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Associations of Retinal Microvascular Density and Fractal Dimension with Glaucoma: A Prospective Study from UK Biobank

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Objective: To explore the association between retinal microvascular parameters and glaucoma.

Design: Prospective study.

Subjects: The UK Biobank subjects with fundus images and without a history of glaucoma.

Methods: We employed the Retina-based Microvascular Health Assessment System to utilize the noninvasive nature of fundus photography and quantify retinal microvascular parameters including retinal vascular skeleton density (VSD) and fractal dimension (FD). We also utilized propensity score matching (PSM) to pair individuals with glaucoma and healthy controls. Propensity score matching was implemented via a logistic regression model with a caliper of 0.1 and a matching ratio of 1:4 no replacements. We conducted univariable Cox regression analyses to study the association between retinal microvascular parameters and incident glaucoma, in both continuous and quartile forms.

Main Outcome Measure: Vascular skeleton density, FD, and glaucoma.

Results: In a study of 41 632 participants without prior glaucoma, 482 cases of glaucoma were recorded during a median follow-up of 11.0 years. In the Cox proportional hazards regression model post-PSM, we found that incident glaucoma has significant negative associations with arteriolar VSD (hazard ratio [HR] = 0.24, 95% confidence interval [CI] 0.11−0.52, $P < 0.001$), venular VSD (HR = 0.34, 95% CI 0.15−0.74, $P = 0.007$), arteriolar FD (HR = 0.24, 95% CI 0.10−0.60, $P = 0.002$), and venular FD (HR = 0.31, 95% CI 0.12−0.85, $P = 0.022$). Subgroup analysis using covariates revealed that individuals aged ≥60 years, nonsmokers, moderate alcohol consumers, and those with hypertension and myopia exhibited P values <0.05 consistently prematching and postmatching, differing from other subgroups within this covariate.

Conclusions: Our study found that reduced retinal VSD and lower FD are linked to elevated glaucoma risk.

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Glaucoma is a chronic and progressive disorder characterized by the degeneration of nerve fibers in the eye structures and the optic nerve, ranking as the primary contributor to irreversible visual impairment worldwide.[1−3] It is estimated that by the year 2040, the number of individuals with glaucoma will reach 111.8 million.[4] In the majority of cases, glaucoma manifests as a persistent condition necessitating continual supervision. The alleviation of ocular pressure is the singular established approach to impede or retard the advancement of glaucoma. Diagnosis is frequently delayed due to the potential asymptomatic nature of the disease until its advanced stages, compounded by constraints in screening and limited access to early detection opportunities.[2,5] There is a pressing demand within the medical community for developing a noninvasive and economically viable diagnostic screening instrument aimed at improving early detection and preventive management of glaucoma.

The associations between glaucoma and factors like blood pressure, intraocular pressure (IOP), vascular constriction, cardiovascular diseases, and ocular blood circulation highlights the important role of vascular elements in advancing glaucomatous conditions.[6] An optimized manner arranges the retinal vascular system to reduce shear stresses caused by blood circulation and to efficiently utilize energy for perfusion, thereby ensuring adequate energy provision with minimal expenditure.[7] Alterations in the morphology of retinal blood vessels have been previously documented to be linked with a diverse array of ocular disorders.[8] The fundus serves as a window for evaluating the microvascular system in the human body and the progress in fundus photography and

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image processing software has greatly improved the evaluation of retinal microvasculature. Advances in deep learning technology have increased the accuracy and speed of measuring retinal features in fundus images, providing critical information for diagnosing and treating ocular conditions.[9] The Retina-based Microvascular Health Assessment System (RMHAS), utilizing artificial intelligence technology, facilitates the automated segmentation and quantitative analysis of retinal vessels.[10] Retinal fundus images provide a noninvasive method to observe diverse characteristics within the retinal vasculature, encompassing fractal dimension (FD) and vascular skeleton density (VSD).

Some studies indicate a relationship between FD and VSD with glaucoma. Ocular hypertension is correlated with a reduction in retinal vascular FD.[11] Research has shown a reduction in macular vessel density as glaucoma advances.[12,13] We need further research to investigate the clinical relevance of the 2 retinal microvascular parameters mentioned above to glaucoma, considering some studies' cross-sectional nature and inconsistent results. Therefore, we merged clinical data from the UK Biobank, a significant community database, to discuss the association between retinal microvascular parameters as biomarkers and predicting the onset of glaucoma.

