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Association between visual impairment and psychosis: A longitudinal study and nested case-control study of adults

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ABSTRACT

Background: Theories propose that visual impairment might increase the risk of psychosis, and vice versa. We aimed to investigate the relationship between visual impairment and psychosis in the UK Biobank cohort.
Study design: In a nested case control study of ~116,000 adults, we tested whether a Schizophrenia Spectrum Disorder (SSD) diagnosis as exposure was associated with visual impairment. We also tested longitudinally whether poorer visual acuity, and thinner retinal structures on Optical Coherence Tomography (OCT) scans in 2009 were associated with psychotic experiences in 2016. We adjusted for age, sex, depression and anxiety symptoms; and socioeconomic variables and vascular risk factors where appropriate. We compared complete case with multiple imputation models, designed to reduce bias potentially introduced by missing data.
Results: People with visual impairment had greater odds of SSD than controls in multiply imputed data (Adjusted Odds Ratio [AOR] 1.42, 95 % Confidence Interval [CI] 1.05–1.93, $p = 0.021$). We also found evidence that poorer visual acuity was associated with psychotic experiences during follow-up (AOR per 0.1 point worse visual acuity score 1.06, 95 % CI 1.01–1.11, $p = 0.020$; and 1.04, 95 % CI 1.00–1.08, $p = 0.037$ in right and left eye respectively). In complete case data (15 % of this cohort) we found no clear association, although confidence intervals included the multiple imputation effect estimates. OCT measures were not associated with psychotic experiences.
Conclusions: Our findings highlight the importance of eye care for people with psychotic illnesses. We could not conclude whether visual impairment is a likely causal risk factor for psychosis.

1. Introduction

A cross-sectional association exists between visual impairment and Schizophrenia-Spectrum Disorders (SSDs), or psychotic symptoms more broadly (Shoham et al., 2021a). Possible explanations include: SSDs increase the risk of visual impairment (hypothesis 1) (Viertiö et al., 2007a); visual impairment increases the risk of SSDs (hypothesis 2) (Landgraf and Osterheider, 2013); or a common neuropathological process, or confounding by other factors, underlies both (Adams and Nasrallah, 2018). Understanding the mechanisms of association might inform preventative strategies for these conditions.

Regarding hypothesis 1, SSDs might contribute causally to visual impairment through reducing access to optical care (Viertiö et al., 2007b); antipsychotic medication side effects (Richa and Yazbek, 2010); or raised incidence of comorbidities such as diabetes and hypertension (Osborn et al., 2015). The 'Protection against Schizophrenia' (PaSZ) model proposes that whilst congenital blindness could be protective, impaired visual capacity might predispose to psychosis, as per hypothesis 2 (Landgraf and Osterheider, 2013).

Our Mendelian Randomisation (MR) study of adults supported hypothesis 1: that SSDs contribute causally to poorer vision. This study found no evidence that myopia (the most common form of visual

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impairment) was causally associated with subsequent SSD, contrary to hypothesis 2 (Shoham et al., 2022). One possible explanation for this is that an unidentified third factor(s), for example early life influences or lower socioeconomic status, contribute to both schizophrenia and eyesight problems in traditional observational studies, with their influence being eliminated by the MR study design. Alternatively, if visual impairment is only a causal risk factor for psychosis at a younger stage of development, this might not have been captured by the MR study, which measured lifetime exposure to visual impairment; possibly diluting this effect. Findings regarding visual impairment and future psychosis in older adults have been mixed, likely due to different measures of psychosis and visual impairment used (Blazer et al., 1996; Hamedani et al., 2020; Stafford, 2019). For example, one study looking at Very Late-Onset Schizophrenia-Like Psychosis (VLOSLP) and blindness or low vision found a negative association (Stafford, 2019); whereas studies looking at the broader categories of psychotic symptoms and visual impairment found a positive association (Blazer et al., 1996; Hamedani et al., 2020).

Some causes of visual impairment damage retinal structures, which can be measured objectively (Singh et al., 2020). The retina is an extension of the central nervous system that can be easily visualised and often mirrors cerebral changes (Komatsu et al., 2022). Optical Coherence Tomography (OCT) involves non-invasive, high resolution imaging of the retina (Komatsu et al., 2022). Relative to healthy controls, OCT studies have found reductions in macular thickness, macular volume, and ganglion cell-inner plexiform and retinal nerve fiber layer thickness in schizophrenia (Komatsu et al., 2022; Silverstein et al., 2020). Neural cell loss, common to the brain and the retina, has been proposed to underlie these findings (Silverstein et al., 2022). Recent evidence shows associations between retinal thinning and poorer visual acuity in ophthalmic and neurologic populations, but it is unclear to what extent retinal changes correlate with poorer visual acuity seen in people with SSDs, and whether retinal changes may explain poorer visual acuity in this population (Abd Hamid et al., 2021; Cheema et al., 2014; Lin et al., 2022).

Using data from the UK Biobank adult cohort, we conducted the largest (nested) case control study to test the hypothesis that participants with visual impairment would have higher odds of an SSD diagnosis. We also tested whether visual acuity and thinner retinal neural layers at baseline were associated with psychotic experiences during follow-up, to test hypothesis 2; and whether retinal structure thickness was associated with visual acuity in this population, to test whether retinal damage might underlie any association between SSDs and poorer vision.

