

Supplementary Online Content

Multimodal retinal ophthalmology in schizophrenia: findings from the AlzEye study

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eMethods

All retinal images in this report were macula-centered. OCTs captured a 6.0mm x 6.0mm area with 512 A scans per B scan and 128 horizontal B scans per volume.

Both AutoMorph and VAMPIRE take, as input, a color fundus photography image file and consecutively pre-process the image, quantify image quality, segment the retinal vasculature and optic nerve using state-of-the-art deep learning methods, extract clinically relevant oculomic features and output a comma-separated value file of numerical outputs (for AutoMorph, this includes a continuous score of image quality). All features are extracted using standard formulae. Further details for VAMPIRE are available at <https://vampire.computing.dundee.ac.uk>; for AutoMorph, details and access to the models are available at <https://rmaphoh.github.io/projects/automorph.html>. For this study, we included only images categorised as ‘good’ or ‘usable’ by AutoMorph. Further details for how this is computed can be found elsewhere¹. Retinal sublayers for the four parafoveal subfields, defined by the Early Treatment for Diabetic Retinopathy Study were averaged for analysis (i.e. we did not include the fovea or outer subfields)².

The mGC-IPL layer corresponds to the cell body and dendrites of the retinal ganglion cells (RGC) while the RNFL represents the axons of the RGCs as they project towards the optic nerve and visual pathways. Retinovascular indices in the study included calibre, tortuosity, vessel density and fractal dimension. Calibre is a measure of the width of the retinal vessels. Tortuosity is a quantitative metric of the curvature of the retinal vessels. Vessel density reflects the number of pixels with the image occupied by retinal vessels. Fractal dimension is a measure of self-similarity derived from non-linear dynamics where a higher number

equates to a greater level of complexity. The cup-disc ratio is a measure of optic nerve morphology calculated by dividing the vertical cup size by the vertical disc size.

Index of multiple deprivation (IMD decile) was estimated by permuting the IMD 2015 rank from the patient's postcode through Lower Super Output Areas followed by aggregation into deciles³. The IMD is provided by the UK Ministry of Housing, Communities and Local Government.

Imaging device	Schizophrenia (n=485)	No schizophrenia (n=100, 931)	p-value
1000-MK2	12 (2.5)	2,285 (2.3)	0.233
3DOCT-2000	7 (1.4)	867 (0.9)	
3DOCT-2000SA	380 (78.4)	81,676 (80.9)	
FD_OCT	82(16.9)	15,422 (15.3)	
Triton plus	4 (1)	699 (0.7)	

eTable 1: Distribution of retinal imaging devices for individuals with and without schizophrenia.

mGCIPL		No schizophrenia		Schizophrenia	
		Regression coefficient (95% CI)	p value	Regression coefficient (95% CI)	p value
Age	Per decile	-2.54 (-2.62, -2.46)	<2.0 x 10 ⁻¹⁶	-3.20 (-4.40, -1.99)	3.4 x 10 ⁻⁷
Sex	Female	Reference		Reference	
	Male	0.71 (0.52, 0.89)	1.4 x 10 ⁻¹³	-0.88 (-3.77, 2.02)	0.56
Socioeconomic status	Per decile	0.22 (0.18, 0.26)	<2.0 x 10 ⁻¹⁶	-0.05 (-0.66, 0.56)	0.87
Hypertension	Absent	Reference		Reference	
	Present	-1.23 (-1.45, -1.00)	<2.0 x 10 ⁻¹⁶	4.14 (0.23, 8.03)	0.039
Diabetes mellitus	Absent	Reference		Reference	
	Present	-0.84 (-1.08, -0.60)	2.9 x 10 ⁻¹²	-1.47 (-4.72, 1.78)	0.38
Image quality	Per SD increase	1.05 (0.97, 1.13)	<2.0 x 10 ⁻¹⁶	0.23 (-0.94, 1.40)	0.70

eTable 2: Adjusted regression coefficients for secondary exposure variables stratified by those with schizophrenia versus those without schizophrenia.