Methods

Study Design and Participants

The UK Biobank is a large community-based cohort of 502 656 United Kingdom residents aged 40–69. Wide-ranging touchscreen questionnaires and physical measures were carried out at 22 study assessment centers across the United Kingdom, during 2007–2010. The UK Biobank conducts follow-up primarily through integration with national and other diverse datasets. Initial outcomes identified through electronic and semiautomated sources are validated and classified further by retrieving case records, imaging data, or stored tissue samples.[14] The UK Biobank data are available through its Access Management System (https://biobank.ndph.ox.ac.uk/showcase/).

Between June 2009 and July 2010, baseline eye examinations, such as visual acuity, refraction, IOP, and fundus photography were conducted, and a subgroup of 67 321 participants underwent retinal photography.[15] Images of the macular and optic disc were obtained by Topcon 3D OCT-1000 Mark II equipment.

We initially included 53 008 participants with right eye fundus images focusing on the macular center and complete follow-up results. Patients with poor quality fundus photos, prior glaucoma diagnosis, or history of ocular surgery/laser treatment for glaucoma or intraocular hypertension were excluded sequentially. After excluding participants who met the exclusion criteria,

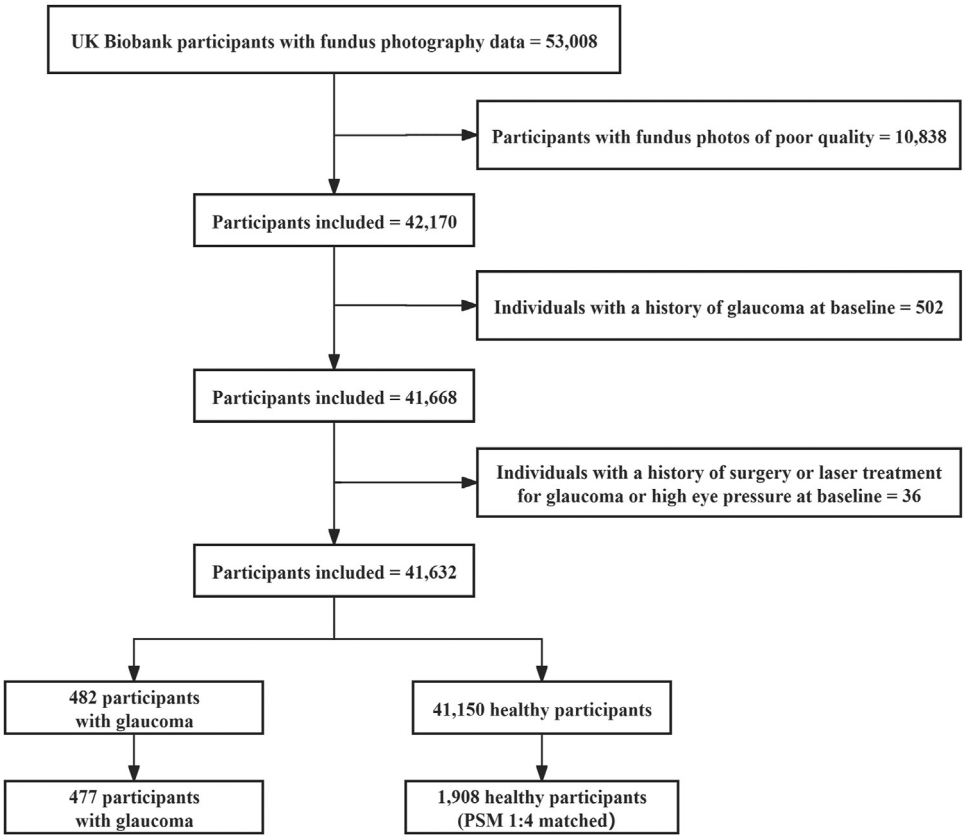

Figure 1. Flowchart of participants' inclusion. PSM = propensity score matching.

patients with glaucoma were matched with healthy volunteers at a ratio of 1:4 (Fig 1).

Ethical Approval

The study was approved by the North West Multi-Centre Research Ethics Committee (reference no. 06/MRE08/65), and informed consent was obtained by the UK Biobank study with adherence to the principles outlined in the Declaration of Helsinki. The UK Biobank website contains further information on the project www.ukbiobank.ac.uk/.

