PhD Thesis Report

Visual impairment and psychosis: cause, consequence or neither?

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Declaration

I, Natalie Shoham, confirm that the work presented in this thesis is my own. Where information is attributable to other sources, this has been indicated in the thesis.

Date: 8th March 2023

Signature: Natalie Shoham

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Abstract

Introduction: I investigate the potential bidirectional association between visual impairment and psychosis. I consider the implications for the detection, understanding, prevention and treatment of each condition.

Methods: I conducted a systematic review and meta-analysis to collate existing evidence regarding an association between these conditions. Next, I investigated whether worse visual acuity at ages 7-11 is associated with psychotic symptoms at ages 17-24 using the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort. I investigated whether genetic evidence supports a causal association between visual impairment and schizophrenia. These analyses were based on two-sample Mendelian Randomisation (MR) using data from the UK Biobank and Psychiatric Genomics Consortium, and genome-wide association studies of myopia and refractive error. I used the UK Biobank cohort of adults aged 40-69 to test whether poorer visual acuity and size of retinal structures were associated with psychotic experiences 8 years later, and whether cases with visual impairment were more likely to have a Schizophrenia-Spectrum Disorder (SSD) diagnosis than controls without.

Results: Existing cross-sectional studies consistently showed an association between visual impairment and psychosis, whereas findings from longitudinal studies were mixed. In ALSPAC, poorer visual acuity at age 11 was associated with psychotic experiences in young people. In the Mendelian Randomisation study, I found no evidence that poorer visual acuity was a causal risk factor for schizophrenia, though there was evidence for the converse. In Biobank participants, poorer visual acuity was associated with psychotic experiences 8 years later, though thinner retinal structures were not. People with visual impairment were more likely to have been diagnosed with SSD.

Conclusions:

I found evidence that psychotic illnesses contribute causally to visual impairment, but not the converse. Future research to understand the mechanisms by which psychotic illnesses could be causal risk factors for visual impairment will aid prevention.

Impact Statement

Potentially, preventative action could be taken to reduce cases of visual impairment in people with psychotic illnesses based on my finding from this thesis; that psychotic illnesses increase the risk of visual impairment. The 2019 NHS long-term plan has a focus on reducing health inequalities, particularly for people with serious mental illness.[2] It recommends that barriers between separate healthcare services are reduced, and that a more proactive approach to preventing chronic ill health is taken.[2] In the UK, Integrated Care Systems (ICSs) have been established to improve coordination of care and make it place-based.[3] In keeping with this, my work could theoretically lead to consideration of visual acuity testing at the already established annual physical health check for people with serious mental illnesses. This could be incorporated into guidelines, such as National Institute of Clinical Excellence guidelines.[4] My thesis could also elicit consideration of pathways through which high street opticians can interlink patients with mental health services when necessary. A further relevant recent policy is the World Health Assembly 2013 Global Action Plan, which launched the 'Right to Sight' strategy aiming to reduce preventable visual impairment worldwide by 25% before 2019.[5] Unfortunately, this goal was not achieved, showing that more assertive approaches are needed.

To improve the chance of benefit to patients and the public from this work, I have collaborated with six people with lived experience of mental health service use, visual impairment, or caring for someone with psychotic-like experiences. Publications from this thesis are freely available in open access journals read by healthcare professionals. I have also disseminated findings by presenting them at meetings and conferences frequented by healthcare professionals. These included a poster entitled *Associations Between Psychosis and Visual Acuity Impairment: A Systematic Review and Meta-Analysis* at the Royal College of Psychiatrists academic trainees' conference on 28th April 2021; a video abstract presentation at the UCL Institute of Mental Health conference entitled *Association between childhood visual acuity and late adolescent psychotic experiences: a prospective birth cohort study* on 15th September 2021; a poster of the same at the National Institute of Mental Health Research Academy conference 23rd -24th November 2021; and a poster presentation

entitled *Association between myopia and schizophrenia: a Mendelian Randomisation study* at the Royal College of Psychiatrists International Congress on 22nd June 2022.

Academic Impact

This work could influence the course of future research, by leading other researchers to focus on the mechanisms by which psychotic illness could contribute causally to visual impairment and whether this is preventable. I have suggested questions for further research in the discussion sections of the publications arising from this thesis. I have also presented findings at conferences aimed at researchers: a short virtual presentation of my systematic review from chapter 3 at the UCL Neuroscience Symposium on 15th June 2021,and a presentation entitled *Association between myopia and schizophrenia: a Mendelian Randomisation study* at the UCL postgraduate faculty conference on 27th May 2022. Papers from this thesis have been cited by other researchers.[6-10]

Publications

Shoham, N., Eskinazi, M., Hayes, JF., Lewis, G., Theodorsson, M., Cooper, C. Associations between psychosis and visual acuity impairment: A systematic review and meta-analysis. *Acta Psychiatr Scand*. 2021; 144: 6– 27. https://doi.org/10.1111/acps.13330

Shoham, N., Hayes, JF., Cooper, C., Theodorsson, M., Lewis, G. Association Between Childhood Visual Acuity and Late Adolescent Psychotic Experiences: A Prospective Birth Cohort Study, *Schizophrenia Bulletin*, 2021; https://doi.org/10.1093/schbul/sbab121

Shoham, N., & Cooper, C. (2022). Eyes, the window on psychosis? BJPsych Open, 8(2), E44.doi:10.1192/bjo.2022.16

Shoham, N., Dunca, D., Cooper, C., Hayes, J., McQuillin, A., Bass, N., . . . Kuchenbaecker, K. (2023). Investigating the association between schizophrenia and distance visual acuity: Mendelian randomisation study. *BJPsych Open, 9*(2), E33. doi:10.1192/bjo.2023.6

Shoham, Natalie; Hayes, Joseph F; Lewis, Gemma; Silverstein, Steven M; Cooper, Claudia (2023). Association between Visual Impairment and Psychosis: A Longitudinal Study and Nested Case-Control Study of Adults. Schizophrenia Research. 254: 81-89. https://doi.org/10.1016/j.schres.2023.02.017

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Claudia Cooper, Joe Hayes, Gemma Lewis, and Karoline Kuchenbaecker supervised me for this work. All other authors acted as collaborators for the relevant papers.
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List of Abbreviations

AHR - Adjusted Hazard Ratio

ALSPAC – Avon Longitudinal Study of Parents and Children

ANOVA – analysis of Variance

AOR – Adjusted Odds Ratio

cAMP – cyclic Adenosine Monophosphate

cGMP-PKG – Cyclic Guanosine 3’,5’-Monophosphate Dependent Protein Kinase G

CI – Confidence Interval

CMD – Common Mental Disorder

CREAM – Consortia of Refractive Error And Myopia

CSE – Certificate of Secondary Education

DNA – Deoxyribonucleic Acid

EPDS – Edinburgh Postnatal Depression Scale

ErbB – Epidermal Growth Factor Receptor family

ERG – Electroretinography

ETDRS chart – Early Treatment of Diabetic Retinopathy Screening chart

FUMA – Functional Mapping and Annotation of Genome-Wide Association Studies

GABA – Gamma-Aminobutyric Acid

GERA – Genetic Epidemiology Research in Adult Health and Ageing Cohort

GnRH – Gonadotrophin Releasing Hormone

GWAS – Genome Wide Association Study

HES – Hospital Episode Statistics

HPA axis – Hypothalamic Pituitary Adrenal axis

ICD 10 / 11 – International Diagnostic Criteria version 10 / 11

InSIDE – Instrument Strength Independent of Direct Effect

IQ – Intelligence Quotient

IQR – Interquartile Range

IVW – Inverse Variance Weighted

KEGG2021 – Kyoto Encyclopaedia of Genes and Genomes

LASIK – Laser-Assisted in Situ Keratomileusis

LD – Linkage Disequilibrium

LogMAR – Logarithm of Minimal Angle of Resolution

MAF – Minor Allele Frequency

MAPK – Mitogen-activated Protein Kinase

MAR – Missing At Random

MCAR – Missing Completely at Random

MI – Multiple Imputation

MNAR – Missing Not At Random

MR – Mendelian Randomisation

MRI – Magnetic Resonance Imaging

MR-PRESSO – Mendelian Randomisation Residual Sum and Outlier

N – Number

NHS - National Health Service

NMDA – N-methyl-D-Aspartate

NOS – Newcastle Ottawa Scale

OCT – Optical Coherence Tomography

OCTA – Optical Coherence Tomography Angriography

OR – Odds Ratio

PaSZ model – Protection against Schizophrenia model

PCP – Phencyclidine

PGC – Psychiatric Genomics Consortium

PHESANT – PHEnome Scan Analysis Tool

PLIKSi – Psychotic-Like Symptoms Screening interview

PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RCT – Randomised Controlled Trial

REDCap – Research Electronic Data Capture

RNA – Ribonucleic Acid

RPE – Retinal Pigment Epithelium

RSS – Residual Sum of Squares

SCAN - Schedule for Clinical Assessment in Neuropsychiatry

SCID – Structured Clinical Interview

SDQ – Strengths and Difficulties Questionnaire

SE – Spherical Equivalent

SE – Standard Error

SES – Socioeconomic Status

sMFQ – Short Mood and Feelings Questionnaire

SMI – Serious Mental Illness

SNP – Single Nucleotide Polymorphism

SSD – Schizophrenia Spectrum Disorder

TMS – Transcranial Magnetic Stimulation

VA – Visual Acuity

VLOSLP – Very Late-Onset Schizophrenia-Like Psychosis

WHO – World Health Organisation

Chapter 1 Introduction

1.1 Overall Introduction and thesis remit

Schizophrenia and other psychotic disorders, sometimes combined under the term Schizophrenia Spectrum Disorders (SSDs), have a significant impact on affected individuals, their families, and wider society. Despite existence of treatments, these illnesses continue to confer reduced life expectancy, poorer quality of life, and diminished opportunities.[11, 12] Psychotic illnesses have complex, multifactorial causes. Although many risk factors have been identified, most are difficult to modify.

There has been interest in visual impairment as a theoretical risk factor for psychotic illnesses. Visual impairment is often modifiable, so identification of any causal association might ultimately translate into improved prevention or treatment of psychotic illnesses. One aspect often neglected in this area of research is the possibility of reverse causation: schizophrenia and other psychotic illnesses may cause poorer eyesight. Whilst cross-sectional studies do find evidence of an association between visual impairment and psychosis, longitudinal studies where visual impairment is the exposure give mixed results.[13, 14]

In this thesis, I investigate the association between psychosis and visual impairment. In **Chapter 1**, I provide an overview of the central topics of eyesight, its impairment, and psychotic symptoms and disorders, in relation to published literature. In **Chapter 2**, I outline the aims of this thesis. In **Chapter 3**, I conduct a systematic review and meta-analysis of studies reporting on the existence and strength of an association between the two conditions. Using these findings to identify gaps in the literature, I subsequently investigated this relationship (considering psychotic disorder and symptoms) in three large datasets spanning childhood to older adults. First, I report a birth cohort study investigating the association between childhood visual acuity and adolescent psychotic-like experiences in **Chapter 4**. In **Chapter 5** I carry out a Mendelian Randomisation (MR) study to determine whether there is evidence of a causal association between myopia and schizophrenia in either direction. In **Chapter 6**, I report a longitudinal study into the association between visual impairment and psychotic experiences in a cohort of older adults. In **Chapter 7,** I report a nested case-

control study of adults with and without visual impairment, where I investigated each group's odds of having received a prior Schizophrenia-Spectrum Disorder diagnosis. Finally in **Chapter 8**, I summarise the findings from this PhD and consider potential implications both clinically and for future research. Throughout this thesis, I describe methodology in the relevant research chapter, rather than dedicating a chapter to general methods.

In this first chapter, I summarise the definition, aetiology, and epidemiology of visual impairment, and briefly describe its impact. I cover the same areas with respect to psychosis. Lastly, I introduce three proposed mechanisms by which visual impairment and psychosis might be associated and my three hypotheses, which form the basis of my thesis aims (set out in **Chapter 2**).

1.2 Introduction to the Eye and Visual Impairment

1.2.1 Basic Anatomy and Physiology of the Eye

Figure 1-1: Anatomy of the eye. Source: Karki G; Human Eye: Anatomy, parts and structure.[15] shows the anatomy of the eye, which is referred to in the following sections.

Figure 1-1: Anatomy of the eye. Source: Karki G; Human Eye: Anatomy, parts and structure.[15]

Light enters the pupil through the cornea and anterior chamber, and is directed by the lens onto the retina at the back of the eye.[16] The ciliary muscles adjust the lens to correctly focus light so that it falls accurately onto the retina depending on whether objects are near or further away.[16] The iris, another muscular structure, can also contract and expand to adjust its size, regulating how much light enters the eye, depending on external lighting.[17] The retina contains photoreceptor cells: cones, which detect colours, and rods, which function in dim lighting.[17] These photoreceptor cells convert light into electrical signals, which are passed via the optic nerves and subsequently the optic tracts to the visual cortex in the brain, where the incoming

sensory information is processed.[18] It has been estimated that vision might make up 90% of the information we receive about the world, and that 30% of the human neocortex is involved in visual processing.[19]

Figure 1--2: Anatomy of the retina. Source: Gray's Anatomy 39th[20]

Figure 1-2 shows the layers of cells in the retina. The choroid is the vascular layer at the back.[21] In front of this lies the retinal pigment epithelium, a dark brown / black cell layer which performs much of the eye's essential metabolism, including processing vitamin A.[21] The rod and cone photoreceptor cells are next, and as described above, they detect light entering the eye. Anteriorly to these lie the interneuron cells: a variety of cell types including the amacrine, bipolar, horizontal and interplexiform cells.[21] These have the common function of processing the light signal detected by photoreceptor cells and conveying it to the ganglion cells. The final, ganglion cell layer transmits the signal to the brain and forms the optic nerve. Also found in the retina are two types of immune or glial cells, the Muller cells and microglia, and retinal arteries and veins.[21]

Other key features of the retina include the optic disc, where the optic nerve exits the eye.[21] This creates a small 'blind spot' where no visual information is received.[16] The macula, located to the side of the optic disc, contains a high density of cone cells especially in its innermost part, the fovea.[21]

1.2.2 Development of the Eye and Visual Processes

As my PhD investigates visual functions in children and well as adults, a short summary of ocular development has relevance. In the developing human embryo, the lens and cornea are formed from the surface ectoderm, which also forms the skin; whereas the retina develops from the neural plate, which also forms the brain.[22] This has led some authors to describe the retina as an extension of the brain.[23]

Typically, newborn babies can focus only about 25cm away, and have vision in the long-sighted range.[24, 25] By 3-4 months of age, they become able focus on targets at

the correct distance; an ability called accommodation.[26] Colour perception becomes possible after 34 weeks' gestation; initially red, and gradually other colours with exposure to light.[25] Eye movements appear to develop over the first few weeks of life; initially with jerky movements (saccades) and later smooth movements (smooth pursuit eye movements).[27]

Over the first 1-2 years of life, a process known as emmetropisation occurs, whereby infants' longsightedness decreases. Most corneal growth occurs during these first two years.[17] The length of the eye itself continues to increase over the next two decades of life, and short-sightedness can emerge during this time.[24] The lens also loses its ability to adjust and focus light as people age, meaning that longsightedness often re-emerges in the 5th decade of life.[17]

As the eye develops, so does the visual cortex in the occipital lobe of the brain. By 4 years of age synaptic density in the visual cortex approximates that of an adult.[27] Prior to this there is a peak density at around 6-9 months, followed by a process of selective cell loss; pruning.[27] Binocular vision (ability to fuse images from both eyes) is thought to develop by around 3-6 months, and to result from these changes in the cortex rather than development of the eye itself.[27] Cortical development also allows more complex aspects of vision known as visual processing to develop. These functions include, among others: perception of direction of moving objects, around 7 weeks; ability to track moving objects by 3 months; contrast gain (ability to adapt to different levels of contrast, e.g. in different light levels) by 6 months;[28] contrast discrimination (ability to detect lighter and darker shades);[29] and Vernier acuity (ability to detect misalignment in a contour).[30] These latter two develop well into childhood.[31, 32].

1.2.3 Definitions of Visual Impairment

Visual impairment is referred to by many names including sight loss or low vision. It is typically defined using visual acuity: this means ability to discriminate two stimuli separated by space with high contrast compared to the background.[33] In clinical practice, visual acuity is often determined by Snellen chart testing, where individuals stand a set distance away from lines of printed letters of decreasing size and read the smallest line they can.[34] When a person can read at 6 metres what they are 'expected'

to be able to read at 6 metres, this is known as 6/6 vision (or 20/20 vision in America, referring to feet). The first number indicates the distance at which the letters were read, and the second the distance at which the letters should be readable. The 'expected' line was set by the inventor of the chart Hermann Snellen, a Dutch ophthalmologist, in 1862.[33] He defined standard vision as the ability to read one of his visual stimuli at an angle of one minute of arc (a unit of angular distance equal to 1/60th degree).[33] Theoretically, any visual ability lower than 6/6 could be described as visual impairment. There is however some evidence that changes in eyesight within the 'normal' range can make a difference to the functional ability of individuals.[35]

Figure 1-3: A Snellen Chart. Source: Uveitis Information Group (Scotland): Low Vision.[36]

The World Health Organisation defines mild visual impairment as visual acuity worse than 6/12; worse than 6/18 as moderate impairment; and worse than 6/60 as severe visual impairment[37].

The terms partial sightedness and blindness also have specific definitions. These incorporate not only visual acuity but visual fields; the area over which someone is able to perceive visual stimuli.[38] For certifiable blindness, the criteria according to the Royal National Institute of the Blind are:

- Visual acuity of less than 3 / 60 with a full visual field.
- Visual acuity between 3 / 60 and 6 / 60 with a severe reduction of field of vision, such as tunnel vision.
- Visual acuity of 6 / 60 or above but with a very reduced field of vision, especially if significant sight is missing in the lower part of the field.[34]

Similarly, the criteria for partial sightedness are:

- Visual acuity of 3 / 60 to 6 / 60 with a full field of vision.
- Visual acuity of up to 6 / 24 with a moderate reduction of field of vision or with a central part of vision that is cloudy or blurry.
- Visual acuity of 6 / 18 or even better if a large part of the field of vision is missing.[34]

These standard thresholds are based on distance visual ability, although there is a separate definition for near vision impairment, based on reading text close-up.[37] There are also several other distance visual acuity charts that use the same principles as a Snellen chart, including the Early Treatment of Diabetic Retinopathy Screening (ETDRS) chart,[39] which is often used in research, including my PhD, and the Freiburg (computerised) chart.[40] Although they are not directly interchangeable, suggested approximate equivalent measurements on the Snellen and ETDRS chart can be found in appendix A. Some situations make reading letters an unsuitable test of vision. Examples are very severe visual impairment, intellectual disability, or very young age. In these instances, alternative ways to measure vision include Cardiff cards (based on pictures rather than letters),[41] counting fingers, and perception of light.[42]

Refractive error is another term that I will use in this thesis. It is an umbrella term for disorders in which light entering the eye falls sub-optimally on the retina, leading to a blurred image in some situations. Types of refractive error include short-sightedness (myopia), in which images are blurred at distance; long-sightedness (hyperopia), in which images are blurred close-up; and astigmatism, in which images are blurred at any distance.[43] These disorders can all cause visual impairment.

1.2.4 Epidemiology of Visual Impairment

Approximately 2 million people in the UK live with significant visual impairment; that which affects day-to-day life.[44] Of these, about 360,000 are registered as blind or partially sighted.[44] Globally, the number of people with visual impairment is approximately 2.2 billion.[37] In 50% of cases, this impairment is believed to be preventable.[45]

1.2.5 Aetiology of Visual Impairment

Visual impairment can be congenital but is strongly associated with ageing.[37] In 2015 one in five people over the age of 75 had significant sight loss, which is of particular concern as the number of older people is predicted to continue to rise.[46] Many leading causes of severe visual impairment are associated with ageing. There are many potential causes, and I will outline only the most common types, likely to be relevant to the people who contributed data to my thesis. According to the World Health

Organisation, myopia and cataracts are the two most common causes globally.[37] Of note, these are also two of the most treatable causes.

Other major contributors to the global burden of sight loss are glaucoma, diabetic retinopathy, and age-related macular degeneration.[5] These conditions are less easily corrected.[5]

1.2.5.1 Myopia

Myopia has many synonyms including short-sightedness.[47] As described above, it is one type of refractive error. Myopia can often be corrected using glasses or contact lenses, but these are not accessible to everyone.[37] Of particular concern is severe myopia (high myopia), which may lead to blindness.[48]

Myopia is increasing in prevalence. Currently it affects at least 30% of the population in Europe,[49] and 80% in some populations in East Asia.[24] It is predicted to affect 50% of the world's population by 2050.[50] Myopia often begins whilst children or young people are still at school.[24] The exact reason for its increasing prevalence is unknown, but widespread near-reading is an established risk factor which may be implicated.[51]

There is a sizable genetic contribution to myopia.[52] In chapter 5, I describe a Mendelian Randomisation study, which uses genetic instruments associated with myopia and refractive error and therefore distance visual acuity. Development of the eye appears to be influenced by many Single Nucleotide Polymorphisms (SNPs): changes in a single base pair in DNA. Detection of association between individual SNPs and a polygenic condition typically requires very large samples; 10s or 100s of thousands of participants. Consortia comprising many studies, including the Consortia of Refractive Error and Myopia (CREAM) have therefore been established with the aim of detecting these variants.[53] A recent meta-analysis of such efforts by Hysi and colleagues identified 449 SNPs at novel genetic loci which are associated with myopia. Each of these confers a very small effect individually, but collectively they appear to explain 18.4% of the heritability of myopia, with total heritability estimated at 60-80%.[54] The evidence that these genetic variants directly cause poorer visual acuity is strengthened by functional analyses showing that they are enriched (transcribed more than expected by chance) in the eye and nervous system, and are found in genes

involved in biological pathways implicated in eye conditions such as glaucoma and retinitis pigmentosa, and eye development.[55]

1.2.5.2 Cataracts

Cataract means clouding of the lens in the eye.[56] It is strongly associated with ageing, exposure to ultraviolet light, and genetic predisposition.[56] Although cataract is not preventable and is responsible for approximately half of all blindness globally, it is correctable using a relatively straightforward surgical procedure.[56]

1.2.5.2 Glaucoma

Glaucoma is a group of conditions characterised by progressive damage to the retinal nerves and is the leading cause of irreversible blindness worldwide.[57] Treatment works by lowering intraocular pressure, and the hallmark of the disease appears to be a high intraocular pressure relative to the susceptibility of the optic nerve head to damage from such pressure.[57] This is sometimes due to impaired ability of the aqueous humour to drain as it is replenished. Risk factors include age, African or Asian ancestry, and high myopia.[57]

1.2.5.3 Age-related Macular Degeneration

Age-related macular degeneration is a degenerative disorder associated with ageing. It affects the central region of the retina; the macula, causing progressive impairment of central vision.[58] Early signs include changes in the retinal pigment epithelium and retinal deposits of fats and proteins called drusen.[58] Later in the disease process, development of new retinal blood vessels may be seen, indicating neovascular age-related macular degeneration, which is associated with rapid progression of visual loss. Age-related macular degeneration remains a leading cause of irreversible vision loss worldwide despite modern availability of medical treatments for the neovascular subtype.[58] Prevalence in people aged over 85 has been estimated at 13%, though this figure was based on an Australian population, and might be lower in Asian and African populations.[58] Besides age, the clearest risk factor for age-related macular degeneration is smoking, with evidence for other environmental contributors being mixed.[58] Age-related macular degeneration has been shown to be associated with future depression and Alzheimer's disease.[58]

1.2.5.4 Diabetic Retinopathy

Diabetic retinopathy is another leading cause of vision loss.[59] High blood pressure, poor control of diabetes, and high cholesterol are risk factors.[59] The condition has traditionally been considered to result from damage to the small blood vessels supplying the retina in the presence of raised blood sugar, but pathology may be more complex and likely also involves inflammation causing direct damage to nerves.[59] Various medical and surgical treatments to prevent and manage diabetic retinopathy exist, but progression to significant visual impairment nevertheless remains widespread.[59] Retinopathy affects approximately a third of people with diabetes,[60] and hypertension is known to exacerbate the risk.[59]

1.2.5.5 Congenital and Acquired Blindness

The common causes of visual impairment and blindness I have discussed above are acquired. Blindness present from birth is called congenital blindness. Congenital cortical blindness originates from a defect in the brain or optic tracts, whilst congenital peripheral blindness originates from a defect in the eyes.[61] Although congenital blindness is rare, its relationship to psychosis has been extensively discussed and will be explained later in this introduction.

1.2.6 Provision of Optical Care in the UK

Although the majority of UK healthcare is provided by the publicly-funded National Health Service (NHS), provision of optical care for refractive errors is largely private.[62] Groups entitled to free eye examinations and corrective aids for refractive error include under 16s, people entitled to certain benefits due to low household income, and people in need of complex corrective aids,[63] but this does not cover the majority of people who use corrective aids. Even where the costs are covered, the onus still falls on the individual to arrange an eyesight test, as this is not part of routine NHS screening. The other conditions outlined above would typically be managed within the NHS, but since refractive errors account for a large proportion of visual impairment, it seems likely that the personal cost of optical care presents a barrier to diagnosing and treating a significant number of cases.

1.3 Wider Context of Visual Impairment

There are complex interactions between a person's sociodemographic, economic and general health circumstances and their vision. I discuss this in the next few sections.

1.3.1 Sociodemographic Contexts

Visual impairment is more prevalent in people from more deprived, socioeconomic backgrounds.[64] This may be both because lower income leads to poorer health and reduced ability to correct refractive errors, and because visual impairment limits social and occupational opportunities.[65] A 2015 survey from the Royal National Institute for the Blind found that blind and partially-sighted people reported lower wellbeing than the rest of the population, were more likely to struggle financially, experienced negative attitudes from others, and were less able to work, travel and exercise freely.[45] Nearly half of respondents reported recently being treated unfairly by others due to their sight loss. Only 22% of working age respondents were employed, and half said they would not be able to afford a necessary but unexpected bill for £500.[45] Two thirds were not in employment, and the more severe the visual impairment, the less likely they were to be so.[45]

1.3.2 Economic Costs of Visual Impairment

A 2013 systematic review estimated the annual direct medical costs per patient of visual impairment as US $12,175–14,029 for moderate visual impairment, $13,154–16,321 for severe visual impairment and $14,882–24,180 for blindness.[66] The greatest proportion of these costs was from hospitalisation, medical devices and assistive aids, medical services, and nursing care.[66] Informal care also contributed significantly.

1.3.3 Comorbidities of Visual Impairment

A wide variety of systemic conditions, such as autoimmune and cardiovascular diseases, haematological conditions and cancers, can cause eyesight to deteriorate, and are therefore found co-morbidly with visual impairment more frequently than would be expected by chance.[67] Poorer visual acuity has been shown to associate with age-specific mortality.[68] It is likely that this association is driven by risk factors for visual

impairment, including smoking, hypertension, obesity, and other causes of cardiovascular disease.

Visual impairment has repeatedly been associated with elevated rates of depression and anxiety in cross-sectional studies that treat visual impairment as exposure.[64] The association appears to be particularly strong in older adults with progressive ophthalmological conditions; for example there is evidence that up to one third of people with Age-related Macular Degeneration appear to meet criteria for major depressive disorder.[64] Risk of suicide attempt is elevated in populations with visual impairment.[69] Research has found that levels of distress from visual impairment are comparable to those from acquired immunodeficiency, chronic obstructive pulmonary disease, and bone marrow transplant.[70] The risk of falls and car accidents is also elevated, further contributing to excess mortality.[68]

1.3.4 Health and Social Care: Needs and Barriers

Poorer overall health may also result from the visual impairment. People with significant visual impairment face barriers to accessing healthcare, such as difficulty reading appointment letters, difficulty taking medications correctly, and inability to take transport to appointments or navigate healthcare facilities.[71] At times, embarrassment may serve as a barrier to accessing necessary help with activities such as reading letters about healthcare or asking for guidance when attending appointments. [71] This can mean that appointments and opportunities to optimise physical health are missed.

As with physical comorbidities, the relationship between visual impairment and depression is likely to be bidirectional. Whilst depression could result from the functional and psychological effects of visual impairment, it might also lead to poorer attendance to health and eye care.[64]

The Royal National Institute for the Blind survey referenced above found that the majority of respondents needed some support around the home, for example with preparing food and setting the heating, and this support was most often informal and unpaid.[65]

1.4 Introduction to Psychosis

1.4.1 Definitions of Psychosis

Psychosis is a broad term. It can be used to mean illnesses characterised by psychotic symptoms, or the symptoms themselves, which do not always amount to illness. Psychotic symptoms can be categorised into 'positive' symptoms, meaning additional mental or behavioural experiences to those seen in states of health, and 'negative' symptoms, meaning loss of mental or behavioural functions seen in health.[72] Positive symptoms include: hallucinations, delusions, disorganised thought, disorganised behaviour, and passivity phenomena (experience of being directly controlled by outside forces).[73] Examples of negative symptoms include impairments of cognition, motivation, range of affect, sociability, and enjoyment.[72] The archetypal psychotic illness is schizophrenia. This can take a chronic, intermittent, or single episode course. The full diagnostic description for schizophrenia, as seen in the European classification system the International Diagnostic Criteria version 11 (ICD11) is as follows:

Schizophrenia is characterised by disturbances in multiple mental modalities, including thinking (e.g., delusions, disorganisation in the form of thought), perception (e.g., hallucinations), self-experience (e.g., the experience that one's feelings, impulses, thoughts, or behaviour are under the control of an external force), cognition (e.g., impaired attention, verbal memory, and social cognition), volition (e.g., loss of motivation), affect (e.g., blunted emotional expression), and behaviour (e.g., behaviour that appears bizarre or purposeless, unpredictable or inappropriate emotional responses that interfere with the organisation of behaviour). Psychomotor disturbances, including catatonia, may be present. Persistent delusions, persistent hallucinations, thought disorder, and experiences of influence, passivity, or control are considered core symptoms. Symptoms must have persisted for at least one month [for] a diagnosis of schizophrenia to be assigned. The symptoms are not a manifestation of another health condition (e.g., a brain tumour) and are not due to the effect of a substance or medication on the central nervous system (e.g., corticosteroids), including withdrawal (e.g., alcohol withdrawal).[74]

Other psychiatric diagnoses considered to be psychotic illnesses include schizoaffective disorder and some episodes of bipolar affective disorder. In these illnesses, known as affective psychoses, the psychotic symptoms occur in the context of major mood disturbance.[74] The full list of psychotic illness diagnoses in ICD-11 can be seen below.

Table 1-1: Diagnoses considered psychotic illnesses[74]

Diagnostic code	Diagnosis
6A60.1	Bipolar type I disorder, current episode manic, with psychotic symptoms
6A70.2	Single episode depressive disorder, moderate, with psychotic symptoms
6A70.4	Single episode depressive disorder, severe, with psychotic symptoms
6A60.5	Bipolar type I disorder, current episode depressive, moderate with psychotic symptoms
6A60.7	Bipolar type I disorder, current episode depressive, severe with psychotic symptoms
6A60.A	Bipolar type I disorder, current episode mixed, with psychotic symptoms
6A21	Schizoaffective disorder
6A22	Schizotypal disorder
6A23	Acute and transient psychotic disorder
6A24	Delusional disorder

ICD11 has significant overlap with the American criteria from the Diagnostic and Statistical Manual version 5 (DSM5).[75]

1.4.2 Schizophrenia Spectrum Disorder

I use the term Schizophrenia Spectrum Disorder (SSD) later in this thesis. This has been used in previous research studies to capture a collection of schizophrenia and related diagnoses that are inherently psychotic illnesses.[76] I have included schizophrenia, schizotypal disorder, delusional disorders, schizoaffective disorder, acute and transient psychotic disorders, and unspecified or other nonorganic psychosis in this category. This is based on the previous version of the ICD (ICD10), as diagnoses from this categorisation system are often available in UK data sets.[77]

1.4.3 Psychotic Symptoms in the General Population

Experiencing psychotic symptoms does not usually equate with psychotic illness. In the 2014 UK Adult Psychiatric Morbidity Survey, a general population household survey investigating prevalence of psychiatric morbidity, 5-6% of people reported past-year experiences which could be classed as positive psychotic symptoms, suggesting that these symptoms might be more common than traditionally thought.[78] There is some debate and uncertainty about the nature and relevance of these experiences in healthy populations, and to what extent they represent risk factors for or even milder forms of psychotic illnesses. There is evidence that they are linearly correlated with impairment, strengthening the case for a continuum model where they represent

milder forms of psychotic illness.[79] On the other hand, they have been shown not to associate with a family history of schizophrenia,[80] but do associate with presence of nonpsychotic psychiatric disorders, such as depression and anxiety.[81] Psychotic symptoms are therefore sometimes considered to be a cross-diagnostic feature of mental illness.[82] Psychotic symptoms can also occur frequently in healthy people for example in 'waking dreams' or sleep paralysis, so do not necessarily imply pathology.[83] 'Non-clinical' psychotic symptoms are especially common in childhood and adolescence.[84] They may however also be a sign of a possible psychotic illness prodrome.

