Multimodal retinal oculomics in schizophrenia: findings from the AlzEye study

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Key Points

Question: Do individuals with schizophrenia have measurable differences in retinal morphology?

Findings: In this retrospective cohort analysis of 101,416 patients (485 with schizophrenia), those with schizophrenia had significantly thinner ganglion cell-inner plexiform layers. Retinovascular differences were mostly attributable to higher medical comorbidity among those with schizophrenia.

Meaning: These data indicate that individuals with schizophrenia have reduced thickness of the inner retina, which may indicate heightened neurodegeneration.

Abstract

Importance: The potential association of schizophrenia with distinct retinal changes is of clinical interest but has been challenging to investigate due to lack of sufficiently large and detailed cohorts.

Objective: To investigate the association between retinal biomarkers from multimodal imaging (oculomics) and schizophrenia in a large real-world population.

Design: This cross-sectional analysis used data from the AlzEye study, a retrospective cohort where ophthalmic data of patients attending Moorfields Eye Hospital has been linked with hospital admissions across England between January 2008 and April 2018.

Setting: A secondary care ophthalmic hospital, incorporating a principal central site, four district hubs and five satellite clinics in and around London, United Kingdom.

Participants: A total of 154,830 patients aged 40 years and over and had retinal imaging during the study period.

Main outcome and measure: Retinovascular and optic nerve indices were computed from color fundus photography. Macular retinal nerve fiber layer (RNFL) and ganglion cell-inner plexiform layer (mGC-IPL) thicknesses were extracted from optical coherence tomography. Linear mixed effects models were used to examine the association between schizophrenia and retinal biomarkers.

Results: A total of 485 individuals (747 eyes) with schizophrenia (mean age 64.9 ± 12.2 years, 53.2% female) and 100,931 individuals (165,400 eyes) without schizophrenia (mean age 65.9 ± 13.7, 51.2% female) were included following image quality control and exclusion of potentially confounding conditions. Individuals with schizophrenia were more likely to be hypertensive (83.9% vs 48.0%) and have diabetes mellitus (75.1% vs 27.6%). The schizophrenia group had thinner mGC-IPL (-4.05 microns, 95% CI: -5.40,-2.69, $p=5.4\times10^{-9}$), which persisted when investigating only those without diabetes mellitus (-3.99 microns, 95% CI: -6.67,-1.30, $p=0.004$) or just those aged 55 years and younger (-2.90 microns, 95% CI: -5.55,-0.24, $p=0.033$). On adjusted analysis, retinal fractal dimension, among vascular variables was reduced in individuals with schizophrenia (-0.14 units, 95% CI: -0.22,-0.05, $p=0.001$) although this was not present when excluding those with diabetes mellitus.

Conclusions and relevance: Patients with schizophrenia have measurable differences in neural and vascular integrity of the retina. Differences in retinal vasculature were mostly secondary to the higher prevalence of diabetes and hypertension in patients with schizophrenia. The role of oculomic biomarkers as adjunct outcomes in patients with schizophrenia warrants further investigation.

[349 words]

Introduction

Schizophrenia, a chronic heterogenous neuropsychiatric disorder with an estimated global prevalence of 23 million people in 2019[1], is increasingly recognised as a multisystemic disease[2] with bidirectional dysregulation. Features of endocrine dysfunction, such as impaired glucose tolerance, are present at the first episode of psychosis[3,4] and shared genetic mechanisms have been implicated in diabetes mellitus and psychosis[5]. Treatment with antipsychotics and unhealthy lifestyle practices contribute to a high prevalence of metabolic syndrome among individuals with schizophrenia[6]. Following diagnosis, affected individuals are also more likely to experience cardiovascular disease and premature cognitive decline[7–9] with some researchers positing an association between schizophrenia and accelerated senescence[10].