Measurement of Retinal Vessel Parameters

Photographs of retinal vessels were automatically analyzed via RMHAS.[10] To quantify the retinal vascular morphology, global physical/geometric parameters, and custom region-specific summaries were employed and the retinal vessels were divided into segments at crossings or bifurcations.

Vascular skeleton density was defined as the ratio of vessels' total length to the image's total area at 1 pixel, a measure of overall vessel length within a fundus image. Standardized vessel diameters were used in the skeletonized map, with an emphasis on the capillary-level perfused vasculature, making VSD a useful metric to evaluate capillary density.[16] Fractal dimension was calculated by the box-counting method, demonstrating the density and overall complexity of retinal vasculature in one number.[17] We removed sex-specific extreme outliers by altering the traditional box and whisker upper and lower bounds and compensated for skewness with the robust base tool in R (setting range = 3).[18]

Definition of Incident Glaucoma

Glaucoma diagnosis was ascertained based on a combination of the International Classification of Diseases 9 (ICD9) and 10 (ICD10), and participants' self-reported previous diagnoses. Glaucoma was defined as a disease of the eye and adnexa by diagnosis codes 3650-3652, 3655, and 3659 for the ICD9 in data field 41 271, codes H400-406 and H408-409 for the ICD10 in data field 41 270, and self-reported code 1277 in data field 20 002. The incidence of glaucoma was defined as the emergence of glaucoma events after recruitment and during the follow-up period, while the history of glaucoma was defined as the emergence of glaucoma events before recruitment. The follow-up time was calculated from the enrollment date to the earliest recorded date of glaucoma diagnosis, lost to follow-up, or death (whichever occurred first).

Covariates

Covariates include age, gender, ethnicity (White/Mixed/Asian/Black/Chinese/Other), smoking status (current/ever or never), and alcohol consumption frequency (low [never or special occasions only], moderate [drinking once per month to $\leq$4 times per week], and high [daily or almost daily]). Diabetes mellitus diagnosis was determined through 7 criteria: physician-diagnosed diabetes, insulin therapy, diabetes medications, age at first noncancer illness diagnosis, hemoglobin A1c levels, ICD9 codes, and ICD10 codes. We gathered data about blood pressure treatment and diastolic and systolic blood pressure measurements to comprehensively evaluate hypertension. In ophthalmology, the values representing IOP were articulated as corneal-compensated IOP. The classification of the IOP was into 3 distinct categories: IOP (corneal-compensated IOP $>$21 mmHg), normal IOP (10 mmHg less than or equal to corneal-compensated IOP $\leq$21 mmHg), and low IOP (corneal-compensated IOP $<$10 mmHg). Covariates included trauma to the right eye and excluded individuals who had undergone laser or surgical treatment for glaucoma or high IOP.

Statistical Analysis

We performed propensity score matching (PSM) to match individuals with glaucoma and healthy controls. Confounders were served as the input covariates to account for potential bias and PSM was computed using a logistic regression model with a caliper of 0.1 and a matching ratio of 1:4 with no replacements. The intergroup balance of confounders was measured using the standardized mean difference, and a value of standardized mean difference $<$0.2 indicated an acceptable balance. Subgroup analyses were undertaken encompassing variables including age, gender, hypertension, smoking habits, alcohol intake, myopia, and diabetes, both pre-PSM and post-PSM. We conducted a restricted cubic spline analysis to examine the nonlinear relationship between retinal vascular parameters and the occurrence of glaucoma.

Student *t* test assessed the difference in retinal vessel parameters between groups. Univariable Cox regression analyses were applied to assess the association between retinal microvascular parameters (continuous and quartiles) and incident glaucoma. We used hazard ratios (HRs) and 95% confidence intervals (CIs) to present the results. The statistical significance threshold was $P < 0.05$. The statistical analysis was performed using R 4.3.1 (R Foundation for Statistical Computing) and Stata 16.0 (StataCorp LLC).

Results

Study Participants

A total of 41 632 participants meeting the inclusion criteria were included in the study, with 482 individuals diagnosed with glaucoma. The final effective population included 477 patients with glaucoma and 1908 healthy volunteers, with 5 unmatched participants with glaucoma excluded from the study (Fig 1). Among the 41 632 participants, 55% were female, the mean age at recruitment was 55.2 $\pm$ 8.2 years, and 90.6% were White. The median duration of follow-up was 11.0 (interquartile range, 10.89−11.13) years.

