C: low-density lipoprotein cholesterol; PH: prostatic hyperplasia; SCr: serum creatinine; TC: total cholesterol; TG: triglycerides; UA: uric acid.

6.3 Retinal vascular parameters

AAD: average arterial diameter; AVC: average vascular curvature; AVD: average vessel diameter; AVeD: average venous diameter; AVR: arteriole-to-venule ratio; VD: vessel density; VFD: vascular fractal dimension; VL: vessel length; VAM_Distance: arcade-macula distance; VAPD1_Distance: arcade-to-1-disc-diameter intersection distance; VAPD2_Distance: arcade-to-2-disc-diameter intersection distance.

6.4 Optic disc and cup parameters

CA: optic cup area; CDR: area cup-to-disc ratio; CDR_H: horizontal cup-to-disc ratio; CDR_V: vertical cup-to-disc ratio; DA: optic disc area; DCB: optic disc center-boundary distance; DDM: optic disc-macula distance; DR: optic disc roundness; HCD: horizontal cup diameter; HDD: horizontal disc diameter; LSR: disc long-to-short axis ratio; MaxRD_OC: maximum optic cup rim distance; MCB: macula center-boundary distance; MinRD_OC: minimum optic cup rim distance; OD: optic disc; RID: inferior rim distance; RND: nasal rim distance; RSD: superior rim distance; RTD: temporal rim distance; SLR_OD: disc short-to-long axis ratio; VCD: vertical cup diameter; VDD: vertical disc diameter; VHR_OD_VA: disc vertical-to-horizontal ratio.

6.5 Peripapillary atrophy parameters

AAA: atrophy arc area; AADM: atrophy arc-macula distance; AAH: atrophy arc height; AAH_DDV: atrophy arc height-to-disc vertical diameter ratio; AAR: atrophy arc-to-disc area ratio; AAW: atrophy arc width; AAW_DDH: atrophy arc width-to-disc horizontal diameter ratio.

6.6 Fundus tessellation density parameters

Fundus_FTD: global fundus tessellation density; M_1mm_FTD: macula-centered 1-mm zone FTD; M_3mm_FTD: macula-centered 3-mm zone FTD; M_6mm_FTD: macula-centered 6-mm zone FTD; OD_4.5mm_FTD: optic disc-centered 4.5-mm zone FTD; OD_4.5mm_I_FTD: inferior sector of the optic disc-centered 4.5-mm zone FTD; OD_4.5mm_N_FTD: nasal sector of the optic disc-centered 4.5-mm zone FTD; OD_4.5mm_S_FTD: superior sector of the optic disc-centered 4.5-mm zone FTD; OD_4.5mm_T_FTD: temporal sector of the optic disc-centered 4.5-mm zone FTD.

Declarations

7.1 Ethics approval and consent to participate

The study protocol was approved by the Institutional Review Board of Ganzhou Municipal Hospital (approval number LW2024016H). All participants provided written informed consent. The study adhered to the tenets of the Declaration of Helsinki.

7.2 Consent for publication

Not applicable. The manuscript contains no identifiable individual participant data.

7.3 Availability of data and materials

The de-identified participant-level data are not publicly available because their release is restricted by the Ganzhou Municipal Health Commission. Access for research purposes may be considered upon reasonable request and is subject to approval by the Ganzhou Municipal Health Commission and applicable data-protection requirements.

7.4 Competing interests

The authors declare that they have no competing interests.

7.5 Funding

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7.6 Authors' Contribution

JH and XnZ contributed equally to the study design, data analysis, interpretation of the results, and drafting of the manuscript, and share first authorship. LZ and DC were the principal investigators, responsible for the overall study conception, design, supervision, funding acquisition, and critical revision of the manuscript. WQ, HH, FX, HL, TZ and XaZ were responsible for the acquisition and curation of clinical and imaging data. IMH, AL, JH, MG, and WZ contributed to the data interpretation and provided critical revisions to the manuscript. All authors have read and approved the final manuscript.