The eye provides a promising non-invasive route to elucidating multisystem dysregulation in mammals. As an embryological extension of the primitive forebrain, the eye represents an easily accessible window to direct quantitative imaging of central nervous system tissue through the retinal ganglion cells, nerve fibre layer (i.e. ganglion cell axons) and optic nerve. In addition, shared characteristics between retinal vascular morphology and other microvascular systems, such as those found in the heart, kidney and brain, reinforce the hypothesis that retinal imaging-based oculomics can stratify individuals by risk of cardiovascular disease, renal failure and cerebrovascular disease[11–16]. Retinal changes have also been observed in individuals with schizophrenia. Two recent meta-analyses concluded that there was evidence for thinner peripapillary retinal nerve fiber layer and macular ganglion cell and inner plexiform layer (mGC-IPL) and enlarged cup-to-disc ratio (CDR) but acknowledged an inconsistency in results and low statistical power[17,18]. For example, across six reports, significant mGC-IPL thinning was found in

schizophrenia but only when evaluating right eyes. Optic cup volume is significantly larger in schizophrenia spectrum disorders (SSD) but cup-to-disc area ratio is similar to controls. Preliminary reports also indicate changes in the density of retinal microvasculature in schizophrenia[19–21]. However, most reports exclude participants with other systemic diseases, such as diabetes mellitus and hypertension (both of which impair retinal structure and function), yet these medical comorbidities are highly prevalent in SSD, challenging the generalizability of any findings.

In this analysis drawing on the AlzEye cohort, we investigated associations between schizophrenia and retinal morphology using cross-sectional multimodal imaging in a cohort of 101,416 patients (*n*=485 with schizophrenia) in London, United Kingdom (UK). We hypothesized that individuals with schizophrenia would have enlarged CDR and reduced inner retinal thicknesses, above that which could be explained by the presence of hypertension and diabetes mellitus.

Methods

Design, participants and setting

This analysis used data from the AlzEye project, a retrospective cohort study with individual-level linkage between ophthalmic data and hospital admissions across England of 353,157 participants (154,830 with retinal imaging) who attended Moorfields Eye Hospital NHS Foundation Trust (MEH) between January 1st 2008 and April 1st 2018 (described previously[22]). In brief, participants were aged 40 years or over and had attended MEH, a secondary ophthalmic institution serving an ethnically diverse region of London, UK. Ophthalmic data was deterministically linked with the Hospital Episode Statistics (HES) Admitted Patient Care Database, a repository of all hospital admissions under the National Health Service (NHS) within England[23], which captures > 97% of all hospital admissions in England[24]. HES is coded using the 10th revision of the International Classification of Diseases (ICD)[25]. The primary objective was to assess whether prevalent schizophrenia was associated with a larger CDR and thinner mGC-IPL and RNFL compared to controls. We additionally investigated whether retinal vascular morphology differed in those with schizophrenia.

Variables

The dependent variables were retinal morphological features derived from macula-centred colour fundus photography (CFP) and optical coherence tomography (OCT) (Figure 1). OCT is a non-contact imaging modality, which measures back-scattered light and echo time delay (analogous to ultrasound but using light) to generate cross-sectional images of tissue with histological-like resolution (axial resolution ~5 microns). Retinal vascular morphometric characteristics, including fractal dimension, and CDR were extracted from 45-degree CFPs using two deep

learning-based tools - the Vessel Assessment and Measurement Platform for Images of the REtina (VAMPIRE) and AutoMorph[26,27]. For retinal sublayers, we only examined mGC-IPL and RNFL, defined according to the International Nomenclature for OCT panel[28]. Thicknesses were estimated using the Topcon Advanced Boundary Segmentation Tool (TABS, version 1.6.2.6), a software leveraging dual-scale gradient information for automated segmentation of retinal sublayers [29]. All retinal images were acquired using Topcon (Topcon Corporation, Tokyo, Japan) devices. Across the study period, five different Topcon devices were used but approximately 80% were collected on a single device, distribution of devices among cases and controls was similar and the same software version of TABS was used on all images (eTable1). Images from both eyes, where available, were used.