Table 1 summarizes the baseline characteristics. There is a hypertension disparity as hypertension patients are affected with glaucoma more often than those without hypertension. The average age of glaucoma patients was 60.92, higher than that of the nonglaucoma group. Roughly 40% of glaucoma patients were observed to have high IOP. However, there were no significant differences in the distribution of gender, smoking status, diabetes, ethnicity, ocular injuries, alcohol consumption, or myopia. Almost all differences of confounders before the PSM vanished after the matching. Figure 2 shows the data distribution before and after matching.

Retinal Microvascular Parameters Measurements and Incident Glaucoma

Quantitative measurements were conducted on retinal blood vessels, yielding parameters such as FD and VSD. Table 2 indicates the result of descriptive statistics and *t* tests of independent groups. Vascular skeleton density and FD of both arteriole and venule are highly associated with the incidence of glaucoma.

In the Cox proportional hazards regression model after PSM, the incident glaucoma showed significantly negative associations with arteriolar VSD (HR = 0.24, 95% CI,

Table 1. Baseline Clinical and Demographic Characteristics of Nonglaucoma and Glaucoma Groups

Characteristics	Level	Full Cohort				PSM Cohort			
		Overall	*Nonglaucoma Group*	*Glaucoma Group*	*SMD*	*Overall*	*Nonglaucoma Group*	*Glaucoma Group*	*SMD*
n		41 632	41 150	482		2385	1908	477	
Age (mean [SD])		55.28 (8.21)	55.22 (8.20)	60.92 (6.21)	**0.784**	60.90 (6.19)	60.90 (6.19)	60.87 (6.22)	0.005
Sex no.%	Female	22 895 (55.0)	22 656 (55.1)	239 (49.6)	0.11	1214 (50.9)	976 (51.2)	238 (49.9)	0.025
	Male	18 737 (45.0)	18 494 (44.9)	243 (50.4)		1171 (49.1)	932 (48.8)	239 (50.1)	
Smoking status no.%	Never smoker	23 754 (57.1)	23 482 (57.1)	272 (56.4)	0.013	1379 (57.8)	1110 (58.2)	269 (56.4)	0.036
	Ex-smoker/current smoker	17 878 (42.9)	17 668 (42.9)	210 (43.6)		1006 (42.2)	798 (41.8)	208 (43.6)	
Diabetes no.%	No	39 490 (94.9)	39 056 (94.9)	434 (90.0)	0.185	2185 (91.6)	1753 (91.9)	432 (90.6)	0.046
	Yes	2142 (5.1)	2094 (5.1)	48 (10.0)		200 (8.4)	155 (8.1)	45 (9.4)	
Hypertension no.%	No	21 042 (50.5)	20 867 (50.7)	175 (36.3)	**0.294**	860 (36.1)	687 (36.0)	173 (36.3)	0.005
	Yes	20 590 (49.5)	20 283 (49.3)	307 (63.7)		1525 (63.9)	1221 (64.0)	304 (63.7)	
Ethnicity no.%	White	37 735 (90.6)	37 302 (90.6)	433 (89.8)	0.059	2205 (92.5)	1777 (93.1)	428 (89.7)	0.151
	Mixed	1197 (2.9)	1182 (2.9)	15 (3.1)		55 (2.3)	40 (2.1)	15 (3.1)	
	Asian	170 (0.4)	168 (0.4)	2 (0.4)		8 (0.3)	6 (0.3)	2 (0.4)	
	Black	1249 (3.0)	1230 (3.0)	19 (3.9)		55 (2.3)	36 (1.9)	19 (4.0)	
	Chinese	1003 (2.4)	993 (2.4)	10 (2.1)		42 (1.8)	32 (1.7)	10 (2.1)	
	Other	278 (0.7)	275 (0.7)	3 (0.6)		20 (0.8)	17 (0.9)	3 (0.6)	
IOP no.%	Low IOP	1406 (3.4)	1402 (3.4)	4 (0.8)	**0.729**	17 (0.7)	13 (0.7)	4 (0.8)	0.02
	Normal IOP	36 751 (88.3)	36 446 (88.6)	305 (63.3)		1515 (63.5)	1211 (63.5)	304 (63.7)	
	Intraocular hypertension	3475 (8.3)	3302 (8.0)	173 (35.9)		853 (35.8)	684 (35.8)	169 (35.4)	
Injury-patient no.%	No	41 549 (99.8)	41 068 (99.8)	481 (99.8)	0.002	2381 (99.8)	1905 (99.8)	476 (99.8)	0.012
	Yes	83 (0.2)	82 (0.2)	1 (0.2)		4 (0.2)	3 (0.2)	1 (0.2)	
Alcohol consumption no.%	Low	8412 (20.2)	8292 (20.2)	120 (24.9)	0.171	538 (22.6)	420 (22.0)	118 (24.7)	0.079
	Moderate	24 784 (59.5)	24 535 (59.6)	249 (51.7)		1261 (52.9)	1014 (53.1)	247 (51.8)	
	High	8385 (20.1)	8272 (20.1)	113 (23.4)		584 (24.5)	472 (24.7)	112 (23.5)	
	Prefer not to answer	51 (0.1)	51 (0.1)	0 (0.0)		2 (0.1)	2 (0.1)	0 (0.0)	
Myopia no.%	No	25 659 (61.6)	25 384 (61.7)	275 (57.1)	0.094	1453 (60.9)	1181 (61.9)	272 (57.0)	0.099
	Yes	15 973 (38.4)	15 766 (38.3)	207 (42.9)		932 (39.1)	727 (38.1)	205 (43.0)	

