# Association Between Retinal Features From Multimodal Imaging and Schizophrenia: findings from the AlzEye Study

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## Purpose

The potential association of schizophrenia with distinct retinal changes is of clinical interest, primarily due to the potential for (i) monitoring disease progression and (ii) identifying those at risk of debilitating sequelae, such as cognitive decline and dementia.

However, research in this area has been challenging due to lack of sufficiently large and detailed cohorts. We investigated the association between retinal biomarkers from multimodal imaging (oculomics) and schizophrenia in a large real-world population.

## Methods

This cross-sectional analysis used data from the AlzEye study [1], a retrospective cohort of 154,830 patients over the age of 40 who had retinal imaging at Moorfields Eye Hospital from 2008-2018. Ophthalmic data were deterministically linked with the Hospital Episode Statistics (HES) Admitted Patient Care Database, which is coded in ICD-10.

*Variables*

Retinovascular indices and optic nerve characteristics were extracted from colour fundus photography using the *Automorph* [2] and *VAMPIRE* [3] automated segmentation tools. Thicknesses of the macular retinal nerve fiber layer (RNFL) and ganglion cell-inner plexiform layer (mGCIPL) were extracted from optical coherence tomography via the Topcon Advanced Boundary Segmentation (TABS) system [4].

The primary objective was to assess whether those with the primary exposure, prevalent schizophrenia (ICD-10: *F20*), were associated with a larger optic cup-disc ratio (CDR) and thinner mGC-IPL and macular retinal nerve fiber layer (RNFL) compared with controls. We additionally investigated whether retinal vascular morphology differed in patients with schizophrenia. Secondary exposure variables were age, sex, hypertension (ICD-10: *I10*, *I15*), diabetes (ICD-10: *E10*, *E11*), and index of multiple deprivation.

*Statistical modelling*

Linear mixed effects models were used to examine the association between schizophrenia and retinal biomarkers.

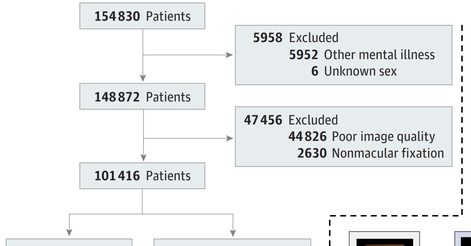



*Figure 1*: Flowchart of included patients and exclusion criteria

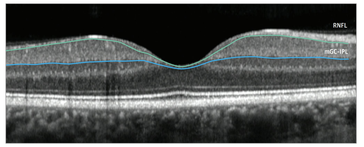



*Figure 2*: Optical Coherance Tomography scan, with the RNFL and mGC-IPL layers highlighted.

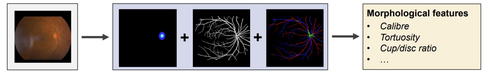



*Figure 3*: *Automorph* pipeline for colour fundus photographs

## Results

| Characteristic | Mean (SD) Schizophrenia (n = 485) | No schizophrenia (n = 100 931) | *P* value |
|---|---|---|---|
| **Demographic data** | | | |
| Age, y | 64.9 (12.2) | 65.9 (13.7) | .08 |
| Sex, No. (%) | | | |
| Female | 258 (53.2) | 53 253 (52.8) | .37 |
| Male | 227 (46.8) | 47 678 (47.2) | |
| Socioeconomic status | 4.1 (2.3) | 5.3 (2.6) | <.001 |
| Comorbidity, No. (%) | | | |
| Hypertension | 407 (83.9) | 49 971 (48.0) | <.001 |
| Diabetes | 364 (75.1) | 28 762 (27.6) | <.001 |
| Glaucoma | 38 (7.8) | 7602 (7.3) | .71 |
| Age-related macular degeneration | 19 (3.9) | 5322 (5.3) | .18 |
| Cataract | 123 (25.4) | 20 383 (20.2) | .007 |

*Table 1*: Baseline and summary statistics for the cohort.

Results are shown at the level of individual; those from retinal imaging represent the mean of the 2 eyes.