The primary exposure was schizophrenia, defined as an HES episode with ICD code F20. HES-based diagnostic codes for schizophrenia in the UK have previously been validated and demonstrated 90% agreement when compared to a psychiatrist-based hierarchical lifetime diagnosis using longitudinal psychopathology and diagnostic information from individual health records in London, UK[30]. We used the most recent HES admission codes for defining whether an individual had schizophrenia as this demonstrated a positive predictive value of 91%. For image selection, we then chose the earliest "good" or "usable" quality image following a HES episode with a diagnostic code for schizophrenia to reduce the potential bias imparted by ophthalmic treatment (e.g. retinal laser). Further information on how image quality is categorised can be found in AutoMorph's description[26]. Among those who had multiple images on that same date, we chose the image with the highest image quality score, as outputted by AutoMorph. Controls were individuals in the cohort similarly attending MEH and had received retinal imaging during

the study period but who did not have an ICD code of schizophrenia (further details available in our previous report[22]). Secondary exposure variables were age, sex, hypertension (ICD: I10, I15), diabetes mellitus (ICD: E10, E11) and socioeconomic status (SES). SES was estimated using the index of multiple deprivation (IMD), a composite score linked to postcode covering income, employment, education, health, and barriers to housing and services, crime and living environment[31]. Given some previous evidence of similar retinal findings in mood disorders, we excluded individuals with ICD codes for bipolar affective disorder (F30-F31), SSD (other than schizophrenia, F21-F29) and unipolar depression (F32-F33) [30,32,33]

Statistical analysis

Continuous variables were compared between groups using the Wilcoxon-Mann-Whitney test and categorical variables through the *U*-Statistic test[34]. We fitted linear mixed effects models using maximum likelihood estimation in line with the Advised Protocol for OCT Study Terminology and Elements (APOSTEL) recommendations[35]. These models included random effects on the intercept to account for the multilevel structure of eyes within individuals, and were adjusted for age, sex, diabetes mellitus, hypertension, socioeconomic status and image quality. Sex, diabetes mellitus and hypertension were coded as categorical variables for modelling. We adjusted for image quality as this has been found previously to be associated with certain retinal vascular features[36]. Degrees of freedom were estimated using Satterthwaite's approximation[37]. We performed two subgroup analyses. Firstly, given the high prevalence of diabetes mellitus among individuals with schizophrenia and its impact on retinal vasculature, and to mitigate the risk of residual confounding conferred by comparing individuals with mild diabetes mellitus to those with more severe disease or those who had received retinal laser

treatment, we performed all analyses on a subgroup excluding individuals with diabetes mellitus. Secondly, to examine the association in younger individuals with schizophrenia, we performed an additional analysis stratifying individuals in the cohort to those <55 and ≥55 years of age. Statistical significance was set at $p<0.05$. All analyses were conducted in R version 4.1.0 (R Core Team, 2021. R Foundation for Statistical Computing, Vienna, Austria) and used the `USP`, `lmer` and `lmerTest`package[38–40].

Reporting is in line with the guidelines set by the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) and its extension, the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statements[41,42].

Approvals

Data from this project were derived from the AlzEye study, which received institutional and ethical review board approval including an exemption of informed consent (REC reference: 18/LO/1163).

Results

Of the initial sample of 154,830, 485 individuals (747 eyes) with schizophrenia and 100,931 individuals (165,400 eyes) without had macula-centered images deemed of sufficient image quality and met our inclusion criteria (Figure 2). Individuals with schizophrenia had a similar distribution of age and sex to those without the condition but were more likely to have hypertension (83.9% versus 48.0%, $p<0.001$), diabetes mellitus (75.1% versus 27.6%, $p<0.001$) and lived in areas of greater deprivation (Table 1). On unadjusted analysis, individuals with schizophrenia had significantly reduced fractal dimension, vessel density, tortuosity density and increased arteriolar and venular calibre (all $p<0.001$). In addition, they had reduced mGC-IPL and RNFL thickness. The schizophrenia group had slightly larger CDR (0.47 ± 0.09 versus 0.46 ± 0.09, $p<0.001$) but a similar prevalence of glaucoma (Table 1).