Ex-smoker = experienced smoker; Injury-patient = eye(s) affected by injury or trauma resulting in loss of vision; IOP = intraocular pressure; PSM = propensity score matching; SD = standard deviation; SMD = standardized mean difference.
Values were presented as no.% for categorical variables and mean (SD) for continuous variables. Statistical significance was determined based on SMD values obtained before and after PSM.
Boldface type was used to highlight SMD values >0.200.

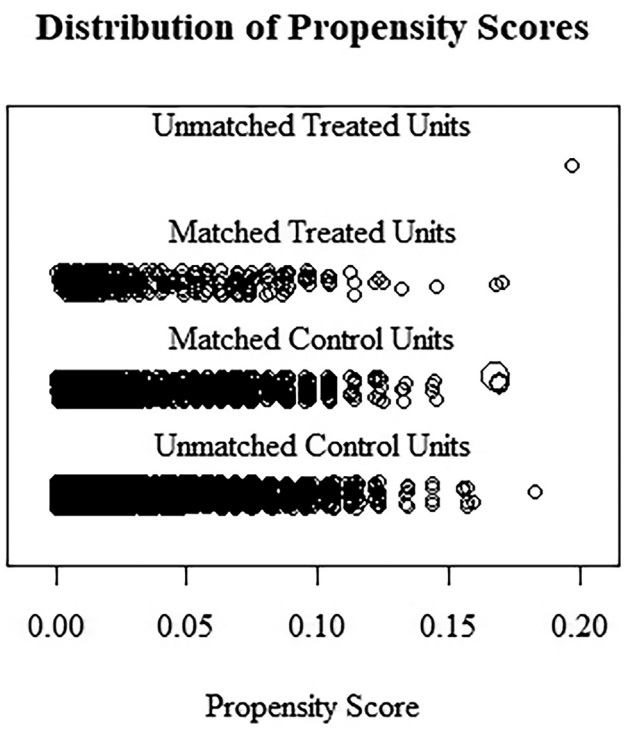

Figure 2. Distribution of propensity scores before and after matching.

0.11−0.52, $P < 0.001$), venular VSD (HR = 0.34, 95% CI, 0.15−0.74, $P = 0.007$), arteriolar FD (HR = 0.24, 95% CI, 0.10−0.60, $P = 0.002$), and venular FD (HR = 0. 31, 95% CI, 0.12−0.85, $P = 0.022$) (Table 3).