1.4.4 Epidemiology of Psychotic Illnesses

Diagnosable psychotic illnesses were estimated to affect 0.7% of the population over the past year in the UK in 2014.[85] Schizophrenia alone affects at least 26 million people worldwide.[12] A 2019 systematic review found a pooled incidence rate of 26.6 per 100,000 person-years for all psychotic disorders internationally, 18.7 per 100,000 person years for non-affective, and 4.8 for affective psychotic disorders.[86]

1.4.5 The Biopsychosocial Model and Aetiology of Psychotic Illnesses

The risk factors for psychotic illnesses can be broadly divided into biological, psychological, and social factors. A paradigm shift in psychiatry occurred when the biopsychosocial model was first described by Engel in 1977.[87] He argued that the traditional biomedical model, to which all medical disciplines including psychiatry were perhaps expected to conform, was overly reductionist and unsuitable not just for psychiatry but the whole of medicine.[87] By contrast, a model allowing for psychological and social factors to contribute to illness development would give a fuller, more explanatory picture. This is highly relevant for any research concerning the aetiology of schizophrenia. Visual impairment also encompasses biological, social and psychological components. Throughout this thesis I will consider variables that could fall under any of these headings in the aetiology of psychotic illness as confounding and mediating variables.

1.4.5.1 Biological Aetiology of Psychotic Illnesses

Psychotic illnesses are likely to be highly multifactorial, and their genesis in unlikely to be explained in terms of a single genetic or environmental exposure. In this section I will outline several key proposed contributors.

1.4.5.1.1 The role of dopamine

The dopamine hypothesis was described as an explanation of how schizophrenia develops several decades ago.[88] It proposes that excessive activity of the cerebral neurotransmitter dopamine is key in causing the illness. It has since been revised to suggest that there is frontal hypoactivity of dopamine, with subcortical hyperactivity.[88]

Evidence to support the dopamine hypothesis includes the efficacy of antipsychotic medications, which act as antagonists at dopamine receptors and reduce dopaminergic activity.[88] Further, the efficacy of antipsychotics is directly related to their affinity for the dopamine receptor, and drugs which cause release of dopamine can precipitate psychosis.[88] Functional brain imaging studies of people affected by schizophrenia show elevated presynaptic dopamine availability in the striatum in keeping with this theory.[88] Alterations in dopamine activity are therefore frequently viewed as a likely 'final common pathway' to schizophrenia, with other risk factors acting to disrupt this.[88]

1.4.5.1.2 The role of glutamate

Glutamate is another neurotransmitter believed to be implicated in schizophrenia. Glutamate is the principal excitatory neurotransmitter in the brain, with three types of receptors, of which the N-methyl-D-Aspartate (NMDA) receptor is particularly implicated.[89] Glutamate plays a role in learning and memory.[89] Observations that drugs of abuse which alter glutamate expression, such as PCP and ketamine, can cause schizophrenia-like symptoms, has led to suggestions that NMDA receptor hypofunction underlies at least some cases of schizophrenia.[89]

1.4.5.1.3 Genetics

The heritability of schizophrenia has been estimated at approximately 80%, suggesting that a high proportion of population variance can be explained by genetics.[90] Most of this heritability is attributable not to rare genetic variants of large

effect, although Copy Number Variants of this type do exist.[91] Rather, the variation is due to hundreds of minor allelic variants of small effect, called Single Nucleotide Polymorphisms (SNPs). In 2014, the Psychiatric Genomics Consortium (PGC) combined many case-control samples to identify 108 genetic loci associated with schizophrenia.[91] In 2021, they were able to identify 270, showing that knowledge of genetic contributors to schizophrenia has expanded rapidly during this time.[92] Known variants are spread throughout the genome. Some have plausibly relevant biological functions, such as regulating dopamine metabolism or signalling, or regulating neuronal differentiation and development.[93] Individually, each of these SNPs confers a very small effect on a person's risk of schizophrenia, and even combining the SNPs into a Polygenic Risk Score does not currently have clinical utility.[91] Polygenic Risk Scores do have potential utility in identifying possible biological mechanisms behind schizophrenia, and I use these SNPs as instruments in my Mendelian Randomisation study (Chapter 5).

1.4.5.1.4 Environmental risk factors

As outlined above, there is evidence that use of some recreational drugs, especially drugs known to increase dopaminergic release and activity, is a risk factor for psychotic episodes.[94] Insults to the developing brain have also been identified as potential risk factors. These include birth trauma, such as hypoxia and in utero infection.[95] Similarly in adults, cerebral infection or inflammation is associated with psychotic symptoms, though these episodes are typically given medical diagnoses such as encephalitis and delirium rather than being recorded as psychosis; a term which seems reserved for episodes which have less immediately obvious biological determinants.[96]

1.4.5.2 Psychological and Social Risk Factors for Psychotic Illnesses

Broader risk factors include poverty, discrimination, urban living, migration, childhood trauma, and sleep deprivation.[97, 98] Of note, the first two of these are also risk factors for visual impairment, as outlined above. Childbirth can also be a precipitant of a psychotic episode, especially for people with Bipolar Affective Disorder.[99] One commonality to these risk factors is the capacity to inflict major stress on an individual, and this may be a further common pathway leading to development of psychotic illness, possibly occurring ahead of dopamine or glutamate dysregulation in the

pathway. The stress-diathesis model proposes that development of psychotic illness occurs when individuals with genetic vulnerability are exposed to stressors, which leads to sustained alteration in the functioning of the Hypothalamic Pituitary Adrenal (HPA) axis, ultimately causing the neurotransmitter abnormalities described above which drive the illness.[100]

Whilst many risk factors for psychotic illness are known, most are difficult to modify. Genetic factors, stress, and downstream effects on neurotransmitters are all difficult or arguably impossible to target for prevention. There is therefore significant potential benefit in identifying easily modifiable risk factors. Since a large proportion of visual impairment is due to refractive errors and myopia that are correctable with simple aids, identifying whether visual impairment is indeed a causal risk factor for psychosis could either identify or exclude a genuine target for prevention.

1.4.6 Treatment of Psychotic Illnesses

1.4.6.1 Antipsychotic Medications

Antipsychotic medications are the mainstay of treatment for established psychotic illnesses.[101] Fundamentally, all work by antagonising the action of dopamine at dopaminergic receptors throughout the cortex.[12] Cognitive Behavioural Therapy for psychosis is another treatment recommended for all patients with psychotic illnesses by the National Institute of Clinical Excellence,[101] although a 2018 systematic review found the effect of Cognitive Behavioural Therapy for psychosis on distress and quality of life to be small.[102] Other aspects of treatment for psychotic illnesses include family therapy and support with finances, occupation, and building social networks, which may include peer support.[101]

A newer treatment which has been trialled is Cognitive Remediation Therapy, a type of training which aims to reduce the cognitive impact of illness to enable sustained improvements in day-to-day functioning.[103] Cognitive Remediation Therapy has some evidence of benefit, and this has been shown to correlate with neuroimaging findings, such as greater preservation of grey matter volume.[103] The size of the effect on functioning appears to be small to moderate.[104] I will reference Cognitive Remediation Therapy when discussing potential implications of findings from this PhD.

1.4.6.2 Physical Health Monitoring in Psychotic Illnesses

Individuals who qualify for a diagnosis of psychotic illness have on average a life expectancy that is reduced by 10-20 years compared to individuals without these illnesses.[11, 12] Much of the excess mortality in psychotic illnesses is attributable to elevated rates of cardiovascular disease.[105] People with psychotic illnesses have higher rates of multiple cardiovascular risk factors such as high cholesterol, smoking, diabetes, hypertension, obesity, poor diet and sedentary lifestyles.[105] There has been a growing focus on how to reduce this mortality gap, for example the recent PRIMROSE trial, which aimed to lower cholesterol through a behavioural intervention delivered in primary care,[106] 2022 trial of metformin administration to improve glucose regulation,[107] a trial using omega-3 supplementation to reduce cardiovascular risk,[108] and multiple trials testing dietary and physical activity interventions.[109]

UK guidelines recommend that all people with psychotic illness diagnoses are offered an annual physical health check including monitoring of weight, height, blood pressure, electrocardiogram, and blood tests including cholesterol, and blood glucose..[101] Similar guidelines exist in other high-income countries.[110] Eyesight checks such as Snellen chart testing are not currently included in UK recommendations, but notably American guidelines specify that these should be conducted every 1-2 years.[110]

1.4.6.3 The Psychosis Prodrome and Tertiary Prevention

Schizophrenia and other psychotic illnesses are often preceded by a prodromal phase, in which signs of their impending onset might be apparent. These might represent an early stage of the illness, before diagnostic criteria are clearly met and when a full episode might still be averted. There has been considerable research interest in defining and identifying this prodrome, with a view to intervening before definitive illness is established, as a form of secondary prevention.[111] Key criteria believed to indicate a high level of individual risk for developing a psychotic illness include being aged 15-25 with a drop in functioning for one month, accompanied by either family history of psychotic illness, or presence of either attenuated or “brief limited intermittent psychotic symptoms”.[112] Attenuated psychotic symptoms are symptoms considered sub-threshold for diagnosis of a psychotic disorder, whilst brief limited intermittent psychotic symptoms may be more severe but resolve within seven days.[111] These

criteria have been associated with an elevation in risk of developing a psychotic disorder that is around 400 times the population risk over three years.[113]

There is so far no strong evidence to support use of either antipsychotic medications or Cognitive Behavioural Therapy to prevent transition to psychotic illness among people experiencing a potential prodrome.[111] If visual impairment is a causal risk factor for psychotic illness, however, then this could be an important group of people in which to support optimisation of eyesight.

1.4.7 Prognosis of Psychotic Illnesses

When a person presents with difficulties consistent with a psychotic illness, there has been a move towards using the term “first episode psychosis” to describe the episode, rather than making a diagnosis of an illness at the outset. Up to 90%+ of individuals with first episode psychosis achieve remission of positive symptoms for three months.[114] Unfortunately, almost half who recover relapsing over two years.[115] A recent systematic review found that just 14% of people with first episode psychosis had achieved both clinical and functional recovery over two years, highlighting the importance of prevention.[116]

Individuals who qualify for a diagnosis of psychotic illness have on average a life expectancy that is reduced by 10-20 years compared to individuals without these illnesses, due primarily to excess cardiovascular disease.[11, 12, 105] Besides shortening life, psychotic illnesses can significantly diminish its quality. A 2014 report noted that people with schizophrenia are 6-7 times less likely to be employed than people without, and in Europe up to 15% have experienced homelessness.[12] People with schizophrenia are also more likely to come into contact with the criminal justice system, and more than twice as likely to be victims of homicide.[12, 117]

1.5 The Association between Visual impairment and Psychosis

Psychosis is associated with a wide variety of physical and mental health conditions.[118] Among these, an association between visual impairment and psychosis has been demonstrated cross-sectionally, and longitudinally where visual impairment is the exposure.[118] It has also been associated with both psychotic diagnoses[119] and

symptoms.[120] Paradoxically, congenital cortical blindness has been postulated to be protective against psychosis, due to an absence of reported cases of the two conditions occurring together.[121] This is unusual since very few negative associations between psychosis and physical health conditions have been identified.[122] It is also recognised that severe loss of vision can directly lead to visual hallucinations (one type of psychotic symptom), in a condition named Charles Bonnet Syndrome.[123] Based on these observations it seems that an association between visual impairment and psychosis may exist, but the association is complex and not well-understood. In my systematic review in chapter 3 I will describe studies investigating the association between visual impairment and psychosis in detail, but in this section I will outline the theoretical basis for investigating the association.

1.5.1 Studies supporting the existence of an association between visual impairment and psychosis

Although the following studies were identified in my systematic review, I outline them here since they were integral to developing my research questions for this PhD. The existence of an association between visual impairment and psychosis is supported by a cross-sectional population study in Finland carried out by Viertio and colleagues.[119] They investigated a nationally representative sample of over 6,500 people who had visual acuity objectively measured using an Early Treatment of Diabetic Retinopathy Screening (ETDRS) chart. Psychiatric diagnoses were confirmed using the Research Version of the Structured Clinical Interview for DSM-IV-TR (SCID-I), or case notes if this was not possible. The study found strong evidence that people with schizophrenia had over five times the odds of distance visual impairment, and six times the odds of near vision impairment compared to the rest of the population, after adjusting for age and sex.[119] People with schizophrenia were also markedly less likely to have been to the optician within the past five years (44% vs 70%).[119] They reported more subjective eyesight problems than participants without psychotic illness, but still tended to under-recognise their impairments.[119] Antipsychotic use was not associated with visual impairment in this study, except for an association between phenothiazines (an older class of antipsychotics) and near vision.[119] Phenothiazine use is less common in current clinical practice, as guidelines tend to favour newer medications.[101] Diabetes rates were elevated in people with schizophrenia as expected, but surprisingly,

diabetes was not associated with visual impairment in this group.[119] Of note, people with affective psychoses and other non-affective psychoses besides schizophrenia did not have greater odds of poor visual acuity.[119]

As the visual tests in this study were performed with participants' usual visual aids such as glasses rather than ideal visual aids, it is likely that uncorrected refractive error contributed significantly to the visual deficits seen in people with schizophrenia. This is further supported by subgroup analyses showing that among glasses-wearers, rates of visual impairment were not different according to schizophrenia case status.[119] The authors concluded that the most likely reason for the association was that people with schizophrenia were at higher risk of non-receipt of optical care leading to poorer de facto vision, and that facilitation of eyesight tests should be incorporated into routine physical health checks for people with schizophrenia every one to two years.[119]

The existence of an association is further supported by studies of psychiatric inpatients. A 2002 cross-sectional evaluation in Hong Kong found that of 428 institutionalised patients with chronic psychiatric conditions, 75% had distance visual impairment, and 39% had myopia, with only a small proportion using adequate correction.[124] This clearly leaves a large number of patients with distance acuity impairment not explained by myopia. The reasons for this are unknown, but this might be explained by visual processing difficulties, or retinal conditions.

A 2015 study conducted in China also measured visual acuity with the ETDRS chart, in 356 psychiatric patients, wearing their spectacles if applicable.[125] This study found much lower rates of distance visual impairment in inpatients with schizophrenia; 13%.[125] However, this rose to 38% when the authors used the same cut-offs as the study from Hong Kong (20/40 or worse). A further, small cross-sectional study of inpatients with schizophrenia in Australia in 1997 found that almost 70% had untreated visual acuity problems on eye examination.[126] All were taking antipsychotic medications. In 2006, a small cross-sectional study of UK psychiatric inpatients found that two thirds had impairment of distance visual acuity,[127] and 61% reported not having been to an optician for five years or more.[127] Over three quarters of the sample took antipsychotic medications. All of these studies appear to highlight a burden of unmet visual need amongst people with psychosis or serious mental illness, and all

study authors concluded that greater support to access optical care was warranted in this population. Since these studies were all cross-sectional, it cannot be assumed that the psychiatric illness preceded the deterioration in vision.

1.5.2 Visual Processing and Psychotic Illnesses

A distinction must be made between visual impairment (the focus of this PhD), and visual processing, which has been more widely researched in schizophrenia. In fact, a trial of a visual remediation programme for schizophrenia, aimed at training visual processing skills and thereby related cognitive processes and real-world functioning, is already underway.[128]

Processing of visual information is a complex task that by necessity incorporates the function of the eye itself. It also involves activity of the optic tracts, visual cortex, and conceptual linking in related brain areas.[128] A vast range of components of visual processing have been identified. These can be divided into: lower-level functions, which are more likely to occur at eye level, such as visual acuity; medium level functions, such as visual perceptual organisation or putting together of visual components; and higher level functions, such as using existing knowledge to adapt visual perceptions.[128]

Findings that many aspects of visual processing are altered in schizophrenia are well-replicated.[128] Impaired contrast sensitivity and impaired perceptual organisation are two of the most well-established findings.[128] An example of perceptual organisation disturbance is given in this quote by a patient from 1966: *"I have to put things together in my head. If I look at my watch I see the watch, watchstrap, face, hands, and so on, then I have got to put them together to get it into one piece."*[129]

One study found that colour vision processing was impaired in first-episode schizophrenia, but improved with antipsychotic treatment, and that this was correlated also with improvement in cognitive scores.[130] Another found that contrast sensitivity was worse in people with both schizophrenia and bipolar affective disorder than healthy controls, and that this was correlated with illness duration, symptom severity, and medication dosage, particularly in the case of lithium.[131]

Proponents of visual processing research in schizophrenia emphasize that visual science is understood more than any other aspect of our neural functioning and cognition and could be a marker for more generalised cognitive functioning in schizophrenia.[132] Leading authors in this field also acknowledge that although visual processing impairments are often assumed to result from deficiencies in cortical function, they may be impacted by changes to the eye itself; a factor that has often been overlooked.[76] The retina is considered the candidate ocular region for this; but visual acuity, a function of the whole eye, is relatively seldom investigated.[35]

There are three prominent hypotheses which aim to explain the observed cross-sectional association between visual impairment and psychosis. I will outline these in the next few sections. It should be noted that the below hypotheses are not mutually exclusive.

1.5.3 Hypothesis 1: Psychotic illnesses are a causal risk factor for visual impairment.

Of the three hypotheses I will outline, the suggestion that psychotic illness might be a causal risk factor for visual impairment is perhaps the most intuitive. Visual impairment could cause as well as result from the mechanisms below, compounding this once it is established.

1.5.3.1 Direct health effects

People with psychotic illnesses might be less able to engage with the process of arranging private optical care, which is necessary to identify and correct common refractive errors. This could occur as a direct consequence of psychotic symptoms, for example if delusions make someone paranoid and unable to trust opticians, or if negative symptoms prevent them from organising appointments. Further, higher rates of comorbidities including diabetes and hypertension seen in (and potentially resulting from) psychotic illnesses would be expected to increase the rates of eyesight damage.[105, 133] This could occur through direct eyesight damage (such as diabetic retinopathy or age-related macular degeneration) or indirectly, for example via stroke.

1.5.3.2 Reduced Social Support

Reduced optician attendance could also occur through decreased social support, as sometimes individuals realise that their eyesight is poor only when comparing it to that of others, and people with psychotic illnesses typically have smaller social networks.[134]

1.5.3.3 Reduced Economic Resources

Loss of earnings induced by having a psychotic illness could also make optical care unaffordable.

1.5.3.4 Side Effects of Antipsychotic Medications

Antipsychotic medications have a wide range of recognised potential ocular side effects. These include oedema of the cornea, mydriasis (excess activation of the muscles of the iris), changes in accommodation, increased risk of glaucoma, and increased risk of cataracts.[135] In the case of some older antipsychotic medications, there is also a risk of damaging deposits in the retina that can lead to severe visual loss.[135] A less serious, but common, side effect is blurring of vision through anticholinergic mechanisms.[135]

1.5.3.5 Implications of Hypothesis 1

The impact of undiagnosed visual impairment in schizophrenia and other psychotic illnesses could be substantial and add to disease burden in a group of people whose health state already leads to disadvantage. There is to my knowledge no prior longitudinal evidence for hypothesis 1. Such evidence could highlight a need to optimise eye care for people with psychiatric illnesses, perhaps by including basic Snellen chart testing in the annual physical health check and raising awareness of access to free correction aids, as are available for some people through an NHS scheme in the UK, where appropriate.[63]

1.5.4 Hypothesis 2: Visual impairment may be a causal risk factor for psychosis.

In this section, I will outline theories proposing that visual impairment might be a causal risk factor for psychosis. Firstly, I describe the Protection against Schizophrenia

(PaSZ) model, followed by a brief description of the relevance of Bayesian psychiatry, and the condition of Charles Bonnet Syndrome.

1.5.4.1 The Protection against Schizophrenia (PaSZ) model

Hypothesis 2 is based on the Protection against Schizophrenia (PaSZ) model, which broadly states that congenital blindness protects against schizophrenia whilst loss of vision later in life has the opposite effect.[136] I will begin with a brief explanation of the somewhat surprising first claim of this model.

In 2003 Sanders and colleagues argued, perhaps boldly, that total blindness abolishes the possibility of developing schizophrenia.[137] They based this on their investigations in 2000-2001, which consisted of extensive database searches, and surveys of healthcare professionals and research institutes, which failed to identify a case of a blind person with schizophrenia.[137] There remain no reported cases of a congenitally cortically blind person developing schizophrenia.[61, 138, 139] This has sustained the theory that early-life blindness, especially congenital cortical blindness, might protect against schizophrenia. Further discussion of this is available in the literature, with some experts arguing that absence of a case report of two rare conditions co-occurring is not conspicuous and highlighting the enormous sample size required to test this statistically,[140] and others arguing that it is significant given that the two conditions share risk factors, and that such a case would be considered noteworthy.[141] A more recent review found cases of early-life or congenital peripheral, but not cortical blindness occurring with psychosis, although further scrutiny suggests many of these may not have described a psychotic illness by modern diagnostic criteria.[139]

In the Protection against Schizophrenia (PaSZ) model, based on the above theory, Landgraf and Osterheider argue that impaired visual capacity is a causal risk factor for schizophrenia, with both supra-normal ‘perfect’ and congenitally absent vision being protective, and the risk of schizophrenia being highest in people with some degree of visual impairment, as shown in the middle of the curve.

Figure 1-4: The Protection against Schizophrenia Model by Landgraf and Osterheider[136]

The level of visual capacity impairment associated with peak risk of schizophrenia or psychosis is theoretical; its location as yet undetermined through experiment. The model also makes no overt assumptions about the shape of the relationship between visual capacity and psychosis, for example whether it is linear or exponential, and claims only to be a basis for further epidemiological investigations.

Despite its name, the PaSZ model aims to represent a spectrum of psychiatrically-relevant phenomena, rather than a risk of binary schizophrenia status, so could apply to psychotic experiences as well.[136] It views psychosis as a late stage in a process of cognitive deterioration. Visual capacity is deemed to include visual acuity, as well as other visual functions such as sensitivity to light, motion and colour, and depth perception.[136] Oculomotor (eye movement) deficits, which have been extensively demonstrated in schizophrenia, are highlighted as another means by which visual capacity can be disturbed. The model proposes that acquisition and / or processing of visual information at some point during the life of an individual is necessary, but not sufficient, for psychosis to develop, and that disturbed visual processing is in some cases sufficient.

Several other claims made by the PaSZ model warrant discussion. Landgraf and Osterheider note that in both schizophrenia and acquired visual impairment, some areas of the brain are utilised for purposes other than those seen in healthy states. For example, they cite one Transcranial Magnetic Stimulation (TMS) experiment which showed that in a state of induced temporary disruption of occipital activity, auditory processing deteriorated in sighted individuals.[142] Landgraf and Osterheider triangulate this with evidence that in people with schizophrenia, brain areas are not optimally employed as individuals use more sequential processing of sensory information, to suggest that functional reorganisation of the brain is pivotal in psychosis development. They propose that the increased use of sequential processing is a compensatory mechanism for reduced multisensory integration in individuals with schizophrenia. In congenital blindness, functional reorganisation occurs early and is then stable through life, perhaps preventing later disruption to existing cognitive processing pathways.

Lastly, the PaSZ model proposes that improved understanding of the impaired visual capacity at different stages of schizophrenia could lead both to better prediction of who is at risk, and therapeutic gains. It describes cognitive training that might benefit schizophrenia patients. It suggests that both increasing attention to visual information, similarly to individuals with optimal visual capacity, and reducing reliance on visual input and instead reorganising neurofunctional sensory processing pathways similarly to congenitally blind people, could have the effect of improving cognitive functioning in schizophrenia, by moving individuals away from the peak risk region of impaired vision or visual processing.

1.5.4.2 Rationale for the PaSZ model

Silverstein and colleagues have described in detail these proposed mechanisms by which blindness could be protective.[121] They observe that multiple higher-order cognitive alterations seen in congenitally blind people allow them to perceive and process their surroundings optimally without vision. These include, compared to sighted individuals: more efficient auditory perception and attention; increased olfactory ability; superior working memory capacity (allowing parts of an object to be held in mind whilst other parts are touched and a full image formed); superior sequential processing ability; and reduced overgeneralisation of language concepts.[121] These adaptations are the reverse of the typical cognitive deficits seen in schizophrenia, and are therefore hypothesised to provide a buffering effect, reducing the individual's susceptibility to the cognitive syndrome of schizophrenia. These authors state that they are not suggesting vision itself is a risk factor for schizophrenia; rather that impaired vision might be, and congenital blindness precludes this.[121]

The neural mechanisms that might underlie these changes are also partially understood. It has been noted that in congenitally blind people, regions of the brain usually reserved for visual input are repurposed to allow more effective processing of haptic and auditory information.[121] This allows the dorsal and ventral streams; important pathways which process visual information; to function as well as they would in fully sighted individuals but based on alternative sensory input.[121] The dorsal stream appears to determine where an object is and guide action, whilst the ventral stream determines what an object is, so these are sometimes termed the 'what and where' pathways.[121] These streams have been shown to function abnormally in

schizophrenia.[121] If this is related to changes in visual processing, then congenitally blind individuals may again be protected from this. There is also some evidence of prolonged plasticity in the occipital cortex in congenital or early blindness, again the opposite to the reduced late-onset plasticity associated with schizophrenia.[121] Further, based on observations from dark-reared animals, early blindness is thought to cause upregulation of NMDA receptors in the brain, the reverse of the hypofunction seen in schizophrenia.[121] NMDA hypofunction is thought to particularly underlie the cognitive deficits seen in schizophrenia, which is highly relevant if schizophrenia is conceptualised as a disorder of cognition.[136]

Silverstein and colleagues also comment that congenital deaf-blindness seems to remove any protective effect of blindness.[121] This may be because the addition of deafness prevents the development of the purportedly protective enhanced cognitive processes that overcome the hurdle of blindness on perceiving the world.[121]

1.5.4.3 Bayesian Explanations

Computational psychiatry also has relevance to the hypothesis that visual impairment could be a causal risk factor for schizophrenia. Friston and colleagues have proposed that mismatch between prior expectations and sensory perceptions may contribute to the development of psychotic illnesses through faulty metacognition.[143] In their Bayesian brain theory of psychosis, it is suggested that our interpretation of the world is informed by prior beliefs, which are a probability distribution of our expectations before perceiving something, and which may be broad or precise. We update our expectations after having perceived something. This leads to posterior beliefs (beliefs which have now been updated based on the new sensory information). Another component in this theory is meta-cognition: beliefs about beliefs. These relate to the expected precision of beliefs. If either prior or posterior beliefs are given too much or too little weight, then delusions and hallucinations might develop. This could occur if, for example, momentary fluctuations in sensory perception are assumed to be wholly accurate and more precise than prior beliefs, even when the perceptions are unlikely.[143] An over-emphasis on the accuracy of sensory input rather than prior expectations in schizophrenia has been replicated in multiple studies. For example, people with schizophrenia often accurately perceive images of concave faces to be concave, whereas healthy individuals tend to perceive them (wrongly) to be convex

since the brain understands that faces are never concave, the latter indicating that more weight has appropriately been given to prior beliefs than sensory input.[144] This resistance to the depth inverson illusion in schizophrenia appears to be state-related and associated with positive symptom severity.[144]

An extension of Bayesian explanations might be that sustained incorrect sensory input (due to visual impairment) could lead to the precision attributed to prior and posterior beliefs being updated, triggering this mechanism of psychotic symptom generation. Sighted individuals are thought to have less stable prior beliefs about the world than blind people because their beliefs are dependent on continuous visual feedback, making them susceptible to cognitive errors and possibly psychosis when the visual feedback is lost.[138]

1.5.4.4 Charles Bonnet Syndrome

There is one psychotic symptom which can be caused by severe visual impairment: hallucinations. Charles Bonnet Syndrome is a well-recognised phenomenon in which hallucinations occur secondary to visual loss.[145] Charles Bonnet Syndrome was first described by Charles Bonnet in 1860, in a published description of an affliction affecting his grandfather; who reportedly had no cognitive impairment or psychiatric illness, and yet saw images of men, women, birds, carriages and buildings appearing and disappearing in front of him in clear consciousness after he lost vision due to cataracts.[146]

Subsequently, the exact definition of the syndrome has been subject to debate. Cases of Charles Bonnet Syndrome occurring without overt visual loss have been described, and association of visual hallucinations with cognitive impairment in older individuals has been identified.[147] de Morsier insisted that the hallucinations resulted from cerebral changes and not ocular visual loss; a viewpoint which has not become mainstream.[148, 149] In fact, visual hallucinations have also been reported after prolonged blindfolding of healthy participants, which contradicts de Morsier's view and suggests that eyesight loss is unimportant to their development.[150] A systematic review of diagnostic criteria for Charles Bonnet Syndrome found that key commonalities were visual loss, visual hallucinations, and exclusion of other neuropsychiatric disorders.[123] Prevalence of Charles Bonnet Syndrome has been

variably reported to be between 11% and 21% in patients with low vision, but may be under-reported by patients due to stigma and fear of being labelled as 'mad'.[146, 151] Severity of visual loss has been shown to correlate with the risk of Charles Bonnet Syndrome.[146] Charles Bonnet Syndrome is usually considered distinct from psychotic disorders insofar as affected individuals typically have isolated hallucinations, without other positive symptoms, and do not believe that the hallucinations are real.[146]

My PhD is not focussed on Charles Bonnet Syndrome, about which extensive research already exists, but this phenomenon demonstrates a link between vision and positive psychotic symptoms and relevant questions as to how, neurologically, a change in level of vision might lead to these. Deafferentation of specific brain structures, predominantly the visual cortex, is one proposed pathway.[146] Burke has suggested that such deafferentation occurs after partial inactivation of the retina, which leads to increased activity of NMDA receptors, and ultimately cortical hyperexcitability which drives the hallucinations.[151] Other authors have also implicated NMDA receptors in mediating any association between visual loss and hallucinations.[121, 137]

1.5.4.5 Comorbidities

In addition to the relatively direct association proposed above, visual impairment could be a causal risk factor for psychosis through more indirect mechanisms. Research shows that sensory impairment is associated with anxiety disorders and depression,[120] which are themselves potential precursors to psychotic illness, and associated with psychotic experiences.[81] This relationship could be bidirectional, as these illnesses may serve as barriers to accessing good eyecare and corrective aids for refractive error, and might also reduce healthy lifestyle behaviours that lessen the chance of developing diabetes, hypertension, or other causes of ocular damage.

1.5.4.6 Socioeconomic factors

People with sight loss also face on average greater social adversity which might elevate stress levels,[152] again a possible mechanism by which psychosis risk is increased. Visual impairment might remove factors that protect to some extent against mental illness, such as meaningful employment and access to supportive social networks and healthcare.[45]

1.5.4.7 Hearing Impairment

For comparison, the other common sensory impairment, hearing impairment, is an accepted risk factor both for psychotic experiences and psychotic illnesses.[153] There are specialist mental health services for d/Deaf people, with the capital D denoting cultural Deafness. This is largely due to the need for an environment in which d/Deaf people can communicate with others around them in sign language. Unlike blindness, congenital deaf/Deafness is not considered protective against schizophrenia, suggesting only a linear, rather than n-shaped relationship between the two.[153]

1.5.4.8 Implications of Hypothesis 2

If hypothesis 2 (that visual impairment is a causal risk factor for psychosis) is supported, then addressing the root causes of myopia and other visual impairment might reduce the number of cases of psychotic illnesses. This type of preventative strategy could be primary (addressing visual impairment in the whole population), or secondary (targeting optical care towards people who have been identified as at high risk of psychosis; either due to family history or short-lived or attenuated psychotic symptoms).[154] In the PaSZ model, Landgraf and Osterheider suggested that visual training might improve cognition in people with established psychotic disorders.[136] Therefore, evidence for hypothesis 2 could also support this avenue of exploration in treating psychosis. In describing the proposed mechanisms which may explain a negative association between congenital blindness and psychosis, Silverstein and colleagues specify that their main aim is to inform development of training interventions to treat and prevent schizophrenia.[121] Indeed, they are now carrying out an early-stage trial of such a visual training intervention in people with a schizophrenia diagnosis.[128] This might also be described as a form of tertiary prevention, since it aims to mitigate further social,occupational, and quality of life effects of the illness.

1.5.5 Alternative Hypothesis: Visual impairment may be share underlying neuropathology with psychosis

Another possible explanation for the association between visual impairment and psychosis is that a third factor (or confounder) causes both; such third factors might include shared neuropathology affecting the brain and eye. Confounding by shared neuropathology is of interest since in this case, studying visual impairment in

psychosis could potentially provide clues as to the underlying neural mechanisms of psychosis, since the eye is the part of the central nervous system that is most accessible for study.[76] My thesis does not directly test this, but it has relevance throughout. In this section I outline retinal imaging studies which support this alternative hypothesis.