Adjusting for age, sex, SES and image quality, schizophrenia was associated with reduced mGC-IPL thickness, reduced fractal dimension, reduced vessel density, greater tortuosity density and enlarged CDR (Table 2). There was no association between schizophrenia and RNFL. When additionally adjusting for hypertension and diabetes mellitus, there was no association between schizophrenia and retinovascular characteristics except VAMPIRE-based fractal dimension (-0.14, 95% CI: -0.22, -0.05], $p = 0.001$). Individuals with schizophrenia maintained a larger CDR (0.01, [0.00, 0.02], $p=0.041$) and thinner mGC-IPL (-4.05 microns, 95% CI: -5.40, -2.69, $p=5.4 \times 10^{-9}$). Increasing age was associated with thinner mGC-IPL in both the schizophrenia and control groups. In those with schizophrenia, mGC-IPL was 3.20 microns (95% CI: -4.40, -1.99, $p= 3.4 \times 10^{-7}$) thinner while in those without schizophrenia, the mGC-IPL was 2.54 microns (95% CI: -

2.62, -2.46, $p < 2.0 \times 10^{-16}$, eTable 2) thinner per ten years of age. On adjusted analysis, we found no significant difference in RNFL between those with schizophrenia and those without.

Restricting the analysis to individuals without diabetes mellitus left a sample of 121 individuals (192 eyes) with schizophrenia and 73,574 controls (122,673 eyes, eTable 3). A strong association persisted between mGC-IPL and schizophrenia (-3.99 microns, 95% CI: -6.67, -1.30, p=0.004); the schizophrenia group no longer had enlarged CDR. No retinovascular indices were associated with schizophrenia in this subgroup.

We next stratified the cohort into those aged <55 and ≥55 years (eTable 4). Regardless of age, mGC-IPL was reduced in those with schizophrenia; however, the effect estimate was more extreme for older patients (younger group: -2.90 microns, 95% CI: -5.55, -0.24, p=0.033, older group: -4.43 microns, 95% CI: -6.00, -2.85, $p = 3.6 \times 10^{-8}$, Table 3). Reduced fractal dimension (VAMPIRE system) was seen in those with schizophrenia in both the older (-0.11 per SD increase, 95% CI: -0.20, -0.01, p=0.027) and younger (-0.23 per SD increase, 95% CI: -0.41, -0.04, p=0.016) subgroups.

Discussion

Among the AlzEye cohort of 101,416 individuals who had eye imaging of sufficient quality for analysis, people with schizophrenia had thinner mGC-IPL and slightly enlarged CDR compared to those without schizophrenia after adjustment for multiple demographic and medical factors, suggesting retinal neural atrophy. However, associations with retinovascular morphology could be explained by the increased prevalence of hypertension and diabetes mellitus among those with schizophrenia. Our report is the largest to date to examine multimodal retinal oculomics in individuals with schizophrenia and supports evidence of heightened retinal neurodegeneration in this disease that accelerates with advanced age.

Retinoneural associations with schizophrenia

We report evidence of reduced thickness of the inner retinal layers, which would be consistent with a neurodegenerative process in schizophrenia. The effect size for mGC-IPL thickness was similar to what has been reported in the literature on Alzheimer's disease[43,44] and prominent even when people with diabetes mellitus were excluded. A link between schizophrenia and mGC-IPL has been proposed but with inconsistent evidence thus far. In a meta-analysis of seven studies comprising 453 participants, thinner mGC-IPL was associated with schizophrenia but only in right eyes[17]. In another meta-analysis of three studies comprising 169 participants with SSD, mGC-IPL thickness was reduced but significance was lost when excluding one published report and the overall quality of evidence was deemed to be very low[18].