In the PSM cohort, the incidence of glaucoma was 45% and 43% higher in participants in the lowest quartile of arteriolar and venular VSD, compared with participants in the largest quartile (Table 3). Participants with arteriolar and venular VSD in the second (HR = 1.26, 95% CI, 0.97−1.63, $P = 0.084$; HR = 1. 11, 95% CI, 0.86−1.45, $P = 0.422$) and third (HR = 1.03, 95% CI, 0.78−1.34, $P = 0.844$; HR = 1. 01, 95% CI, 0.77−1. 32, $P = 0.963$) quartiles had similar risks of incident glaucoma event compared with those in the fourth quartile, respectively. Participants in the lowest quartile of arteriolar FD (HR = 1.36, 95% CI, 1.06−1.76, $P = 0.018$) had a distinctly increased risk of incident glaucoma event, compared with those in the fourth quartile. Participants with arteriolar FD in the second quartile had a 29% increased risk of incident glaucoma event. In comparison, those in the third quartile had a 10% higher risk than individuals in the fourth quartile. There was no significant difference across 4 venular FD quartiles regarding the risk of incident glaucoma (Fig S3, available at www.ophthalmologyscience.org). In restricted cubic spline analysis, the nonlinear relationship between retinal vascular parameters and the onset of glaucoma is not significant (Fig S4, available at www.ophthalmologyscience.org).

Subgroup Analysis before and after Matching

We utilized subgroup analysis to investigate the association between retinal microvascular parameters and glaucoma stratified for age, gender, hypertension, smoking status, alcohol consumption, diabetes, and myopia. The significant findings are only evident upon conducting subgroup analysis after the matching process. Individuals aged ≥60 years may influence the negative association between retinal microvascular parameters and glaucoma ($P < 0.05$). The association between venular FD and glaucoma demonstrated heightened significance among male individuals (HR = 0.15, 95% CI, 0.04−0.62, $P = 0.01$), as did venular VSD (HR = 0.22, 95% CI, 0.07−0.67, $P = 0.01$). The connection is more evident in never-smokers and moderate drinkers when considering smoking and drinking habits in subgroup analysis. The link between venular FD and glaucoma is particularly significant in individuals with diabetes (HR = 0.01, 95% CI 0−0.27, $P = 0.01$). We have also observed a more pronounced association between retinal microvascular parameters and glaucoma in populations with hypertension and myopia ($P < 0.05$) as shown in Figures S5−12 (available at www.ophthalmologyscience.org).

Discussion

The present investigation delved into the relationship between retinal microvascular parameters among 41 632 individuals sourced from the UK Biobank. The study results highlight a notable association between the predisposition to VSD and FD with glaucoma progression, as demonstrated through an exhaustive examination integrating both continuous and categorical factors following thorough

Table 2. Comparison of Retinal Parameters in Participants without Incident Glaucoma vs. Participants with Incident Glaucoma

	Participants without Incident Glaucoma	Participants with Incident Glaucoma	*P* Value
Arteriolar VSD	0.72 ± 0.11	0.70 ± 0.11	**0.015**
Venular VSD	0.76 ± 0.11	0.75 ± 0.11	**0.010**
Arteriolar FD	0.80 ± 0.10	0.79 ± 0.10	**0.004**
Venular FD	0.83 ± 0.09	0.82 ± 0.09	**0.021**

FD = fractal dimension; VSD = vascular skeleton density.
P values were calculated by *t* tests. $P < 0.05$ denoted statistical significance, with noteworthy associations highlighted in bold.

Table 3. Univariate Conditional Cox Regression Analysis for Glaucoma in the PSM Cohort and the Relationship between Retinal Microvascular Parameters Stratified by Quartile and Glaucoma

Retinal Microvascular Parameters	HR (95% CI)	*P* Value	Quartile	HR (95% CI)	*P* Value
Arteriolar VSD	0.24 (0.11, 0.52)	**<0.001**	Q1	1.45 (1.13, 1.87)	**0.004**
			Q2	1.26 (0.97, 1.63)	0.084
			Q3	1.03 (0.78, 1.34)	0.844
			Q4	Reference	Reference
Venular VSD	0.34 (0.15, 0.74)	**0.007**	Q1	1.43 (1.11, 1.83)	**0.005**
			Q2	1.11 (0.86, 1.45)	0.422
			Q3	1.01 (0.77, 1.32)	0.963
			Q4	Reference	Reference
Arteriolar FD	0.24 (0.10, 0.60)	**0.002**	Q1	1.36 (1.06, 1.76)	**0.018**
			Q2	1.29 (1.00, 1.68)	0.051
			Q3	1.10 (0.84, 1.44)	0.492
			Q4	Reference	Reference
Venular FD	0.31 (0.12, 0.85)	**0.022**	Q1	1.26 (0.98, 1.61)	0.07
			Q2	1.03 (0.79, 1.33)	0.824
			Q3	0.97 (0.74, 1.26)	0.797
			Q4	Reference	Reference