1.5.5.1 Oculomics

As explained earlier in this chapter, the retina is an embryological extension of the brain.[23] Further, it shares multiple aspects of anatomy and physiology with the brain, including layered architecture, neural circuitry, neurotransmitters, and glial cells.[6, 155] It has been suggested that the retina may therefore offer a unique opportunity to image processes of neuronal damage in neurological conditions, potentially including psychotic disorders, directly using non-invasive procedures. In neurological diseases such as dementia, retinal changes correlate with cerebral volume loss on MRI, and seem to precede and predict disease status.[6] The emerging field concerned with studying eyes to identify ocular signs of systematic diseases has been termed oculomics.[6]

1.5.5.2 Optical Coherence Tomography (OCT) Studies

Modern mechanisms for studying the retina include Optical Coherence Tomography (OCT), where cross-sectional images of the retina are produced using light.[156] OCT is a non-invasive form of imaging able to identify cellular layers on the retina, making its resolution unusual in the level of detail that can be obtained.[157] It can determine retinal nerve fibre layer thickness, macular thickness, macular volume, and foveal thickness.[23]

Figure 1-5: OCT Image of a healthy retina[158]

A 2018 systematic review of retinal structural and functional imaging studies in schizophrenia highlighted reduced retinal thickness on OCT scans in affected people compared to healthy individuals.[23] The macula in particular has been found to have reduced thickness and volume in schizophrenia across studies.[6] One study in the

review found that this applied to people with chronic illness, but not people in an acute first episode.[159] It is thought that OCT changes could therefore develop as illness progresses, rather than preceding it.

1.5.5.3 Electroretinography (ERG) Studies

OCT is a form of structural imaging, but functional imaging of the retina is also possible, in the form of Electroretinography (ERG). ERG measures retinal response to a light stimulus, in the form of an evoked potential, indicating rod and cone cell functioning.[23] This can be done by placing an electrode near the eye, or for a stronger signal, onto the eye using a contact lens.[160] Studies of ERG recordings in schizophrenia have found evidence of altered retinal waveforms, which did not correlate with dose or duration of antipsychotic treatment, and therefore are not thought to be medication side-effects.[23] Hébert and colleagues found ERG abnormalities in non-affected children of people with both schizophrenia and bipolar affective disorder, implying that these changes were not a result of the illness, but might be predictive of risk.[146] In a more recent paper, they showed that having a 'schizophrenia-like' ERG profile was predictive of psychotic experiences in high-risk offspring of parents with a psychotic illness.[161] Further, adjusting for antipsychotic medication use increased the relative risk of having a schizophrenia-like ERG, perhaps meaning that medication use was not a confounder but rather something that might normalise the ERG to some extent.[161] It has been suggested that this work is the strongest evidence to date that ERG could have diagnostic utility in schizophrenia.[100] In a review of the literature, it has also been noted that some ERG changes appear to be state-related and others trait-related.[6]

1.5.5.4 Retinal Photography Studies

A third technique for investigating ocular function in schizophrenia assessed in the 2018 systematic review was retinal photography, which can be used to image retinal vasculature, as a proxy for cerebral vasculature.[23] Studies have correlated vascular dysfunction, possibly at the level of the smallest blood vessels (capillaries) with schizophrenia.[157] Genome-Wide Association Studies (GWAS) also identify a number of risk genes for schizophrenia that are associated with vascular development.[157] It is proposed that microvasculature changes might be an inherent feature of the development of the illness.[157] Studies employing retinal photography found that retinal

venules were wider in people with schizophrenia when compared to people with other medical and psychiatric conditions, including diabetes, hypertension, tobacco dependence, depression, and healthy controls.[162] Unaffected twins also had wider venules. Of note, wider retinal venules are considered a risk factor for stroke and cerebrovascular disease, in line with elevated cardiovascular risk seen in schizophrenia.[23] Photography has even been used to show that crypts and pigment dots in the iris of the eye are more commonly seen in people with schizophrenia.[130]

1.5.5.5 Optical Coherence Tomography-Angiography (OCT-A)

A newer method for assessing the retina is Optical Coherence Tomography Angiography (OCTA). This is a functional extension of OCT that generates angiograms.[157] The first studies using OCTA in schizophrenia show alterations in vascular density, which vary depending on the region of the retina.[157]

1.5.5.6 Further findings from retinal imaging studies

Some studies have correlated the above structural and functional imaging findings with psychotic symptom level.[23] Various mechanisms have been speculated to cause retinal imaging abnormalities, including dysregulation of glutamate, dopamine, and serotonin; omega-3 fatty acid depletion; and inflammation, which again might be implicated in the genesis of schizophrenia.[23]

1.5.5.7 Limitations of retinal imaging studies

Major limitations of retinal imaging studies in schizophrenia include small sample sizes in some studies, case-control designs which restrict ability to determine when in illness course changes occur, and inability to account for possible confounding effects of comorbidities and antipsychotic medications.[23] Nevertheless, these studies show that the association between psychosis and visual impairment could potentially be explained by shared underlying neuropathology. Until recently, it was not clear how retinal changes related to visual impairment. Research has now begun to link them to some visual processing deficiencies, for example lower contrast sensitivity.[76, 163]

1.5.5.8 Implications of alternative hypothesis

Whilst this alternative hypothesis; that visual impairment and psychosis share underlying neuropathology; will not be tested directly in my PhD, I will consider it

throughout as an alternative explanation for findings. If this hypothesis is correct, then it is possible that retinal imaging might have diagnostic or prognostic utility in psychotic illnesses,[164] or may give insights into an underlying neurodegenerative process, potentially informing the development of new treatments.[165] Proposed advantages of studying the retina over relying on brain imaging include its sensitivity to change, and the relative ease of acquiring an image of the retina, which can take less than one second.[6]

1.6 Demographics, Visual Impairment, and Psychosis

1.6.1 Psychosis and visual impairment do not affect demographic groups equally. I discuss below social characteristics that are associated with a greater risk of both conditions, which could thus potentially confound any relationship between vision and psychosis. . While I describe these separately, I note their intersectionality. Age

The nature of the relationship between visual impairment and psychosis may not be consistent across age groups, since common causes of both conditions vary by age. There could be a critical period of exposure to visual impairment in determining the risk of psychosis in children or adolescents, who undergo ocular and cerebral development throughout the first two decades of life.[27, 166, 167].

Visual impairment is however far more common among older people.[5] There may be a differential effect of visual impairment between older and younger adults, as visual impairment early in life could impair the development of occupational and social roles, whilst later visual loss could lead to grief and loss of existing networks and roles. Older people continue to face stigma and discrimination in our society, particularly when they possess other characteristics against which discrimination occurs.[168] This could inhibit their access to optimal healthcare and social inclusion.[168] This may mean that actions to reduce visual impairment or address the limitations it imposes on an individual are undertaken less proactively in older people, compounding its effects, particularly when discrimination due to the visual impairment itself co-occurs.

The prevalence of different types of visual impairment also varies across age groups, with older people being more likely to experience severe visual impairment than younger people, which may create different associations with psychosis between age groups given the non-linear shape of the PaSZ model across degrees of visual impairment.[169]

I have so far discussed psychosis primarily in the context of psychotic illnesses such as schizophrenia, which typically begin with a prodrome in adolescence and can be considered neurodevelopmental disorders. It is not unusual however for psychotic experiences and psychotic illnesses to occur for the first time in later life.[170] It has been noted that older people are frequently excluded from research in this area, meaning that less is understood about the epidemiology of late-onset psychosis than other forms.[170] Current research shows that psychotic symptoms occurring for the first time in older people commonly have a different aetiology in older people in that they can be a manifestation of dementia.[171] Psychosis is more common in dementia, and more likely to manifest in the form of visual hallucinations or illusions when dementia is the cause, particularly in Lewy-body or Parkinson's disease dementia.[172] One variant of dementia, posterior cortical atrophy, is characterised by impairment of processing visual stimuli.[173]

Primary psychotic illnesses arising de novo in old age are also associated with increased risk of future dementia diagnosis, particularly over the subsequent year, again raising the possibility that a dementia prodrome is the cause, although this is certainly not true in all cases.[174]

Visual impairment, much like hearing impairment, appears to be a risk factor for dementia, although it is not known whether this relationship is causal.[175] If it is, then this is an additional possible mechanism by which visual impairment could cause psychosis in older people, and a further reason why the relationship between visual impairment and psychosis is potentially distinct between younger and older people.

I will therefore consider, particularly in chapters 4, 6, and 7 of this thesis, that any association between visual impairment and psychosis may not be uniform across age groups.

1.6.2 Ethnicity

People from ethnic minority backgrounds in the UK, especially people with Afro-Caribbean backgrounds, are more likely to have visual impairment, in part due to higher rates of some precursors to visual impairment such as diabetes.[176] Ethnic minority groups are also more likely be excluded from services that might preserve vision, for example through lack of written information in an appropriate language, or services that are not culturally competent.[176]

It is well established that being in an ethnic minority group or being migrant is risk factor for development of psychotic illnesses.[177] People from Black Caribbean backgrounds in the UK in particular are at elevated risk.[178] There has been much speculation as to why this is. One case study found that it might be because Black Caribbean people are more likely to experience social disadvantage including unemployment and living in rented accommodation.[178] People from ethnic minority groups in the UK are also disproportionately likely to experience a first contact with mental health services through being detained under the mental health act or contact with the police, rather than through voluntarily accessing community services.[179] A systematic review found that the most likely reasons for this include increased prevalence of psychotic illness (rather than other types of mental illness), increased perceived risk of violence by practitioners, and ethnic disadvantages (perhaps due to structural racism).[179] Due to this, the effects of both visual impairment and psychotic illness are likely to be heightened, on average, in ethnic minority groups, and any association between visual impairment and psychosis might be stronger.

1.6.3 Gender

Visual impairment is more prevalent among women than men.[180] A Spanish household survey found that women waited longer than men to access cataract surgery, despite women having higher rates of obtaining medical care.[180] It is speculated therefore that gender discrimination affects access to corrective procedures.[181] There may be both biological reasons for higher rates of visual impairment in women (such as hormonal differences) and societal reasons (such as greater exposure to domestic work which can predispose to stress and ill health).[181]

Men have a higher incidence of psychosis compared to women.[86] Although the peak age of incidence is in young adulthood for both sexes, women have a second peak around the age of menopause, perhaps suggesting distinct triggers.[86] Previous research has also identified differential associations between environmental risk factors and psychosis; for example, childhood physical and sexual abuse may have greater relevance in women, whilst urban living might show a stronger association in men.[182] I will consider gender as a putative confounder of the association between visual impairment and psychosis in the upcoming chapters of this thesis.

1.6.4 Socioeconomic Factors

Inequalities in access to care will affect treatment of visual impairment and psychosis.[183] In addition to age, ethnic group, and even sexual orientation, geographical factors and deprivation are associated with poorer experiences of accessing primary care.[183] Visual impairment is associated with lower household income in both low- and high-income countries.[181] This relationship is likely to be bidirectional, since low income can act as a barrier towards paying the costs of eyecare, and visual impairment can also limit opportunities for employment and earning.[181] It is likely that lower income further reduces ability to compensate for visual impairment, for example by paying for help or accessing equipment that might mitigate against its effects on quality of life.[64] Ultimately, the burden of visual impairment is distributed unequally across socioeconomic groups.

Findings from some studies that lower socioeconomic status is associated with psychotic illness has long prompted debate as to whether this is caused by social drift (people with psychosis drifting into lower socioeconomic classes due to illness) or whether the stress of adversity contributes to causing psychosis.[184] Studies showing that childhood socioeconomic status is associated with adulthood psychosis suggest that the latter is true to some extent, but again this relationship is most likely to be bidirectional.[185] Similarly to visual impairment, the effects of psychotic illness on one's life may also be influenced by income, education, and social support networks.

In the research chapters of this thesis, I consider socioeconomic status as a further possible confounder of the association between visual impairment and psychosis.

Although I have discussed demographic factors individually in this section, intersectionality means that inequalities in the likelihood and consequences of health conditions are likely to be greatest, on average, in people with more than one marginalised characteristic[186], as discrimination compounds.

1.7 Multiple Long-Term Conditions

Co-existent long-term health conditions can also interact to cause particularly deleterious effects on an individual.[187] The situation where two or more diseases or health conditions cluster in a population leading to higher health burden has been termed a 'syndemic' by The Lancet.[188] Syndemics are more likely to occur where there is health inequality such as that caused by poverty, stress or stigma; which not only creates the conditions for co-occurrence of diseases but also heightens their effects.[188] Identifying clusters of multiple long term conditions and improving outcomes in this context is therefore a priority for the National Institute of Health and Care Research.[187] My PhD fits with this aim as I focus on the association between two long-term conditions.

1.8 Summary and gaps in the literature I will address

In this chapter, I have given an overview of visual impairment and psychosis, and described the two hypotheses that I will aim to test in this PhD, as well as an alternative hypothesis that I will refer to throughout. Here, I highlight key gaps in the literature.

Numerous studies comparing visual processing abilities in people with schizophrenia and people without exist and have been recently reviewed,[189] but studies measuring visual acuity have not received the same attention. At the most recent (1993) systematic review, studies investigating the potential association between sensory (visual and hearing) impairments and psychosis were collated in older, but not younger, adults.[190] The literature pertaining to visual impairment at that time was deemed to be inconsistent, with methodological flaws such as lack of appropriate control groups, and unreliable measurement of visual impairment.[190] More recently, there have been large observational studies investigating the association between visual acuity impairment and psychosis, which have not previously been systematically

reviewed.[13, 14, 118] I will critically appraise these in the relevant chapters of this thesis. The lack of an up-to-date synthesis of studies investigating associations between visual impairment and psychosis, or any synthesis across age groups, is one literature gap that I have aimed to address in my systematic review (Chapter 3).

To date, there are no studies of which I am aware exploring whether childhood visual impairment is a risk factor for future psychotic experiences, as opposed to schizophrenia. This is another gap that I have aimed to address in chapter 4.

Clearly, Randomised Controlled Trials (RCTs) investigating whether visual impairment is a causal risk factor for psychosis, and vice versa, are impossible. It is therefore imperative that the best use is made of observational data in assessing whether there is a causal relationship between the two conditions. Mendelian Randomisation is a relatively new technique, described later, which attempts to simulate an RCT using observational data. As this technique has not previously been applied to this research question, I have made use of it in chapter 5.

There is no large population study investigating the association between psychotic experiences and retinal measures derived from OCT scans, and how this relates to visual acuity. I will report such a study in chapter 6.

To my knowledge, case control studies investigating the association between visual impairment and psychosis to date have used small samples. Most had other significant limitations, including selecting cases and controls from circumscribed populations, or excluding people with visual impairment above a certain level. These are gaps which I try to address in chapter 7.

In the next chapter, I briefly describe the aims of my PhD.

Chapter 2 Aims of Thesis

2.1 Aims of this PhD

The aims of my PhD were to make the best use of observational data to directly test hypotheses 1 (that psychotic illnesses are a causal risk factor for visual impairment) and 2 (that visual impairment is a causal risk factor for psychotic illnesses), and to consider throughout how the evidence might indirectly support my alternative hypothesis (that visual impairment and psychotic illness might share underlying neuropathology).

2.2 Objectives

2.2.1 Objective 1

My first objective is to collate and synthesise existing studies reporting on the presence and strength of an association between visual acuity impairment and psychosis in a systematic review and meta-analysis (chapter 3). I include any eligible quantitative study in this review, and meta-analysed results where possible. This enables me to identify the boundaries of current knowledge to identify gaps in the literature and build upon it. Evidence of an association in my systematic review is supportive of both hypothesis 1 and 2, and my alternative hypothesis.

2.2.2 Objective 2

My second objective is to investigate the association between visual acuity impairments in childhood and psychotic symptoms in adolescence in a longitudinal analysis, separately from other aspects of ocular function with which they have only been investigated in combination previously (chapter 4). In this study I aim to test hypothesis 2; that visual impairment is a causal risk factor for psychotic illnesses, in a younger group where neurodevelopment was still occurring, and where the incidence of both myopia and psychotic illnesses were reaching their peak.

2.2.3 Objective 3

I assess genetic evidence for a causal association between myopia and schizophrenia using Mendelian Randomisation (chapter 5). Mendelian Randomisation aims to test both hypotheses 1 and 2. Using this study design allows me to make use of observational data to do this, since a randomised controlled trial cannot be undertaken to address my hypotheses. I use samples including the UK Biobank, Psychiatric Genomics Consortium (PGC), and Consortium of Myopia and Refractive Error (CREAM) for this study.

2.2.4 Objective 4

I assess for longitudinal evidence of an association between visual acuity impairment and alterations in retinal structures, and psychotic experiences in a cohort of working age and older adults in the UK Biobank (chapter 6). Here, I aim to test hypothesis 2 in a sample of older adults where neurodegenerative factors could lead to a different relationship between visual impairment and psychosis compared to the younger cohort.

2.2.5 Objective 5

I investigate whether cases (with visual impairment) have a higher odds of having a Schizophrenia-Spectrum Disorder (SSD) diagnosis than controls (without visual impairment) in a sample of adults from the UK Biobank (chapter 7). Through this study I test hypothesis 1 (that psychotic illnesses are a causal risk factor for visual impairment).

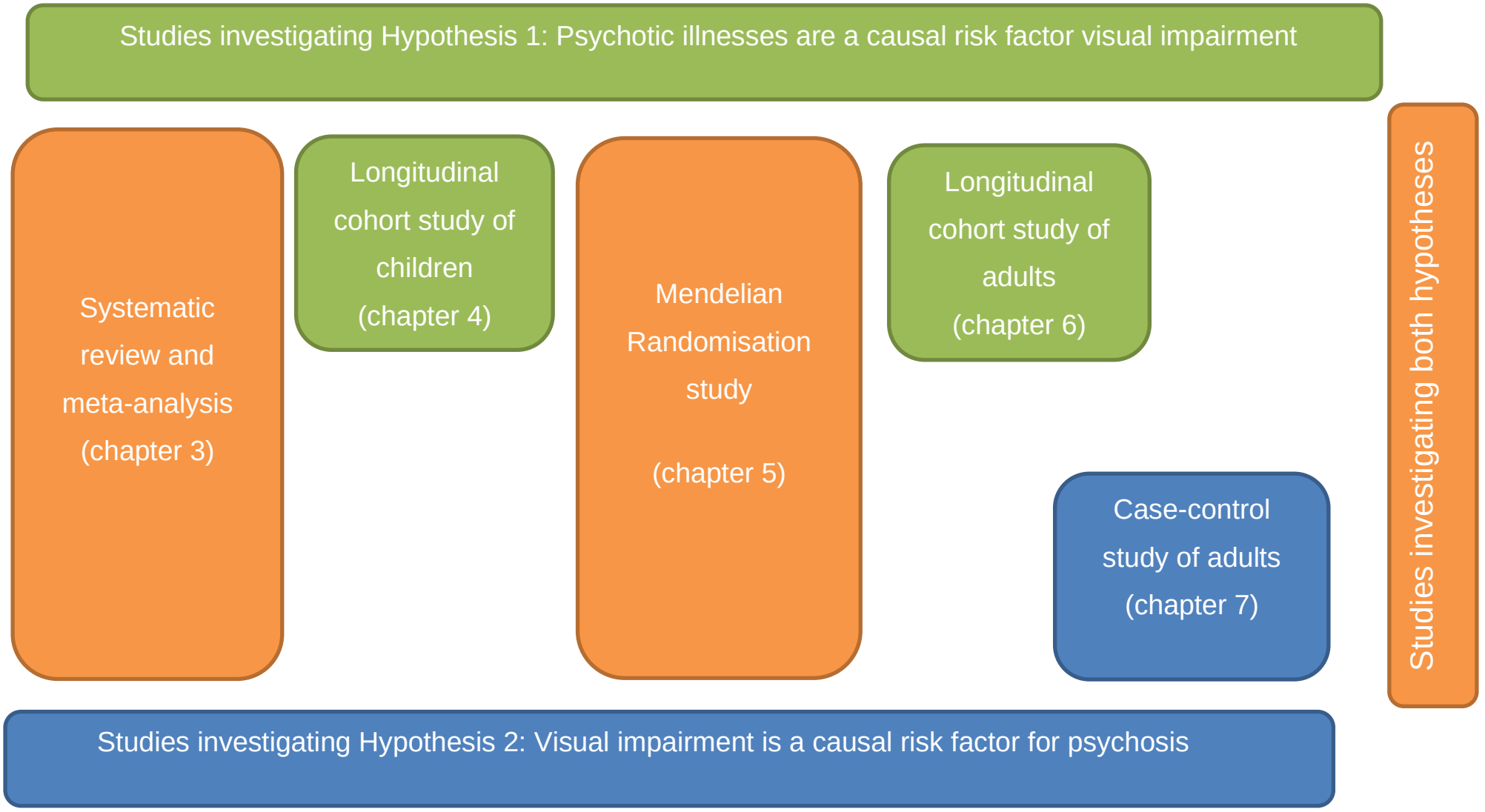

Figure 2-1: Studies in PhD. = testing hypothesis 1 = testing hypothesis 2 = testing both hypotheses

Chapter 3 Associations Between Psychosis and Visual Acuity Impairment: A Systematic Review and Meta-Analysis

An amended version of this chapter was published in Acta Psychiatrica Scandinavica:

Shoham, N, Eskinazi, M, Hayes, JF, Lewis, G, Theodorsson, M, Cooper, C. Associations between psychosis and visual acuity impairment: A systematic review and meta-analysis. Acta Psychiatr Scand. 2021*; 144: 6– 27. https://doi.org/10.1111/acps.13330*

3.1 Introduction

In the previous chapter, I gave an overview of the literature which suggests that psychosis may be a risk factor for visual impairment, or the converse. If either hypothesis 1 (schizophrenia is a causal risk factor for visual impairment) or 2 (visual impairment is a causal risk factor for psychosis) is true, then existing cross-sectional and case-control studies would be expected to consistently show an association between the two conditions. If hypothesis 1 were true, then longitudinal studies with psychosis as exposure would also be expected to show an association with visual impairment; and if hypothesis 2 were true, then the relationship ought to be apparent in longitudinal studies reversing this exposure and outcome. Any association, regardless of temporality, would also be consistent with the alternative hypothesis (that visual impairment and psychosis share underlying neuropathology).

I referred to a previous systematic review of sensory impairments and psychosis in the introduction. This was conducted in 1993 by Prager and Jeste.[190] They reviewed published studies investigating a possible association between visual or hearing impairment and late life psychosis.[190] It appears that at the time, a possible role of sensory impairment in contributing causally to late-onset schizophrenia and psychotic illness was broadly acknowledged, but the potential link in younger adults less so. Prager and Jeste appear not to have restricted by study design, and include one single case report in their narrative review.[190] They identified 27 studies in total, of which nine assessed both visual and hearing impairments, three assessed visual impairment alone, and two omitted to mention which type of impairment they investigated.[190] Of

the twelve studies investigating visual impairment, one had no control group; and nine used patients with other psychiatric conditions as the control group (typically paraphrenia - an older term for late-onset schizophrenia - vs another diagnosis). These control groups often included other psychotic disorders, limiting their utility in assessing the true nature of the association between visual impairment and psychosis.[190] Results from these studies were mixed, with some finding an association between visual impairment and paraphrenia and some not, allowing no firm conclusions to be drawn.[190] One study tested for differences in psychotic symptoms between hearing impaired and visually impaired patients, and patients with both impairments.[191] This found that blind patients had more persecutory delusions than the other groups.[191] Just two studies compared patients with psychotic illnesses to healthy individuals or community controls.[192, 193] Of these, one found a higher rate of visual impairment in patients,[192] and the other found no difference.[193] The number of participants in both studies was relatively small; one had 40 participants with psychotic illness,[192] and the other 43.[193]

This shows that prior to my systematic review, there was no synthesis of studies of visual acuity impairment and psychosis in studies including younger adults or children; no synthesis of cohort-studies, and no synthesis of large, high-quality studies in this area. The overall comparatively low quality of studies in the 1993 review has restricted ability to draw conclusions as to whether there is consistent evidence of an association between visual impairment and psychosis.

3.1.1 Rationale for Method and Key Decisions

I aimed to address the gap in the literature identified above. Systematic review is a key method for collating existing knowledge, and allowed me to identify more specific gaps and limitations in existing literature, so that I could ensure my PhD built on and did not duplicate previous knowledge. One of Bradford-Hill's criteria in establishing casual relationships is strength: a strong association between variables can support causality.[1] Conducting a meta-analysis combining compatible effect estimates allowed me to estimate the size of an association between these two conditions, and compare it to effect sizes of other known risk factors for psychosis. Systematic review also has

the potential to test a second Bradford Hill criterion; consistency of results across settings and populations.[1]

My preliminary searches found no relevant studies of younger people prior to Prager and Jeste's review. Therefore, I made the decision to restrict the dates of included studies to 1992 onwards, for the avoidance of duplication with this previous review.

My preliminary searches also made it clear that many studies of visual processing in schizophrenia exist, typically assuming participants to have 'normal' visual acuity and implying that the level of any impairment is not at the level of the eye itself. These have been collated and discussed by other authors, sometimes under the umbrella term of 'visual impairment'.[194, 195] To distinguish my review from these, I used the term 'visual acuity impairment' rather than visual impairment. I also used a broad definition of psychosis, to include either a diagnosed psychotic illness (whether by self-report, diagnostic interview or medical records) and psychotic symptoms (whether by self-report or rating scale). This was to account for the fact that psychotic symptoms can occur outside the context of primary psychotic illnesses, and any association may generalise to these experiences.

Regarding study design, I excluded qualitative studies and case reports or case series, since information required to measure strength of association and could not be obtained from these papers. I did not however exclude any type of quantitative study design, since cohort, case-control, and cross-sectional studies can all estimate strength of an association. Initial searches identified several studies measuring the association not as a primary outcome of the study; for example, studies of visual processing in schizophrenia where visual acuity had been measured in both case and control groups. I did not exclude these if they gave an estimate of association with visual acuity, or at least allowed one to be calculated. I decided a priori to use the Newcastle Ottawa Scale (NOS) to assess risk of bias in all studies, since this is standardised and widely used in systematic reviews, and can be adapted for each relevant study design.[196] I assessed studies according to their risk of bias in measuring the association between visual impairment and psychosis, rather than the study's stated aim.

Further rationale for the methodology is described in the next section.

3.2 Methods

I registered the advance protocol for this review on PROSPERO (CRD42019129214).[197]

3.2.1 Search Strategy

I used the OVID interface to search the databases MEDLINE, Embase, and PsychINFO on 18th August 2020, limiting studies to human subjects and English-language. I also searched the databases Open Grey[198] and Web of Science 19th August and 10th September 2020 respectively. I combined search terms encompassing visual acuity impairment with terms related to psychosis. To finalise these search terms, I consulted an ophthalmologist (Magnus Theodorsson - MT), and checked papers identified in initial searches for synonyms.

Final search terms were:

(Visual impairment OR low vision OR visually impaired OR impaired vision OR visual disability OR sight loss OR short-sighted OR myopia OR myope OR myopic OR near-sighted OR refractive error OR eyesight OR visual loss OR vision loss OR partially sighted OR far-sighted OR long-sighted OR nearsightedness OR vision disorder OR farsightedness OR hypermetropia OR hyperopia OR staphyloma OR hypermetrope OR hypermetropic OR hyperope OR ambylopia OR amblyope OR astigmatism OR visual acuity)

AND

(psychosis OR psychotic OR schizophren OR schizoaffective OR paranoi* OR delusion* OR hallucinat* OR paraphrenia)*

3.2.2 Inclusion and Exclusion Criteria

My inclusion criteria were:

1) Quantitative studies that compared psychotic symptoms or illnesses as the outcome in people with visual acuity impairment relative to people without; or

2) Quantitative studies that compared visual acuity impairment as the outcome in people with psychotic symptoms or illnesses relative to people without.

I included research studies published from 1st January 1992 onwards where:

Visual acuity was defined as either measured visual acuity on objective testing or self-reported visual clarity.

Psychosis was defined as either reporting psychotic symptoms, or diagnosis of psychotic disorder whether self-reported or determined by psychiatric interview or from medical records.

Exclusion criteria were:

Studies with fewer than 30 exposed participants, due to limited validity relating to low power to detect an association.[199]

Studies reporting a measure of colour blindness or visual processing but without a measure of objective visual acuity or self-reported visual clarity.

Studies that excluded participants with visual acuity worse than 20/20 on Snellen chart or equivalent from participation; since no participants meeting standard definitions of visual impairment would then be included.

Studies which only measured visual hallucinations and no other psychotic symptoms. I added this criterion to avoid overestimating any effect due to studies focused on Charles Bonnet Syndrome, given consensus that Charles Bonnet Syndrome is not a psychotic disorder.[123]

I exported search results into two software packages: EndNote[200] and then Covidence,[201] to facilitate co-screening and record-keeping by separate reviewers,

and to automatically remove software using inbuilt duplicate detection software in these packages.

In advance of conducting the review, I planned to hand-search reference lists of included studies and email several experts in the field to find out whether they could retrieve papers that the search strategy had not. I identified experts who had authored relevant papers in my preliminary searches.

I screened the titles and abstracts of retrieved studies before a 10% random sample was independently screened by my co-reviewer Dr Michelle Eskinazi (ME). I subsequently confirmed eligibility of studies from full texts, and ME independently checked >20% of these. Disagreement at each stage was resolved through discussion and consensus, if necessary, including with senior authors Claudia Cooper (CC) or Joseph Hayes (JH). I report both percentage agreement and the Cohen's Kappa statistic as calculated by *Covidence* software[201] as a measure of interrater reliability, and pre-specified that a score greater than 0.8 would be acceptable without co-screening of a larger proportion of retrieved studies.[202]

3.2.3 Data Extraction

I extracted pre-specified data from all included studies and recorded this in a Microsoft Excel spreadsheet, and then in tables in Microsoft Word for results reporting. Extracted data varied by study type but included: study type; country; year; population; sample size; number of exposed individuals; definitions of exposure and outcome; odds ratio, hazard ratio, or other statistical result; and covariates reported. ME cross-checked data extraction for 10% of included studies.

3.2.4 Assessing Risk of Bias

ME and I separately assessed risk of bias for each study individually, using the Newcastle Ottawa Scale (NOS) for cross sectional, case-control, or cohort studies as appropriate.[196, 203] The NOS for each study type is available in appendix B. I agreed with co-authors, regarding the interpretation of the NOS for cross sectional studies, that we did not require: assessment of outcome to be blinded, if it was objective; studies to include a power calculation if the sample size was > 1000, nor for studies to

have established comparability between respondents and non-respondents if the response rate was > 90%. In these cases, we allocated studies the corresponding number of points regardless of whether they met the criterion. I defined a quality score of 7+ as indicating a low risk of bias, and studies with a score of <4 to have a high risk of bias, consistent with published systematic reviews.[204, 205] We resolved any disagreements regarding NOS score through discussion.

3.2.5 Reporting of Results

I reported findings according to study type, and prioritised studies with a low risk of bias in the narrative review. I also graphically presented results where possible using Forest plots. Where multiple relevant results were reported, I reported odds or hazard ratios with the most robust level of adjustment in the Forest plots.[206-208] I report distance visual acuity impairment where both near and distance vision were reported on separately, for comparability with other studies and consistency with criteria for certifiable visual impairment.[34] Similarly, I chose schizophrenia when multiple psychotic disorder diagnoses were assessed, for comparability.

3.2.6 Comparisons between studies

Where there were enough studies rated as at low risk of bias, I compared studies of older and younger adults to account for psychotic symptoms in older adults potentially having different aetiology, such as neurodegenerative disease.[209] For the cross-sectional studies, I also compared studies that reported only on psychotic symptoms and those that included psychotic diagnoses; and studies that used objective (measured) or subjective reports of visual impairment. This was not possible for other study types.

3.2.7 Assessing Strength of the Evidence

I summarised the level of evidence using the Evidence Based Medicine Consult guidelines.[210] These classify research evidence into one of four grades:

A=consistent evidence from randomised controlled trials

B=consistent evidence from observational studies

C=extrapolations from observational studies at higher risk of bias

D=troublingly inconsistent evidence from studies at any level.[210, 211]

As randomised controlled trials are not possible in this field, the highest obtainable grade was B.

3.2.8 Meta-Analysis

I planned to conduct random effects meta-analysis if three or more studies with low risk of bias could be combined.[197] This would be determined by studies of the same type reporting equivalent effect estimates. Random effects meta-analysis can account for differences between study designs by including a measure of estimated between-study heterogeneity in the weighting, to avoid giving an overly precise estimate as might occur with fixed effects meta-analysis.[212] For the meta-analysis, I calculated compatible effect estimates (Odds Ratios) from raw data where only raw data was given. I also used fully adjusted odds ratios where possible, due to evidence and guidelines suggesting that this is likely to obtain the least biased pooled estimate,[206-208] but I also separately combined unadjusted odds ratios where these were provided or could be calculated, as a sensitivity analysis to reduce heterogeneity. I treated studies that used visual acuity impairment as exposure and psychosis as outcome and the converse separately, since these odds ratios are not theoretically interchangeable when adjusted.