2. Methods

2.1. Sample

The UK Biobank cohort comprises over half a million participants who were recruited aged 40–69 in 2006–2010. UK Biobank participants contribute to a large biomedical database by donating biological samples and answering questionnaires. The North West Multi-Centre Research Ethics committee provided ethical approval. Further details are available: https://www.ukbiobank.ac.uk/. Our sample includes 116,012 participants in whom ocular testing was undertaken in 2009 (Sudlow et al., 2015).

2.2. Nested case control study

Hypothesis: people with below-normal visual acuity are more likely to have a prior diagnosis of a schizophrenia-spectrum disorder compared to people with normal visual acuity.

2.2.1. Outcome variable: visual impairment

Habitual distance visual acuity was tested separately in each eye (in 2009) using any current corrective aids, giving a measurement consistent with participants' day-to-day visual acuity (Littlejohns et al., 2021). Standard scoring was used to determine logMAR score (Littlejohns et al., 2021), with 0 being roughly equivalent to a 6/6 or 20/20 Snellen chart reading; positive numbers indicate poorer vision; and negative numbers indicate better vision. Scores across the UK Biobank baseline sample ranged from −1.06 to 1.35 (UK Biobank, n.d.-a; UK Biobank, n.d.-b). Our primary outcome variable was binary visual impairment status, with visual impairment defined as a measurement >0 in either eye (Cumberland et al., 2015).

2.2.2. Exposure variable: Schizophrenia Spectrum Disorder

Our exposure variable was an International Classification of Diseases 10 (ICD10) diagnosis code F20-29 (Schizophrenia-Spectrum Disorder), derived from Hospital Episode Statistics (HES) data from linked hospital records. We coded participants with any F20-F29 code prior to outcome measurement (in 2009) as having a preceding SSD, and other participants as not having these disorders. We also coded participants as positive if they had an equivalent ICD9 diagnosis.

2.2.3. Confounders

We adjusted for participant age in years; and sex, reported as male/female. We also adjusted for three variables associated with Socioeconomic Status (SES): average household income before tax (categorised as <£18,000/£18,000 to £30,999/£31,000 to £51,999/£52,000); age of leaving full time education (a discrete self-reported variable in years); and Townsend deprivation score. The latter is a logmar score designed to measure relative area level deprivation (Yousaf and Bonsall, 2017). We adjusted for SES variables separately, as these could reduce access to optical care and be causal mechanisms, as well as confounders, in the hypothesised relationship between SSD and visual acuity (Meehl, 1971; Miller and Chapman, 2001).

2.2.4. Statistical analyses

We ran logistic regression models in Stata/MP versions 16 and 17 (StataCorp, 2019, 2021). We ran models unadjusted; and adjusted for putative confounding variables.

2.2.5. Missing data

Missing data are substantial in the UK Biobank, reducing power to detect associations and potentially introducing bias. We used multiple imputation through chained equations for primary analyses, with imputation including all model variables and multiple auxiliary variables to improve prediction of missing variables (included in supplementary information). We used the Stata command *mi impute chained* (StataCorp, 2021) to generate 20 imputations, and combined these for analysis using Rubin's rules (White et al., 2011). We included only participants with a measured logMAR score in the left eye (the ocular measure with least missing data). We repeated analyses using only participants with complete data as a sensitivity analysis. This was not the primary analysis because multiple imputation gives less biased results than complete case analysis provided data are missing in relation to observed variables (Sterne et al., 2009), and the volume of missing data in our sample was substantial and liable to bias findings. We also report, in a supplement, results from multiple imputation analyses that included only participants with an observed logMAR score in both eyes; i.e. where no outcome data is imputed.

2.3. Cohort study

Hypothesis: There will be an association between poorer visual acuity/macular and retinal pigment layer thickness on OCT scan and subsequent psychotic experiences.

2.3.1. Outcome variable: psychotic experiences

Participants completed an online questionnaire on symptoms and

experiences of mental illness in 2016. It was developed based on validated measures in consultation with a reference panel (Davis et al., 2019). Four questions measured psychotic-like experiences: believing in an unreal conspiracy against the self; believing in unreal communications or signs; hearing an unreal voice; and seeing an unreal vision. Participants were asked whether they had ever had these, and if so at what age the experience first occurred. We classed psychotic experiences as positive if participants reported any except for seeing an unreal vision, to avoid categorising cases of Charles Bonnet Syndrome as psychosis (Hamedani and Pelak, 2019). We discounted psychotic experiences where the reported age of first occurrence was older than age at vision testing.

2.3.2. Exposure variables: visual acuity, macular and retinal pigment epithelium layer thickness

Our primary exposure variables were continuous logMAR scores in each eye separately at baseline (2009), as described above.

Additionally, 67,321 participants underwent retinal imaging between 2009 and 2010 using a spectral domain OCT device, which has an axial resolution of </=6 μm and a transverse resolution of approximately 15 μm (Keane et al., 2016). Automated software analysed the images, as described in detail elsewhere (Keane et al., 2016). We tested as secondary exposure variables baseline macula and retinal pigment epithelium (RPE) layer thickness in micrometres. The macula is the area of the retina associated with highest visual acuity, whilst the RPE is a highly metabolically active layer which plays a crucial supportive and regulatory role in nourishing photoreceptors (Sharma et al., 2020).