There are several biologically plausible reasons for the thinner mGC-IPL we observed in schizophrenia. Firstly, mGC-IPL thinning may result from a central neurodegeneration which, through retrograde trans-synaptic degeneration (RTSD), manifests as inner retinal thinning, such as that found in multiple sclerosis, ischaemic stroke and chiasmal compression[45–47]. Some have advocated RTSD as the mechanism for inner retinal thinning in Alzheimer's disease and other forms of dementia, diseases which are more common in people with schizophrenia, however conclusive evidence for this in schizophrenia is lacking[7,48–50].Our subgroup analysis showed a more modest reduction in mGC-IPL among younger individuals with schizophrenia compared to those older in the cohort corroborating evidence from other disciplines of accelerated neurodegeneration. Affected individuals have progressive gray and white matter volume loss, beyond that of healthy controls[51] and gene expression patterns suggest accelerated molecular ageing[52]. Even in the absence of confounding anti-psychotic therapy, individuals with schizophrenia show exaggerated cognitive decline[53]. Further evidence for a neurodegenerative phenomenon in schizophrenia comes from data on a different biomarker for neurodegeneration, neurofilaments, which were significantly increased in the blood of affected individuals[54,55]. Findings on retinoneural structure in those presenting with a first episode of psychosis have thus far been conflicting. While some have found no observable differences in retinal sublayer thicknesses[56], others have identified reductions in total retinal thickness and visual cortex gray matter volume in small samples[57]. Future work should assess the relationship between mGC-IPL thinning and other indices of accelerated ageing in schizophrenia, such as gene expression and blood neurofilament protein levels.

Alternatively, mGC-IPL thinning may result from bidirectional multisystemic associations with schizophrenia. Chronic psychosis is associated with a greater prevalence of systemic comorbidities, such as hypertension, which influence mGC-IPL thickness[58] and adjustment for medical comorbidities and age diminishes effect estimates between retinal thickness and schizophrenia[59]. Furthermore, schizophrenia has well-established epidemiological and genetic co-distribution with metabolic dysfunction[3–5] and there is increasing evidence that retinal thinning may pre-date overt diabetes mellitus[60,61]. In our sensitivity analysis, we excluded all patients with diabetes mellitus during the study period to mitigate this; however it is conceivable that individuals within our population had early or undiagnosed metabolic syndrome. The finding that individuals with first-episode psychosis exhibit an initially accelerated but self-limiting decline in retinal thinning and brain gray matter has also led some to hypothesise a pharmacological aetiology for degeneration[62]. Finally, even certain health behaviours and lifecourse exposures, which may be more frequent in schizophrenia, are linked with reduced mGC-IPL. For example, alcohol misuse is highly prevalent among those with schizophrenia [63] and is known to lead to thinner mGC-IPL[64].

Retinovascular associations with schizophrenia

We noted an apparent association between schizophrenia and reduced fractal dimension, increased tortuosity and increased vascular calibre; however these differences were mostly accounted for by diabetes mellitus and hypertension. Appaji and Rao also noted increased tortuosity and wider venules, but found increased retinal fractal dimension and narrower arterioles[32,65,66]. The reasons likely relate to our contrasting study populations. While our cohort

consisted of older patients (mean age 64.9 years) attending an ophthalmic hospital, Appaji et al studied younger participants (early 30s) in a community setting and excluded those with significant medical comorbidity. Retinal metrics are known to differ between those with chronic disease and those recovering from a first episode of psychosis[56]. Recent investigations using OCT angiography (OCTA), a newer modality providing visualization of retinal vessel density and perfusion, highlight the complex relationship between disease duration and retinovascular indices. While several reports have shown reduced microvascular vessel density in schizophrenia[19,20,67], another has shown increased superficial vessel density in early-course patients[68] leading some to hypothesise that layer-specific changes may occur as disease progresses[21]. Further analyses should investigate the association between retinovascular and retinal layer changes. Incorporating longitudinal analyses would shed light on the temporal dynamics of retinovascular changes in psychosis.

A novel aspect of our work was the use of state-of-the-art retinal image analysis tools for fully automated extraction of retinovascular features in schizophrenia. We used two separate deep learning-based models - the VAMPIRE fractal dimension estimation module, based on a robustly validated U-Net segmentation algorithm developed by the Universities of Dundee and Edinburgh[69,70] and AutoMorph, an openly available fully automated pipeline for the extraction of retinal features[26]. Rejection rate based on image quality was similar to previous reports using retinal imaging[71,72]. Given the challenges in the agreement between different segmentation tools[27], we can have greater confidence in our findings on retinal fractal dimension where results by two independent fully automated segmentation systems.