I reported the I^2 statistic to estimate the proportion of variation in results caused by study heterogeneity rather than chance. If studies are truly measuring the same effect, I^2 is expected to be low.[213] I^2 has advantages over Cochran's Q statistic in that it is less sensitive to distortion by small or large numbers of included studies, and estimating degree of heterogeneity is arguably more useful than stating whether or not heterogeneity exists in a binary manner.[213] Consistent with standard interpretation, I classed 25% as evidence of low heterogeneity, 60% as moderate, and 75% as high.[213] For data analysis, I used STATA version 16.[214]

3.3 Results

3.3.1 Search results

I screened all 5700 titles and abstracts discovered through searches for inclusion, and ME co-screened 570 (10%). The Cohen's Kappa coefficient for inter-rater reliability was > 0.8, with agreement for > 99% abstracts. 280 full texts were screened, of which ME co-screened 65 (23%), giving a Cohen's Kappa of 0.63, with 88% agreement. The reasons for exclusion of full texts are shown in the PRISMA diagram. ME also checked data extraction from four (10%) of studies, with complete agreement. Forty papers which reported on 31 studies were finally included in the review. I emailed four experts in the field, which did not identify any additional papers, although three experts responded and one (Professor Steven Silverstein) suggested papers which had already been identified.

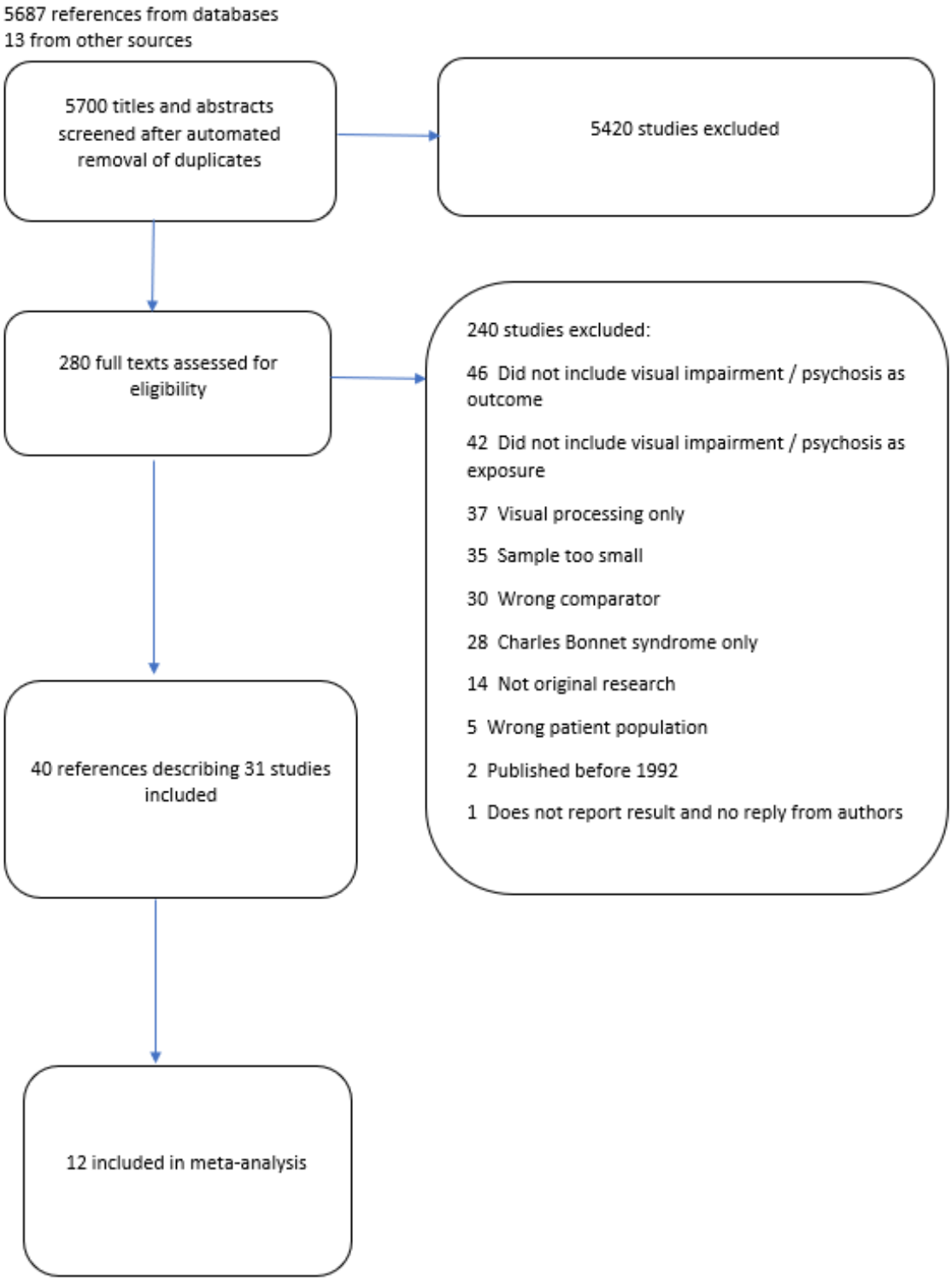

Figure 3-1 PRISMA Flow Diagram

3.3.2 Description of studies

Included studies comprised a total of 7,369,169 participants ranging from 16 to 102 years of age. I identified 7 cohort studies, 7 case-control studies, and 11 cross

sectional studies which reported on the relationship between psychosis as an outcome and visual acuity impairment as exposure. Relatively few studies reported on the converse relationship, and all were cross-sectional in design (n=6).

Eleven studies restricted analysis to older age groups, by using cut-offs of age 50 or older, or by recruiting from facilities primarily for older adults.[147, 171, 215-223] Two cohort studies investigated visual problems in childhood specifically.[224, 225]

In total 19 (61%) studies had a low risk of bias,[13, 14, 118-120, 125, 147, 170, 218, 219, 221-229] whilst an additional two met low risk of bias criteria for cross-sectional but not longitudinal results.[216, 220]. All other studies were rated as having a moderate risk of bias.[171, 190, 215, 217, 230-235]

3.3.3 Cohort Studies (Table 3-1, Figure 3-2)

Seven cohort studies were identified.[13, 14, 170, 216, 220, 224, 225] Collectively, they reported on over 4,830,050 participants. All reported the relationship between psychosis as an outcome and visual acuity impairment as exposure.

3.3.3.1 Studies classed as at low risk of bias

Five out of seven cohort studies were rated as having a low risk of bias.[13, 14, 170, 224, 225] These recruited three distinct populations: young male military conscripts,[13, 14] older people,[170] and children.[224, 225]

Two very large studies investigated whether, in young male military conscripts, refractive error predicted future diagnosis of psychotic illness.[13, 14] Both measured visual acuity with Snellen charts and used linked hospital records to determine subsequent psychotic illness diagnosis status, but they found opposing results. A Swedish study of >1 million young men[13] found that worse visual acuity increased the risk of psychotic illness; whilst an Israeli study[14] of > 650,000 young men found that it reduced the risk of schizophrenia. I noted some key differences between these studies. The Israeli study focused exclusively on schizophrenia and assessed corrected visual acuity.[14] It did not state length of follow-up or describe the measure of visual acuity impairment in detail and reported a lower prevalence of myopia than another study using the same data, suggesting that a stringent cut-off was used.[236]

This could however be explained by the second study using a more recent wave of the data, since prevalence of myopia is increasing over time. The Swedish study assessed multiple measurements of the exposure including uncorrected visual acuity, and additionally tested non-affective psychotic disorder as an outcome.[13] It included a sensitivity analysis excluding participants who developed psychosis within five years of the exposure measurement to ensure prevalent psychosis was not driving the findings, which were robust to this.[13] Both studies also included a discordant sibling pairs analysis to account for environmental and genetic confounding, which did not alter results.

A study of older adults used Swedish national registry data from >3 million people aged 60 in 1980 and investigated whether visual acuity impairment predicted diagnosis of Very Late-Onset Schizophrenia-Like Psychosis (VLOSLP) up to 31 years later.[170] Contrary to the authors' hypothesis, visual acuity impairment predicted a significantly lesser likelihood of being diagnosed with VLOSLP. The authors comment that this finding was unexpected and suggest that using register-based diagnoses may have led to artificial evidence of negative association as people with psychotic illness can be less able to access healthcare and are therefore less likely to have visual acuity impairment recorded.[170] They may also be more likely to be subject to 'diagnostic overshadowing', where physical complaints are wrongly attributed to psychiatric illness.[170] Further, survivor bias is possible, as participants who received a diagnosis of psychosis earlier in life were not included.[170]

Two smaller studies from Denmark and Sweden (n= 242 and n=110) examined children including offspring of parents with psychotic illness, and matched comparators.[224, 225] Both found that ophthalmic problems in childhood were associated with a future diagnosis of schizophrenia spectrum disorder. Schizophrenia spectrum disorder typically means schizophrenia and other psychotic disorder diagnoses combined, but excludes bipolar disorder. These studies measured visual acuity at ages 4[225] and 11-13[224] and followed children up for 18 and 20 years respectively. In both studies, visual acuity was combined with other aspects of ocular function, such as referral to an eye specialist or eye movement disorders, to make a composite ocular dysfunction score as the exposure.

There were only two cohort studies in similar populations that reported results compatible with combination in meta-analysis; the studies of adolescent male military conscripts.[13, 14] As these results were contradictory it was not appropriate to combine them.

3.3.3.2 Moderate and higher risk of bias studies

The 2/7 cohort studies classed as having moderate risk of bias both reported data on older adults and found that visual acuity impairment was associated with subsequent psychotic symptoms.[216, 220]

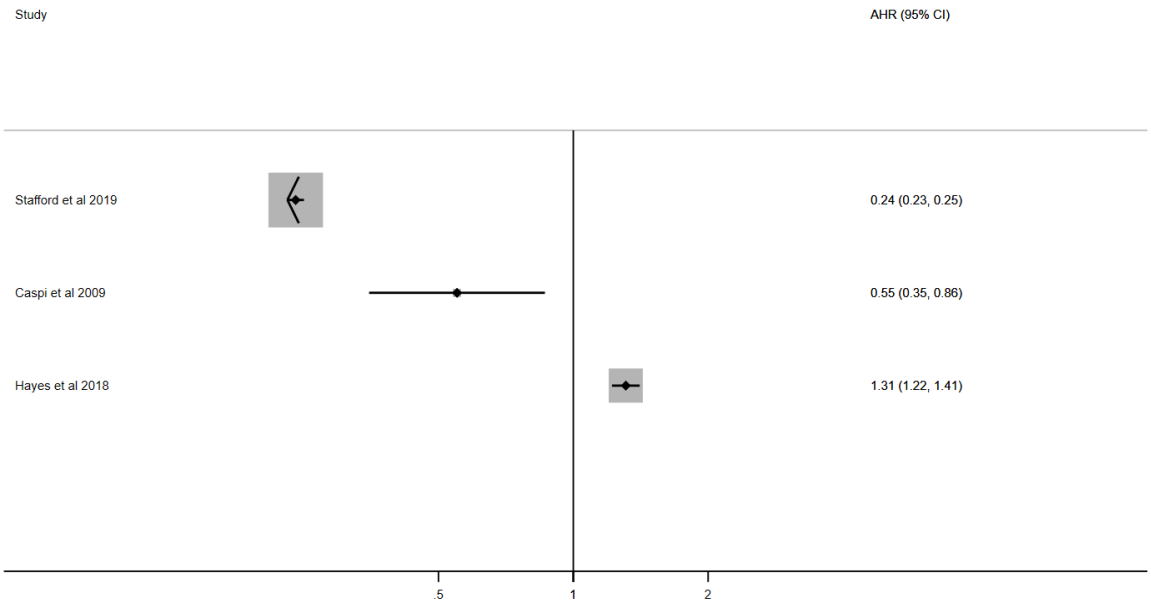

Figure 3-2: Forest plot showing cohort studies investigating association between visual impairment as exposure and psychosis as outcome.

Table 3-1: Cohort Studies Reporting on Psychosis in Visual Impairment

Study and Country	Population	Sample Size (Exposed Participants)	Exposure	Outcome	Maximum Length of Follow-up (years)	Factors Adjusted for in results shown	Results (for people with exposure relative to people without)	Risk of Bias Rating
Hayes et al 2018 Sweden [13]	Male military conscripts aged 18 - 19 from 1974 -1997	1,140,710 (84,663 mild visual impairment 62,678 moderate visual impairment 90,142 severe visual impairment)	Snellen chart acuity, both corrected uncorrected, recorded as decimal where 20 / 20 vision = 1.0	Inpatient diagnosis of schizophrenia or other non-affective psychotic disorder from linked hospital records	38 (Mean 24.75)	Age, year of interview, SES, IQ History of CMD, parental SMI, alcohol use disorder, substance use disorder	<u>For uncorrected acuity < 1.0 (decimal based on Snellen chart)</u> AHR schizophrenia: 1.31, 95% CI 1.22–1.41 AHR other psychotic illness: 1.17, 95% CI 1.08–1.26 <u>For best corrected acuity < 1.0 (decimal)</u> AHR any psychotic illness: 1.21, 95% CI 1.15–1.2	Low
Caspi et al 2009 Israel [14]	Unselected population of Israeli-born male adolescents aged 16-17	678,674 (40,201)	Refractive error based on best corrected visual acuity measured using Snellen chart	Inpatient diagnosis of schizophrenia from linked hospital records	NR	Intelligence, years of education, SES	AHR 0.55, 95% CI 0.35–0.8	Low
Stafford et al 2019	Whole population sample of adults	Total = 3,007,378	Visual impairment according to	Very late-onset schizophrenia-like	31	Age, sex,	AHR 0.24, 95% CI 0.23–0.25.	Low

Sweden [170]	aged 60+ from national registers for psychiatric illness, followed from 1980	(2037)	National Patient Register	psychosis; defined as ICD diagnosis of nonaffective psychotic disorder since 1980 recorded in National Patient Register.		age-sex interaction, offspring with nonaffective psychosis, region of origin, birth period, disposable income, death of child, death of partner, hearing impairment		
Schubert et al 2005 Sweden [225]	'High risk' sample of offspring of women with psychosis and matched controls born in 1973-1977.	Total = 110 52 high risk offspring 58 controls	Severity of visual dysfunction aged 4 measured by visual acuity at age 4 or referral to specialist due to vision problems before age 4	Diagnosis of schizophrenia-spectrum disorder made using SCID	18	-	OR 16.07 95% CI 1.85-139.60, p=0.003	Low
Schiffman et al 2006 Denmark [224]	All children born in one hospital from 1959 to 1961 whose parent had a specialist diagnosis of schizophrenia. Controls whose parent had another psychiatric diagnosis Controls with no parental psychiatric diagnoses	Total = 242 at follow-up From initial cohort of 265: 90 offspring of a parent with schizophrenia 93 offspring of a parent with another psychiatric diagnosis 82 offspring of parents with no psychiatric	Composite eye examination score which included eye alignment and related deficits, suppression, depth perception, pursuit movements and visual acuity (measured using the Stycar Vision Test at age 11-13 and categorised as normal or abnormal).	Diagnosis of schizophrenia-spectrum disorder made by psychiatrist when participants were aged 31-33 using SCID and PSE; or hospital records.	20	-	Schizophrenia-spectrum group mean eye score =147.90 Comparison group mean eye score =118.32 p =0.035	Low

		diagnoses	Higher scores indicate worse visual function.					
Hamedani et al 2020 USA [220]	Data from two longitudinal studies were analysed: NHATS: a nationally representative study of medicare beneficiaries aged 65 or older.	NR	Distance and near vision, and blindness assessed using yes / no questions.	Proxy reported visual or auditory hallucinations	7	Age, sex, ethnicity, income, hypertension, diabetes, smoking, stroke, education, depression, anxiety, dementia, hearing loss	AOR in near vision impairment 1.77 95% CI 1.43–2.17 AOR in distance vision impairment: 1.74 (1.43–2.11) AOR in blindness: 1.62 (0.98–2.68)	Medium
	HRS: a nationally representative survey of US adults over the age of 50	NR	Overall eyesight, distance vision and near vision assessed using questions.	Proxy reported visual or auditory hallucinations	12	Age, ethnicity, sex, income, hypertension, diabetes, smoking, stroke, education, nursing home status, physical functional impairment, hearing loss	AOR in overall visual impairment: 1.40 95% CI 1.22 – 1.60 AOR in near vision impairment: 1.42 (1.23–1.63) AOR in distance vision impairment: 1.63 (1.41–1.87) AOR in blindness: 1.79 (1.10–2.92)	Medium
Blazer et al 1996	Community sample of older adults over 65,	2936	Visual deficit measured on a continuous scale	Paranoia measured using CES-D	3	NR	AOR 1.32 95% CI 1.02 -1.71 p<0.05	Medium

USA [216]	identified using four-stage stratified sampling design from census		based on six questions.					

SES= Socioeconomic status, IQ= Intelligence Quotient, CMD= Common Mental Disorder, SMI = Serious Mental Illness, AHR = Adjusted Hazard Ratio, 95% CI = 95% Confidence Interval, NR= Not Recorded, ICD= International Classification of Diseases, SCID = Structured Clinical interview for DSM-III-R, OR = Odds Ratio, PSE=Present State Examination, AOR = Adjusted Odds Ratio, NHATS= The National Health and Aging Trends Study, HRS= The Health and Retirement Study, CES-D=Center for Epidemiological Studies Depression Scale.

3.3.4 Case-Control Studies (Table 3-2)

There were seven case-control studies, reporting data on 723 people aged over 18.[190, 226, 230-234] These all compared people with a diagnosed psychotic illness to controls without psychosis. Two studies investigated differences in visual acuity impairment as a primary aim,[190, 230] with the remainder assessing acuity purely to establish comparability between groups in visual processing or retinal thickness experiments.[226, 231-234, 237]

All case-control studies measured objective visual acuity impairment using Snellen, LogMAR, Freiburg, or similar charts. Five studies allowed some degree of correction of impairment using aids during the measurement,[190, 226, 231, 232, 234] and two did not state whether correction was employed.[230, 233] The number of participants in each study ranged from 60 to 130.

Of note, four studies excluded participants with myopia above a certain level of impairment,[226, 231-233] one broadly matched groups by visual acuity (but still tested for a difference),[234] and one selected controls from an eye clinic.[230] This likely limited the ability of case-control studies to detect an association and reduced the magnitude of any detected differences between groups with and without psychotic illnesses.

3.3.4.1 Studies classed as at low risk of bias

Only one case-control study was rated as having low risk of bias.[226] This study reported on a group of 30 adults with schizophrenia attending a secondary care centre and 30 controls.[226] Controls were hospital staff and volunteers and were matched to cases by age, sex, and ethnicity. This study excluded people with myopia requiring lenses greater than 2.0 Dioptres. There was a slightly lower mean visual acuity score in the schizophrenia group compared to the control group (100 vs 102), but the results from a T-test did not support this difference being unrelated to chance (p=0.068).

3.3.4.2 Studies classed as at moderate or higher risk of bias

Three of the six case-control studies at moderate risk of bias found evidence of lower visual acuity in the groups with psychotic illness for at least some types of vision,[190, 232, 233] while the remaining three found no difference between the groups.[230, 231, 234]

One study found that the lower visual acuity applied to people with established schizophrenia, but not people with first episode psychosis.[232]

Table 3-2: Case-Control Studies Reporting Odds of Visual Impairment in Psychosis

Study and Country	Cases	Controls	Sample Size Total (Cases)	Measure of Visual Acuity	Results	Risk of Bias Rating (for outcome of interest)
Lee et al 2013 Malaysia [226]	Consecutive patients with schizophrenia attending a secondary care centre. Diagnosis based on psychiatric examination and DSM IV-TR criteria. People with myopia >2.0 dioptres excluded.	Hospital staff and volunteers matched for age, sex, and ethnicity. Psychiatric disorders were excluded using SCID	60 (30)	Best corrected visual acuity measured with Snellen chart and refraction	Patient mean visual acuity score: 100.00 Control mean visual acuity score: 102.17 No statistically significant difference between groups using independent t-test (p=0.068)	Low
Prager and Jeste 1993 USA [190]	Patients with schizophrenia aged 45+ recruited primarily from Veterans Affairs clinic. Diagnosis confirmed using SCID. Organic mental disorder was excluded by investigation.	Comparison group with no major psychopathology recruited from other studies at the clinic.	Total = 87 16 with late-onset schizophrenia 25 with early-onset schizophrenia 20 with mood disorder	Near-vision acuity measured using Lebensohn chart. Distance-vision acuity measured using Snellen chart, both with and without correction. Groups compared using Kruksal-Wallis test	Uncorrected near-visual acuity: no group differences. Corrected near visual acuity: All psychiatric groups had worse acuity than controls. The differences reached significance for left-eye and binocular vision. Uncorrected distance visual acuity: no group differences Corrected distance visual acuity: all psychiatric groups had worse mean acuity. The differences reached significance	Medium

					for patients with Early Onset Schizophrenia on left-eye and binocular vision and for mood disorder patients on left-eye vision. Significance level p<0.05	
Cumurcu et al 2015 Turkey 230	Patients with DSM IV-TR schizophrenia diagnosis aged 18-65 evaluated at the Eye Outpatient Clinic. All had been treated with an antipsychotic medication for 2+ years and had no medical comorbidity.	Patients visiting the same institution matched for age, sex, and education.	130 (70)	Visual acuity measured by Snellen chart	No evidence of difference in incidence of refractive error between the two groups using two-sided t-test (p=0.082).	Medium
Brittain et al 2010 UK 231, 237	Patients with a DSM-IV diagnosis of schizophrenia recruited from outpatient and long term assisted living settings Diagnosis was confirmed by their treating clinician, chart review and SCID. People with best corrected visual acuity <0.8 decimal were excluded.	Control status was determined using the psychotic screening SCID. Potential control subjects were excluded if any of their first-degree relatives had a history of psychotic illness.	129 (64)	Best corrected visual acuity measured using Freiburg visual acuity test.	Patient mean visual acuity: 1.31. Control mean visual acuity: 1.33 This difference was not statistically significant at p<0.05 level using t-test	Medium
Keane et al 2019 USA 232, 238, 239	People aged 18-65 with first episode psychosis or schizophrenia / schizoaffective disorder assessed using SCID or electronic medical record.	Controls without 4-year college degrees were preferentially recruited. Controls had no diagnosis	120 49 with schizophrenia or schizoaffective disorder	Visual acuity measured using LogMAR chart In-house visual acuity correction kit used when necessary	Using ANOVA, the group with schizophrenia / schizoaffective disorder had poorer visual acuity than controls (p<0.001) and people with a first episode of psychosis (p<0.05).	Medium

	People with visual acuity poorer than 20/32 were excluded.	of any psychotic or mood disorder, no current psychotropic medication, and no first-degree relative with schizophrenia or schizoaffective disorder.	23 with first episode psychosis			
Schechter et al 2005 USA [233]	Patients with schizophrenia or schizoaffective disorder recruited from a state psychiatric facility. Diagnosis was confirmed by chart review, consultation with physicians and SCID. Participants with visual acuity < 20/32 were excluded	Healthy volunteers with no history of SCID defined psychiatric disorder, neurological or ophthalmologic disorders, alcohol or substance dependence within the last six months or abuse within the last month.	106 (57)	Visual acuity measured using ETDR Chart	Patients had poorer mean visual acuity assessed using t-test: Patient mean 0.88 Control mean 1.07 P<.001	Medium
Silverstein et al 2014 Denmark [234]	Patients aged 18–60 and diagnosed with schizophrenia or first episode psychosis, referred to the study by mental health inpatient staff. All patients were receiving antipsychotic medication. Diagnoses were confirmed by SCID. Groups were matched on visual acuity, but between-group acuity was still tested due to small differences.	Healthy controls without diagnosable lifetime psychiatric conditions (confirmed using SCID); no use of psychotropic medication over the preceding 6 months, and no first-degree relatives with psychotic illness.	91 22 with first episode psychosis 34 with schizophrenia	Measured visual acuity in LogMAR units.	The groups did not differ in acuity using ANOVA.	Medium

SCID=Structured Clinical Interview for Diagnostic and Statistical Manual (DSM), DSM=Diagnostic and Statistical Manual, IQ= Intelligence Quotient, LogMAR = Logarithm of Minimal Angle Resolution, ETDR= Early Treatment Diabetic Retinopathy, ANOVA= Analysis of Variance

3.3.5 Cross-sectional studies (Table 3-3, Table 3-4, Figure 3-3)

Nineteen studies reported on the cross-sectional association between visual acuity impairment and psychosis.[118-120, 125, 147, 171, 215-223, 227-229, 235] These covered a total of 2,541,332 people aged over 16. Two studies reported data both cross-sectionally and longitudinally: only the cross-sectional data is included here.[216, 220]

3.3.5.1 Studies classed as at low risk of bias (n=15)

Fifteen out of nineteen studies were classified as having low risk of bias.[118-120, 125, 147, 216, 218-223, 227-229] Five of these investigated general population samples including adults of any age;[118-120, 227, 228] seven investigated community samples of older adults;[147, 216, 218-221, 223] one a community sample of adults with intellectual disability;[229] and two recruited patients from psychiatric facilities, of which one focused on older adults.[125, 222] Two had very large samples (>200,000 participants).[118, 228]

In determining presence of visual acuity impairment, three studies used formal measures including LogMAR chart and Kay's pictures;[119, 125, 229] two used undescribed standardised physical examinations;[147, 223] one used diagnosis of blindness or low vision in healthcare records;[228] three used judgements from clinicians or carers;[218, 219, 222] and six used self-report.[118, 120, 216, 221, 227]

Ten studies investigated psychotic symptoms rather than diagnoses [120, 125, 147, 216, 218-221, 223, 227, 240]. Two used either psychotic symptoms or diagnosis;[118, 119] and three used diagnoses (from clinical records or research interview).[222, 228, 229]

In total, 11/15 studies found evidence of a positive association between visual acuity impairment and psychosis,[118-120, 147, 218, 220-222, 227-229] with Adjusted Odds Ratios (AORs) ranging from 1.20 to 13.19 (Figure 3-3: Meta-analysis of cross-sectional studies investigating association between visual impairment and psychosis). This included 5/8 studies of older adults [147, 220-223] and 6/7 studies of adults of any age.[118-120, 227-229] In the remaining studies, no evidence of an association was found (as opposed to finding a negative association).

3.3.5.2 Studies Including Adults of any Age

3.3.5.2.1 Objective Measures of Visual Impairment

Four of the seven studies including younger adults used objective measures of visual acuity impairment; either LogMAR test score, Kay's pictures, or a diagnosis of blindness or low vision in clinical records.[119, 125, 228, 229] They include the only study of younger adults which did not find evidence of association at the $p<0.05$ level.[125] This took place in a psychiatric facility and was relatively smaller than the other studies (n=356). The point estimate for the odds ratio for visual acuity impairment in schizophrenia relative to other diagnoses was still suggestive of an association.[125]

3.3.5.2.2 Subjective measures of Visual Impairment

Three studies including younger adults reported the association between self-reported sight difficulty and psychosis.[118, 120, 227] All found evidence of association, including one international study with over 2 million participants.[118] Adjusted odds ratio point estimates ranged from 1.64 – 2.16.

3.3.5.3 Studies that recruited older adults

3.3.5.3.1 Objective Measures of Visual Impairment

Only 1/8 studies of older adults used an objective measure of visual acuity impairment.[147] This measured (either) visual defects according to examination; or participants having been informed by a doctor that they could be registered as blind or partially sighted.[147] The study found an association between visual acuity impairment and psychotic symptoms.

3.3.5.3.2 Subjective Measures of Visual Impairment

Seven older adult studies used self-report or carer-report of reduced vision.[216, 218-223] Four reported a significant, positive association between visual acuity impairment and psychotic symptoms;[218, 220-222] one found evidence of an association with hallucinations (in any sensory modality) but not other psychotic symptoms;[223] one found a small difference in visual acuity impairment scores between groups with and without psychosis but with statistical evidence at the $0.05<p<0.1$ level;[219] and one found no evidence of association.[216]

3.3.5.4 Psychotic Diagnosis vs Psychotic Symptoms

Of all 15 cross-sectional studies with low risk of bias, 7/9 that reported exclusively on psychotic symptoms found evidence for an association with visual acuity impairment at the level $p<0.05$ [120, 147, 218, 220, 221, 223, 227] compared to 5/6 that reported on psychotic illness diagnoses.[118, 119, 222, 228, 229]

3.3.5.5 Studies at moderate or higher risk of bias

Three out of four studies at moderate risk of bias found evidence of association between visual acuity impairment and psychosis; two in older adults,[171, 215] and one in adults.[235] The other study found an association between visual acuity impairment and paranoid ideation, but not delusions or hallucinations in older adults.[217]

Table 3-3: Cross-Sectional Studies Reporting on Association between Psychosis and Visual Impairment in People of Any Age

Study and Country	Sample	Year of Data Collection	Sample Size (number of exposed participants)	Exposure	Outcome	Factors Adjusted for	Results (for exposed relative to unexposed participants)	Risk of Bias Rating
Saha et al 2011 Australia [227]	General population household survey of people aged 16 to 85	2007	8771 (593)	Positive response to the question: have you ever had sight problems lasting more than 6 months?	Possible psychosis based on CIDI	Age, sex, marital status, migrant status, alcohol / drug abuse, anxiety disorder, depressive disorder, family history of psychosis	AOR 1.64, 95% CI 1.11 - 2.41, p<0.01	Low
Shoham et al England [120]	Nationally representative household sample of people aged 16+	2014	7107 (934)	Self-reported difficulty reading a newspaper or seeing a face across the room, even with visual aids.	Psychotic symptoms elicited by PSQ.	Age, sex, ethnicity, employment, education, housing, AUDIT score	AOR 1.81, 95% CI 1.33–2.44, p<.001.	Low
Zheng et al 2015 China [125]	Patients aged 18+ consecutively admitted to a psychiatric centre 44% schizophrenia diagnosis; 33% bipolar affective disorder diagnosis, 23% major depressive disorder.	2013	Total = 356 (87)	Presenting visual acuity measured by LogMAR chart with spectacles, if required. Distance visual impairment defined as LogMAR score ≥ 0.5	Severity of psychotic symptoms on BPRS Raw numbers with visual impairment provided for each diagnostic category	-	For schizophrenia relative to other diagnoses: OR 1.51 95% CI 0.81-2.82 」 No association between mean BPRS score and distance visual impairment p=0.63	Low

Cooper et al 2007 Scotland [229]	Community sample: all persons aged 16+ known to their GP with intellectual disability within a defined region	NR	1020	The C21st Health Check: includes Kay's pictures and caregiver report	Diagnosis of psychosis made by a psychiatrist in people who scored positive on PAS-ADD	Age, gender, level of ability previously having lived in a long-stay hospital, special communication needs, epilepsy, smoking, type of accommodation/ support.	AOR 1.97 95% CI 1.04 – 3.74 p=0.038	Low
Viertio et al 2007 Finland [119, 241, 242]	Nationally representative population survey of people aged 30+	2000 - 2001	Total sample = 6588 (56 schizophrenia, 72 other nonaffective psychosis, 38 affective psychosis)	SCID diagnosis in people reporting diagnosis of psychotic disorder / possible psychotic or manic symptoms on CIDI, at Interview, or from hospital case notes.	Visual Acuity on logMAR chart and near vision chart with usual visual aids. Distance visual impairment defined as acuity < 20/40	Age, sex	<u>Schizophrenia:</u> Distance vision impairment: AOR 5.04 95%CI 1.89–13.48 p< 0.001 Near vision impairment: AOR 6.22 95% CI2.61–14.82 P< 0.001 <u>Other non-affective psychosis or affective psychosis</u>: no evidence of association	Low
Moreno et al 2013 Stubbs et al 2016 Koyanagi et al 2016	World Health Survey Data: randomly selected household sample of people aged 18+ across 70 countries Moreno et al:	2002 - 2004	Moreno et al 224,254 (NR) In Stubbs et al	Psychotic symptoms elicited from CIDI 3.0 Self-reported diagnosis of psychotic illness	Self-reported presence (yes/no) of vision problems	Sample weighting was applied. Koyanagi et al: Age, sex, wealth, education, alcohol consumption, anxiety, country	Moreno et al: In people with psychotic symptoms but no diagnosis: OR 1.67, 95% CI 1.59 to 1.75 In people with psychotic symptoms	Moreno and Stubbs: Low Koyanagi et al: Medium

Multinational 118, 243, 244	sample from 52 countries. Stubbs et al: sample from 48 low- and middle-income countries. Koyanagi et al: sample from 44 low- and middle-income countries. Excluded people with lifetime diagnoses of psychotic disorders or who reported psychotic experiences in the absence of depression.		242,952 (NR) Koyanagi et al 195,479 (2.7% subsyndromal depression, 3.0% brief depressive episode, 7.1% depressive episode).				and psychosis diagnosis: OR 2.16, 95% CI 1.80 to 2.58 Stubbs et al: Evidence of association between both visual impairment and psychosis diagnosis and visual impairment and subclinical psychosis (p<0.0001). Koyanagi et al Linear regression co-efficient for vision problems in people with depression only relative to people with depression and psychotic experiences was -0.05, 95% CI -1.72 to 2.61	
Gabilondo et al 2017 Spain 228	Everyone registered in Population Stratification Programme (healthcare dataset covering population of Basque country)	2011	2,255,406 (7731)	Healthcare records: diagnosis of schizophrenia (F20, ICD10) made by a mental health specialist in a public mental health resource.	Diagnosis of blindness or low vision in healthcare records	Age, sex, deprivation Index	AOR 1.20 95% CI 1.02 1.42, p=0.032	Low
Kinoshita et al 2009	Household survey of people aged 18+	2001 to 2003	2322 (85)	Visual impairment elicited by	Auditory hallucinations elicited using CIDI	Sex Stratification by age	AOR 2.16, 95%CI 0.87–5.33, P=0.10	Medium

USA [235]				asking: [Do you have] a vision problem that prevents you from reading a newspaper even when wearing glasses or contacts?			The association was significant in people aged 18-39: AOR 13.25, 95% CI 2.99 to 58.75, p<0.001.	