2.3.3. Confounders and covariates

Few participants with a prior diagnosis of SSD completed the follow-up questionnaire, and none reported psychotic experiences at follow up. No baseline measure of the outcome was available. We adjusted models for two separate scores: one derived from the Patient Health Questionnaire 2 (PHQ2) (Kroenke et al., 2003); and the response to the question "Over the past two weeks, how often have you felt tense, fidgety or restless?" with a score 1–4 allocated based on possible answers not at all/several days/more than half the days/nearly every day (Spitzer et al., 2006). We intended to account for baseline depression and anxiety symptoms which are known to be associated with psychotic symptoms (Bourgin et al., 2020).

We also adjusted for age and sex as described above. In further models, we adjusted for vascular risk factors, since these are risk factors both for retinal and eyesight damage (Silverstein et al., 2020) and neurodegenerative states (Livingston et al., 2020), which are associated with psychosis (Aarsland, 2020). These were: Body Mass Index (BMI) as a continuous measure; diabetes as a binary self-reported variable; and self-reported categorical smoking status (past smoker/current smoker/never smoker). In a final model, we adjusted for all putative confounders, including the socioeconomic variables described above.

We tested separately whether baseline OCT measures were cross-sectionally associated with baseline logMAR scores, unadjusted, and adjusted for age and sex.

2.3.4. Statistical analyses

We ran analyses in Stata/MP versions 16 and 17 (StataCorp, 2019, 2021). We used logistic regression models where the outcome was binary (psychotic experiences), and linear regression where it was continuous (visual acuity). We ran models unadjusted; and adjusted for putative confounding variables.

2.3.5. Missing data

As described in the previous section, we used multiply imputed data for primary analyses. We excluded participants who did not have an observed left eye logMAR score, or for whom a date of death had been recorded prior to 2017. We again report results from complete case data as a sensitivity analysis, and in a supplement, we report multiply imputed data using only participants with observed data for each exposure.

3. Results

Fig. 1 shows where missing data occurred.

3.1. Demographics of sample (Table 1)

116,012 participants with an observed left eye logMAR score constituted the sample for multiply imputed data in the case-control analysis. After excluding participants who died during follow-up, 113,044 participants remained in the multiply imputed cohort analysis.

In the baseline analytic sample, participants with visual impairment were more likely to have an SSD diagnosis (0.2 % vs 0.1 %), and more likely to be in the lowest bracket for household income (21.3 % vs 15.2 %). They also had an older median age (60 vs 55) and were more likely to have died during follow-up (3.1 % vs 1.8 %).

3.2. Case control study

3.2.1. The association between schizophrenia-spectrum disorder and visual impairment (Tables 2a and 3)

The complete case sample were more likely to be in the lowest bracket for household income than the sample in the multiply imputed analyses (28.5 % vs 11.9 %), but were otherwise similar and no more likely to have an SSD diagnosis. Details of the differences can be seen in Table 2a.

Using the multiply imputed dataset ($N = 116{,}012$), we found evidence of an association between SSD diagnosis and visual impairment in the unadjusted model (Odds Ratio [OR] 1.52, 95 % CI 1.14–2.03, $p = 0.005$). Following adjustment for age and sex, the association was strengthened (Adjusted Odds Ratio [AOR] 1.89, 95 % CI 1.40–2.54, $p < 0.001$). Evidence of the association attenuated but remained after further adjustment for socioeconomic status (AOR 1.42 95 % CI 1.05–1.93, $p = 0.021$).

In the complete case analyses however, we found no evidence of association between visual impairment and SSD in any model (final AOR 1.13, 95 % CI 0.76–1.69, $p = 0.549$). We noted that the confidence intervals overlapped with those from multiply imputed data.

As a post-hoc analysis, we measured the linear association between visual acuity and SSD prior to 2009 in the entire Biobank sample. There was no association in complete case data either before adjustment or following adjustment for sex, age, and socioeconomic variables (mean adjusted difference in left eye 0.079, 95 % CI −0.083–0.242, $p = 0.337$; right eye 0.103, 95 % CI −0.056–0.261; $p = 0.204$). In multiply imputed data ($n = 502{,}412$) there was an association (adjusted mean difference for left eye 0.044, 95 % CI 0.009–0.079, $p = 0.015$; right eye 0.049, 95 % CI 0.013–0.084; $p = 0.009$), consistent with our primary analyses.

3.3. Cohort study (Tables 2b, 4 and 5)

3.3.1. The association between baseline visual acuity and thinner retinal structures and psychotic experiences at follow-up

The complete case sample were less likely to have had an SSD diagnosis than the multiply imputed sample (<0.1 % vs 0.2 %) and less likely to be current smokers (8.3 % vs 10.1 %), but had similar rates of reporting psychotic experiences at follow-up. They were slightly less likely to have visual impairment (55.3 % vs 57.5 %) Details can be seen in Table 2b.