This study should be considered within the broader limitations of retrospective observational research. Firstly, there are likely confounders which we could not adjust due to a lack of data. For example, smoking is more prevalent among individuals with psychosis[73] and is known to affect retinal vasculature[74]. Secondly, our case definition of schizophrenia was based on ICD codes from hospital admissions data which may be prone to misclassification bias. However, our strategy for identifying individuals with schizophrenia was such that any misclassification bias would likely underestimate our effect measure[30]. Thirdly, the average age and prevalence of medical comorbidities, such as diabetes mellitus, of individuals with schizophrenia was relatively high in our study and as such our findings may not reflect the situation in younger patients without other systemic diseases presenting with a first episode of psychosis[19]. However, given the corroboration of our results with other studies where similar associations were found in younger groups and those with medical comorbidities excluded, the possibility of a unique sample effect seems unlikely.

In conclusion, we show that individuals with schizophrenia have both altered retinovascular indices and thinner mGC-IPL. While the former was accounted for by comorbid diabetes mellitus and hypertension, we found independent associations with thinner inner retinal features similar to those observed in other neurodegenerative conditions, such as multiple sclerosis and Alzheimer's disease[75]. The absence of some of these findings in younger individuals presenting with a first episode of psychosis supports a neurodegenerative mechanism which could relate to a primary degenerative phenomenon or secondary to metabolic impairment. Longitudinal analyses, which incorporate multimodal imaging and ancillary investigations of neurodegeneration, such as the blood neurofilament protein concentration and gene expression, are needed to elucidate the

developmental course of these changes[19,56]. Further investigations are warranted into whether oculomic biomarkers could help characterise disease course, predict treatment response or even risk-stratify those patients most at risk of developing cognitive decline, cardiovascular disease and other devastating sequelae of schizophrenia.

Author Contributions

Dr Wagner and Professor Keane had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Wagner, Cortina-Borja, Silverstein, Alexander, Pontikos, Denniston, Rahi, Petzold, Keane

Acquisition, analysis or interpretation of data: All authors

Drafting of the manuscript: Wagner, Silverstein, Liu, MacGillivray, Alexander, Denniston, Petzold, Rahi

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Data Sharing Statement:

National and international collaborations are welcomed however the data are subject to the contractual restrictions of the data sharing agreements between National Health Service Digital, Moorfields Eye Hospital and University College London and are therefore not available for access beyond the AlzEye research team. Researchers should contact the Chief Investigator at p.keane@ucl.ac.uk.

Conflict of Interest Disclosures

Professor Trucco, Dr MacGilivray, Mr Hogg and Dr Mookiah are developers of the VAMPIRE retinal analysis system. Mr Zhou, Dr Wagner, Professor Alexander and Professor Keane developed the AutoMorph retinal analysis system. Dr Khawaja has acted as a consultant to Abbvie, Aerie, Google Health, Novartis, Reichert, Santen and Thea.

The authors have no other conflicts of interest to disclose.

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Figure Legends

Figure 1: Retinal images representing optical coherence tomography with the retinal nerve fibre layer and macular ganglion cell-inner plexiform layer indicated (A), the nine regions of the ETDRS grid centred on the fovea (B) and an example colour fundus photograph (C). Note that for variables from optical coherence tomography, only measurements from the inner ETDRS regions were included.

C: Centre, II: inner inferior, IN: inner nasal, IS: inner superior, IT: inner temporal, mGC-IPL: macular ganglion cell-inner plexiform layer, OI: outer inferior, ON: outer nasal, OS: outer superior, OT: outer temporal. RNFL: retinal nerve fibre layer.

Figure 2: Flow chart of included patients with patient-level and image-level inclusion and exclusion criteria detailed.