CI = confidence interval; FD = fractal dimension; HR = hazard ratio; PSM = propensity score matching; VSD = vascular skeleton density.
The initial quartile signifies the minimum level of retinal microvascular parameters, whereas the final quartile denotes the maximum level of retinal microvascular parameters.
P values were determined through univariate Cox regression analysis. $P < 0.05$ denoted statistical significance, with noteworthy associations highlighted in bold.

adjustments. This indicates that retinal microvascular characteristics could play a significant role in the pathogenesis of glaucoma, thereby opening up the prospect of utilizing retinal fundus images to develop a deep learning predictive model to assess the risk of glaucoma.

Vascular skeleton density is a validated measure frequently employed to assess capillary density, which is determined by the proportion of blood vessel length to the overall area in the skeletonized vessel map. Vascular skeleton density proves to be particularly responsive to alterations in perfusion occurring at the delicate capillary level.[19] Studies have shown associations between changes in VSD and the severity of diabetic retinopathy,[20] cardiovascular diseases,[21] and all-cause mortality.[22] Previous research examining the initial phases of glaucoma has revealed notable declines in macular vascular density, indicating that retinal vascular density reduction may commence early in glaucoma progression.[12,13] Takuhei Shoji et al conducted a longitudinal study that revealed that OCT angiography can identify a decline in macular vessel density over time in glaucomatous eyes. Assessing retinal vasculature in the macula can enhance the detection of glaucomatous changes due to the high metabolic demands and reliance on local capillary networks of retinal ganglion cells (RGCs). The decreased vessel density in glaucomatous eyes may suggest a reduced metabolic demand for RGCs.[23] The key features in diagnosing glaucoma involve alterations in the optic nerve head and retinal nerve fiber layer, which reflect RGC demise and optic nerve fiber depletion. These changes can be observed through ophthalmoscopic examination. However, the RGCs could be lost before detectable defects in standard visual field testing.[5] A study conducted earlier found that the diagnostic accuracy of macular vessel density surpassed that of ganglion cell complex thickness in discerning between preperimetric glaucoma and healthy eyes,[24] and another study revealed that vascular changes precede detectable visual field damage.[25] Furthermore, there was no correlation between IOP and decreased rates in macula vessel density. However, a significant association was observed between IOP and rates of thinning in the ganglion cell complex. This indicates that alterations in macular vessel density in glaucoma might not rely heavily on IOP.[12] In patients with glaucoma with normal IOP, early detection of vascular density can enhance prevention and treatment strategies.

Furthermore, beyond the evaluation of retinal vessel density, a significant association was found between the FD of retinal vessels and the presence of glaucoma. The FD elucidates the extent to which a pattern occupies areas in 2 dimensions, serving as a comprehensive metric that encapsulates the entirety of the branching structure within the retinal vascular network.[26,27] Fractal analysis can provide valuable insights into retinal blood vessel issues,[28] with the FD of these vessels showing promise in predicting both ocular and systemic conditions. Alterations in the FD have demonstrated associations with conditions such as diabetes, stroke, coronary heart disease, and glaucoma.[9,29–31] Marco et al demonstrated a notable decrease in the FD among individuals with advanced glaucoma compared with the control group, while Wu et al identified an association between the decline in FD and ocular hypertension.[11,29] The diminished FD of the retinal vasculature in individuals with glaucoma indicates potential compromise in the optimization of vascular circulation, as alterations in the geometric patterns suggest deviations from the ideal structure and function of the microcirculation, resulting in reduced efficiency and impaired circulatory transport.[7,32]

The retina is a metabolically active tissue reliant on a continuous supply of nutrients and oxygen for proper function. Deviation from the ideal structure and function of the retinal microvasculature can impair circulatory transport efficiency.[6] Glaucoma types linked to vascular factors, like neovascular, secondary to diabetes, or venous occlusion, show a strong connection to vascular dysfunction or impaired vascular self-regulation.[31,32] The static characteristics of retinal microcirculation may be related to vascular phenomena in glaucoma.[6] Studying early changes in retinal microvascular parameters is clinically valuable for diagnosing glaucoma linked to vascular factors. Further research is needed to investigate the associations between retinal microvasculature density and FD with glaucoma caused by vascular factors.