People with poorer baseline logMAR score in either eye had higher odds of psychotic experiences at follow-up in primary analyses including following adjustment for age, sex, and vascular risk factors (for right eye: AOR per 0.1-point increase in logMAR score 1.08, 95 % CI 1.03–1.13, $p = 0.003$; and left eye 1.05, 95 % CI 1.02–1.09 $p = 0.004$). The association was attenuated but remained following adjustment for

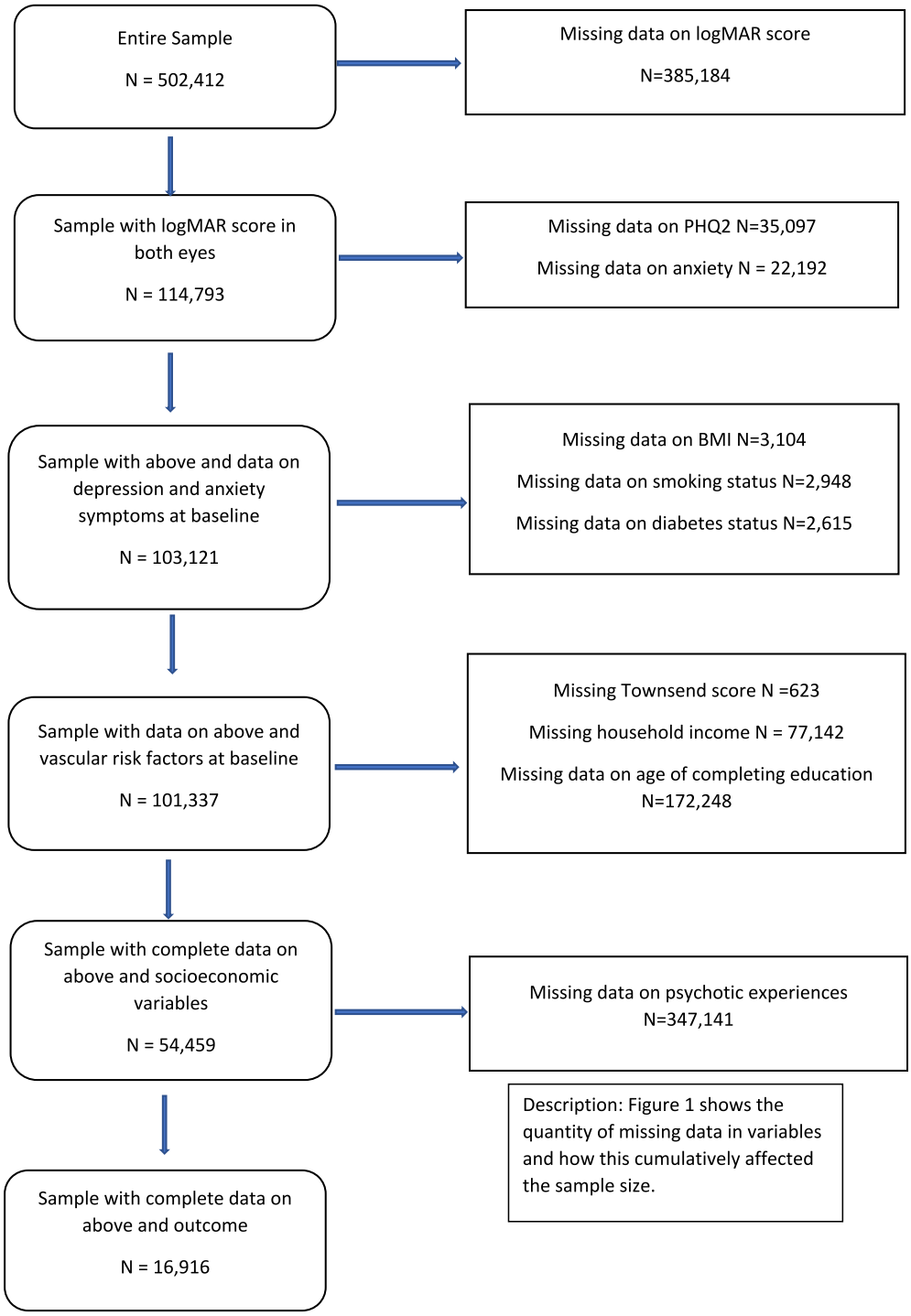

Fig. 1. Missing data flowchart for cohort analyses.

SES (AOR 1.06, 95 % CI 1.01–1.11, $p = 0.020$; AOR 1.04, 95 % CI 1.00–1.08, $p = 0.037$ for right and left eye). These associations were not seen in complete case data, which had a much smaller sample size of 16,916. The final AOR for the right eye was 0.94 (95 % CI 0.80–1.11, $p = 0.460$; for left eye 1.02, 95 % CI 0.89–1.16, $p = 0.775$). Again, these confidence intervals overlapped with those from MI data.

We found no evidence of any association between OCT measures and subsequent psychotic experiences in any analyses (Table 5).

There was evidence that OCT measures (increased RPE layer thickness and lower macular thickness) were associated with visual acuity, including following adjustment for age and sex (supplementary Table 1). Confidence intervals were similar overall in complete case data.

4. Discussion

4.1. Main findings

In line with our hypothesis that schizophrenia-spectrum disorders will be associated with visual impairment, we found that individuals with any degree of visual impairment (cases) had higher odds of a preceding SSD diagnosis than controls in primary analyses. This could occur through suboptimal correction of refractive errors, degenerative

Table 1
Demographics of sample with observed left eye visual acuity according to visual impairment status in 2009.