CI: confidence interval, mGCIPL: macular ganglion cell-inner plexiform layer, SD: standard deviation

	Characteristic	Schizophrenia (n=121)	No schizophrenia (n=73,574)	p-value ¹
Demographics	Age (years)	66.6 +/- 12.9	64.5 +/- 12.0	0.09
	Female sex (n (%))	67 (55.4)	39,250 (53.3)	0.70
	Socioeconomic status (1=most deprived)	4.3 +/- 2.4	5.5 +/- 2.7	<0.001
Comorbidity	Hypertension (n (%))	94 (77.7)	24,754 (33.6)	<0.001
	Glaucoma (n (%))	10 (8.2)	5,416 (7.4)	0.87
	Age-related macular degeneration (n (%))	8 (6.6)	4,404 (6.0)	1
	Cataract (n (%))	31 (25.6)	13,034 (17.7)	0.033
CFP	Image quality	0.88 +/- 0.13	0.91 +/- 0.12	0.008
	Cup-disc ratio ²	0.47 +/- 0.10	0.45 +/- 0.09	0.029
	Arteriolar calibre (µm)	64.3 +/- 8.5	63.2 +/- 8.0	0.13
	Venular calibre (µm)	73.7 +/- 9.9	71.4 +/- 9.1	0.009
	Fractal dimension	1.46 +/- 0.06	1.48 +/- 0.05	0.002
	Fractal dimension (VAMPIRE) ³	1.51 +/- 0.04	1.52 +/- 0.03	0.16
	Vessel density	0.065 +/- 0.015	0.069 +/- 0.014	0.004
	Distance tortuosity	3.46 +/- 1.6	3.37 +/- 1.2	0.57
	Tortuosity density	0.70 +/- 0.04	0.70 +/- 0.03	0.07
OCT	RNFL (µm)	25.9 +/- 15.1	26.8 +/- 13.1	0.003
	mGC-IPL (µm)	77.9 +/- 20.9	83.3 +/- 16.0	<0.001

eTable 3: Characteristics of the subgroup without diabetes mellitus.

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 Optic nerve measurements were available for 106 individuals with schizophrenia and 65,241 without.

³ Note that for VAMPIRE, data from 104 individuals with schizophrenia and 67,416 controls were available.

CFP: color fundus photography, mGC-IPL: macular ganglion cell-inner plexiform layer, OCT: optical coherence tomography, RNFL: retinal nerve fiber layer.

	Characteristic	Schizophrenia (n=111)	No schizophrenia (n=24,847)	p-value ¹
Demographics	Age (years)	48.0 +/- 5.4	47.2 +/- 5.2	0.06
	Female sex (n (%))	44 (39.6)	10,842 (43.6)	0.43
	Socioeconomic status (1=most deprived)	4.0 +/- 2.3	4.9 +/- 2.6	<0.001
Comorbidity	Hypertension (n (%))	83 (74.8)	4,643 (18.7)	<0.001
	Diabetes mellitus (n (%))	84 (75.7)	4,183 (16.8)	<0.001
	Glaucoma (n (%))	*	*	0.85
	Age-related macular degeneration (n (%))	*	*	0.48
	Cataract (n (%))	12 (10.8)	1,885 (7.6)	0.26
CFP	Image quality	0.91 +/- 0.13	0.95 +/- 0.09	<0.001
	Cup-disc ratio ²	0.48 +/- 0.07	0.45 +/- 0.08	<0.001
	Arteriolar calibre (µm)	66.0 +/- 10.1	63.6 +/- 7.7	0.006
	Venular calibre (µm)	73.2 +/- 12.5	70.1 +/- 8.4	0.013
	Fractal dimension	1.48 +/- 0.05	1.50 +/- 0.05	<0.001
	Fractal dimension (VAMPIRE) ³	1.52 +/- 0.03	1.54 +/- 0.03	<0.001
	Vessel density	0.07 +/- 0.01	0.08 +/- 0.01	<0.001
	Distance tortuosity	3.23 +/- 1.0	3.07 +/- 0.9	0.11
	Tortuosity density	0.69 +/- 0.03	0.69 +/- 0.02	0.36
OCT	RNFL (µm)	27.5 +/- 25.5	26.6 +/- 11.5	0.022
	mGC-IPL (µm)	81.7 +/- 15.4	87.1 +/- 14.5	<0.001

eTable4: Characteristics of the young subgroup (<55 years of age).

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 Optic nerve measurements were available for 106 individuals with schizophrenia and 65,241 without.

³ Note that for VAMPIRE, data from 104 individuals with schizophrenia and 67,416 controls were available.

*Raw values suppressed due to small numbers

CFP: color fundus photography, mGC-IPL: macular ganglion cell-inner plexiform layer, OCT: optical coherence tomography, RNFL: retinal nerve fiber layer.

References

1. Zhou Y, Wagner SK, Chia MA, et al. AutoMorph: Automated Retinal Vascular Morphology Quantification Via a Deep Learning Pipeline. *Transl Vis Sci Technol.* 2022;11(7):12.
2. Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema. *Arch Ophthalmol.* 1985;103:1796-1806.
3. Ministry of Housing, Communities, Local Government. English indices of deprivation 2015. Published online September 30, 2015. Accessed October 10, 2022. <https://www.gov.uk/government/statistics/english-indices-of-deprivation-2015>