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Figures

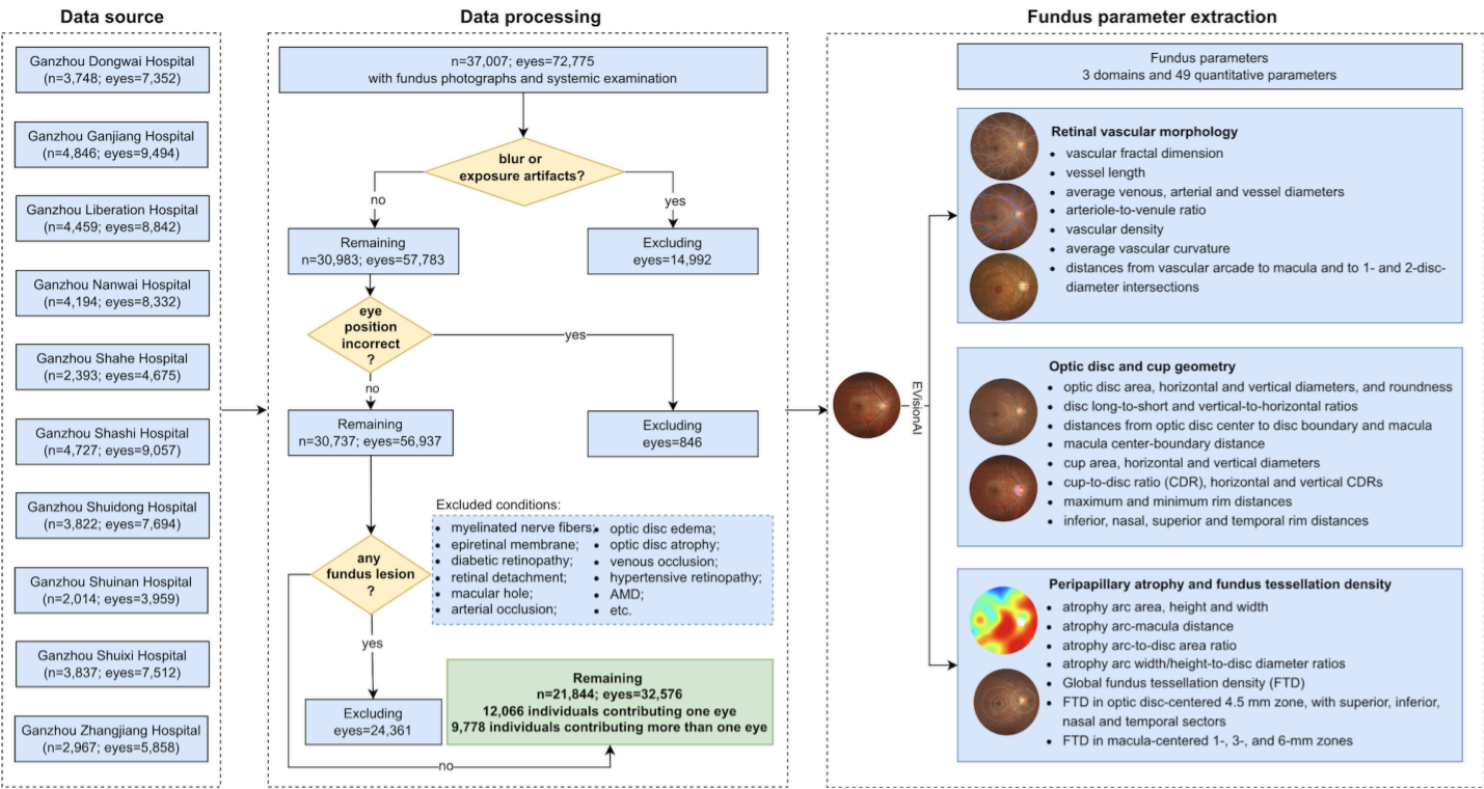


Figure 1

Study flowchart. Flow diagram illustrating participant inclusion and exclusion. From 37,007 participants with 72,775 eye-level fundus records in the Ganzhou Community Health Screening Program, records were excluded for poor image quality or exposure artifacts (14,992 records), incorrect positioning (846 records), or documented fundus pathology (24,361 records). Model-specific analyses used complete