N = 116,012 (23.1 %)	Total (%)	Group without visual impairment	Group with visual impairment
Visual impairment (LogMAR score >0 in either eye)	65,991 (56.59)	–	–
Date of death recorded prior to 2017	2968 (2.6)	898 (1.8)	2031 (3.1)
Schizophrenia Spectrum Disorder diagnosis prior to 2009	208 (0.2)	67 (0.1)	136 (0.2)
Reported psychotic experiences at follow-up	109 (0.1)	49 (0.1)	58 (0.1)
Female	63,124 (54.4)	25,722 (52.7)	36,787 (55.8)
Average household income before tax			
<£18,000	21,760 (18.8)	7409 (15.2)	14,059 (21.3)
£18,000–£30,999	24,746 (21.3)	9809 (20.1)	14,667 (22.2)
£31,000–£51,999	25,292 (21.8)	11,612 (23.8)	13,446 (20.4)
£52,000+	27,189 (23.4)	13,825 (28.3)	13,165 (20.0)
Smoking status			
Never	63,996 (55.2)	27,411 (56.2)	35,909 (54.4)
Past	39,636 (34.2)	16,446 (33.7)	22,811 (34.6)
Current	11,609 (10.0)	4680 (9.6)	6787 (10.3)
Diabetes	6789 (5.9)	2189 (4.5)	4494 (6.8)
Median (interquartile range)			
Age	58 (50–63)	55 (47–62)	60 (53–65)
Age of completing full-time education	16 (15–18)	16 (16–18)	16 (15–18)
Townsend deprivation score	−1.6 (−3.3–1.07)	−1.7 (−3.4–0.8)	−1.5 (−3.2–1.3)
Body mass index	26.7 (24.1–29.9)	26.6 (24.1–29.7)	26.8 (24.2–30.0)
Patient Health Questionnaire 2 Score	2 (2–3)	2 (2–3)	2 (2–3)
Anxiety score	1 (1–2)	1 (1–2)	1 (1–2)
Right retinal pigment epithelium thickness (μm)	24.7 (23.2–26.9)	24.8 (23.3–27.0)	24.6 (23.1–26.7)
Left retinal pigment epithelium thickness (μm)	24.8 (23.2–27.0)	24.9 (23.3–27.2)	24.7 (23.1–26.9)
Mean (SD)			
Right macular thickness (μm)	276.7 (25.4)	277.7 (24.0)	276.0 (26.1)
Left macular thickness (μm)	274.0 (25.3)	275.2 (24.2)	273.2 (26.1)

Proportion of missing data N(%): Visual Impairment 1219 (1.1); SSD diagnosis prior to 2009 0; psychotic experiences at follow-up 76,492 (65.9); sex 0; household income 17,025 (14.7); smoking status 771 (0.7); diabetes 783 (0.7); age 0; age of completing full time education 42,894 (37.0); Townsend deprivation score 140 (0.1); BMI 655 (0.1); PHQ2 8248 (7.1); anxiety score 5466 (4.7); right retinal pigment epithelium thickness 50,321 (43.4); left retinal pigment epithelium thickness 50,742 (43.7); right macula thickness 50,321 (43.4); left macula thickness 50,742 (43.7).

neuronal alterations in the retina (Adams and Nasrallah, 2018), or other factors typically over-represented in people with SSD such as diabetes, hypertension, obesity, smoking, or antipsychotic medications (Silverstein et al., 2020). Poorer visual acuity was correlated with lower macular thickness, but with increased thickness of the retinal pigment epithelium. The latter could reflect RPE layer oedema in eye disease (Kaiser et al., 2021). This supports one possible mechanism by which SSDs may predispose to visual impairment; through retinal deterioration seen in later stages of the illness.

In the cohort study, we found that poorer visual acuity was associated with broadly defined subsequent psychotic symptoms. There are

Table 2a
Comparison of sample with and without missing data for case control study.

	Sample with missing data N [%]	Complete case sample N [%]
Total	55,834 [48.1]	60,178 [51.9]
Visual impairment	30,694 [56.2]	35,297 [58.7]
Schizophrenia-spectrum disorder diagnosis before 2009	99 [0.2]	109 [0.2]
Female	31,036 [55.6]	32,088 [53.3]
Average household income before tax		
<£18,000	4614 [11.9]	17,146 [28.5]
£18,000–£30,999	7403 [19.1]	17,343 [28.8]
£31,000–£51,999	10,464 [27.0]	14,828 [24.6]
£52,000+	16,328 [42.1]	10,861 [18.1]
Median (interquartile range)		
Age	58 [50–63]	59 [51–64]
Age of completing full-time education	16 [15–17]	16 [15–18]
Townsend deprivation score	−1.44 [−3.25–1.18]	−1.73 [−3.32–0.98]

Table 2b
Comparison of sample with and without missing data for primary cohort analysis.