There are several clinical application benefits of RMHAS. Clinical practitioners can conduct in-depth research and exploration thanks to the extensive data repository provided by the RMHAS database. They can use this resource to look into the relationships between different diseases and information from current medical evaluations. By investigating these connections, we can improve early disease detection and progression prediction, explore potential underlying mechanism of related diseases, and encourage patient-centered precision medicine.

Finding correlations with clinical relevance is a particularly efficient way to use the database. Following that, focused clinical investigations are then designed and carried out to experimentally validate these links. Moreover, by employing sophisticated research tools, particularly molecular biology techniques, the association between diseases and their clinical manifestations can be meticulously examined and elucidated.

The present study presents notable advantages and drawbacks that warrant consideration. This study's notable strength lies in the predictive value of retinal vascular analysis at baseline before the onset of glaucoma, with a large sample size comprising 477 patients with glaucoma and 1908 eligible healthy controls. Furthermore, implementing matching techniques effectively mitigated potential biases within the study cohort. Further investigation through stratified subgroup analysis was conducted to examine the association between retinal vascular parameters and glaucoma among diverse populations, highlighting the importance of tailored preventive measures in optimizing the accuracy of glaucoma management strategies. Retina-based Microvascular Health Assessment System's remarkable efficiency and accuracy render it well-suited for practical medical implementations relying on quantitative modeling. Glaucoma is a neural degenerative disease, so this study may have implications for systemic neural diseases. Research has shown an association between retinal microvascular parameters and multiple sclerosis with ganglion cell complex thickness changes akin to glaucoma.[33] This suggests that investigating retinal microvascular parameters may open new avenues for diagnosing neurological diseases.

Our study is limited in that it relies on a compilation of glaucoma cases determined through self-report and relevant ICD codes data from the UK Biobank. Defining glaucoma cases solely through ICD codes may be specific but could overlook a substantial number of genuine patients with glaucoma not included in hospital databases. Conversely, self-reporting may detect more cases but carries the potential for misclassification and recall bias.[34] Due to the reliance on self-reporting in a substantial portion of our study cases and the lack of detailed classification for glaucoma in the UK Biobank dataset, the absence of specific glaucoma categorization represents a limitation in our research. Besides, the absence of follow-up eye examinations and ophthalmic testing potentially leads to overlooked incident glaucoma cases and incorrect assignments. The prevalence of glaucoma in our study is low. This discrepancy is mainly attributed to volunteer bias, the low response rate (5.5%) in the UK Biobank,[15] and the underdiagnosis of the condition.[35] Another limitation is that glaucoma has a certain genetic predisposition,[36] but due to the absence of glaucoma in the family history sample repository at the UK Biobank, the genetic aspect of this disease has not been adequately explored. In data analysis, PSM can only control for known confounding factors, leaving the possibility of unknown confounders influencing the outcomes. The predominantly European descent in the UK Biobank may limit the generalizability of findings to other populations. However, risk factor associations in UK Biobank appear generalizable.[37]

Our research findings indicate that decreased retinal microvascular density and FD are associated with an increased risk of glaucoma. Further studies should explore the clinical application potential of deep learning models based on retinal microvascular parameters, which could aid in the early screening and prediction of glaucoma.

Footnotes and Disclosures

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HUMAN SUBJECTS: Human subjects were included in this study. The study was approved by the North West Multi-Centre Research Ethics Committee (reference no. 06/MRE08/65), and informed consent was obtained by the UK Biobank study with adherence to the principles outlined in the Declaration of Helsinki.

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Abbreviations and Acronyms:
CI = confidence interval; **FD** = fractal dimension; **HR** = hazard ratio; **ICD9** = International Classification of Diseases 9; **ICD10** = International Classification of Diseases 10; **IOP** = intraocular pressure; **PSM** = propensity score matching; **RGC** = retinal ganglion cell; **RMHAS** = Retina-based Microvascular Health Assessment System; **VSD** = vascular skeleton density.

Keywords:
Fractal dimension, Fundus photography, Glaucoma, UK Biobank, Vascular density.

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