eye-level records for the outcome and covariates required for each model. The final dataset included 21,844 participants and 32,576 eye-level fundus records; 12,066 participants contributed one eye-level record and 9,778 contributed two or more eye-level records because of bilateral eyes, same-day repeat imaging, or both. Abbreviations: AMD, age-related macular degeneration; FTD, fundus tessellation density; CDR, area cup-to-disc ratio.

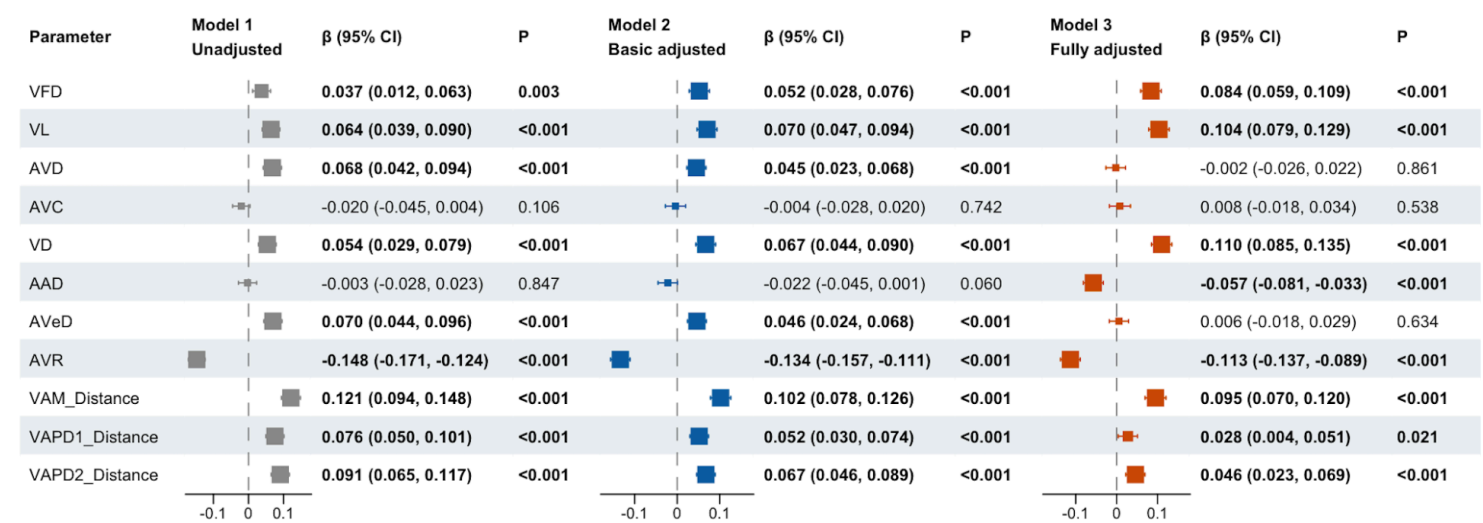


Figure 2

Sex differences in retinal vascular morphology. Three generalized estimating equation models are shown side by side: Model 1, unadjusted; Model 2, adjusted for age and age squared (age^2); Model 3, additionally adjusted for 20 binary systemic factors. β is the standardized mean difference (male versus female) in standard-deviation units; box size reflects the P-value category and bold values denote FDR-adjusted $P < 0.05$. Abbreviations: VFD, Vascular fractal dimension; VL, Vessel length; AVD, Average vessel diameter; AVC, Average vascular curvature; VD, Vessel density; AAD, Average arterial diameter; AVeD, Average venous diameter; AVR, Arteriole-to-venule ratio; VAM_Distance, Arcade-macula distance; VAPD1_Distance, arcade-to-1-disc-diameter intersection distance; VAPD2_Distance, arcade-to-2-disc-diameter intersection distance.