Characteristic	Sample with missing data N (%)	Complete case sample N (%)
Total	96,128 (85.0 of total)	16,916 (15.0 of total)
Visual impairment	54,610 (57.5)	9350 (55.3)
Reported psychotic experiences at follow-up	61 (0.3)	48 (0.3)
Diagnosis of Schizophrenia Spectrum Disorder before 2009	195 (0.2)	6 (<0.1)
Female	52,325 (54.4)	9632 (56.9)
Average household income before tax		
<£18,000	17,639 (22.2)	3221 (19.0)
£18,000–£30,999	19,266 (24.2)	4761 (28.1)
£31,000–£51,999	19,913 (25.0)	4869 (28.8)
£52,000+	22,794 (28.6)	4065 (24.0)
Smoking status		
Never	53,918 (56.5)	8959 (53.0)
Past	31,815 (33.4)	6558 (38.8)
Current	9650 (10.1)	1399 (8.3)
Diabetes	5676 (6.0)	690 (4.1)
Median (interquartile range)		
Age	58 (50–63)	58 (51–63)
Age of completing full-time education	16 (15–18)	17 (16–18)
Townsend deprivation score	−1.5 (−3.3–1.2)	−2.1 (−3.5–0.3)
Body mass index (BMI)	26.7 (24.1–29.9)	26.6 (24.1–29.7)
Patient Health Questionnaire 2 score	2 (2–3)	2 (2–3)
Anxiety score	1 (1–2)	1 (1–1)
LogMAR score – right eye	−0.02 (−0.10–0.12)	−0.04 (−0.12–0.10)
LogMAR score – left eye	−0.04 (−0.10–0.10)	−0.04 (−0.12–0.08)
Right retinal pigment epithelium thickness μm	24.7 (23.2–26.9)	24.6 (23.1–26.7)
Left retinal pigment epithelium thickness μm	24.8 (23.2–27.0)	24.8 (23.2–26.9)
Mean (SD)		
Right macular thickness μm	276.7 (25.4)	276.7 (24.5)
Left macular thickness μm	274.0 (25.1)	274.5 (26.1)

however several reasons that mitigate against concluding that this relationship is causal. Perhaps most persuasively, we found no evidence that reduced thickness of retinal structures was associated with

Table 3
Results from nested case control study: odds of prior schizophrenia-spectrum disorder diagnosis in group with visual impairment compared to group without.

	Model 1: Unadjusted odds ratio [95 % CI]	*P*-value	Model 2: Adjusted odds ratio [95 % CI]	P-value	Model 3: Adjusted odds ratio [95 % CI]	P-value
Multiply imputed dataset N = 116,012	1.52 [1.14–2.03]	0.005	1.89 [1.40–2.54]	<0.001	1.42 [1.05–1.93]	0.021
Complete case sample *N* = 60,178	1.22 [0.82–1.80]	0.325	1.44 [0.96–2.14]	0.076	1.13 [0.76–1.69]	0.549

Model 2: adjusted for age and sex.
Model 3: adjusted for age, sex, Townsend deprivation score, and household income and age at leaving full time education.

Table 4
Odds of reporting psychotic symptoms at follow-up according to visual acuity at baseline.

Exposure	Model 1 Unadjusted odds ratio [95 % CI]	P-value	Model 2 Adjusted odds ratio [95 % CI]	P-value	Model 3 Adjusted odds ratio [95 % CI]	P-value	Model 4 Adjusted odds ratio [95 % CI]	P-value
Multiply imputed data								
Poorer logMAR Score by 0.1 – right eye *N* = 113,044	1.07 [1.02–1.12]	0.005	1.08 [1.03–1.13]	0.002	1.08 [1.03–1.13]	0.003	1.06 [1.01–1.11]	0.020
Poorer logMAR Score by 0.1 – left eye N = 113,044	1.05 [1.01–1.08]	0.009	1.06 [1.02–1.09]	0.001	1.05 [1.02–1.09]	0.004	1.04 [1.00–1.08]	0.037
Complete case data								
Poorer logMAR Score by 0.1 – right eye *N* = 16,916	0.91 [0.77–1.08]	0.278	0.96 [0.82–1.12]	0.597	0.96 [0.82–1.12]	0.587	0.94 [0.80–1.11]	0.460
Poorer logMAR Score by 0.1 – left eye *N* = 16,916	1.00 [0.87–1.15]	0.968	1.03 [0.91–1.18]	0.635	1.03 [0.90–1.17]	0.673	1.02 [0.89–1.16]	0.775

Model 2: adjusted for baseline anxiety and depression scores, age, and sex.
Model 3: adjusted for baseline anxiety and depression score, age, sex, smoking status, body mass index (BMI), and diabetes status.
Model 4: adjusted for baseline anxiety and depression score, age, sex, smoking status, body mass index (BMI), diabetes status, age of leaving full time education, Townsend deprivation score, and household income.

Table 5
Odds of reporting psychotic symptoms at follow-up according to retinal structure thickness at baseline.