CIDI = Composite International Diagnostic Interview, AOR= Adjusted Odds Ratio, 95% CI = 95% Confidence Intervals, PSQ=Psychosis Screening Questionnaire, , AUDIT = Alcohol Use Disorders Test, BPRS=Brief Psychopathological Rating Scale, OR= Odds Ratio, ⌋ = Calculated from raw numbers by authors, SCID = Structured Clinical Interview for DSM-IV-TR, CIDI = Composite International Diagnostic Interview, LogMAR= Logarithm of Minimal Angle of Resolution, NR = Not Recorded, C21st= 21st century, PAS-ADD = Psychiatric Assessment Schedule for Adults with Developmental Disabilities Checklist, NR = Not Recorded

Table 3-4: Cross-Sectional Studies Reporting on Association between Psychosis and Visual Impairment in Older Adults

Study and Country	Sample	Year of Data Collection	Sample Size (number of exposed participants)	Exposure	Outcome	Factors Adjusted for	Results (for exposed relative to unexposed participants)	Risk of Bias Rating
Livingston et al 2001 England [221]	Household sample of people aged 65+	NR	720 (137)	Uncorrected visual impairment elicited by asking: `Do you have any problems with your sight?'; and whether this had been adequately corrected.	Perceptual distortion and affective response to delusions or hallucinations elicited from GMSE	Analysis repeated restricted to people with dementia	OR 2.8 p<0.02 When analysis was restricted to people with dementia: OR 3.9 p<0.05	Low
Subramaniam et al 2016 Singapore [223, 245]	Population-based study of people aged 60+	2011	2166 2.7% with paranoid ideation 2.8% with persecutory ideation 2.7% with hallucinations	Presence of paranoid ideation, delusions, and hallucinations assessed by GMSE	Eyesight problems elicited from WHO Disability Assessment Schedule	Sociodemographic variables (specifics not given)	Paranoid ideation: AOR 1.4 95% CI 0.6-2.9 p=0.432 Persecutory delusions: AOR 1.3 95% CI 0.6 - 2.7 p=0.550 People with hallucinations: AOR 2.1 95% CI 1.01 - 4.2 p=0.046 Any of these symptoms: AOR 1.55 95% CI 0.9 - 2.7 p=0.121	Low
Ballard and Bannister 1995 England [147]	People aged 65+ with mild or moderate dementia and informant contact at	NR	124 (83)	Psychotic symptoms elicited using Burns' Symptom Checklist	Visual defects according to CAMDEX, or participants who were registered blind or partially		Visual impairment was significantly associated with psychotic symptoms using Wald Test, p=0.02	Low

	least weekly, recruited from consecutive referrals to old-age psychiatry services				sighted or having been informed by a doctor that they could be.			
Matsuoka et al 2015 Japan [Letter] [222]	Consecutive outpatients aged 60+ seen at department of psychiatry between April 2009 and March 2013.	2009 - 2013	979 (157)	Visual impairment defined as poor visual capacity in the clinical examination and daily life, based on reports from participants and their caregivers	ICD10 diagnosis of psychosis occurring after age 60	Age, gender, hearing impairment	OR 13.19; 95% CI 4.05–43.00, P<0.001	Low
Forsell and Henderson 1998 Sweden [218]	Community sample of people aged 75+ All residents in the region, including people living in institutions.		1220	Visual problems assessed by physicians as causing clinical distress	Paranoid ideation elicited through PRS	Cognitive dysfunction	OR 1.6 95% CI 1.1-2.0. This was 'not significant' after controlling for cognitive dysfunction.	Low
Hamedani et al 2020 USA [220]	NHATS: a nationally representative sample of people aged 65+	2002 to 2014	1520	Distance vision impairment defined as self-reported difficulty seeing someone	Proxy-reported hallucinations ascertained by asking 'Does he or she ever see or hear things that are not there?'	Age, sex, ethnicity, income, hypertension, diabetes, smoking, stroke, education, depression, anxiety, dementia, hearing loss	In near-vision impairment: AOR 1.77, 95% CI 1.32–2.39. In distance vision impairment: AOR 2.48, 95% CI: 1.86 to 3.31 In blindness: AOR 2.05, 95% CI: 0.88–4.78)	Low

				across the street.				
	HRS: nationally representative survey of people aged 50+		3682	Overall eyesight, distance vision and near vision assessed using scales	Proxy-reported hallucinations ascertained by asking 'Does he or she ever see or hear things that are not there?'	Age, sex, ethnicity, income, hypertension, diabetes, smoking, stroke, education, nursing home status, physical functional impairment, hearing loss	In impaired overall eyesight: AOR 1.32 95% CI 1.08-1.60 In distance vision impairment: AOR 1.61 95% CI 1.32-1.96 In near vision impairment: AOR 1.52 95% CI 1.25 - 1.85 In blindness: AOR 1.99, 95% CI: 0.94–4.19	Low
Blazer et al 1996 USA [216]	Community sample of adults aged 65+ identified using four-stage stratified sampling design from census	NR	3869	Visual deficit measured on continuous scale based on 6 questions	Paranoid symptoms elicited using CES-D	Age, sex, ethnicity, marital status, education, income, ADLs, functional limitations, mobility, social network, social interaction, negative life events, depressive symptoms, cognitive impairment	AOR 0.84, 95% CI 0.61-1.14, p>0.05	Low
Henderson et al 1998 Australia [219]	Sample drawn from the electoral roll for Canberra, aged 70+	1990 to 1991	935	Psychotic symptoms elicited using questions from CIE.	Scale for visual impairment based on respondent report and interviewer observations.		Mean visual impairment score 7.8 in group with psychosis Mean visual impairment group 7.2 in group without psychosis. p=0.07	Low
Bayón and Sampedro 2017 Spain	Patients examined consecutively in cognitive	NR	Total=843 13.3% had recorded	Clinical records noting visual changes interfering with functional	Delusions or hallucinations recorded in clinical notes.		Delusions and hallucinations were more prevalent in people with visual changes (p<0.01)	Medium

[171]	neurology clinic. 607 had mild cognitive impairment or dementia. Subjects aged 65+ accounted for 80.5% of the total.		visual changes	capacity in patients whose vision could not be corrected with lenses.				
Bazant et al 2003 [Conference abstract] USA [215]	People presenting for geriatric assessment. Over half had dementia. Mean age 79	1997 - 2000	447	Visual acuity assessed using LNVAT. Impairment defined as score < 20/40.	Hallucinations and delusions assessed using NPI Clinical diagnosis of psychosis		Multivariate analysis showed visual Impairment < 20/60 level to be associated with hallucinations (OR = 3.17) and impairment < 20/40 to be associated with delusions (OR = 1.85). Visual acuity at all levels failed to meet significance threshold with respect to clinical diagnosis of psychosis.	Medium
Ostling and Skoog 2002 Sweden [217]	Residents of Gothenburg aged 85 selected from census by systematic sampling	1986-1987	305 (58)	Delusions, hallucinations, or paranoid ideation elicited using CPRS, triangulated with informant interview and medical records.	Visual deficits that interfered with conversation and execution of tasks as observed at psychiatric examination.		Hallucinations: OR 3.4; 95% CI 1.0-11.1 Paranoid ideation: OR 3.6; 95% CI, 1.2-10.5 Delusions: OR 1.4 95% CI 0.2-6.9	Medium

GMSE= Geriatric Mental State Examination, OR= Odds Ratio, 95% CI = 95% Confidence Intervals, WHO= World Health Organisation, AOR= Adjusted Odds Ratio, CAMDEX=Cambridge Mental Disorders of the Elderly Examination, ICD=International Classification of Diseases, NR = Not Recorded, CPRS= Comprehensive Psychopathological Rating Scale, NHATS= The National Health and Aging Trends Study, HRS = The Health and Retirement Study, CES-D = Center for Epidemiological Studies Depression Scale, CIE = Canberra Interview for the Elderly, LNVAT = Lighthouse Near Visual Acuity Test, NPI= Neuropsychiatric Inventory, CPRS = Comprehensive Psychopathological Rating Scale

3.4 Meta-Analysis (Figure 3-3)

I combined results for the twelve cross-sectional studies with low risk of bias that reported an odds ratio or allowed one to be calculated, dividing these according to whether they treated visual acuity impairment (n=8) or psychosis (n=4) as the exposure (Figure 3-3: Meta-analysis of cross-sectional studies investigating association between visual impairment and psychosis).[118-120, 125, 216, 218, 220, 222, 223, 227-229] I included two samples reported in one study separately.[220] I used fully adjusted odds ratios where possible.[206, 207] The meta-analysis gave a pooled odds ratio where visual acuity impairment was the exposure of 1.76 (95% CI 1.34-2.31); and for psychosis as exposure of 1.85 (95% CI 1.17 – 2.92). Heterogeneity was high in both groups: I^2 statistic=78.7%, p<0.001 and 89.2% p<0.001 respectively. In view of this, I tested heterogeneity in subgroups of studies with adults and older adults. I found that where visual acuity impairment was the exposure, there was no evidence of heterogeneity among younger adult studies (I^2=0, p=0.920), but heterogeneity remained high in older adult studies (I^2=89.1%, p<0.001). Even after excluding two outlying older adult studies,[216, 222] heterogeneity remained moderate. The pooled OR for younger adult studies was 1.74 (95% CI 1.40 – 2.15). For older adult studies it was 1.87 (95% CI 1.18 – 2.98) (Figure 3-3: Meta-analysis of cross-sectional studies investigating association between visual impairment and psychosis). There were too few studies to test subgroups when the exposure was psychosis.

There was no strong evidence of publication bias from Egger's test (p=0.386 where visual acuity impairment was the exposure, and p=0.593 where psychosis was the exposure). The funnel plot however did show some mild evidence of asymmetry, consistent with publication bias or other small study effects (Figure 3-4: Funnel Plot).

I also combined unadjusted odds ratios from six studies that provided sufficient information [118, 120, 125, 218, 220, 228, 229] (Figure 3-3: Meta-analysis of cross-sectional studies investigating association between visual impairment and

psychosis). This gave a pooled OR of 2.07 (95% CI 1.38 – 3.11) and did not reduce heterogeneity (I^2=95.2%, p<0.001).

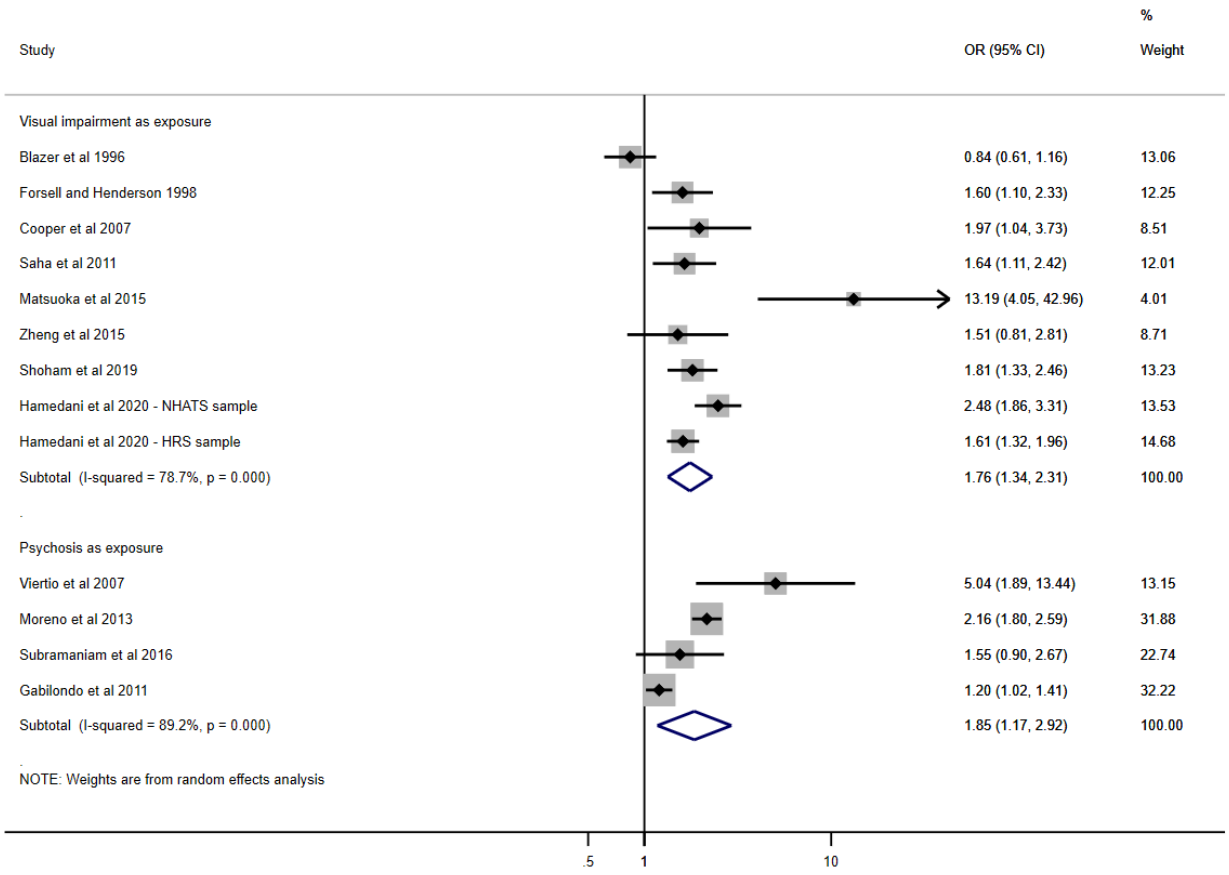

Figure 3-3: Meta-analysis of cross-sectional studies investigating association between visual impairment and psychosis

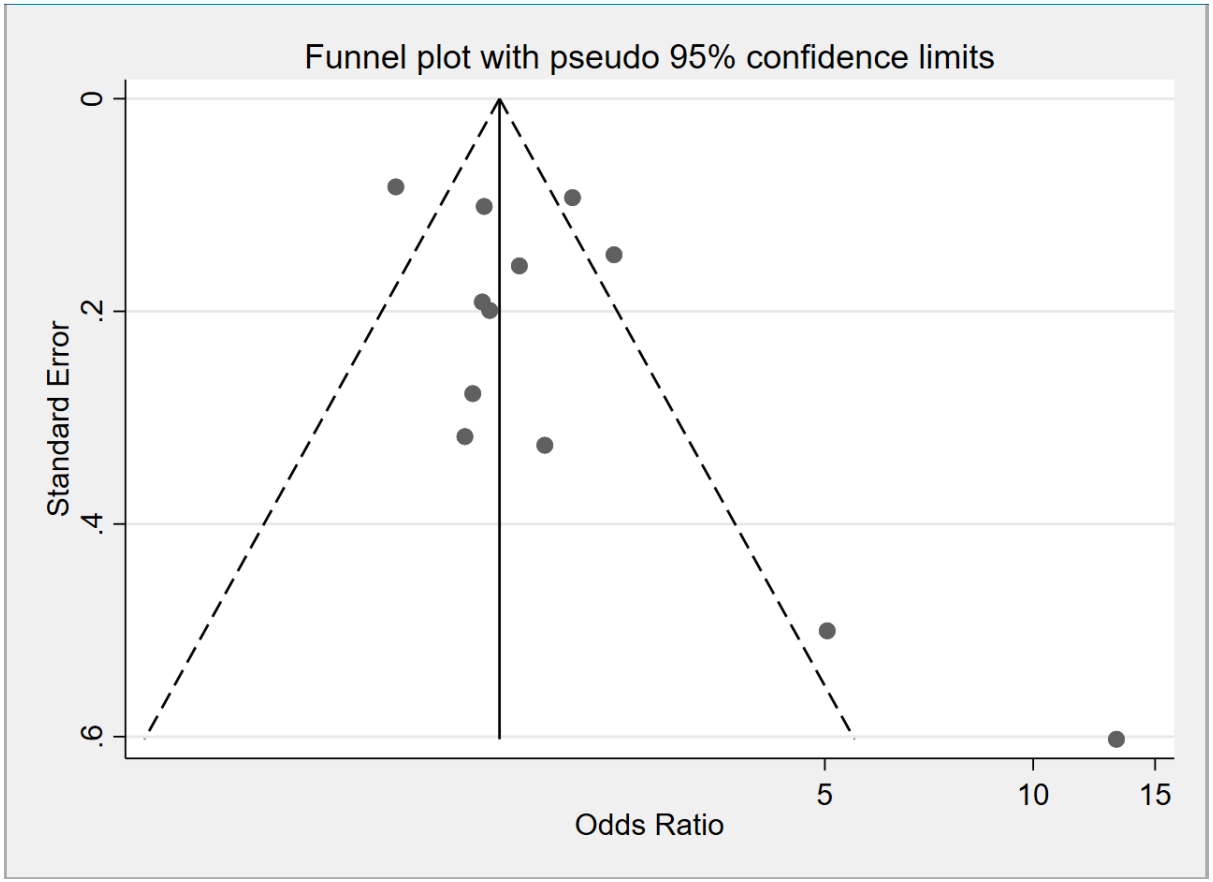

Figure 3-4: Funnel Plot

3.4.1 Summary of Evidence

Overall, I found grade D (troublingly inconsistent) evidence for an association between objectively measured visual acuity impairment as an exposure and schizophrenia as an outcome in longitudinal studies. This classification is based on the two highest quality studies to investigate this giving conflicting results. I found no longitudinal studies that investigated the converse relationship (psychosis as an exposure, and visual acuity impairment as an outcome). I also found grade D (troublingly inconsistent) evidence for an association between visual acuity impairment and psychosis from case-control studies. I found grade B (consistent evidence from observational studies) evidence however for a cross-sectional association between visual acuity impairment, whether measured objectively or subjectively, and psychosis.

3.5 Discussion

Most included studies (22/31) found evidence of a positive association between impaired visual acuity and greater risk of either psychotic illness or symptoms of psychosis in at least one analysis.[13, 118-120, 147, 171, 190, 215-218, 220-225, 227-229, 232, 233, 235] This was also true of most (15/21) that were rated as at low risk of bias.[13, 118-120, 147, 218, 220-225, 227-229]

3.5.1 Longitudinal Studies

For a longitudinal relationship between visual acuity impairment as exposure and psychosis as outcome, evidence was conflicting in both adolescent / young adult and older adult populations.[13, 14, 170, 216, 220] Both (small, cohort) studies of children found evidence of an association;[224, 225] suggesting that ophthalmic problems during a critical developmental phase may be implicated on the causal pathway to a future diagnosis of psychosis. These studies did not allow me to distinguish visual acuity impairments from other ocular abnormalities, like eye movement disorders, however, so it is unclear which aspects of ocular function explained the associations.

The two cohort studies with the strongest designs for investigating the longitudinal association between visual impairment as exposure and psychotic illness diagnosis as outcome gave conflicting results in adolescents.[13, 14] I can only speculate on the reasons for this. It might be because the association is genuinely different between the Israeli and Swedish populations, though this seems unlikely. A more plausible explanation might be that the study based in Israel used a more stringent cut-off for defining visual impairment (inferred from low rates of refractive error), and therefore found a negative association between severe visual impairment and psychosis, which might be consistent with the n-shaped PaSZ model. The study based on Swedish data appears to have employed more robust methodology, for example, testing different cut-offs for visual impairment, incorporating numerous confounding variables, and using a long duration of follow-up (up to 38 years). It provides more detail about this methodology than the other study.

The conflicting findings in older adult studies appear most likely to be driven by different measures used to define visual impairment and psychosis in these studies. I will discuss this further in chapter 6, in the introduction to my own study of working age and older adults.

Findings from the two studies of children are discussed further in the next chapter.

3.5.2 Case-control Studies

No firm conclusions can be drawn from case-control studies, since so few of these studies were designed to investigate the presence and strength of an association between visual impairment and psychosis, and as such were subject to major limitations in terms of testing this, further discussed below.

3.5.3 Cross-sectional Studies

The evidence for a cross-sectional association between visual impairment and psychosis was reasonably strong and consistent. It applied across the lifespan,

and in studies where psychotic symptoms and visual impairment were both professionally diagnosed and self-reported.

3.5.4 Secondary Findings

There is some suggestion from two studies that the association may be larger for schizophrenia than for other psychotic illness diagnosis.[13, 35] Arguably, this could support the hypothesis that visual impairment is a consequence rather than a risk factor for psychosis, because schizophrenia is typically associated with poorer functioning than some other causes of psychosis and therefore more likely to impair eye-care.[246] Alternatively, it could support a hypotheses that visual impairment is specifically a risk factor for schizophrenia,[121] or that visual impairment results from neuropathology seen in schizophrenia more commonly than related illnesses.

The positive associations between visual impairment and symptoms were greater for hallucinations than delusions in three studies which separated these out,[215, 217, 223] raising the possibility that visual hallucinations partially drove the associations seen similarly to Charles Bonnet Syndrome. I was however unable to separate these from other types of hallucination in these studies, as reporting combined hallucinatory modalities.

3.5.5 Discrepant Findings between Cross-Sectional and Longitudinal Studies

The discrepancy in findings between cross-sectional and longitudinal studies warrants further attention. It could suggest that psychosis leads to visual impairment, rather than the converse, as no studies have yet tested the longitudinal association between psychosis as exposure and visual acuity impairment as outcome. It might also be that psychosis and visual impairment co-occur and are not causally associated. Visual acuity impairment might reflect faulty neural processing resulting from the neuropathology of psychosis.[247]

Nevertheless, given that the most robustly conducted longitudinal study found a temporal association which was strongest for acuity that could not be corrected to normal,[13] the hypothesis that visual acuity impairment could be an aetiological factor contributing to the development of psychosis remains possible. With this in mind, I noted that the pooled cross-sectional odds ratios are larger than those for some established risk factors for schizophrenia, for example, obstetric complications, and birth seasonality;[248, 249] but smaller than or similar to those for others, such as having an affected parent or childhood trauma.[98, 249] Specutatively then, if the association were causal, visual impairment could be making a notable contribution to the burden of psychosis.

3.5.6 Strengths and Limitations

My systematic review is the first to bring together studies of visual acuity impairment and psychosis across the lifespan. I searched multiple databases and incorporated a wide variety of designs. I included studies where the visual acuity impairment-psychosis relationship was not the primary focus of the study. I follow these strengths with a discussion of some limitations of the review.

The strength of my findings is inevitably dependent on the methodology of the included studies. Clearly, RCTs are not possible in this area, so all studies were observational. While I found several large cohort studies at low risk of bias, their findings were conflicting. This may be due to measurement differences, differences in severity of visual acuity impairment, or different lengths of follow-ups. The tendency in most case-control studies to exclude people with visual acuity below a certain level, and the use of inappropriate control groups for my research question, likely reduced their power to detect an association with detrimental effects on the conclusions that I can draw from these. Consequently, I concluded that the evidence from study designs that might allow interpretation of the direction of association between visual acuity impairment and psychosis was inconsistent, and that it is not possible to surmise from this review whether a potential causal relationship exists.

A key limitation of the cross-sectional studies was that most used subjective measures of visual acuity such as asking participants whether they had eyesight difficulties, and the majority also relied on self-reported psychotic symptoms. No cross-sectional studies report adjusting for antipsychotic medication use, which may affect associations, in primary analyses.

There was statistical evidence of high heterogeneity between studies, except for four studies investigating a cross-sectional association between visual acuity impairment as exposure and psychosis as outcome in adults of any age.[120, 125, 227, 229] The high heterogeneity in the remaining studies is to some extent expected given the variation in study settings, and exposure and outcome measures, but means that caution is needed in interpretation of the pooled odds ratios. Meta-analysis of observational data should be interpreted with caution, given the tendency for variation in study designs and unmeasured confounding.[250] After careful consideration, I decided that pooling of cross-sectional study results would still be the most useful way to present overall evidence of strength of association.

There were also limitations of the review methodology. It is possible that studies reporting no association may have been missed due to not being indexed in databases. Although the Egger's test did not show evidence of publication bias, the funnel plot appeared mildly asymmetrical, which could be the result of small study effects including publication bias, heterogeneity or chance.[251] I did not collate studies that used objective measures of retinal function, such as visual evoked potentials or electroretinograms, although this has been done previously.[252] I was unable to search for studies that were not written in or translated into English, which might have led to a language bias, since studies with negative findings might be less likely to be published in English.[253] I excluded the search term 'blind', due to its having alternative meanings (such as allocation concealment) that would bring up a very large number of irrelevant studies. Nevertheless, through hand-searching reference lists and contacting experts, I aimed to ensure that any relevant studies not captured in the original search were still detected. I was unable to arrange for co-screening of all abstracts and studies, but the high concordance between

reviewers in the subset co-screened suggests that doing so would have had minimal impact on the results of the review. I attempted to contact authors for additional details regarding some studies and frequently did not receive replies. There is some evidence that inter-rater reliability on the Newcastle-Ottawa Scale (NOS) is lower than ideal, but I aimed to mitigate this by discussing the NOS with ME for all studies.[254] I decided not to include studies that excluded participants with vision above the 20/20 level, but in doing so could have missed a small number of studies that measured group differences within the 'normal' range.[35]

3.5.7 Conclusions and Implications for further PhD Research

Overall, the evidence summarised above supports the existence of a cross-sectional association between visual acuity impairment and psychosis. This appears to span working-age and older adult age groups. There are potential clinical implications to this. Regardless of whether a causal relationship exists between visual impairment and psychosis, the evidence to date suggests that clinicians caring for people with psychotic illnesses should be alert to the increased chance that their patients will have impaired visual acuity. Facilitation of optical testing could improve eye care for this group.[119] Wider uptake might also mean that complications of comorbidities associated with psychotic illnesses such as diabetes are detected earlier, preventing sight loss.[105, 255] Similarly, clinicians caring for people with visual impairment should be aware of the potential for mental illness, so that patients can be signposted to appropriate support when needed.

There are also several implications for the remainder of my PhD research. As discussed, I was unable to either infer or exclude the possibility that visual impairment is causal risk factor for psychosis from this review. I will investigate this relationship further in the longitudinal studies described in Chapters 4 and 6, the Mendelian Randomisation study in Chapter 5, and the case control study in Chapter 7. Through the systematic review I established that the possibility of psychosis leading to subsequent visual acuity impairment does not appear to have been tested longitudinally. Again therefore, I cannot draw any

conclusions from the systematic review regarding whether psychosis is a likely causal risk factor for visual impairment. This underlines the importance that in my own research, I investigate the bidirectional association between these two conditions longitudinally where possible, rather than exclusively focusing on visual impairment as exposure as has typically been done in previous longitudinal studies.

Young children were the only age group where longitudinal research consistently showed an association between visual impairment and subsequent psychosis (schizophrenia). The two studies in this category however used relatively small samples, were unable to adjust for confounders, and importantly did not separate visual acuity from other aspects of ocular function, such as eye movement disorders, making it impossible to determine which aspects drove the association. This led to my decision, in a birth cohort study in Chapter 4, to investigate these aspects of ocular function separately where available.

There were multiple studies of older adults, but the longitudinal studies of this age group gave mixed findings, with some showing a clear association between visual impairment and subsequent psychosis, and some showing no association. This led me to conduct a study focused on middle-aged and older adults in Chapters 6 and 7, again looking at the bidirectional association between conditions where possible. In the next chapter, I will describe the first of the data studies I carried out in my PhD, which investigates whether poorer visual acuity and other aspects of eyesight in children aged 7 and 11 is associated with psychotic experiences reported at ages 17 and 24.

Chapter 4 Association between childhood visual acuity and late adolescent psychotic experiences: a prospective birth cohort study

A modified version of this chapter has been published here:

Natalie Shoham, Joseph F Hayes, Claudia Cooper, Magnus Theodorsson, Gemma Lewis, Association Between Childhood Visual Acuity and Late Adolescent Psychotic Experiences: A Prospective Birth Cohort Study, *Schizophrenia Bulletin*, 2021; sbab121, https://doi.org/10.1093/schbul/sbab121

4.1 Introduction

Establishing a temporal association between variables is a key facet of inferring causality.[1] As described in the last chapter, there is a paucity of longitudinal studies investigating the association between childhood visual acuity impairment and subsequent psychosis when older; just two studies emerged from the systematic review. In investigating whether visual impairment might be a causal risk factor for psychosis, childhood is an important period to investigate. The peak incidence of both psychotic symptoms and diagnoses occurs in adolescence,[80, 81, 185] and any primary or secondary prevention strategies aimed at reducing exposure to causal risk factors might be most effective during neurodevelopment and before this peak.[167] As outlined in the introduction, psychotic symptoms are broader than psychotic illnesses. Many people with psychotic symptoms will not be diagnosed with a psychotic illness, but experiencing psychotic symptoms does increase the risk both of psychotic illnesses and other mental illnesses.[256]

Both previous childhood studies were carried out in Scandinavian populations. They had relatively small samples, which included selected high-risk offspring of people with psychotic illnesses.[224, 225] Neither study adjusted for confounders in their main analyses, so confounding by other variables such as socioeconomic status or IQ is possible. Further, both studies combined various

aspects of ocular function into one measure, making it impossible to determine whether visual acuity impairment specifically was a risk factor. It is important to investigate visual acuity specifically since the other aspects of ocular function included would require different strategies for correction and affect fewer people over the lifespan, so preventative measures based on these would be quite different.

The first study comprised 110 participants from the 1973 to 1977 Swedish high-risk for psychosis study cohort.[225] Fifty-two participants were 'high-risk' offspring of mothers with psychotic disorder diagnoses, and 58 were controls whose mothers were matched for age, parity, social class, and formal marital status with case mothers. The children were followed from the prenatal period into adulthood. They were assigned to a visual dysfunction category based on results of a Well Baby Clinic check aged 4.[225] Measures included visual acuity testing based on an adapted age-appropriate Snellen chart or Boström Nordlöw-Joachimsson test (designed for young children).[257] Referrals to an eye specialist also contributed points into the score. Referrals could be for eye alignment abnormalities, such as strabismus, as well as measured visual acuity deficit. The resulting score was either 0 (no known visual dysfunction), 1 (deviant vision test), 2 (referral to eye specialist after test), or 3 (eye disorder diagnosed, wearing glasses, and/or repeatedly managed by eye specialist). The odds ratio for developing schizophrenia-spectrum disorder by age 22 in the presence of visual dysfunction compared to no visual dysfunction was 16.07, although confidence intervals were very broad (1.85 – 139.6).[225] This finding was predominantly driven by diagnoses in the high-risk cohort (6 out of 7 diagnoses). SSD was also associated with greater severity of visual dysfunction. No other adulthood psychiatric diagnoses were associated with childhood visual dysfunction presence or severity in this sample. Of note, visual dysfunction was also associated with deviant neurological examination findings aged 6. The authors concluded that visual dysfunction was a potential marker of neurological mal-development, and that their findings supported a neurodevelopmental hypothesis of schizophrenia.

The second Danish study followed a cohort of children born at one hospital in 1959 to 1961. Ninety offspring of a parent with diagnosed schizophrenia were included, as well as 93 offspring of a parent with another psychiatric diagnosis, and 82 control offspring of parents without psychiatric diagnoses. A composite ocular function score was derived from visual assessment aged 11-13. Measures assessed were: eye alignment and related deficits (such as strabismus, also called squint), suppression (reduced vision in one eye), depth perception, abnormalities of pursuit (smooth tracking) eye movements and visual acuity.[224] This study found that children who developed adulthood Schizophrenia-Spectrum Disorders (SSD) had higher composite ocular dysfunction scores and strabismus scale scores, as assessed by Mann-Whitney U test (mean rank 147.9 vs 118.32 p=0.035; and mean rank 152.88 vs 117.72 p=0.005 respectively).[224, 225] Differences were also found when comparing groups who had an SSD diagnosis and no mental illness in adulthood, but not between other mental illness diagnosis and no mental disorder. The median scores on the eye examination scale were 1.22 in the SSD group, and 1.11 in both the 'no mental illness' and 'other mental illness' groups. The conclusion was that eye deficits, particularly strabismus, might be useful in predicting development of schizophrenia in youth at risk, based on these results.