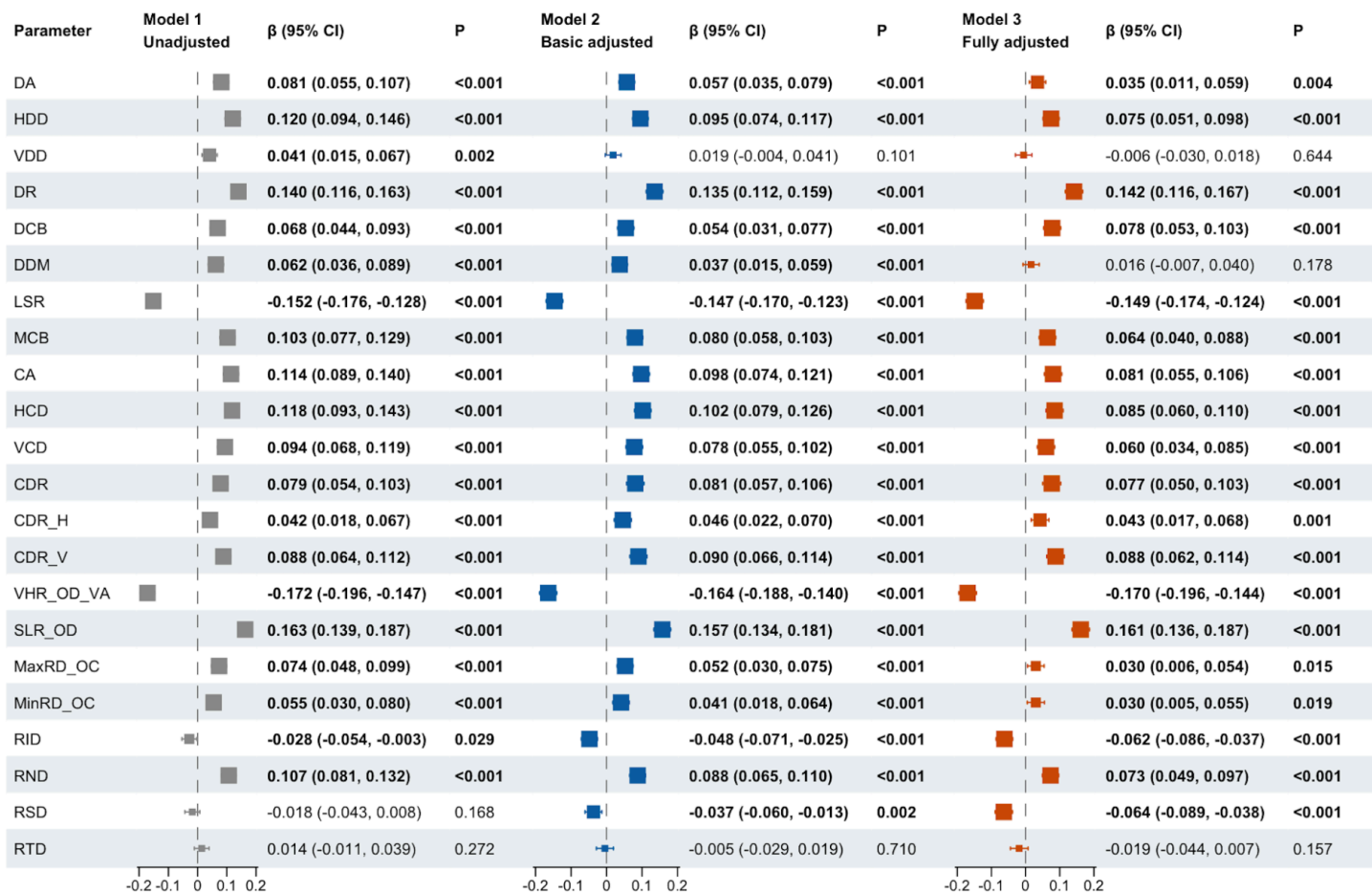


Figure 3

Sex differences in optic disc and cup geometry. Models as in Figure 2. β is the standardized mean difference (male versus female) in standard-deviation units; box size reflects the P-value category and bold values denote FDR-adjusted $P < 0.05$. Abbreviations: DA, Optic disc area; HDD, Disc horizontal diameter; VDD, Disc vertical diameter; DR, Disc roundness; DCB, Disc center-boundary distance; DDM, Disc-macula distance; LSR, Disc long/short axis ratio; MCB, Macula center-boundary distance; CA, Optic cup area; HCD, Cup horizontal diameter; VCD, Cup vertical diameter; CDR, area cup-to-disc ratio; CDR_H, Horizontal CDR; CDR_V, Vertical CDR; VHR_OD_VA, disc vertical-to-horizontal ratio; SLR_OD, disc short-to-long axis ratio; MaxRD_OC, Max rim distance; MinRD_OC, Min rim distance; RID, Rim inferior distance; RND, Rim nasal distance; RSD, Rim superior distance; RTD, Rim temporal distance.