Exposure	Model 1 Unadjusted odds ratio [95 % CI]	P-value	Model 2 Adjusted odds ratio [95 % CI]	P-value	Model 3 Adjusted odds ratio [95 % CI]	P-value	Model 4 Adjusted odds ratio [95 % CI]	P-value
Multiply imputed data								
Right macular thickness - per μm *N* = 113,044	1.00 [0.99–1.00]	0.477	1.00 [0.99–1.00]	0.451	1.00 [0.99–1.00]	0.526	1.00 [0.99–1.00]	0.654
Left macular thickness - per μm *N* = 113,044	1.00 [0.99–1.00]	0.731	1.00 [0.99–1.00]	0.681	1.00 [0.99–1.00]	0.840	1.00 [1.00–1.00]	0.977
Overall right retinal pigment epithelium thickness - per μm N = 113,044	1.00 [1.00–1.00]	0.349	1.00 [1.00–1.00]	0.446	1.00 [1.00–1.00]	0.463	1.00 [1.00–1.00]	0.590
Overall left retinal pigment epithelium thickness - per μm N = 113,044	1.00 [1.00–1.00]	0.287	1.00 [1.00–1.00]	0.328	1.00 [1.00–1.00]	0.360	1.00 [1.00–1.00]	0.479
Complete case data								
Right macular thickness - per μm *N* = 10,022	1.00 [0.98–1.02]	0.858	1.00 [0.98–1.02]	0.915	1.00 [0.98–1.02]	0.891	1.00 [0.99–1.02]	0.810
Left macular thickness - per μm *N* = 9962	1.01 [1.00–1.02]	0.125	1.01 [1.00–1.02]	0.217	1.01 [1.00–1.01]	0.234	1.01 [1.00–1.01]	0.274
Overall right retinal pigment epithelium thickness - per μm N = 9962	1.00 [0.98 0 1.01]	0.923	1.00 [0.98–1.02]	0.918	1.00 [0.98–1.02]	0.902	1.00 [0.98–1.01]	0.842
Overall left retinal pigment epithelium thickness - per μm *N* = 10,022	1.00 [0.99 0 1.01]	0.711	1.00 [0.99–1.01]	0.643	1.00 [0.99–1.01]	0.643	1.00 [0.99–1.01]	0.683

Model 2: adjusted for baseline anxiety and depression scores, age, and sex.
Model 3: adjusted for baseline anxiety and depression score, age, sex, smoking status, body mass index (BMI), and diabetes status.
Model 4: adjusted for baseline anxiety and depression score, age, sex, smoking status, body mass index (BMI), diabetes status, age of leaving full time education, Townsend deprivation score, and household income.

subsequently measured psychotic experiences; if the relationship were causal, retinal changes might be expected to also predict future psychosis. An alternative conclusion is that impaired visual processing is part of a psychosis prodrome which adversely affects acuity testing, as research shows that visual acuity is associated with visual processing function (Keane et al., 2015).

4.2. Strengths and limitations

This is the largest case control study, to our knowledge, to explore the association between SSD and visual impairment as outcome. We believe it is also the first to explore associations between OCT scan results and psychotic experiences and visual acuity in a sample of thousands of participants. There are however limitations.

First, the association between visual acuity and psychosis was not statistically evidenced in complete case data, though this is likely explained by the larger imputed sample size (only 15 % of whom were included in complete case analysis). The inclusion of fewer people who had SSD at baseline (48 vs 109) also reduced the power to detect this association. Secondly, the effect was small, so the clinical significance is uncertain.

As widespread OCT and acuity measures were only available at baseline and psychotic symptoms only at follow-up, we cannot be certain whether exposures truly occurred before outcomes, despite testing variables longitudinally. We adjusted for depression and anxiety symptoms, but this is not equivalent to psychotic symptoms, although they are associated (Bourgin et al., 2020). We did not investigate duration or severity of schizophrenia, which are also likely to affect the relationship with visual impairment. Due to missing data neither did we investigate cognitive measures, which may be a mediator in the relationship between visual impairment and psychosis, and a more stable marker of psychotic illnesses than psychotic symptoms themselves (Silverstein et al., 2012). Further, the number of participants with complete data for all relevant variables represent approximately a fifth of the entire sample. Relatively few participants included had been diagnosed with SSD or had psychotic experiences (for SSD: $N = 208$, for psychotic experiences, $N = 109$). This reduced power to detect associations and increased the risk of type 2 error in complete case analyses. The large quantity of missing data may have led to bias if people with psychotic experiences were more likely to drop out, again reducing apparent evidence of an association. We sought to overcome these limitations using multiple imputation. Nevertheless, multiple imputation is only unbiased when data are missing in relation only to observed variables (White et al., 2011). Although this assumption cannot be proven, we used multiple auxiliary variables to increase the chances of this, meaning that MI data is likely to be less biased by attrition than complete case data (Sterne et al., 2009). We were also limited in the number of imputations we could create, due to intensive computing resources required.

The UK Biobank sample is not representative of the UK population. It had a low response rate of just 5.5 % (Stamatakis et al., 2021). A healthy volunteer effect is recognised, whereby participants are on average older, more likely to be female, white, and to live in socioeconomically advantaged areas, and less likely to have serious health conditions, compared to the general population (Fry et al., 2017). This can adversely affect the validity of associations found in the UK Biobank (Keyes and Westreich, 2019; Stamatakis et al., 2021; van Alten et al., 2022). Consistency of our findings with previous research is reassuring in this regard, but caution should be applied when generalising findings.

As with all observational studies, we cannot exclude a possible influence of residual and unmeasured confounding. Recruitment occurred at age 40+, meaning we could not account for potential confounding variables from earlier in life, such as birth trauma or in utero infection. Variables such as smoking and diabetes could not be included in the case-control study due to being collected contemporaneously with the outcome, and ethnicity in either study due to small numbers in most categories.

We discounted visual hallucinations to avoid confounding by severe eye disease and Charles Bonnet Syndrome. In so doing, we likely excluded people with psychotic experiences not driven by severe eye disease, as visual hallucinations may affect 20–30 % of people with schizophrenia (McCarthy-Jones et al., 2017); therefore our findings are likely to be a conservative estimate of associations. The use of corrected visual acuity may also have led to an underestimate of the association between visual impairment and SSD or psychotic experiences.