To my knowledge there are no prior studies investigating whether childhood vision is associated with psychotic symptoms, as opposed to diagnoses, in adolescence and adulthood, and no studies in general population samples. I aimed to fill this gap in the literature and to address limitations of the previous studies by conducting the first study of the association between childhood visual acuity; and other ocular measures separately, with subsequent psychotic symptoms.

4.1.1 Aims

I investigated whether poorer visual acuity at ages 7 or 11 was associated with psychotic experiences at ages 17 and 24. A temporal association between these variables would support my second PhD hypothesis: that visual

impairment is a potential causal risk factor for psychotic illnesses and symptoms; but would also be consistent with shared underlying neuropathology (hypothesis 3; my 'alternative' hypothesis for this PhD). I also assessed, as secondary exposures: tests of binocular vision, near vision impairment, and eye movements; in line with other studies, as described further below.[224, 225 120]

4.2 Methods

I published the advance protocol for this study on *protocols.io.*[258] Publication of study protocols is increasingly encouraged to improve transparency and prevent selective reporting of results.[259]

4.2.1 Sample

The Avon Longitudinal Study of Parents and Children (ALSPAC) is an ongoing UK birth cohort designed to further knowledge of health determinants.[260, 261] I chose this cohort for several reasons. Firstly, it has a significantly larger sample size than the cohorts used in previous studies on this topic. Approximately 15,000 pregnancies were originally registered in the ALSPAC cohort.[262] The fact that families were followed from before the child was born meant that a variety of perinatal confounders could be accounted for. Information was also collected from mothers and partners, allowing for adjustment for various family-level confounding variables. Further, visual acuity was objectively measured in eye clinics at ages 7 and 11 and therefore can be considered more reliable than self-report data.

All pregnant women in the ALSPAC study catchment area with a due date between 1st April 1991 and 31st December 1992 were eligible for invitation to participate in the study at antenatal appointments and through advertisements.[260, 261, 263] The catchment area was defined by four NHS District Health Authorities in and around the city of Bristol, in the Southwest UK. 14,541 pregnant women out of 20,248 deemed eligible were originally recruited.[263] At age seven, 913 additional children who had originally been eligible but did not participate were enrolled.[261, 264] In total, 14,901 infants

surviving to age one were included.[265] Children were followed into adulthood through regular questionnaires and 'Focus' clinic appointments at various ages.[263] Questionnaires were also administered to mothers and mothers' partners. The ALSPAC Law and Ethics Committee and Local Research Ethics Committees provided ethical approval for the study and participants gave written informed consent. Study data were collected and managed using the REDCap electronic data capture tool hosted at the University of Bristol: a secure, web-based software platform.[266]

Further details of the cohort profile and a fully searchable data dictionary can be obtained through the study website (https://www.bristol.ac.uk/alspac/).

Figure 4-1: The Catchment Area of the Avon Longitudinal Study of Parents and Children (ALSPAC)[263]

4.2.2 Outcome Variable

The Psychotic-Like Symptoms Screening Interview (PLIKSi) is a semi-structured interview based on the Schedule for Clinical Assessment in Neuropsychiatry (SCAN),[267] designed to assess psychotic experiences in non-clinical populations.[240] It includes 11 core questions about psychotic experiences (hallucinations, delusions, and thought interference).[268] The PLIKSi has been validated in ALSPAC and was administered by trained interviewers.[268] An advantage of measuring psychotic symptoms / experiences rather than diagnoses was that these are widespread in the general population, allowing detection of individuals who would not present to psychiatric services or receive a diagnosis, and increasing the power to detect an association with the exposures.[268] Experiencing psychotic symptoms has been shown to increase the risk of being diagnosed with psychotic illness sin the future in a systematic review.[256] As young people in the ALSPAC cohort completed the PLIKSi at ages 11, 17 and 24, this outcome could be taken from multiple time-points. PLIKSi result at age 11 has however been shown to be poorly predictive of development of a psychotic disorder, and not strongly

predictive of psychotic experiences aged 18, suggesting a positive result at this age is more likely to represent a transient developmental phenomenon.[268] Therefore, I decided to include only PLIKSi result at ages 17 or 24 as a binary outcome variable (suspected or definite psychotic experiences / none). Consistent with standard use of the PLIKSi, I did not include symptoms occurring only in partial sleep states or fever.[269] Sleep-related hallucinations can be distinguished from other types of psychotic experiences and overlap with dreaming,[270] whereas psychotic experiences in the context of fever are suggestive of delirium, which is a transient state not usually reflective of broader psychopathology in younger people.[271]

4.2.3 Exposure Variables

I consulted an ophthalmologist (Dr Magnus Theodorsson - MT) regarding which measures of eyesight in ALSPAC would give the most useful information for this study.

In the 'Focus at age 7' and 'Focus at age 11' clinics, trained orthoptists performed visual assessments. To test visual acuity, children sat four metres away from the light box used to present the test.[272] Carers reported whether children wore glasses. Children who had used glasses in the preceding six months wore these, and carers supported with matching cards if the child did not know the alphabet. The test used was the Early Treatment Diabetic Retinopathy Study (ETDRS) chart, which gave a Logarithm of Minimal Angle of Resolution (LogMAR) score ranging from -0.3 to 1.0.[273] Zero is roughly equivalent to Snellen chart 'normal' 6/6 or 20/20 vision, with negative numbers indicating 'better than normal' and positive numbers indicating 'worse than normal' vision.[16] The test continued until the child read a whole line wrong. Visual Acuity (VA) was then derived from the formula:

VA= -0.3 x (total errors x 0.02).

Testing was performed using patches to occlude one eye and repeated using a pinhole; a simple device to improve acuity in the presence of refractive errors

including myopia.[16] Best corrected visual acuity was the better measurement; with or without the pinhole, in the best eye.[272]

My primary exposure variable was best corrected visual acuity at ages 7 and 11, as a continuous logMAR score. LogMAR score gives the most detailed information about visual acuity from the eyesight measures available.

Uncorrected visual acuity was not measured in ALSPAC, so I was unable to draw comparisons between visual acuity impairments that could be corrected by aids and those that could not, as was done in the previous Swedish study of adolescents by Hayes et al.[13] However, I also tested 'suboptimal vision': a composite binary measure of 'normal' vision (logMAR </= 0) without glasses, or visual impairment (reduced vision, i.e. logMAR > 0; or normal vision with glasses). I analysed, as a binary exposure, glasses use in past 6 months (yes / no) at ages 7 and 11 as well. By including the latter two exposure variables I aimed to capture participants who required corrective aids but may have scored highly on logMAR testing with those aids.

I tested further secondary exposure variables based on previous studies. I assessed between-eye visual acuity difference at ages 7 and 11, due to the study of Swedish adolescents by Hayes et al finding this to be associated with subsequent schizophrenia.[13] There is evidence that binocular visual acuity approximates best-eye monocular visual acuity, so this measure could detect monocular deficits not captured when only the better eye result was used.[274]

All the above measures were available both at age 7 and age 11, but I also tested several measures which were only collected at age 7 in ALSPAC. Firstly, I used measures of eyesight that were included in the composite measures from the two previous childhood studies,[224, 225] to see whether these could account for their identified associations with psychosis. The first of these was presence of manifest strabismus on cover test. Strabismus, also known as squint, occurs when the eyes are misaligned and is a common cause of double vision in adults.[275] Treatment at a young age is essential for children to achieve satisfactory depth perception.[275] In the cover test, the person

undergoing assessment focusses on an object whilst one eye is covered. In the presence of manifest strabismus, the uncovered eye moves to readjust, denoting a positive test.[275] Strabismus in childhood has previously been associated with adulthood psychiatric illness, and people with schizophrenia have been noted to have higher rates of strabismus than healthy controls.[276, 277]

Ambylopia means reduction of visual acuity in one eye that is not due to problems with the eye structure or visual pathways.[278] It can result from multiple causes including strabismus, or difference in refractive error between eyes.[278] It must be addressed early in life for the visual cortex to be able to develop as well as that of someone without this impairment. Parents or carers of ALSPAC children were asked whether the child had ever had patches for the better eye, which would be a treatment for amblyopia.[278] I therefore used history of patch as a proxy for amblyopia.

The Worth four dots test is described as a test of ability to receive two separate images from each eye and perceive them as one; binocular fusion.[272] It is based on being able to see different coloured lights at the corners of vision, requiring input from the two eyes to be incorporated.[272] Seeing two or three lights indicates suppression of the image from one eye, whereas seeing five indicates failure of fusion. To increase power, I dichotomised the result of this test at age 7 into a binary variable (normal / abnormal). Worth Four Dots test was also used in the previous composite eye measure reported in the introduction to this chapter.[224]

Although not used in the two previous childhood studies, I also tested binary prism cover test result (normal /abnormal) alongside Worth Four Dots result, since the prism cover test also measures binocular fusion and was available in ALSPAC.[272] In this test, a prism is placed in front of one eye to displace its image, with lack of compensatory eye movement indicating a deficit of fusion.[272]

Differences in eye movements between people with schizophrenia and healthy controls are widely replicated.[279] A distinction can be drawn between pursuit (smooth) and saccadic (jerky) eye movements. ALSPAC vision clinic examiners observed children's pursuit eye movements in all positions of gaze, and both horizontal and saccadic eye movements using a picture target and a light.[272] I tested both of these as binary exposures as reported by examiners (normal / abnormal).[280]

Near vision impairment has separately been associated with psychiatric symptoms cross-sectionally in adults.[281] The autorefractor is a device which estimates errors in focussing of light on the retina in Dioptres; a measure of lens strength required for correction, with positive numbers indicating near visual impairment.[282] [283] Children had autorefractometry performed three times in each eye, and an average taken.[272] I defined near vision impairment as >/= +2.00 Dioptres in either eye on autorefraction as a final exposure. This cut-off, in the mild near vision impairment range, is in line with a previous study using ALSPAC data.[284]

4.2.4 Putative Confounding Variables

I selected confounding variables *a priori* based on available literature and included these in final models if missing data did not preclude complete case model analyses.

There is some evidence that male gender increases risk of psychosis,[285] and literature suggests that men have lower rates of seeking physical healthcare.[286] Being in a lower socioeconomic group has been found to be a psychosis risk factor[287] and may lessen opportunity to access opticians. I therefore included sex of child and socioeconomic status of mother as confounding variables. I did not include ethnicity of parents, owing to small numbers in all ethnic groups except White British (96%).[261]

I used several perinatal factors measured in ALSPAC as potential confounders. There is evidence that maternal use of tobacco during pregnancy increases the risk of both psychosis and ocular pathology in offspring,[288] and

similar evidence exists for in-utero exposure to infection.[289-291] Both variables were established by questionnaires administered to expectant mothers, and I assessed these as binary confounding variables (present / absent). I included maternal vitamin D consumption estimated from a dietary questionnaire at 32 weeks' gestation as a continuous variable, as vitamin D deficiency has also been shown to be associated with both myopia and schizophrenia.[292, 293] Higher parity may increase risk of psychosis[294] whilst being first-born increases risk of myopia[295], leading to a possibility of negative confounding by birth order, so I also included mother's parity as a discrete variable.

Intellectual disability has been found to be a risk factor for psychosis[229] and is associated with visual impairment.[296] Conversely higher educational level has been found to predispose to myopia,[297] and might be a protective factor against psychosis,[285] so could lead to negative confounding. I included Intelligence Quotient (IQ) score at age 8 as a continuous variable, only in analyses when the exposure was measured subsequently (at age 11), and parental education, a categorical variable for each of mother and mother's partner (CSE / O level / A level / vocational / degree), as a proxy for participant educational level.

Psychotic experiences in the general population are known to be associated with anxiety and depression, and parental depression could also plausibly also affect capacity to seek optical care for children, or result from visual impairment in parents.[81, 281] The Strength and Difficulties Questionnaire (SDQ) is a measure of childhood adjustment and psychopathology.[298] Parents completed this when children were aged 6-7, and I included the resulting total score as a continuous measure of baseline psychopathology. I included maternal Edinburgh Postnatal Depression Scale (EPDS) score when children were 2-3 years old to account for maternal depression.[299] I did not include fathers due to a high proportion of missing data.

4.2.5 Analysis

4.2.5.1 Descriptive Statistics

I calculated numbers and percentages for categorical variables. I report mean and standard deviation for continuous variables that appeared normally distributed on visual inspection, and median and Interquartile Range (IQR) for skewed variables.

4.2.5.2 Missing Data

A key limitation of the ALSPAC dataset is a relatively high level of attrition. Some participants dropped out and others missed assessments intermittently. In this context, ignoring the missing data and using complete case analysis would risk introducing bias. If, for example, people who had poorer vision were more likely both to drop out and to have psychosis, then the effect size could be reduced. An exception to missing data introducing bias is the situation where data are Missing Completely at Random (MCAR): i.e. missing not in relation to any observed or unobserved variables.[300] Even in this situation, using complete case analysis would decrease the sample size and therefore increase standard errors and reduce power to detect an association. In my study however, it is likely that at least some data are missing in relation to observed variables (Missing At Random - MAR) since previous work using ALSPAC has linked missingness to variables in the dataset.[301]

Multiple imputation is a widely used technique to reduce this bias when data are MAR. Unfortunately, multiple imputation assumes that data are MAR and not MNAR. The MNAR scenario cannot be disproven, particularly when the unobserved outcome itself, psychosis, might affect retention in a study. To increase the likelihood that the MAR assumption is met, multiple auxiliary variables (variables associated with both observed variables and with missingness) can be used.[300] A simulation study shows that even when some data are missing in relation to the missing outcome variable (Missing Not At Random), multiple imputation using a linked proxy variable for the outcome still reduces bias and increases efficiency compared to complete case analysis.[302]

To maximise the sample size and reduce potential attrition bias, my main analyses used a multiply imputed dataset. This comprised participants with a LogMAR score at age 7 and at least one of 10 available short Mood and Feelings Questionnaire (sMFQ) scores taken from ages 9 through to 22. The sMFQ is a 13-item self-report measure of depressive symptoms[303] which is associated with the PLIKSi in the ALSPAC cohort and improves prediction of missing PLIKSi values.[304] For example, for the sMFQ score with least missing data (at age 9), the odds of scoring positive on the PLIKSi were increased by 11% for each additional point (OR 1.11, 95% CI 1.07 – 1.16).

I used chained equations through the command *mi impute chained* in STATA version 16.0[214] to generate the imputed dataset, with 100 imputations, including all exposure, confounder and outcome variables. This process uses a 'burn-in' of 10 cycles for each imputation. I imputed binary variables using logistic regression, ordinal variables using ordered logistic regression, and continuous variables using linear regression. Where continuous variables were non-normally distributed, I used progressive mean matching via the *pmm* command to impute only observed values drawing from 10 nearest neighbours, making the distribution of imputed variables consistent with the observed dataset.[300]

I used as auxiliary variables: mother's housing situation, family income, conduct disorder score, and mother's marital status, which are associated with missingness in the ALSPAC data.[304 305]

Missing outcome data was divided between ages 17 and 24, with some individuals providing outcome data at only one of these timepoints. I used multilevel modelling to include anyone who reported outcome data at one or both time points, whilst accounting for within-individual clustering of observations.[306] This served to further increase my sample size. Not accounting for correlation of observations within individuals could lead to artificial inflation of standard errors, giving overly precise results.[306]

4.2.5.3 Primary Analyses

I used multilevel logistic regression (on the multiply imputed dataset) in *Stata version 16.0.*[214] I combined imputed data following Rubin's rules,[300] producing an odds ratio for scoring positive on the PLIKSi at ages 17 or 24 for each 0.1 point deterioration in logMAR score. My model accounted for clustering of PLIKSi scores within individuals at ages 17 or 24 using a random intercept for individual. I repeated this analysis using each exposure; unadjusted and adjusted for putative confounding variables. I did not use Bonferroni corrections because my multiple exposures for visual acuity were testing the same *a priori* hypothesis, and there is evidence that Bonferroni tests may increase the chance of a type II error without significant benefit in this situation.[307]

4.2.5.4 Sensitivity Analyses

I report results from the complete case sample for comparison.

Additionally, I repeated my primary analyses in the complete case sample excluding individuals who reported visual hallucinations (except in states of fever, intoxication or sleep states), to assess whether experiences related to Charles Bonnet syndrome drove any association.[145]

4.3 Results

4.3.1 Description of the sample (Table 4-1)

Characteristics of participants according to visual acuity ((‘normal’ vision (LogMAR</=0) and reduced vision (LogMAR > 0)) are shown in Table 4-1.

Table 4-1: Characteristics of Sample with complete data for visual acuity at age 7

Characteristic **Total N = 7,166**	**Whole Sample** **N (%)**	**Group with LogMAR score </=0** **N (%)**	**Group with LogMAR score >0** **N (%)**
Male	3,584 (50.1)	3,135 (50.3)	449 (48.9)
Maternal socioeconomic status based on occupation			
Professional Managerial and technical Skilled non-manual Skilled manual Partly skilled Unskilled	248 (4.2) 1,871 (32.0) 2,512 (43.0) 205 (3.5) 849 (14.5) 159 (2.7)	228 (4.5) 1,661 (32.5) 2,184 (42.7) 175 (3.4) 728 (14.3) 134 (2.6)	20 (2.7) 210 (28.6) 328 (44.7) 30 (4.1) 121 (16.5) 25 (3.4)
Maternal educational level			
CSE Vocational O level A level Degree	839 (12.9) 546 (8.4) 2,337 (35.9) 1,733 (26.6) 1,052 (16.2)	689 (12.1) 464 (8.2) 2,045 (40.0) 1,532 (26.9) 958 (16.8)	150 (18.3) 82 (10.0) 292 (35.7) 201 (24.5) 94 (11.5)
Mother's partner's educational level			
CSE Vocational O level A level Degree	1,229 (19.4) 493 (7.8) 1,439 (22.7) 1,767 (27.9) 1,402 (22.2)	1,009 (18.3) 430 (7.8) 1,245 (22.5) 1,577 (28.5) 1,265 (22.9)	220 (27.4) 63 (7.8) 194 (24.1) 190 (23.6) 137 (17.0)
Infection during 1st trimester of pregnancy	1,467 (23.6)	1,269 (23.4)	198 (25.2)
Maternal smoking in pregnancy	1,248 (18.8)	1,068 (18.5)	180 (21.3)
Mother's parity in pregnancy	Median 1 IQR 0-1	Median 1 IQR 0-1	Median 1 IQR 0-1
IQ aged 8	Mean 105.2 SD 16.1	Mean 105.9 SD 15.7	Mean 99.6 SD 17.5
SDQ score aged 81 months	Median 6 IQR 4 – 10	Median 6 IQR 4-10	Median 7 IQR 4-11
Maternal EPDS score in Pregnancy	Median 6 IQR 3-9	Median 6 IQR 3-9	Median 6 IQR 3-10
Maternal vitamin D consumption in pregnancy in micrograms	Median 3.5 IQR 2.5 – 5.4	Median 3.5 IQR 2.5 – 5.4	Median 3.3 IQR 2.3 – 5.1
LogMAR score aged 7	Mean -0.06 SD 0.07		
LogMAR score aged 11	Mean -0.15 SD (0.09)	Mean -0.16 SD 0.07	Mean -0.06 SD 0.1
Needed glasses aged 7	754 (10.6)	452 (7.3)	302 (32.9)
Needed glasses aged 11	989 (18.2)	691 (14.5)	298 (44.4)
Visual Impairment (LogMAR > 0 or needing glasses) at age 7	1,370 (19.2)		
Visual Impairment (LogMAR > 0 or needing glasses) at age 11	1,030 (19.4)	708 (15.2)	322 (49.5)
Manifest Strabismus aged 7	144 (2.0)	81 (1.3)	63 (6.9)
Abnormal Prism test aged 7	746 (10.5)	612 (9.8)	134 (14.6)
History of eyepatch aged 7	226 (3.2)	143 (2.3)	83 (9.0)
Abnormal Worth's Four Dots test aged 7	209 (3.8)	129 (2.7)	80 (12.0)
Impaired near vision aged 7	278 (3.9)	149 (2.4)	129 (14.1)

Abnormal saccadic eye movements aged 7	361 (5.8)	293 (5.4)	68 (8.6)
Abnormal smooth pursuit eye movements aged 7	522 (7.3)	433 (6.9)	89 (9.7)
Scored positive on PLIKSi aged 17	261 (7.4)	228 (7.2)	33 (8.3)
Scored positive on PLIKSi aged 24	291 (10.1)	254 (9.9)	37 (11.4)
Scored positive on PLIKSi at either age	481 (11.5)	419 (11.3)	62 (12.6)

LogMAR= Logarithm of Minimal Angle of Resolution, where 0 = "normal" vision, <0 = " better than normal" vision, and >0 = reduced vision; EPDS = Edinburgh Postnatal Depression Scale; SDQ = Strengths and Difficulties Questionnaire; PLIKSi = Psychotic-like Experiences Symptoms Interview.

Missing data (%): Sex (0.2); maternal ethnicity (9.5); maternal socioeconomic status (18.5); maternal educational level (9.2); mother's partner's educational level (11.7); infection during first trimester of pregnancy (13.3); maternal smoking in pregnancy (7.4); mother's parity in pregnancy (8.8); IQ aged 8 (18.0); SDQ score aged 81 months (20.3); maternal EPDS score in pregnancy (13.2); maternal vitamin D consumption in pregnancy (11.3); glasses use aged 7 (0.03); glasses use aged 11 (24.3); visual impairment aged 7 (0.3); visual impairment aged 11 (25.9); manifest strabismus aged (0.1); prism test aged 7 (0.4); Worth's Four Dots test aged 7 (23.1); impaired near vision aged 7 (0.3); saccadic eye movements aged 7 (12.5); pursuit eye movements aged 7 (0.1); PLIKSi aged 17 (50.4); PLIKSi aged 24 (59.7); no PLIKSi result at either age (41.5).

Participants with 'below normal' best corrected visual acuity at age 7 had on average a lower parental socioeconomic status and educational level, lower IQ, higher rates of maternal smoking in pregnancy, and higher rates of other abnormal ocular examination findings than children with 'normal' visual acuity.

6,686 individuals provided visual acuity scores aged seven and at least one sMFQ score. These individuals comprised the multiply imputed sample in primary analyses. Complete data on the primary exposure at age 7, all confounders, and outcome data at one or both of ages 17 and 24 were available for 3,058 individuals. These individuals comprised the complete case sample. From the sample with complete visual acuity data at age seven, 481 (11.5%) individuals with primary exposure data scored positive on the PLIKSi at one or more time points; 261 (7.4%) at age 17 and 291 (10.1%) at age 24.

Differences between participants with and without missing data (i.e. those in the imputed and complete case sample vs complete case sample only) are shown in Table 4-2.

Table 4-2: Characteristics of participants with and without missing analytic data from sample with primary exposure data at age 7 and at least one short Mood and Feelings Questionnaire score

Characteristic	Sample with missing Data N (%)	Sample without missing data N (%)
Total	3,637 (54.4)	3,049 (45.6)
Male	1,944 (53.6)	1,361 (44.6)
Mother's socioeconomic status based on occupation		
Professional	65 (2.6)	177 (5.8)
Managerial and technical	697 (28.2)	1,102 (36.1)
Skilled non-manual	1,106 (44.7)	1,254 (41.1)
Skilled manual	99 (4.0)	101 (3.3)
Partly skilled	413 (16.7)	369 (12.1)
Unskilled	92 (3.7)	46 (1.5)
Maternal educational level		
CSE	515 (16.7)	235 (7.7)
Vocational	304 (9.8)	208 (6.8)
O level	1,143 (37.0)	1,057 (34.7)
A level	752 (24.3)	914 (30.0)
Degree	377 (12.2)	635 (20.8)
Mother's partner's educational level		
CSE	671 (22.2)	450 (14.8)
Vocational	256 (8.7)	210 (6.9)
O level	693 (23.6)	668 (21.9)
A level	792 (26.9)	898 (29.5)
Degree	528 (18.0)	823 (27.0)
Infection during 1st trimester of pregnancy	661 (23.6)	716 (23.5)
Maternal smoking in pregnancy	722 (22.6)	408 (13.4)
Mother's parity in pregnancy	Median: 0 IQR: 0-1	Median: 0 IQR: 0-1
IQ aged 8	Mean: 102.5 SD: 15.8	Mean: 108.3 SD: 15.7
SDQ score aged 81 months	Median: 7 IQR: 4-11	Median: 6 IQR: 4-9
Maternal EPDS score in Pregnancy	Median: 6 IQR: 3-10	Median: 6 IQR: 3-9
Maternal vitamin D consumption in pregnancy in micrograms	Median: 3.4 IQR: 2.3 – 5.2	Median: 3.6 IQR: 2.6 – 5.6
LogMAR score aged 7	Mean: -0.06 SD: 0.08	Mean: -0.06 SD: 0.07
LogMAR score aged 11	Mean: -0.14 SD: 0.09	Mean: -0.15 SD: 0.08
Needed glasses aged 7	381 (10.5)	309 (10.2)
Needed glasses aged 11	485 (18.9)	498 (17.6)
Visual Impairment (LogMAR > 0 or needing glasses) at age 7	700 (19.3)	551 (18.1)
Visual Impairment (LogMAR > 0 or needing glasses) at age 11	505 (20.1)	520 (18.7)
Manifest Strabismus aged 7	67 (1.8)	64 (2.1)
Abnormal Prism test aged 7	358 (9.9)	336 (11.1)
History of eyepatch aged 7	108 (3.0)	106 (3.5)
Abnormal Worth's Four Dots test aged 7	117 (4.1)	76 (3.3)
Impaired near vision aged 7	150 (4.1)	106 (3.5)
Abnormal saccadic eye movements aged 7	173 (5.4)	152 (5.8)
Abnormal smooth pursuit eye movements aged 7	239 (6.6)	237 (7.8)

Scored positive on PLIKSi aged 17	75 (8.0)	184 (7.1)
Scored positive on PLIKSi aged 24	85 (11.7)	204 (9.5)
Scored positive on PLIKSi at either age	141 (12.7)	336 (11.0)

N = Number, CSE = Certificate of Secondary Education, IQ = Intelligence Quotient, LogMAR= Logarithm of Minimal Angle of Resolution, where 0 = “normal” vision, <0 = “ better than normal” vision, and >0 = reduced vision; EPDS = Edinburgh Postnatal Depression Scale; SDQ = Strengths and Difficulties Questionnaire; PLIKSi = Psychotic-like Experiences Symptoms Interview.

The sample with missing data had: a higher proportion of males and maternal smoking in pregnancy; a lower proportion of participants with parents in the highest socioeconomic and educational level groups; and a lower average IQ than the group without missing data.

Potential confounders which I considered but did not include due to a high proportion of missing data (%) included: resuscitation at birth (46), gestational age at birth (44), and polygenic risk score for schizophrenia (28). Bivariable models in the sample with all available data suggested that these were not significant confounders, however.

4.3.2 Primary Results

Results are presented in Table 4-3.

In the Multiple Imputation (MI) analysis, I found evidence that the odds of adolescent psychotic experiences increased with each 0.1-point deterioration in LogMAR score at age 7: Odds Ratio (OR) 1.26 (95% CI 1.06 – 1.49), and at age 11: OR 1.31 (95% CI 1.13 – 1.51). Evidence of these associations attenuated but remained after adjustments; at age 7: Adjusted Odds Ratio (AOR) 1.18, (95% CI 1.00 – 1.40), and at age 11: AOR 1.23, (95% CI 1.06 – 1.42). Visual inspection of histograms suggested that greater variation in the exposure could account for the stronger evidence of association at age 11 relative to age 7.

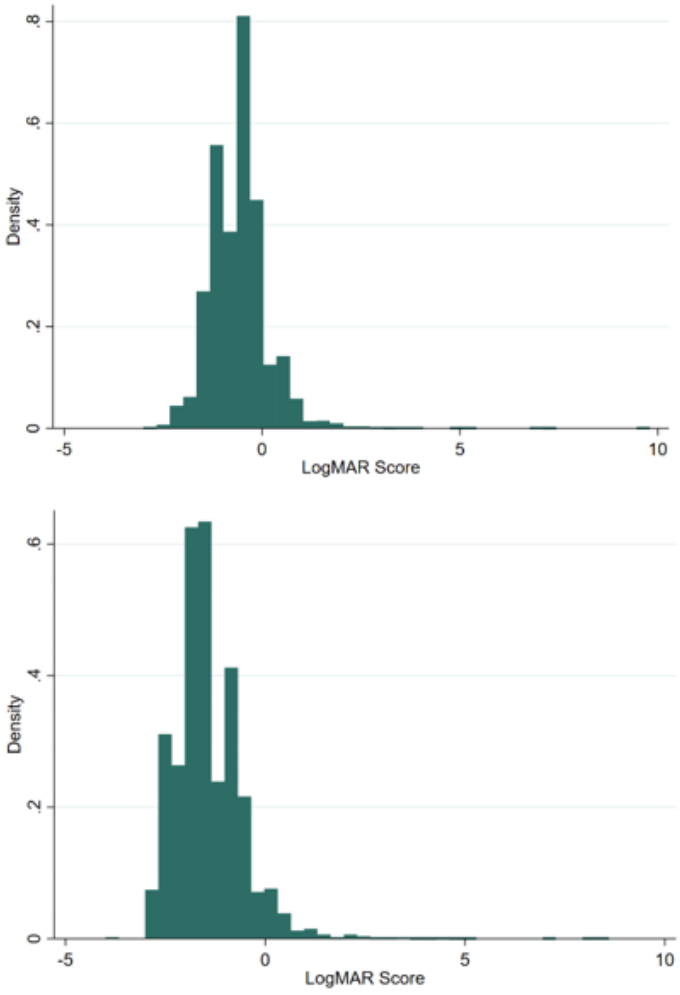

Figure 4-2: Distribution of LogMAR scores in the ALSPAC sample aged 7 (top) and 11 (bottom)

4.3.3 Secondary Analyses

Following adjustment there was evidence of association between psychotic experiences at ages 17 or 24 and needing glasses (AOR 1.63, 95% CI 1.21 – 2.19); and any visual impairment (LogMAR >0 or requiring glasses) (AOR 1.64, 95% CI 1.23 – 2.19), at age 11. AORs were also suggestive of a positive association with logMAR score at age 7, but statistical evidence was too weak to confirm this.

There was no evidence of an association with the outcome of psychotic experiences for between-eye visual acuity difference at either age, or with manifest strabismus, abnormal prism test, history of eye patch, abnormal Worth Four Dots test, impaired near vision, or abnormal saccadic or pursuit eye movements at age 7, either before or after adjustment.

Table 4-3: Odds of Psychotic-Like Symptoms Interview (PLIKSi) Score Consistent with Psychotic Experiences According to Eyesight Variables in Multiply Imputed Data

Exposure	N	OR (95% CI)	P-value	AOR (95% CI) ʟ	P-value
Outcome: Positive result on PLIKSi aged 24 or aged 17					
Best corrected visual acuity aged 7 ɬ	6,686	1.26 (1.06 – 1.49)	0.008*	1.18 (1.00 – 1.40)	0.057
Best corrected visual acuity aged 11 ɬ	6,686	1.31 (1.13 – 1.51)	<0.001*	1.23 (1.06 – 1.42)	0.006*
Difference in acuity between eyes aged 7 ɬ	6,686	1.05 (0.88 – 1.25)	0.565	1.03 (0.86 – 1.22)	0.782
Difference in acuity between eyes aged 11 ɬ	6,686	0.94 (0.70 – 1.25)	0.654	0.92 (0.69 – 1.23)	0.571
Child needed glasses aged 7	6,686	1.56 (1.02 – 2.38)	0.039*	1.42 (0.93 – 2.17)	0.103
Child needed glasses aged 11	6,686	1.73 (1.28 – 2.33)	<0.001*	1.63 (1.21 – 2.19)	0.001*
Normal vision with glasses or subnormal vision aged 7 ɹ	6,686	1.41(1.03 – 1.92)	0.032	1.28 (0.93 – 1.75)	0.125
Normal vision with glasses or subnormal vision aged 11 ɹ	6,686	1.75 (1.31 – 2.34)	<0.001*	1.64 (1.23 – 2.19)	0.001*
Manifest Strabismus aged 7	6,686	0.56 (0.19 – 1.65)	0.292	0.46 (0.15 – 1.37)	0.161
Abnormal prism test aged 7	6,686	1.25 (0.83 – 1.89)	0.290	1.20 (0.79 – 1.82)	0.389
History of eyepatch aged 7	6,686	1.07 (0.54 – 2.12)	0.841	0.97 (0.49 – 1.92)	0.936
Abnormal Worth Four Dots Test aged 7	6,686	0.85 (0.39 – 1.88)	0.693	0.79 (0.36 – 1.74	0.555
Impaired near vision aged 7	6,686	0.62 (0.29 – 1.31)	0.209	0.57 (0.27 – 1.21)	0.140
Abnormal saccadic eye movements aged 7	6,686	0.82 (0.45 – 1.49)	0.521	0.73 (0.40 – 1.33)	0.300
Abnormal pursuit eye movements aged 7	6,686	0.68 (0.40 – 1.18)	0.169	0.64 (0.37 – 1.11)	0.112

N = Number of individuals in analysis; OR = Odds Ratio; 95% CI = 95% Confidence Interval; AOR = Adjusted Odds Ratio; ɬ per 0.1 point deterioration; ɹ = relative to group with normal vision without glasses.