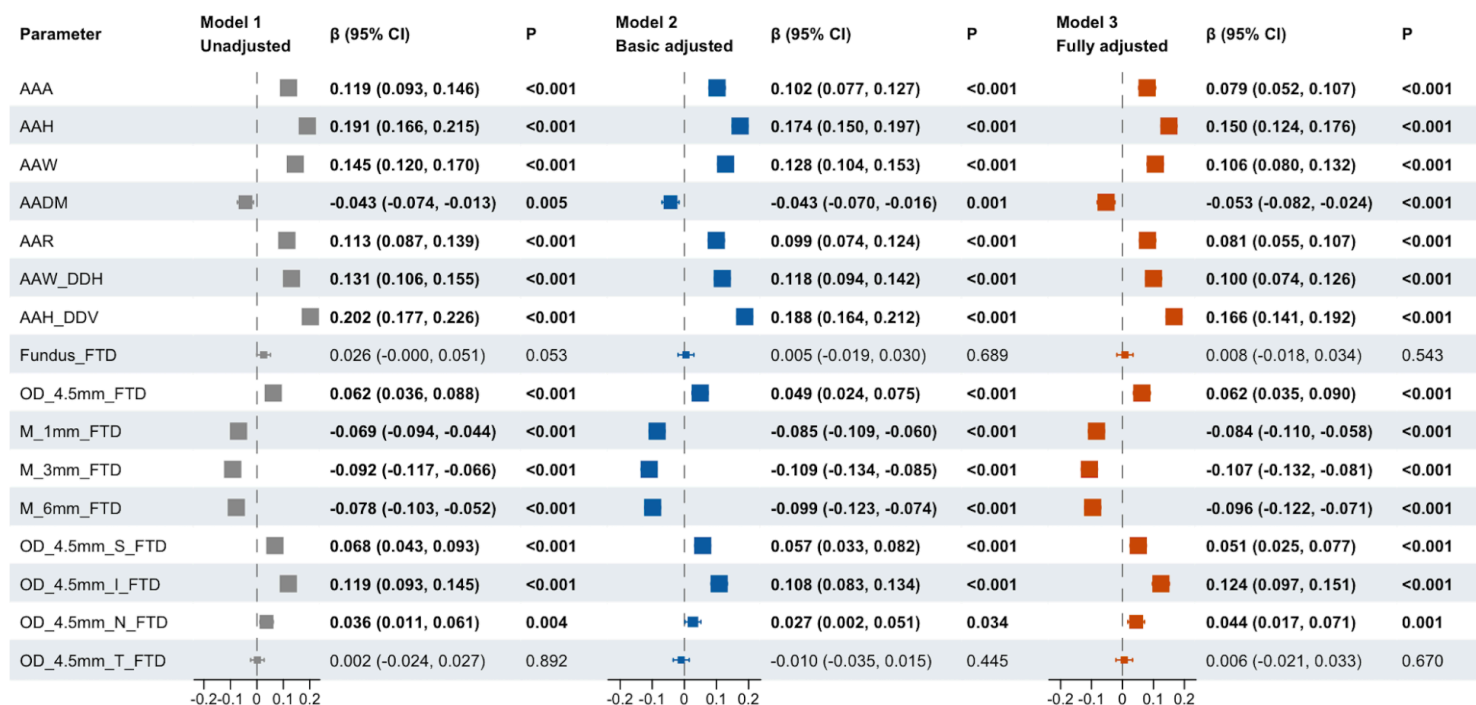


Figure 4

Sex differences in peripapillary atrophy and fundus tessellation density. Models as in Figure 2. β is the standardized mean difference (male versus female) in standard-deviation units; box size reflects the P-value category and bold values denote FDR-adjusted $P < 0.05$. Abbreviations: AAA, Atrophy arc area; AAH, Atrophy arc height; AAW, Atrophy arc width; AADM, Atrophy arc-macula distance; AAR, Atrophy arc/disc area ratio; AAW_DDH, atrophy arc width-to-disc horizontal diameter ratio; AAH_DDV, atrophy arc height-to-disc vertical diameter ratio; Fundus_FTD, Fundus FTD (global); OD_4.5mm_FTD, OD 4.5mm FTD; M_1mm_FTD, Macula 1mm FTD; M_3mm_FTD, Macula 3mm FTD; M_6mm_FTD, Macula 6mm FTD; OD_4.5mm_S_FTD, OD 4.5mm superior FTD; OD_4.5mm_I_FTD, OD 4.5mm inferior FTD; OD_4.5mm_N_FTD, OD 4.5mm nasal FTD; OD_4.5mm_T_FTD, OD 4.5mm temporal FTD.

discovery rate < 0.05 (filled), $P < 0.05$ uncorrected (open) and not significant. The dashed line marks $P = 0.05$. Abbreviations: AAD, average arterial diameter; AADM, atrophy arc-macula distance; AAH, atrophy arc height; AAH_DDV, atrophy arc height-to-disc vertical diameter ratio; AAR, atrophy arc-to-optic disc