Tables

	Characteristic	Schizophrenia (*n*=485)	No schizophrenia (*n*=100, 931)	*p*-value[1]
Demographics	**Age (years)**	64.9 ± 12.2	65.9 ± 13.7	0.08
	Female sex (*n* (%))	258 (53.2)	53,253 (51.2)	0.37
	Socioeconomic status (1=most deprived)	4.1 ± 2.3	5.3 ± 2.6	**<0.001**
Comorbidity	**Hypertension (*n* (%))**	407 (83.9)	49,971 (48.0)	**<0.001**
	Diabetes mellitus (*n* (%))	364 (75.1)	28,762 (27.6)	**<0.001**
	Glaucoma (n (%))	38 (7.8)	7,602 (7.3)	0.71
	Age-related macular degeneration (n (%))	19 (3.9)	5,322 (5.3)	0.18
	Cataract (n (%))	123 (25.4)	20,383 (20.2)	**0.007**
CFP	**Image quality**	0.59 ± 0.34	0.51 ± 0.35	**<0.001**
	Cup-disc ratio[3]	0.47 ± 0.09	0.46 ± 0.09	**<0.001**
	Arteriolar calibre (μm)	65.1 ± 8.4	63.6 ± 8.0	**<0.001**
	Venular calibre (μm)	73.5 ± 10.1	72.0 ± 9.2	**<0.001**
	Fractal dimension	1.46 ± 0.06	1.47 ± 0.05	**<0.001**
	Fractal dimension (VAMPIRE)[4]	1.51 ± 0.03	1.52 ± 0.03	**<0.001**
	Vessel density	0.072 ± 0.013	0.073 ± 0.012	**0.027**
	Distance tortuosity	3.48 ± 1.3	3.41 ± 1.2	0.58
	Tortuosity density	0.71 ± 0.04	0.70 ± 0.04	**<0.001**
OCT	**RNFL (μm)**	26.6 ± 18.5	26.7 ± 13.4	**<0.001**
	mGC-IPL (μm)	77.4 ± 16.8	82.4 ± 16.1	**<0.001**

Table 1: Baseline and summary statistics for the cohort. Results are shown at the level of the individual - those from retinal imaging represent the means of the two eyes. Except where indicated, all characteristic results are shown as mean ± standard deviation.

[1] *p*-values were obtained using the Mann-Whitney-Wilcoxon test for continuous variables and the *U*-Statistic permutation test of independence for categorical variables.

[2]Socioeconomic status was missing for no individuals with schizophrenia and 343 individuals without schizophrenia.

[3] Optic nerve measurements were available for 450 individuals with schizophrenia and 93,045 without.

[4] Note that for VAMPIRE, data from 443 individuals with schizophrenia and 105,413 controls were available.
CFP: Colour fundus photography, OCT: optical coherence tomography, mGC-IPL: macular ganglion cell-inner plexiform layer, RNFL: retinal nerve fibre layer

Table 2: Adjusted associations between prevalent schizophrenia and retinal oculomic biomarkers from colour fundus photography and optical coherence tomography. All characteristics from colour fundus photography are derived from AutoMorph except where indicated.

		Model 1[1]		**Model 2**[2]		**Non-diabetic subgroup**[3]	
Modality	**Characteristic**	**Regression coefficient**	***p*-value**	**Regression coefficient**	***p*-value**	**Regression coefficient**	***p*-value**
CFP	CDR (ratio)	0.01 (0.01, 0.02)	**6.0×10^{-4}**	0.01 (0.00, 0.02)	0.041	0.01 (0.00, 0.03)	0.08
	Arteriolar calibre (per SD)	0.11 (0.03, 0.19)	**0.010**	0.04 (-0.04, 0.12)	0.34	0.09 (-0.07, 0.25)	0.28
	Venular calibre (per SD)	0.08 (0.00, 0.16)	**0.048**	0.02 (-0.06, 0.10)	0.65	0.13 (-0.02, 0.29)	0.10
	Fractal dimension (per SD)	-0.17 (-0.24, -0.11)	**2.4×10^{-7}**	-0.05 (-0.11, 0.02)	0.14	-0.11 (-0.24, 0.02)	0.10
	Fractal dimension (VAMPIRE) (per SD)	-0.27 (-0.35, -0.19)	**1.1×10^{-10}**	-0.14 (-0.22, -0.05)	**0.001**	-0.05 (-0.21, 0.11)	0.56
	Vessel density (per SD)	-0.15 (-0.22, -0.09)	**1.3×10^{-7}**	-0.06 (-0.12, 0.01)	0.11	-0.09 (-0.23, 0.05)	0.21
	Distance tortuosity (per SD)	0.02 (-0.05, 0.09)	0.60	0.00 (-0.01, 0.15)	0.96	-0.04 (-0.21, 0.07)	0.55
	Tortuosity density (per SD)	0.12 (0.05, 0.20)	**0.002**	0.07 (-0.02, 0.14)	0.08	0.05 (-0.11, 0.20)	0.55
OCT	RNFL (μm)	-0.37 (-1.49, 0.75)	0.52	-0.29 (-1.41, 0.84)	0.61	-1.02 (-3.22, 1.18)	0.36
	mGC-IPL (μm)	-4.87 (-6.22, -3.51)	**2.1×10^{-12}**	-4.05 (-5.40, -2.69)	**5.4×10^{-9}**	-3.99 (-6.67, -1.30)	**0.004**