ʟ = Adjusted for sex; mother's socioeconomic status; educational level of mother and mother's partner; maternal smoking during pregnancy; perinatal infection during first trimester; parity of mother during pregnancy; mother's reported vitamin D intake during pregnancy; Strengths and Difficulties Questionnaire (SDQ) score aged 81 months; and maternal Edinburgh Postnatal Depression Scale (EPDS) score in pregnancy.

At age 11, this was further adjusted for IQ aged 8.

* indicates P<0.05

4.3.4 Complete Case Sample

Results can be seen in Table 4-4.

When I repeated the analyses in the complete case sample, estimates for the association between psychotic experiences and LogMAR scores, glasses use, and visual impairment were similar to MI analyses, with confidence intervals largely overlapping. The association between LogMAR score aged 11 and psychotic experiences was not present after adjustment for confounding variables in this sample, whereas there was an association with LogMAR score aged 7. Unexpectedly, there was weak evidence of a negative association between manifest strabismus (AOR 0.23, 95% CI 0.06 – 0.91), abnormal saccadic eye movements (AOR 0.44, 95% CI 0.20 – 0.98), and abnormal pursuit eye movements (AOR 0.47, 95% CI 0.24 – 0.90) at age 7 and psychotic experiences, that was not seen in MI analyses.

Table 4-4: Odds of Scoring Positive on Psychotic-Like Symptoms Interview (PLIKSi) According to Eyesight Variables in Complete Case Sample

Exposure	N	OR (95% CI)	P-value	AOR (95% CI) ʟ	P-value
Outcome: Positive result on PLIKSi aged 24 or aged 17					
Best corrected visual acuity aged 7 ɬ	3,058	1.37 (1.08 – 1.74)	0.009*	1.29 (1.02 – 1.64)	0.037*
Best corrected visual acuity aged 11 ɬ	3,074	1.23 (1.01 – 1.50)	0.037*	1.16 (0.94 – 1.42)	0.163
Difference in acuity between eyes aged 7 ɬ	3,058	0.93 (0.70 – 1.24)	0.628	0.90 (0.68 – 1.21)	0.498
Difference in acuity between eyes aged 11 ɬ	3,074	0.98 (0.67 – 1.43)	0.919	0.97 (0.66 – 1.43)	0.886
Child needed glasses aged 7	3,379	1.27 (0.78 – 2.06)	0.329	1.16 (0.71 – 1.88)	0.552
Child needed glasses aged 11	3,138	1.97 (1.32 – 2.94)	0.001*	1.91 (1.28 – 2.85)	0.002*
Normal vision with glasses or subnormal vision aged 7 ɻ	3,051	1.36 (0.89 – 2.08)	0.151	1.20 (0.79 – 1.85)	0.393
Normal vision with glasses or subnormal vision aged 11 ɻ	3,073	2.09 (1.40 – 3.11)	<0.001*	1.99 (1.33 – 2.97)	0.001*
Manifest strabismus aged 7	3,382	0.28 (0.07 – 1.07)	0.064	0.23 (0.06 – 0.91)	0.037*
History of eyepatch aged 7	3,387	0.50 (0.19 – 1.29)	0.150	0.42 (0.16 – 1.10)	0.077
Abnormal prism test aged 7	3,373	0.88 (0.53 – 1.44)	0.606	0.83 (0.50 – 1.37)	0.456
Abnormal Worth Four Dots Test aged 7	2,556	0.64 (0.23 – 1.78)	0.392	0.55 (0.20 – 1.51)	0.243
Impaired near vision aged 7	3,368	0.56 (0.22 – 1.39)	0.207	0.50 (0.20 – 1.26)	0.141
Abnormal saccadic eye movements aged 7	2,925	0.51 (0.24 – 1.12)	0.092	0.44 (0.20 – 0.98)	0.044*
Abnormal pursuit eye movements aged 7	3,380	0.46 (0.24 – 0.89)	0.020	0.47 (0.24 – 0.90)	0.023*

N = Number of individuals in analysis; OR = Odds Ratio; 95% CI = 95% Confidence Interval; AOR = Adjusted Odds Ratio; ɬ per one point deterioration; ɻ = relative to group with normal vision without glasses.

ʟ = Adjusted for sex; mother's socioeconomic status; educational level of mother and mother's partner; maternal smoking during pregnancy; perinatal infection during first trimester; parity of mother during pregnancy; mother's reported vitamin D intake during pregnancy; Strengths and Difficulties Questionnaire (SDQ) score aged 81 months; and maternal Edinburgh Postnatal Depression Scale (EPDS) score in pregnancy.

At age 11, this was further adjusted for IQ aged 8.

* indicates P<0.05

4.3.5 Sensitivity Analysis

Results shown in Table 4-5Table 4-5

Excluding outcome measures from individuals who reported visual hallucinations at each time point did not significantly weaken the evidence of associations in the complete case sample, with the exception of needing glasses at age 11, although there was still evidence for this association.

Table 4-5: Odds of Scoring Positive on Psychotic-Like Symptoms Interview (PLIKSi) According to Eyesight Variables Excluding Participants who reported Visual Hallucinations in complete case sample

Exposure	N	OR (95% CI)	P-value	AOR (95% CI) ʟ	P-value
Outcome: Positive result on PLIKSi aged 24 or aged 17					
Best Corrected Visual Acuity aged 7 ɬ	3,005	1.44 (1.12 – 1.85)	0.004	1.41 (1.10 – 1.82)	0.008*
Best Corrected Visual Acuity aged 11 ɬ	3,025	1.29 (1.03 – 1.60)	0.025	1.25 (0.99 – 1.57)	0.051
Difference in Acuity between eyes aged 7 ɬ	3,005	1.00 (0.74 – 1.35)	0.998	0.97 (0.72 – 1.32)	0.863
Difference in Acuity between eyes aged 11 ɬ	3,025	1.04 (0.68 – 1.59)	0.847	1.06 (0.69 – 1.62)	0.794
Child needed glasses aged 7	3,324	1.42 (0.84 – 2.41)	0.186	1.31 (0.78 – 2.22)	0.306
Child needed glasses aged 11	3,089	1.62 (1.02 – 2.58)	0.040	1.61 (1.01 – 2.55)	0.044*
Normal vision with glasses or subnormal vision aged 7 ɹ	2,999	1.58 (0.99 – 2.50)	0.050	1.49 (0.94 – 2.37)	0.090
Normal vision with glasses or subnormal vision aged 11 ɹ	3,024	1.78 (1.12 – 2.83)	0.014	1.72 (1.09 – 2.73)	<0.001*
Manifest strabismus aged 7	3,326	0.21 (0.04 – 1.16)	0.073	0.18 (0.31 – 1.01)	0.051
History of eyepatch aged 7	3,331	0.59 (0.21 – 1.63)	0.310	0.51 (0.18 – 1.43)	0.199
Abnormal prism test aged 7	3,318	0.93 (0.54 – 1.61)	0.793	0.86 (0.50 – 1.50)	0.602
Abnormal Worth Four Dots Test aged 7	2,517	0.63 (0.20 – 1.99)	0.428	0.56 (0.18 – 1.76)	0.322
Impaired near vision aged 7	3,312	0.56 (0.20 – 1.57)	0.270	0.51 (0.18 – 1.43)	0.201
Abnormal saccadic eye movements aged 7	2,881	0.47 (0.19 – 1.15)	0.099	0.40 (0.16 – 0.99)	0.047*
Abnormal pursuit eye movements aged 7	3,324	0.43 (0.20 – 0.91)	0.028*	0.44 (0.21 – 0.93)	0.032*

N = Number of individuals in analysis; OR = Odds Ratio; 95% CI = 95% Confidence Interval; AOR = Adjusted Odds Ratio; ɬ per 0.1 point deterioration; ɹ = relative to group with normal vision without glasses.

ʟ = Adjusted for sex; mother's socioeconomic status; educational level of mother and mother's partner; maternal smoking during pregnancy; perinatal infection during first trimester; parity of mother during pregnancy; mother's reported vitamin D intake during pregnancy; Strengths and Difficulties Questionnaire (SDQ) score aged 81 months; and maternal Edinburgh Postnatal Depression Scale (EPDS) score in pregnancy.

At age 11, this was further adjusted for IQ aged 8.

* indicates p<0.05

4.4 Discussion

4.4.1 Main Findings

I have considered two main explanations for my findings that best-corrected visual acuity in childhood; needing glasses; and any visual impairment aged 11 are associated with future psychotic experiences. The first is, in line with my hypothesis 2 which this study was designed to assess evidence for; that visual impairment is a causal risk factor for psychosis. Reduced childhood visual acuity may be a causal risk factor for psychotic experiences. This would be consistent with the Protection against Schizophrenia (PaSZ) model, and work by other authors, notably Silverstein and colleagues, proposing this.[121, 136] It should be noted, given that hypothesis 2 is based on the PaSZ model, that I included no known blind participants in my study, so cannot comment on the PaSZ model assertion that absent vision is protective against psychotic experiences. The distribution of visual acuity scores was such that I was predominantly assessing differences in the 'normal range' of visual acuity, potentially the part of the PaSZ curve which distinguishes 'perfect' from slightly poorer vision.

Alternatively, my findings could be explained by early life central nervous system dysfunction predisposing to both visual impairment and psychosis. This would be in line with my alternative hypothesis, which states that visual impairment and psychosis result from a shared underlying process of neuropathology. Differentiating these two hypotheses based on this study is not possible, though I will consider them further after some more detailed discussion of the findings below. I also cannot rule out hypothesis 1 (that psychosis is a causal risk factor for visual impairment) as the mechanism by which these findings occurred, as I was unable to exclude psychotic experiences in participants at baseline and cannot be certain that the onset of visual impairment preceded them. However, my hypothesis 1 relates to psychotic illnesses rather than broadly defined psychotic symptoms, and having a psychotic illness before age 11 would be very rare; making this explanation unlikely.

I will now discuss the findings in more detail. Although I found evidence that glasses use and visual impairment at age 11 are associated with psychotic experiences, there was very weak evidence for these exposures at age 7, and the reasons warrant consideration. This could be due to the way distribution of refractive errors changes with age. Since a process of ocular elongation occurs through childhood, myopia prevalence is expected to increase with age.[24] In my sample, best corrected visual acuity improved overall at age 11 compared to age 7 with a slightly broader distribution of values. In the multiply imputed dataset, more children wore glasses at age 11 however, in keeping with an increase in corrected myopia cases. This allowed greater power to detect the association with glasses use at age 11 relative to age 7.

Some of the negative findings in my study were unexpected. In particular, the finding that eye movement abnormalities and squint were not associated with psychotic experiences seems surprising, given that these are some of the most widely replicated neurological abnormalities in schizophrenia.[308] This might be because these measures are associated with psychotic illnesses but not psychotic symptoms occurring in other contexts. Alternatively, they may occur closer to the time when psychotic experiences are established or result from these. The lack of association could also simply be due to small numbers of participants with these ocular aberrations in the ALSPAC population.

4.4.2 Strengths and Limitations

To my knowledge, this is the first large study to assess the association between reduced childhood visual acuity and psychotic experiences in adolescence. Strengths include the use of a large birth cohort, and the ability to consider a wide range of potential confounders thanks to the detailed information provided by the ALSPAC study. The inclusion of children at age 7 is particularly helpful in the context of vision. The resulting age range for the exposure (7-11 years old) represents the period in which the visual pathway is reaching its final stages of development.[309] Therefore, childhood visual abnormalities are likely to have manifested in this sample of children, and the

subsequent measure of reduced visual acuity would have been identified and included in analysis.[309, 310]

I am aware of several limitations. Firstly, the ALSPAC cohort consists mostly of White British participants,[311] and cannot be considered fully representative of the population of the UK or global community. This may be especially important given that rates of myopia in children vary across cultures and ethnicities,[24] as might access to corrective aids.

Secondly, although I aimed to include a wide range of confounding variables, residual and unmeasured confounding cannot be eliminated, as in all observational studies. Likely major confounders of the association between visual impairment and psychosis include Socioeconomic Status (SES) and IQ. It has been argued that using only some measures of SES at a single timepoint, as I have done, is too crude a measure and likely to overlook aspects of this multi-faceted concept.[312] For example, household income, and neighbourhood deprivation, which I did not adjust for due to concerns about missing data and collinearity, might be the aspects which drive disparities in access to eyecare and psychosis. SES can also change over time, and affect individuals differently in childhood and adulthood.[312] When data are collected at specific timepoints, this may not be fully captured. IQ was only available after age 7, meaning I could not adjust for it when exposures were measured at age 7. Confounders for which I was unable to adjust at all due to missing data or unavailability, such as shared genetic mechanisms or risk factors including birth trauma, could also partially explain the association.[313]

The proportion of attrition and missing data in ALSPAC is substantial and could bias findings. In my sample, 57% of participants with complete primary exposure data aged 7 were missing data in the confounders or outcome. The unexpected negative association with strabismus and eye movements seen in the complete case sample might suggest bias caused by missing data. I have aimed to mitigate this by using MI; simulations in the ALSPAC dataset show that even when outcome data are Missing Not At Random (MNAR), use of

multiple imputation with appropriate auxiliary variables gives less biased results compared to those from complete case analyses.[302]

Although visual acuity was measured objectively, full engagement with the process was required, and children's' motivation may have influenced test results. Reducing visual acuity to a binary measure reduces its sensitivity, and even small differences within the normal range of vision can lead to significant problems in visual processing.[35] However, I still found associations with the binary exposure variable suggesting this was not too great an oversimplification, and I used continuous logMAR score as my primary analyses. I could not assess uncorrected acuity, which likely led to an underestimate of the true strength of associations. Conversely, the PLIKSi relies on self-reporting, and it is possible that psychotic experiences were under-reported due to stigma, which might have weakened my ability to detect an association.

Although I found an association between visual acuity and psychotic experiences, this does not necessarily equate to an association with psychotic illnesses, since these phenomena do not entirely overlap.[81] Psychotic experiences are associated with a range of psychiatric morbidity,[81] and so my findings could be driven by an association between visual impairment and anxiety or depression. Even so, the Protection against Schizophrenia (PaSZ) model describes a gradient of risk of psychotic symptomatology as a continuous phenomenon according to degree of visual capacity and should therefore be generalisable to a broad range of psychotic experiences.[136]

I have not explored possible mediators or effect modifiers of the association in this study. It is possible that environmental influences occurring after the exposure, such as bullying or trauma, might lie on a causal pathway between visual impairment and psychosis.[314]

4.4.3 Comparison with other literature

My findings extend those from the two small cohort studies of children which found that ocular deficits predicted adulthood diagnosis of schizophrenia.[224,

[225] I have demonstrated this association in a large sample, using psychotic experiences rather than diagnoses, and adjusting for multiple confounders. I have found that visual acuity impairment specifically, rather than other ocular measures, appears to account for the association. This might however be because visual acuity impairments affect more people, leading to greater power to detect an association. Alternatively, it could be because acuity deficits emerge earlier in the development of central nervous system dysfunction in schizophrenia than do other ocular deficits such as eye movement disorders. My results are also consistent with those from the Swedish cohort study of adolescents, which showed that poorer visual acuity at ages 18-19 was associated with subsequent diagnosis of psychotic illnesses.[13] The Swedish study found that between-eye visual acuity difference was associated with psychotic illness. I did not replicate this finding: perhaps because ALSPAC measured corrected rather than uncorrected visual acuity, so was less likely to detect between-eye differences; or because this association did not exist in my sample, which was younger; or because there is a distinction between psychotic experiences and illnesses.[13]

One of the two previous childhood studies found that a strabismus scale score was strongly associated with future schizophrenia diagnosis.[224] The most likely reason for the discrepancy between this and my study is that the previous study used a cohort of high-risk offspring with higher rates of strabismus, increasing its power to detect a difference despite its smaller sample.

Also relevant is the 2020 systematic review which collated studies that used Optical Coherence Tomography (OCT) and Electroretinography (ERG) to compare ophthalmic structure and function in people with schizophrenia and people without.[100] Across studies, there is evidence of retinal thinning and altered retinal waveforms in schizophrenia, which are conceptualised as objective signs of an underlying neuropathological process.[315] The timing of the development of these alterations is unknown, but rates of ERG abnormalities are elevated in children at high risk of psychotic illness.[316] Reduced visual acuity could therefore result from this process in some children in my study and share an underlying neuropathology or genetic predisposition

with psychosis. This is further supported by the work showing that these alterations also affect healthy relatives of people with schizophrenia.[316]

4.4.4 Conclusions

My findings support a temporal association whereby childhood visual acuity impairment, at least at age 11, is associated with late adolescent psychotic experiences. This temporal relationship is consistent with my second PhD hypothesis: visual impairment is a causal risk factor for psychosis. However, the limitations outlined above mean that a causal relationship cannot be confirmed from this study. Even if I assume that residual and unmeasured confounding by factors such as socioeconomic status or birth trauma does not explain the association, the possibility that my alternative hypothesis does remains (that there is shared neuropathology between visual impairment and psychosis).

I have tried to account for the possibility that psychotic experiences occurring through common mental disorders might drive the association by adjusting for common mental disorder symptoms. Nevertheless, I have only been able to do so this at certain points in time. Depression and anxiety are known to increase the chance of psychotic experiences and are associated with visual impairment, so could still drive the association. One way to overcome these limitations would be to test the association of visual impairment with schizophrenia diagnosis instead. I will do this in the next chapter, where I use Mendelian Randomisation to determine the likelihood of a causal relationship.

Chapter 5 Association between Schizophrenia-Spectrum Disorders and Myopia: A Mendelian Randomisation Study

A modified version of this chapter is published here:

Shoham, N., Dunca, D., Cooper, C., Hayes, J., McQuillin, A., Bass, N., . . . Kuchenbaecker, K. (2023). Investigating the association between schizophrenia and distance visual acuity: Mendelian randomisation study. *BJPsych Open, 9*(2), E33. doi:10.1192/bjo.2023.6

5.1 Introduction and rationale for key decisions

5.1.1 Findings from Chapters 3 and 4

In the third chapter, I showed that there is consistent evidence for a cross-sectional association between visual acuity impairments and psychotic illnesses and symptoms. This would be consistent with any of my PhD hypotheses: either that psychosis is a causal risk factor for visual impairment (hypothesis 1); visual impairment is a causal risk factor for psychosis (hypothesis 2); or visual impairment and psychosis result from shared underlying neuropathology (alternative hypothesis). The remainder of my thesis will focus on trying to distinguish between these. Since I found no previous research studies investigating the longitudinal association between psychotic illnesses as exposures and visual impairment as outcome, I was unable to draw conclusions regarding support for the hypothesis that psychosis leads to visual impairment. Longitudinal evidence as to whether visual impairment as exposure is associated with subsequent psychosis as outcome gave mixed findings, so the hypothesis that visual impairment causes psychosis was again neither strongly supported nor refuted.

In the fourth chapter, I found that evidence that poorer childhood visual acuity is temporally associated with adolescent psychotic symptoms, though not necessarily illnesses. This provides some support for hypothesis 2; that visual impairment is a causal risk factor for psychosis, but it is not conclusive, since

there could be other explanations for this association, including my alternative hypothesis (that psychosis and visual impairment share neuropathology).

One critical problem is that since all the above findings stem from observational data, the possibility that they are driven by confounding cannot be excluded. Further, in my longitudinal study, I was unable to exclude the possibility that the psychotic experiences were already manifest at the time of visual acuity measurement. Reverse causation cannot therefore be entirely disproven. As a result, the implications thus far are therefore somewhat speculative. In this chapter, I will aim to make the best use of observational data to overcome these limitations as far as possible.

5.1.2 Research Questions

My research questions for this chapter are:

Does genetic evidence support a causal association between SSD as exposure and poorer visual acuity as outcome? (To test PhD hypothesis 1, that psychotic illnesses are a causal risk factor for visual impairment).

Does genetic evidence support a causal association between myopia as exposure and SSD as outcome? (To test PhD hypothesis 2; that visual impairment is a causal risk factor for psychosis).

5.1.3 Mendelian Randomisation

Overcoming the above limitations presents challenges. The optimal method to assess for causal effects would be a Randomised Controlled Trial (RCT). Clearly, it is not possible to conduct an RCT assessing whether psychosis is a causal risk factor for visual impairment, or the converse. I have therefore decided to use Mendelian Randomisation (MR), which aims to simulate an RCT. The premise of MR is that genetic variants are randomly allocated to research participants during meiosis and conception, according to Mendel's laws of inheritance.[291] This approximates random allocation of an intervention to participants in an RCT, which is designed to eliminate both known and

unknown confounding. By designating genetic variants that are known to associate with an exposure trait (phenotype) as proxy instruments for that trait, the association between that characteristic and another variable can be investigated, theoretically, without possibility of interference by confounding or reverse causation due to this process of natural randomisation. In practice, assumptions in MR methodology mean that this might not always hold true, and I will consider this further in subsequent paragraphs. Even so, MR is considered to add value to traditional observational studies in assessing causal associations and might sit above them in the traditional hierarchy of evidence.[317]

Figure 5-1 Proposed position of MR studies in the traditional hierarchy of evidence Reference: Davies et al [318]

5.1.4 Genetic Instruments and assumptions of MR studies

Usually, the genetic variants used in MR are Single Nucleotide Polymorphisms (SNPs).[317] These are variations in a single DNA base pair between individuals. To make a useful instrument for MR, a SNP must first be clearly associated with the trait of interest.[317] Knowledge of SNPs associated with various diseases and characteristics has burgeoned in recent years due to widespread implementation of Genome-Wide Association Studies (GWAS), in which scanning of entire genome sequences is conducted in very large samples of participants.[319] To be 'genome-wide significant', a SNP must be associated with the trait of interest with $p<5x10^{-8}$.[319]This stringent cut-off is used to reduce the likelihood of a false positive result occurring through multiple testing when millions of SNPs are examined.[319]

A further assumption of MR studies is that of exclusion restriction. This assumption states that genetic instruments must only be associated with the outcome phenotype through the exposure of interest.[317] This may be demonstrable if the biology of the genetic variant is well-understood, but with so many SNPs in the human genome, this is not often the case.[317] Therefore,

when multiple SNPs are used as instruments, statistical methods have been developed to assess the likelihood that the exclusion restriction assumption has been violated, and I will describe how I have applied these in my methodology. One key threat to these assumptions in MR studies is pleiotropy, or more specifically directional horizontal pleiotropy.[317] Pleiotropy refers to genetic variants having multiple effects on an individuals' characteristics, and horizontal pleiotropy means instruments influencing the outcome via routes other than the exposure. When multiple instruments have such effects in opposite directions, and these are balanced overall, the results of the study will still be valid.[320] When overall the effect of horizontal pleiotropy is in one direction however, this may invalidate results. This could occur if a significant subset of instrument SNPs acted on the same confounder.[321] I will discuss the ways in which I have tried to limit the potential effects of directional horizontal pleiotropy in my MR study findings in the methods.

Figure 5-2: Diagrammatic representation of Mendelian Randomisation

Z_A represents genetic instruments, Trait A and B represent exposure and outcome respectively. Pathways 2 and 3 represent violations of the underlying assumptions of Mendelian Randomisation.

Reference: Davey-Smith et al 2014 [322]

5.1.5 One-sample and two-sample Mendelian Randomisation studies

The first MR studies would measure the association of genetic instruments with the outcome trait in a single sample, to assess for an association. Now, it is common and indeed considered preferable for MR to use two samples; one in which the genetic instruments' association with the exposure has been confirmed, and one in which their association with the outcome has been measured.[317] A practical advantage of this is that very large, precise GWAS can be used, allowing the strongest instruments to represent the exposure to be selected, regardless of whether association with the outcome phenotype has been measured in the same sample.[317] For this reason, I have chosen to

use two-sample MR in this chapter. This comes at the expense of the assumption that the two samples reflect the same underlying population; an assumption which I have aimed to justify by using homogenous ancestry samples.[317] This is explained further in the methods section.

5.1.6 Type of Genetic Instrument

I used summary statistics (published effect sizes and standard errors from GWAS) to conduct bidirectional two-sample Mendelian Randomisation. I have used multiple genetic instruments (SNPs) because individual SNPs relevant to my phenotypes of interest confer only very small effects on the probability of an individual having the phenotype and would therefore constitute weak instruments, whereas using large numbers of available SNPs strengthens the instrument. In addition to markedly increasing instrumental power, using multiple SNPs has allowed me to carry out multiple sensitivity tests to assess the likelihood of MR assumptions having been violated, and reduces the likely influence of pleiotropy on results.

5.1.7 Choice of Phenotypes

I have chosen myopia to represent visual impairment as an exposure because it affects people throughout the lifespan and is the most common cause of visual impairment worldwide.[24] The high prevalence of myopia also means that it has been possible for consortia to collate large samples of affected participants in GWAS studies, increasing the likelihood that genetic variants associated with the phenotype are detected.[54]

Where visual impairment was the outcome, I have chosen habitual visual acuity to represent it. This means visual acuity as measured with whichever glasses or visual aids participants had with them on the day. This is because unlike binary myopia status, this measure incorporates correction or non-correction of refractive error, and non-correction is one mechanism by which I hypothesise SSD might be a causal risk factor for visual impairment.

I chose SSD represent psychotic illnesses, for several reasons. Much theoretical rationale for why visual impairment might be a risk factor for psychosis focusses on schizophrenia specifically, rather than psychotic symptoms or experiences.[136] Further, genetic influences on SSD have been widely researched thanks to the existence of the schizophrenia working group of the Psychiatric Genomics Consortium (PGC).[323]

5.1.8 Choice of Samples

In selecting samples from which to derive instruments, I have aimed to use the largest available up-to-date GWAS which reported the necessary information from the resource *GWAS Catalog*.[324] *GWAS Catalog* is a searchable index of published GWAS studies.[324] In using the largest suitable GWAS studies, my intention was to maximise the number of exposure-associated SNPs detected, and therefore maximise my instrument strength and power to detect an association.[320] Using the largest available samples also allows the best possible precision of estimates of SNPs' association with the exposure and outcome phenotypes.

5.1.9 Genetic Ancestry Groups in Mendelian Randomisation

I analysed data from two separate genetic ancestry groups in this study. Analysing ancestry groups separately is required due to Linkage Disequilibrium (LD). LD occurs when genetic variants are inherited together more frequently than would be expected by chance, for example because they are near to each other on the chromosome.[325] One consequence is that the variants detected as associated with a phenotype through GWAS might not the 'true' causal variants influencing the phenotype, but rather in LD with such a variant.[320] Since LD can differ between ancestry groups, this means that the lead variant from a GWAS in one genetic ancestry group might not be a good proxy variant for the true causal SNP in another ancestry, even though the underlying causal variants are likely to be the same.[317, 326] Using statistics from relatively homogenous ancestry groups therefore reduces the chances of use of invalid instruments in Mendelian Randomisation.

For my primary analyses, I used samples with European ancestry, as the group in which the largest GWAS have been conducted and the most relevant SNPs identified. I analysed data from samples with East Asian ancestry separately to test whether the findings are consistent in other ancestry groups. No published SSD GWAS that is sufficiently large was available for any other ancestry group.

5.2 Methods

5.2.1 Sample used in SSD GWAS

Psychiatric Genomics Consortium (PGC): The PGC is a consortium of case-control samples aimed at identifying genetic variants associated with psychiatric disorders.[323] The dataset established by its schizophrenia working group comprises 90 studies including 67,390 SSD cases and 94,015 controls of which 80% had European ancestry.[323] Across samples, cases could be defined as: diagnosis of schizophrenia, schizoaffective disorder, or schizophrenia-spectrum disorder determined through consensus between psychiatrists; validated diagnostic interview; structured assessment; review of medical records; or a combination of these.[323] Analysed separately were 22,778 SSD cases and 35,362 controls of East Asian ancestry.[327]

5.2.2 Samples used in Myopia and visual acuity GWAS

UK Biobank: Between 2006 and 2010, over 500,000 UK residents aged 40-60 were recruited to the UK Biobank cohort across 22 UK centres.[328] Further details on recruitment are available, and also described further in the next chapter.[329] A wide range of health variables have been assessed by questionnaires, examination, and blood sampling in this ongoing, longitudinal study. Myopia status was determined either by Spherical Equivalent (SE) measured by autorefractor, or inferred using questionnaire and other data: age, sex, age of first spectacle or contact lens wear, and year of birth.[54] Spherical equivalent is a measure of lens strength required to correct refractive error.[330] 102,117 participants had both measured refractive error and genotyping.[54] An additional 108,956 cases and 70,941 controls had inferred

myopia status, based on demographic variables and self-reported age of first use of prescription glasses.[54] Myopia status was meta-analysed and contributed to my myopia exposure instrument.[54]

I also used UK Biobank genetic summary statistics for the separate phenotype of continuous visual acuity, both as an exposure and an outcome. At baseline assessment, 116,011 participants had their habitual visual acuity measured; habitual meaning using any corrective aids they usually wore.[331] Of these, 90,214 had European ancestry, and 923 had East Asian ancestry. This generated a continuous right eye Logarithm of Minimal Angle of Resolution (LogMAR score), with negative numbers indicating ‘better than normal’ and positive numbers indicating ‘worse than normal’ distance vision.[331] Scores ranged from -0.66 to +1.35.[332] Phenome-wide association scans were performed using PHESANT (PHEnome Scan ANalysis Tool), to find SNPs associated with a wide variety of traits in the UK Biobank in a hypothesis-free manner. I extracted from this data the variants associated with habitual LogMAR score.[333, 334] I chose right eye logMAR score, as there was no measure that combined the two eyes and no known reason why they would be affected differently.

I used the summary statistics for dental caries in the UK Biobank as a positive control, again generated in a hypothesis-free manner using PHESANT.[333] ICD-10 diagnosis of dental caries status was established from healthcare records.[335] There were 3,646 cases and 416,885 controls among participants with European ancestry.

In a post-hoc analysis, I also used participant report of glasses use for short-sightedness in the UK Biobank as a binary outcome variable.

23andme: 23andme is a private company offering genotyping to paying customers. Consenting customers were asked: 1) "Have you ever been diagnosed by a doctor with nearsightedness (near objects are clear, far objects are blurry)?"; and 2) "Are you nearsighted (near objects are clear, far objects are blurry)?"; and with the same descriptor for nearsightedness 3) "What vision

problems do you have?” and 4) "Prior to your LASIK eye surgery, what vision problems did you have?". These questions were used to identify 106,086 probable myopia cases and 85,757 controls used in subsequent meta-analysis.[54]

Consortium of Refractive Error and Myopia (CREAM): This consortium, designed to further knowledge of genetics of myopia and refractive error, comprised 34,079 participants aged 25+ who did not have major ocular conditions that could alter refractive error.[54] All had refractive error measured and an average between the two eyes taken.[336] Methods specific to each study within CREAM are described elsewhere.[337] Linear regression was used to identify SNPs associated with spherical equivalent.[54]

The Genetic Epidemiology Research in Adult Health and Aging cohort (GERA): The GERA cohort has been described in detail elsewhere.[338] It is part of the Kaiser Permanente Research Program on Genes, Environment, and Health and includes 34,998 adults who had spherical equivalent measured at least once between 2008 and 2014. Mean spherical equivalent from both eyes at first documented assessment was used in meta-analysis.[54] Linear regression was used to determine SNPs’ association with spherical equivalent.[54]

The above myopia samples were combined in a 2020 meta-analysis by Hysi and colleagues using a Z-score method.[54] This meta-analysis formed the basis of my genetic instruments for the phenotype of myopia.

5.2.2.1 Meta-analysis of Severe Myopia in East Asian and Southeast Asian participants

Meguro and colleagues performed a GWAS meta-analysis of 2,549 patients with severe myopia and 11,547 healthy controls of East and Southeast Asian ancestry, to identify SNPs associated with high (severe) myopia.[339] Strength of lens required for correction, or Spherical Equivalent (SE), is measured in Dioptres. The studies variably defined high myopia as SE in at least one eye of </=-5.0, </=-6.0, or </=-9.0 Dioptres, or having an axial length >26mm.

Controls without myopia were defined as SE >/= -0.50 or >/= -1.0 Dioptres in both eyes. Formal ophthalmic examination was used to determine the phenotype in each study.