area ratio; AVD, average vessel diameter; AVC, average vascular curvature; AVeD, average venous diameter; AVR, arteriole-to-venule ratio; BP, blood pressure; CA, optic cup area; CDR, area cup-to-disc ratio; CDR_H, horizontal cup-to-disc ratio; CDR_V, vertical cup-to-disc ratio; DCB, optic disc center-boundary distance; DDM, optic disc-macula distance; FDR, false discovery rate; FTD, fundus tessellation density; HCD, horizontal cup diameter; HDL-C, high-density lipoprotein cholesterol; HGB, hemoglobin; HDD, horizontal disc diameter; LDL-C, low-density lipoprotein cholesterol; MaxRD_OC, maximum rim distance of optic cup; MCB, macular center-boundary distance; MinRD_OC, minimum rim distance of optic cup; OD, optic disc; PH, prostatic hyperplasia; RID, rim inferior distance; RND, rim nasal distance; RSD, rim superior distance; SD, standard deviation; TC, total cholesterol; TG, triglycerides; VAPD1_Distance, arcade-to-1-disc-diameter intersection distance; VAPD2_Distance, arcade-to-2-disc-diameter intersection distance; VCD, vertical cup diameter; VDD, vertical disc diameter; VD, vessel density; VFD, vascular fractal dimension; VL, vessel length.

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