[1]Adjusted for age, sex, socioeconomic status, and image quality.
[2]Adjusted for age, sex, socioeconomic status, diabetes mellitus, hypertension and image quality.
[3] For AutoMorph and TABS, this was 121 individuals with schizophrenia and 75,627 without. For VAMPIRE, this was 104 (165 eyes) individuals with schizophrenia and 67,416 (111,915 eyes) controls. Adjustment is the same as for model 2 without diabetes mellitus.
CDR: cup-disc ratio, CFP: colour fundus photography, mGC-IPL: macular ganglion cell-inner plexiform layer, OCT: optical coherence tomography, RNFL: retinal nerve fibre layer, SD: standard deviation

		Younger subgroup[1]		Older subgroup[2]	
Modality	**Characteristic**	**Regression coefficient**	***p*-value**	**Regression coefficient**	***p*-value**
CFP	CDR (ratio)	0.01 (0.00, 0.03)	0.19	0.01 (0.00, 0.02)	0.12
	Arteriolar calibre (per SD)	0.17 (0.00, 0.34)	**0.046**	0.01 (-0.09, 0.10)	0.87
	Venular calibre (per SD)	0.09 (-0.08, 0.25)	0.31	-0.01 (-0.10, 0.08)	0.89
	Fractal dimension (per SD)	0.14 (-0.01, 0.28)	0.06	-0.09 (-0.16, -0.01)	**0.025**
	Fractal dimension (VAMPIRE) (per SD)	-0.23 (-0.41, -0.04)	**0.016**	-0.11 (-0.20, -0.01)	**0.027**
	Vessel density (per SD)	0.08 (-0.07, 0.23)	0.28	-0.08 (-0.16, -0.01)	0.037
	Distance tortuosity (per SD)	-0.02 (-0.17, 0.13)	0.79	0.00 (-0.09, 0.08)	0.95
	Tortuosity density (per SD)	-0.01 (-0.26, 0.06)	0.23	0.11 (0.02, 0.20)	**0.017**
OCT	RNFL (μm)	-0.08 (-2.11, 1.96)	0.94	-0.48 (-1.82, 0.86)	0.48
	mGC-IPL (μm)	-2.90 (-5.55, -0.24)	**0.033**	-4.43 (-6.00, -2.85)	**3.6×10^{-8}**

Table 3. Adjusted associations between prevalent schizophrenia and retinal oculomic biomarkers from colour fundus photography and optical coherence tomography stratified by age. All characteristics from colour fundus photography are derived from AutoMorph except where indicated. Models were Adjusted for age, sex, socioeconomic status, diabetes mellitus, hypertension and image quality.

[1]For AutoMorph and TABS, this was 111 individuals (181 eyes) with schizophrenia and 24,847 (44,159) without. For VAMPIRE, this was 100 (166 eyes) with schizophrenia and 23,657 (41,984 eyes) controls.
[2]For AutoMorph and TABS, this was 342 individuals (566 eyes) with schizophrenia and 66,761 (121,241 eyes) without. For VAMPIRE, this was 308 individuals (466 eyes) with schizophrenia and 67,760 (106,958 eyes) controls.

CDR: cup-disc ratio, CFP: colour fundus photography, mGC-IPL: macular ganglion cell-inner plexiform layer, OCT: optical coherence tomography, RNFL: retinal nerve fibre layer, SD: standard deviation