4.3. Comparison with other literature

Our finding that people with visual impairment had a greater odds of SSD diagnosis than people without concords with previous cross-sectional studies (Punukollu and Phelan, 2006; Smith et al., 1997; Viertiö et al., 2007a; Zheng et al., 2015). These studies also found that affected individuals reported lower rates of recent optician attendance than the general population, which may be partially explained by a decline in functioning or available funds making optical care less accessible. This finding is also compatible with our Mendelian Randomisation study suggesting that schizophrenia is causally associated with poorer eyesight (Shoham et al., 2022).

Our finding that poorer visual acuity is associated with subsequent psychotic experiences may contradict our MR study findings that mild visual impairment (in the form of myopia) does not cause schizophrenia. Nevertheless, studies of children and adolescents also found this association between visual acuity and subsequent psychotic disorders and experiences (Hayes et al., 2018; Schiffman et al., 2006; Schubert et al., 2005; Shoham et al., 2021b). One consideration is that psychotic experiences and schizophrenia-spectrum disorders are overlapping but separate phenomena. A polygenic risk score for schizophrenia does not predict psychotic experiences in a well-known childhood cohort (Jones et al., 2016), suggesting that the experiences measured in this cohort were mainly non-pathological, or manifestations of depression and anxiety disorders, rather than indicative of psychotic illness (Davies et al., 2018). Therefore, it could be that visual impairment predisposes to psychotic experiences via broad psychopathology, rather than through psychotic disorder specifically. This is consistent with the view that most young people identified as 'at risk' for a psychotic disorder do not develop one, and so psychotic symptoms may be more an aspect of severe multidimensional pathology, and less an indicator of a psychotic disorder in the majority of cases (Perez and Jones, 2021; van Os and Guloksuz, 2017). One candidate mechanism is visual impairment reflecting altered central nervous system function (including visual processing dysfunction) and predisposition to severe anxiety, depression or psychosis (Perez and Jones, 2021; van Os and Guloksuz, 2017). The fact that our sample included older adults could also show an alternative mechanism for a causal association via dementia, although we did not test this (Demro et al., 2022; Li et al., 2021; Stone et al., 2022; Stroup et al., 2021). This perspective is supported by links between schizophrenia and accelerated aging, as well as with increased rates of dementia in people with schizophrenia, and shared genetic components between schizophrenia and neurodegenerative disorders.

Many case-control studies which found reduced retinal thickness in schizophrenia have previously been systematically reviewed (Adams and Nasrallah, 2018; Silverstein et al., 2020). We did not find an association between thickness of retinal structures and psychotic experiences in this sample. This might be because these changes are specific to SSDs rather than psychotic experiences more broadly. Further, thickness of some retinal structures in schizophrenia has been shown to be negatively correlated with disease duration and number of hospitalisations, and is not typically seen in studies of first episode psychosis (Celik et al., 2016; Komatsu et al., 2022; Lai et al., 2020). This suggests that neural cell loss, a late-stage complication of schizophrenia, develops over the course of the illness, and may not be detectable before diagnosis. Of note, other alterations such as retinal microvasculature changes (Silverstein et al., 2021) and changes in retinal cell firing strength and/or latency (as measured via electroretinography (ERG)) appear to occur sooner, and prior to significant loss of neurites and cell bodies (Maziade et al., 2022). This sequence of changes is consistent with what is observed in other diseases (Asanad et al., 2021; Banitt et al., 2013; Nowacka et al., 2015).

4.4. Conclusions

Our findings appear to confirm previous reports that people with a schizophrenia-spectrum disorder are at greater risk of future visual impairment. Clinically, we highlight the importance of facilitating access to optical care for people with psychosis, perhaps during annual physical health screening. This includes routine preventive exams for young patients, who may be characterised by accelerated central nervous system changes that would otherwise be unexpected and unscreened for in people their age.

Our findings are also consistent with visual impairment acting as a risk factor for psychotic experiences in older adults, but the effect was small and this could reflect shared central nervous system dysfunction rather than a causal relationship. Consistent with this, we did not find evidence of association between thickness of retinal structures and psychotic experiences. This is also consistent with the idea that neural thinning reflects progressive neural and neurite atrophy that becomes evident in patients several years after the first episode of schizophrenia (Lee et al., 2013). Nonetheless, we cannot rule out from these findings the possibility that the relationship is causal. If so, this would contradict findings from our recent MR study that did not find evidence for a causal link, though the difference in outcomes (psychotic experiences as opposed to SSD) in the current study could explain this variation. Further studies are needed which adjust for medical comorbidities and antipsychotic medications, and which exclude presence of the outcome at first measurement of the exposure (Jerotic et al., 2020).

Conflict of interest

The authors have declared that there are no conflicts of interest in relation to the subject of this study.

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Role of the funder

The funder had no role in the design, analysis, interpretation or writing of the report for this study.

Appendix A. Supplementary data

Auxiliary variables used for imputations: Housing score (England); employment score (England); right macular volume (in mm^3); left macular volume (in mm^3); systolic blood pressure (mmHg); ever having seen a doctor for nerves, anxiety, tension, or depression; how often felt loved as a child; disability status; frequency of feeling tired in past two weeks; frequency of drinking alcohol. Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2023.02.017.

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