A total of 485 individuals (747 eyes) with schizophrenia and 100,931 individuals (165,400 eyes) without schizophrenia were included after images underwent quality control and potentially confounding conditions were excluded. Individuals with schizophrenia were more likely to have hypertension (407 [83.9%] vs 49 971 [48.0%]) and diabetes (364 [75.1%] vs 28 762 [27.6%]).

| Characteristic | Model 1 Regression coefficient (95% CI) | Model 1 *P* value | Model 2 Regression coefficient (95% CI) | Model 2 *P* value | Subgroup without diabetes Regression coefficient (95% CI) | Subgroup without diabetes *P* value |
|---|---|---|---|---|---|---|
| **Color fundus photography** | | | | | | |
| CDR (ratio) | 0.01 (0.01 to 0.02) | $6.0 \times 10^{-4}$ | 0.01 (0.00 to 0.02) | .04 | 0.01 (0.00 to 0.03) | .08 |
| Arteriolar caliber (per SD) | 0.11 (0.03 to 0.19) | .01 | 0.04 (−0.04 to 0.12) | .34 | 0.09 (−0.07 to 0.25) | .28 |
| Venular caliber (per SD) | 0.08 (0.00 to 0.16) | .048 | 0.02 (−0.06 to 0.10) | .65 | 0.13 (−0.02 to 0.29) | .10 |
| Fractal dimension (per SD) | −0.17 (−0.24 to −0.11) | $2.4 \times 10^{-7}$ | −0.05 (−0.11 to 0.02) | .14 | −0.11 (−0.24 to 0.02) | .10 |
| Fractal dimension, VAMPIRE (per SD) | −0.27 (−0.35 to −0.19) | $1.1 \times 10^{-10}$ | −0.14 (−0.22 to −0.05) | .001 | −0.05 (−0.21 to 0.11) | .56 |
| Vessel density (per SD) | −0.15 (−0.22 to −0.09) | $1.3 \times 10^{-7}$ | −0.06 (−0.12 to 0.01) | .11 | −0.09 (−0.23 to 0.05) | .21 |
| Distance tortuosity (per SD) | 0.02 (−0.05 to 0.09) | .60 | 0.00 (−0.01 to 0.15) | .96 | −0.04 (−0.21 to 0.07) | .55 |
| Tortuosity density (per SD) | 0.12 (0.05 to 0.20) | .002 | 0.07 (−0.02 to 0.14) | .08 | 0.05 (−0.11 to 0.20) | .55 |
| **Optical coherence tomography** | | | | | | |
| RNFL, µm | −0.37 (−1.49 to 0.75) | .52 | −0.29 (−1.41 to 0.84) | .61 | −1.02 (−3.22 to 1.18) | .36 |
| mGC-IPL, µm | −4.87 (−6.22 to −3.51) | $2.1 \times 10^{-12}$ | −4.05 (−5.40 to −2.69) | $5.4 \times 10^{-9}$ | −3.99 (−6.67 to −1.30) | .004 |

*Table 2*: Adjusted associations between prevalent schizophrenia and retinal oculomic biomarkers from colour fundus photography and optical coherence tomography. Model 1 was adjusted for age, sex, IMD, and image quality. Model 2 was additionally adjusted for diabetes and hypertension status. Regarding the subgroup without diabetes, for AutoMorph and TABS, this was 121 individuals with schizophrenia and 75 627 without. For VAMPIRE, this was 104 individuals (165 eyes) with schizophrenia and 67 416 (111 915 eyes) without. Adjustment is the same as for model 2 without diabetes.

The schizophrenia group had marked thinning in the mGCIPL (-4.05 microns, 95% CI: -5.40, -2.69, p=5.4x10-9), which persisted when investigating only patients without diabetes (-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). Following adjustment for hypertension and diabetes, retinal fractal dimension 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.

## Key Points

**Question**

Do individuals with schizophrenia have measurable differences in retinal morphology?

**Findings**

In this cross-sectional analysis of a cohort of data for 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 patients with schizophrenia.

**Meaning**

In this study, individuals with schizophrenia had reduced thickness of the inner retina, which may indicate heightened neurodegeneration.

## Discussion

In this study, we showed that individuals with schizophrenia have both altered retinovascular indices and thinner mGC-IPL. While the former was accounted for by comorbid diabetes 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 disease [5].

Longitudinal analyses that incorporate multimodal imaging and ancillary investigations of neurodegeneration, such as blood neurofilament protein concentration and gene expression, are needed to elucidate the developmental course of these changes. Further investigations are warranted into whether oculomic biomarkers could help characterize disease course, predict treatment response, or even risk-stratify those patients most at risk of developing cognitive decline, cardiovascular disease, and other sequelae of schizophrenia.

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