5.2.3 Instrument selection

5.2.3.1 Schizophrenia and related disorders

The PGC Schizophrenia Working Group have identified 270 independent genetic loci associated with schizophrenia as a binary phenotype with genome-wide significance.[323] Around 60-80% of the population variance in schizophrenia phenotype can be attributed to genetic factors,[323] and these common genetic variants are estimated to account for 24% of this heritability.[323] Enrichment analyses combined with fine-mapping can detect tissues in which genes are relatively more expressed (translated into proteins) and has increased the credibility of many loci as containing causal genes, with genes preferentially expressed in brain tissues showing enriched associations.[323]

5.2.3.2 Myopia and Visual Acuity

Across 542,934 individuals from the UK Biobank, 23andme, the GERA cohort, and CREAM consortium, 449 genetic loci associated with myopia with genome-wide significance ($p<5x10^{-8}$) have been identified through meta-analysis.[54] These analyses were restricted to participants of European ancestry. Refractive error has a heritability of 60-80%,[340] and collectively, these SNPs are estimated to explain 18.4% of this heritability.[54] The majority are in regions with known, plausible biological pathways to myopia and are preferentially expressed in ocular tissues.[54] The SNPs are distributed across all chromosomes except Y.[127]

In the meta-analysis of genetic variants associated with severe myopia in East Asian and Southeast Asian participants, nine genetic loci were discovered to be associated with high myopia at genome-wide significance level.[339] Two regions had previously been associated with myopia in samples of European ancestry.[339]

5.2.3.3 Individual SNP Selection

Where necessary, I used the following formulae to obtain beta-values for SNPs' associations with myopia and standard errors from the meta-analysis z-scores:

$$\text{Beta} = \text{Z-score} / \sqrt{(2*\text{MAF}(1-\text{MAF})*(N+\text{Z-score}^2))}$$

$$\text{SE} = 1/\sqrt{(2x\text{MAF}(1-\text{MAF})*(N+\text{Z-score}^2))}$$ [318]

Where MAF = Minor Allele Frequency, N=sample size, and SE=Standard Error.

I applied the following criteria to identify instrument SNPs for each exposure:

The SNP must show association with the exposure in the relevant ancestry sample at significance level $p<5x10^{-8}$. This is the standard genome-wide significance level, chosen to mitigate against type 1 error (false positives) due to multiple testing in the detection of SNPs.[92]

The SNP must have Minor Allele Frequency (MAF) > 0.005. Very rare genetic variants are unlikely to constitute strong instruments and are more difficult to accurately impute, as outlined below.[341, 342]

Where applicable, the SNP information quality score (only available for SSD instruments) must be > 0.7. This relates to the fact that many variants are not directly typed in GWAS; and imputation from reference panels is needed to fill in missing data.[342] Information quality scores were derived from a composite of measures including subject missingness, SNP missingness, difference in SNP missingness between cases and controls, and difference in Hardy-Weinberg equilibrium between cases and controls.[323] These scores indicate the accuracy of the imputation of each genetic variant.

The SNP must not be in linkage disequilibrium with another instrument SNP (defined as correlation > 0.2). I determined this using the *clump* command within the *TwoSampleMR* package, which uses ancestry-specific reference databases to detect SNPs which are in linkage disequilibrium.[343, 344] This is to

prevent inflation of associations caused by multiple SNPs representing the same genetic locus.

I also removed palindromic SNPs with MAF > 0.42 (the pre-specified cut-off in the software) using the *TwoSampleMR* package in R, due to potential uncertainty about which was the effect allele.[343, 344]

When deriving SNPs associated with habitual logMAR score from the UK Biobank, I used the more lenient threshold of $P<5x10^{-5}$ to give >5 SNPs, otherwise there would have been too few to conduct an analysis due to the lower power conferred by the unselected sample and multi-phenotype way these GWAS were conducted. I used the same criteria for SNP selection otherwise.

Mendelian Randomisation Analysis

To test hypothesis 1 (that SSD is a causal risk factor for poorer visual acuity), I used SNPs associated with SSD in the PGC as instrumental exposures and tested these SNPs' association with poorer logMAR score in the UK Biobank as the outcome.

To test hypothesis 2 (that myopia is a causal risk factor for SSD), I used summary statistics for SNPs identified in the meta-analysis of myopia and refractive error samples as instrumental exposures, and summary statistics for these SNPs' associations with SSD in the PGC as the outcome. I repeated analyses using SNPs associated with poorer habitual logMAR score as instrumental exposures. In a post-hoc analysis, I also tested instrument SNP association with reporting glasses use for short-sightedness as an outcome (explained further below).

I used the package *TwoSampleMR* to run analyses using R version 4.0.3.[343-345] My primary analyses used the Inverse Weighted Variance (IVW) method, with a random effects model to account for pleiotropy.[346] The IVW method combines the effect of each genetic variant in a fixed effects meta-analysis

model, to give an estimate of the causal effect of exposure *x* on outcome *y*.[346] Each SNP's contribution to the effect estimate is determined by the inverse of the variance of the ratio estimate.[320] The formula for the IVW method is:

$$\hat{\theta}_{IVW} = \frac{\sum_j \hat{\theta}_j \, \mathrm{se}(\hat{\theta}_j)^{-2}}{\sum_j \mathrm{se}(\hat{\theta}_j)^{-2}} = \frac{\sum_j \hat{\beta}_{Yj} \hat{\beta}_{Xj} \, \mathrm{se}(\hat{\beta}_{Yj})^{-2}}{\sum_j \hat{\beta}_{Xj}{}^2 \, \mathrm{se}(\hat{\beta}_{Yj})^{-2}}.$$

Source: Burgess and Thompson 2015[319]

Where:

θIVW represents the estimated causal effect of the exposure on the outcome; θ represents the ratio estimate; $ßYj$ represents the association of each genetic variant with the outcome; $ßXj$ represents the association of each genetic variant with the exposure, and *se* represents standard error.[324]

The approximate standard error of the outcome is then given by the formula:

$$\mathrm{se}(\hat{\theta}_{IVW}) = \sqrt{\frac{1}{\sum_j \hat{\beta}_{Xj}{}^2 \, \mathrm{se}(\hat{\beta}_{Yj})^{-2}}}.$$

Source: Burgess and Thompson 2015[341]

The IVW method is widely used as the primary method in MR studies, because it gives more precise estimates than other methods.[341]

Where the outcome was binary, I converted the association between exposure and outcome to an odds ratio for ease of interpretation.

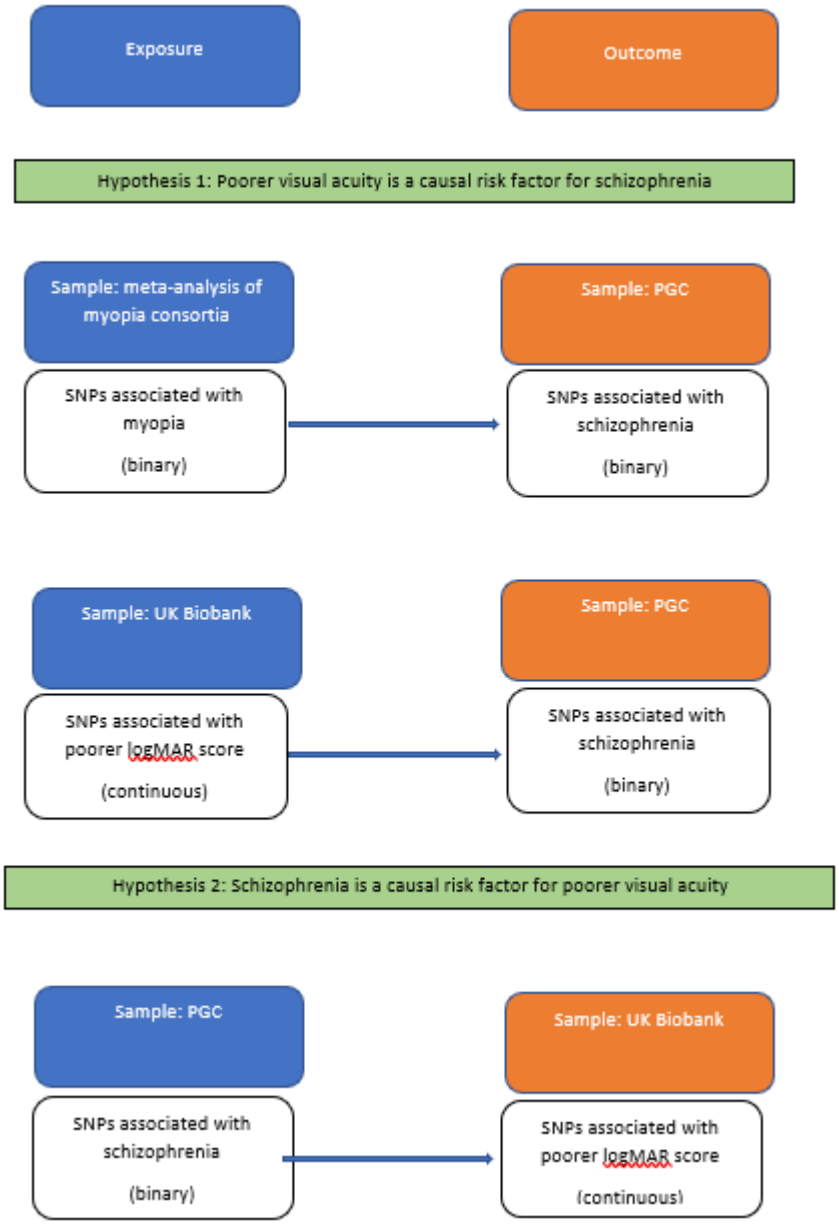

Figure 5-3: Planned Analyses

5.2.4 Sensitivity Analyses

As outlined in the introduction to this chapter, MR methodology assumes absence of directional horizontal pleiotropy, where SNPs influence the outcome via routes other than the exposure creating misleading evidence of an effect. Whilst this assumption cannot be proven, I was able to conduct multiple sensitivity analyses to test the likelihood that pleiotropy caused any association. Firstly, I performed Cochran's Q test for heterogeneity and

generated scatter plots and funnel plots to visually inspect heterogeneity of results. Heterogeneity of the effects of instrumental SNPs in the presence of an overall association could constitute evidence either of horizontal pleiotropy, or other threats to the validity of the study such as confounding by population structure.[317] However, my use of homogenous ancestry groups mitigated against confounding by population structure. Lack of significant heterogeneity would constitute evidence against directional horizontal pleiotropy, as would symmetry of the funnel plot.[347]

I also used other Mendelian Randomisation techniques which give lower statistical power than the IVW method, but are more robust to the violation of the assumption of no directional horizontal pleiotropy.[341] Firstly, I used MR-Egger, which allows the model intercept to be non-zero, unlike the IVW method.[320] This intercept then represents an estimate of the degree of pleiotropy, and in which direction it is acting overall.[320] I report the MR-Egger intercept from random-effects Egger analysis (allowing for greater balanced pleiotropy), and the P-value for statistical significance of the intercept, derived from the *MR Rucker* function in *TwoSampleMR*, with the aim of quantifying pleiotropy.[343]

Limitations of the MR-Egger method are that it remains sensitive to outliers and relies on SNPs' pleiotropic effects being unrelated to their effect on the instrument strength (the Instrument Strength Independent of Direct Effect or InSIDE assumption), which can be violated when the pleiotropy acts via a confounder.[341] Therefore, I also used the weighted median and weighted mode methods. Rather than using the weighted mean, as in the IVW method, the first of these uses the weighted median estimate for the overall ratio of instruments' effect on outcome relative to exposure.[341] This means that provided 50%+ of the variants included in the model are valid instruments, the resulting effect estimate is in the true direction.[346] The weighted-mode method similarly uses the mode estimate (from construction of a normal density) as the estimate.[341] This method is also less sensitive to outliers, as it only relies on the largest group of SNPs being valid instruments.[341]

Although the mode- and median-based methods are less sensitive to outliers, they are not entirely unaffected by them.[341] As a further sensitivity analysis, I conducted the Mendelian Randomisation Pleiotropy Residual Sum and Outlier (MR-PRESSO) test. This feature of the *TwoSampleMR* package has several stages.[343, 344] Initially, it performs the IVW method and calculates the Residual Sum of Squares (RSS) from the regression model.[348] It then omits each SNP from the analysis in turn and compares the new RSS to an expected distribution to identify outlying SNPs.[341] Finally, it re-runs the IVW method excluding all outlying SNPs to give a new estimate. I performed MR-PRESSO with a significance threshold of 0.05 and Negative Binomial Distribution of 8,000, (or 10,000 where logMAR score was the outcome in European participants), to find out whether outlying SNPs had distorted the estimates.[348]

As final sensitivity analyses, I conducted single SNP and 'leave-one-out' analyses. The single SNP analysis performs two-sample MR on each SNP individually and can plot this to allow visual inspection of results, whilst the 'leave-one-out' analysis re-performs the MR leaving out each SNP in turn, to ensure that no single outlying SNP was driving any association.[321] I present results from these analyses graphically.

5.2.5 Comparison with Dental Caries

If a statistically significant association was found, I compared the results where myopia or logMAR score was the phenotypic exposure or outcome to dental caries, with the aim of judging whether overall neglect of physical healthcare was a likely mechanism by which the association could occur.

5.2.6 Post-hoc analysis

I added a final analysis which tested the association between genetically-predicted SSD, as exposure, and reporting glasses use for myopia as a binary outcome variable, since this would give further information regarding whether non-correction of myopia is a likely mechanism by which SSD and poorer visual acuity might be associated.

5.2.7 Functional Gene Ontology

Where an association was found, I report the functions of genes containing instrumental SNPs as determined through the *Functional Mapping and Annotation of Genome-Wide Association Studies (FUMA)* resource.[349, 350] This freely available online resource integrates information about the known function of genes from multiple biological repositories, and is intended to facilitate identification of which of the many disease- and trait-associated SNPs identified from GWAS studies have casual and mechanistic relevance.[350] There are two stages to the mapping: matching SNPs to known genes, and then matching genes to their known functions.[350]

I also report the biological pathways with which these genes are associated with p<0.05 from *Enrichr* output, specifically using the *Kyoto Encyclopaedia of Genes and Genomes 2021 (KEGG2021)* human resource; a similar freely available resource.[351-354] This enabled me to obtain an impression based on biological knowledge of the likelihood that shared effects of genes on both the exposure and outcome had generated the association.

5.3 Results (Table 5-1, Table 5-2, and Figures 5-4 to 5-23)

5.3.1 Hypothesis 1: SSD is a causal risk factor for poorer habitual visual acuity – analyses using summary statistics from European samples

I found evidence of a causal effect of SSD on poorer visual acuity based on SSD instruments' association with the outcome using the IVW method (beta=0.024, 95% CI 0.014 to 0.033, $p=9.63 \times 10^{-7}$). The direction of effect was consistent across the other MR methods. The MR-Egger intercept indicated no evidence of pleiotropy (p=0.877) suggesting a true effect, but Cochran's Q statistic showed some heterogeneity (p=0.029). The funnel plot was broadly symmetrical, however (Figure 5-7: Funnel plot for SSD as exposure, poorer habitual visual acuity as outcome in European ancestry sample). MR-PRESSO did not identify outlying SNPs, and IVW results remained significant in single

SNP and leave-one-out analyses, suggesting outliers were not responsible for the association.

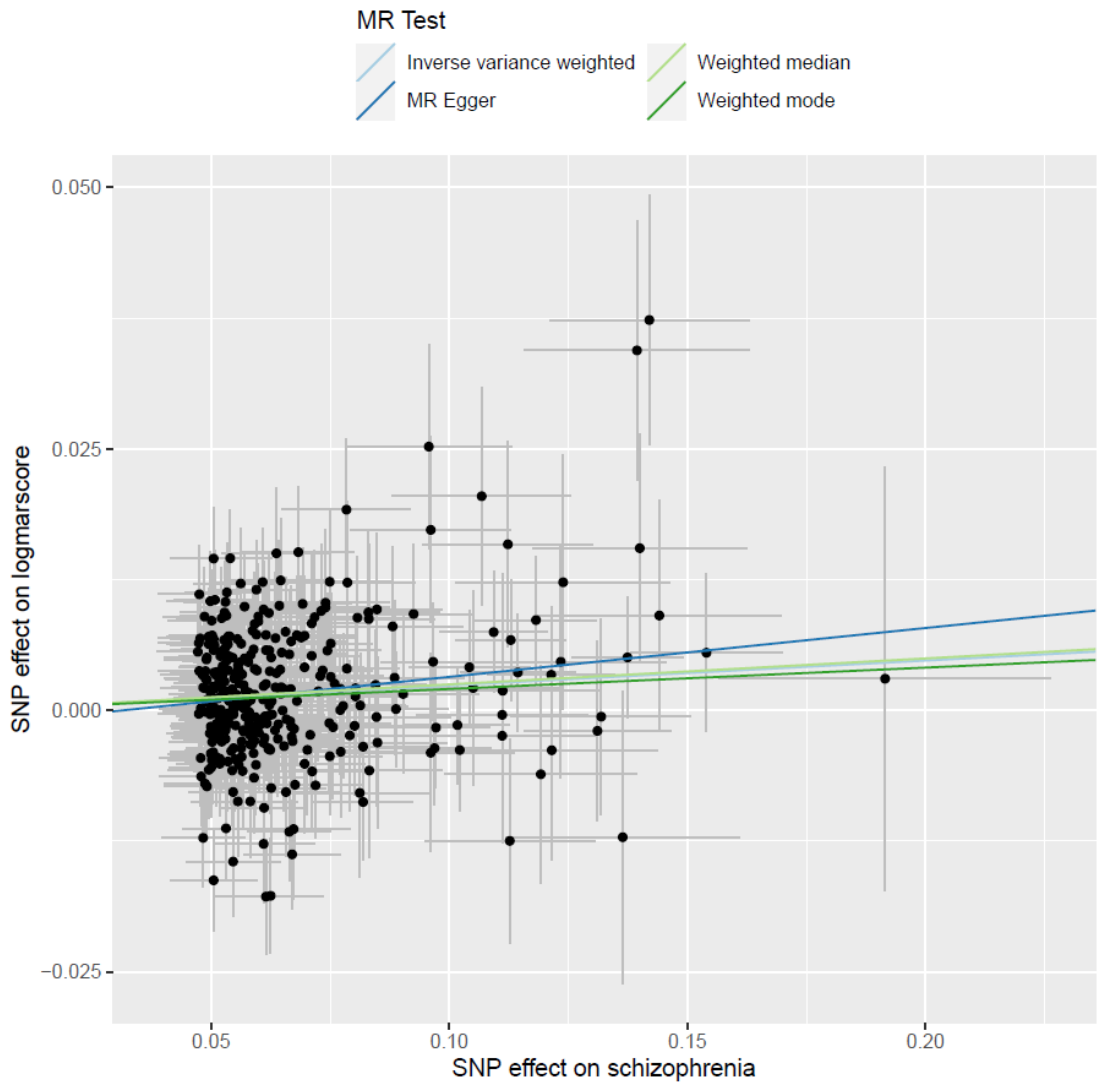

Figure 5-4: SSD as exposure, worse habitual visual acuity (logMAR score) as outcome, European ancestry sample. MR = Mendelian Randomisation; SNP = Single Nucleotide Polymorphism

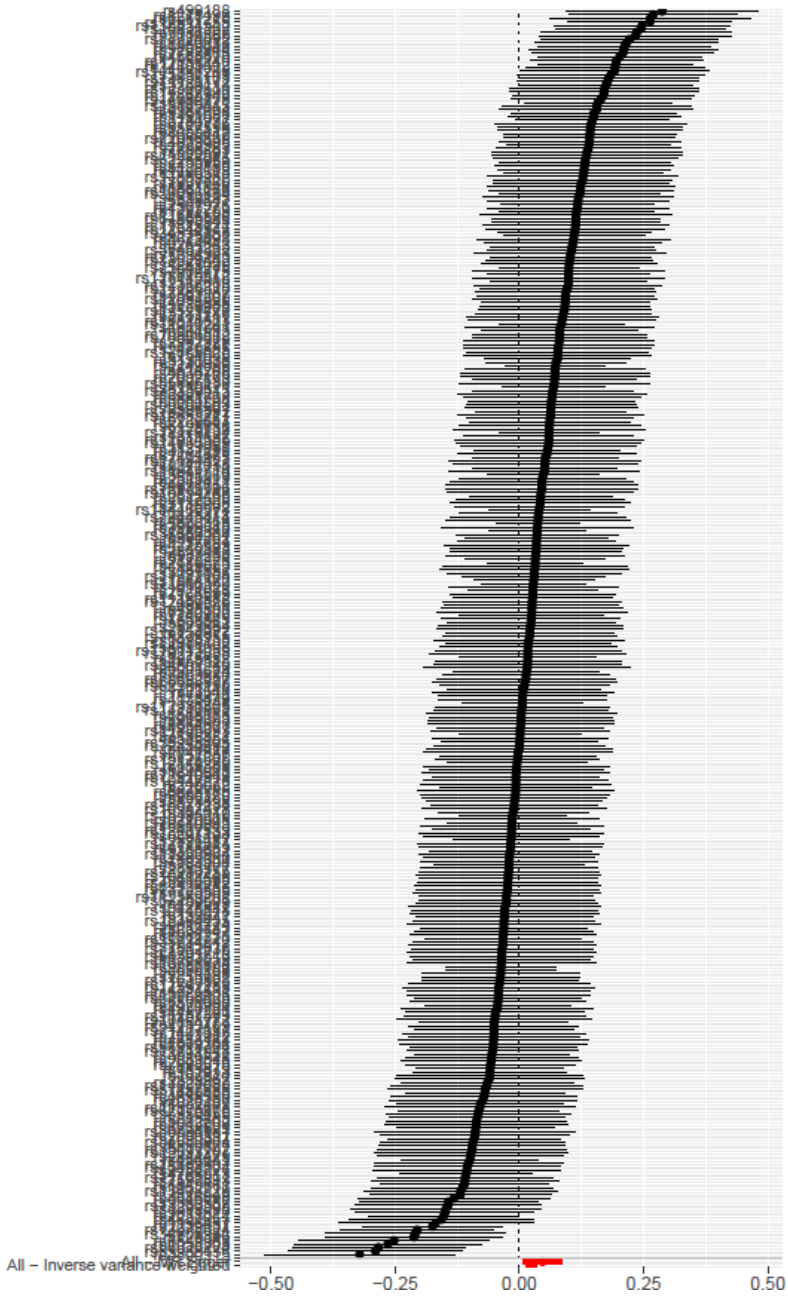

Figure 5-5: Single-SNP Plot for SSD as exposure, poorer habitual visual acuity as outcome in European ancestry sample

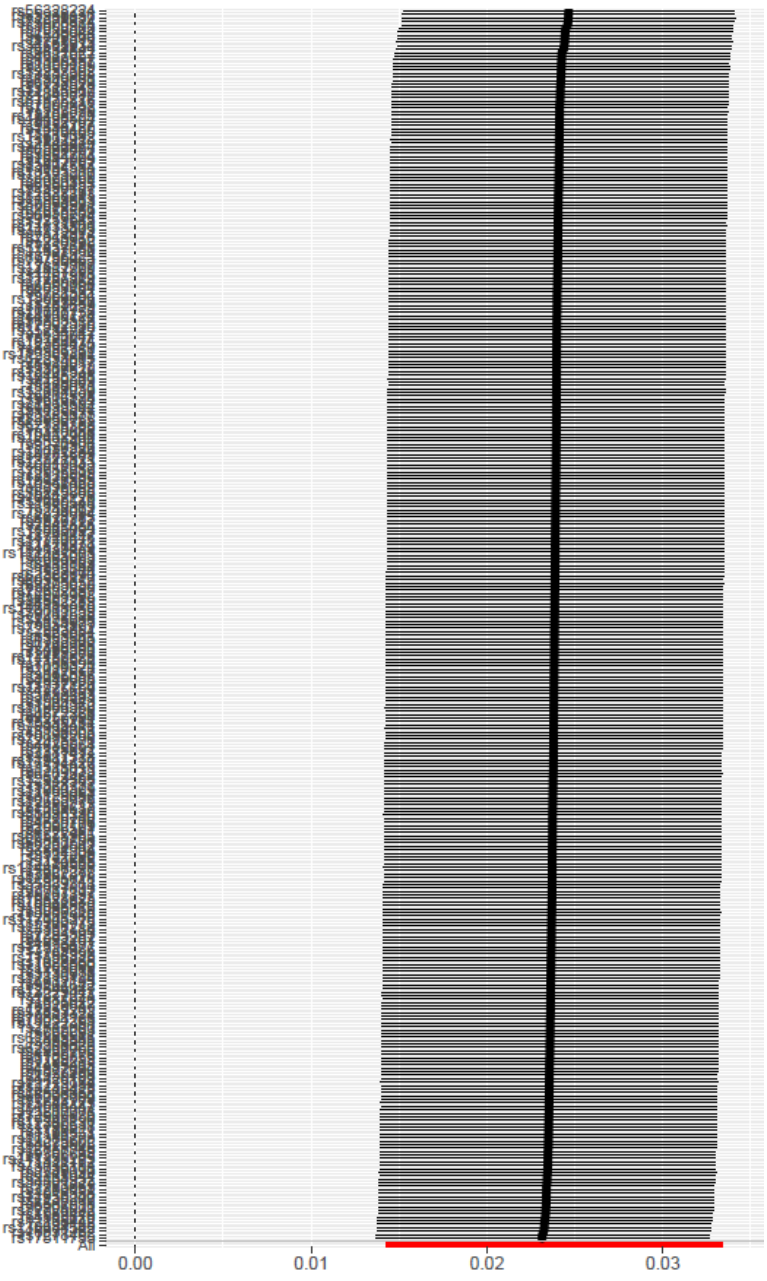

Figure 5-6 Leave-one-out plot for SSD as exposure, poorer habitual visual acuity as outcome in European ancestry sample

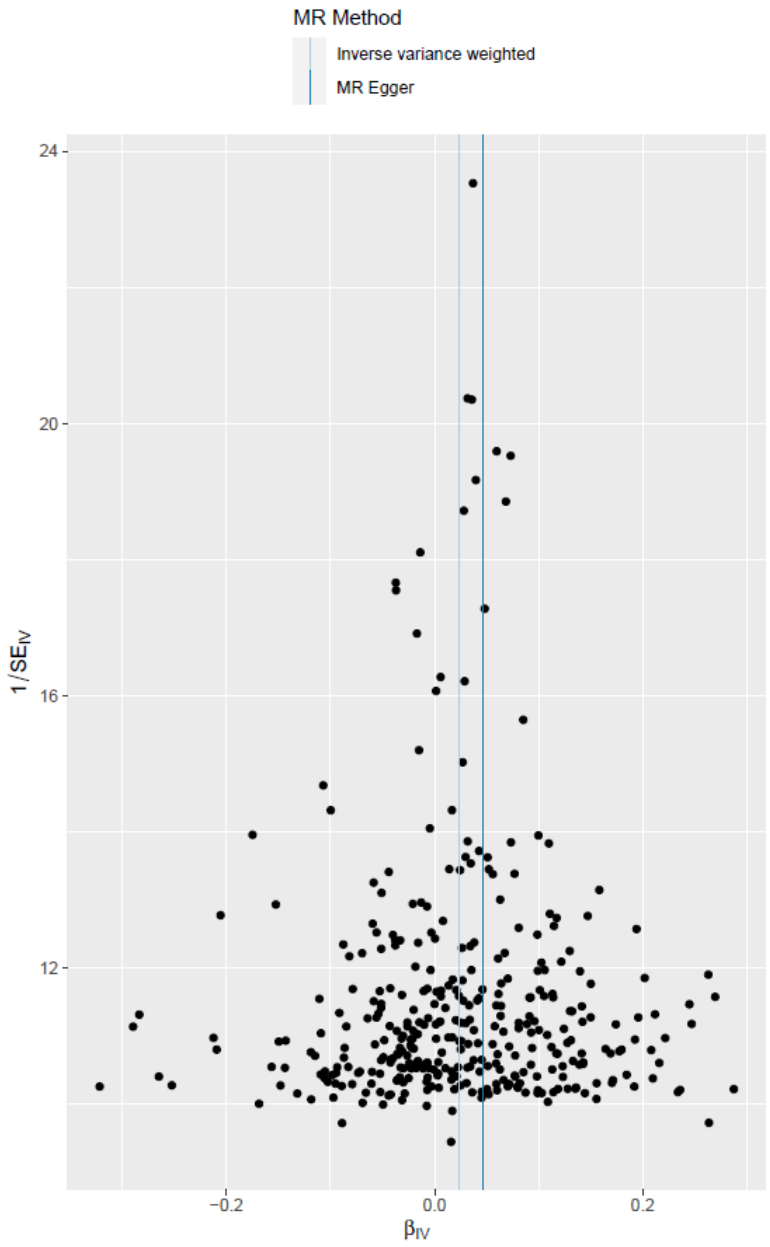

Figure 5-7: Funnel plot for SSD as exposure, poorer habitual visual acuity as outcome in European ancestry sample

5.3.2 Hypothesis 1: SSD is a causal risk factor for poorer habitual visual acuity – analyses using summary statistics from East Asian Samples

The causal estimate for samples with East Asian ancestry was larger (beta=0.186, 95% CI 0.186 to 0.379, p=0.060) and directionally consistent with

the estimate for European ancestry. However, it did not reach the traditional threshold for statistical significance. This may be due to the considerably smaller sample size in people with East Asian ancestry. Notably, the direction of effect was reversed using MR Egger, suggesting an influence from horizontal pleiotropy in the instrument for this analysis, which constituted a much smaller number of SNPs compared to that used in the European samples. The Egger intercept was significant (intercept=0.010, p = 0.019). There was no evidence of heterogeneity on Cochran's Q test (p=0.577), but the funnel plot appeared asymmetrical. MR PRESSO did not identify any outlying SNPs. Single-SNP and leave-one-out plots did not show evidence of association.

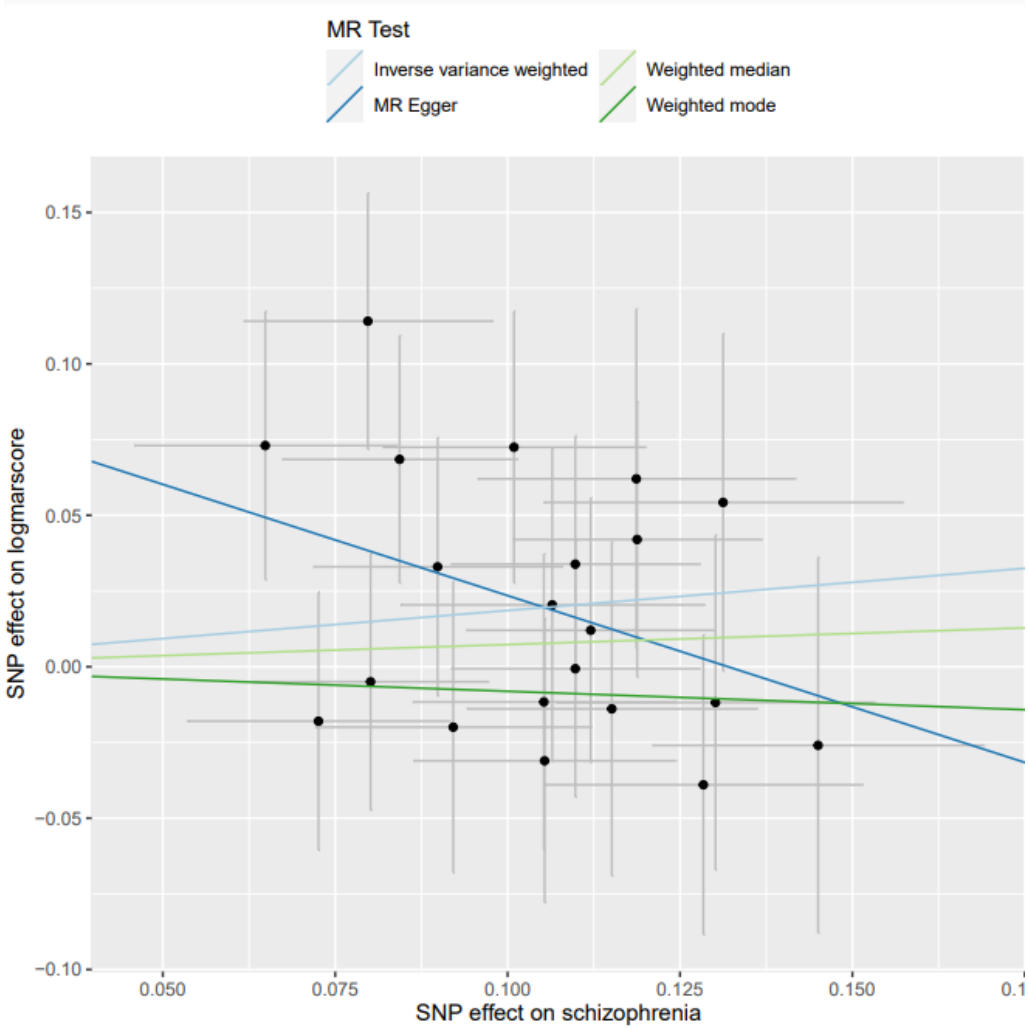

Figure 5-8 Schizophrenia as exposure, habitual visual acuity (logMAR score) as outcome, East Asian ancestry sample; MR = Mendelian Randomisation, SNP = Single Nucleotide Polymorphism

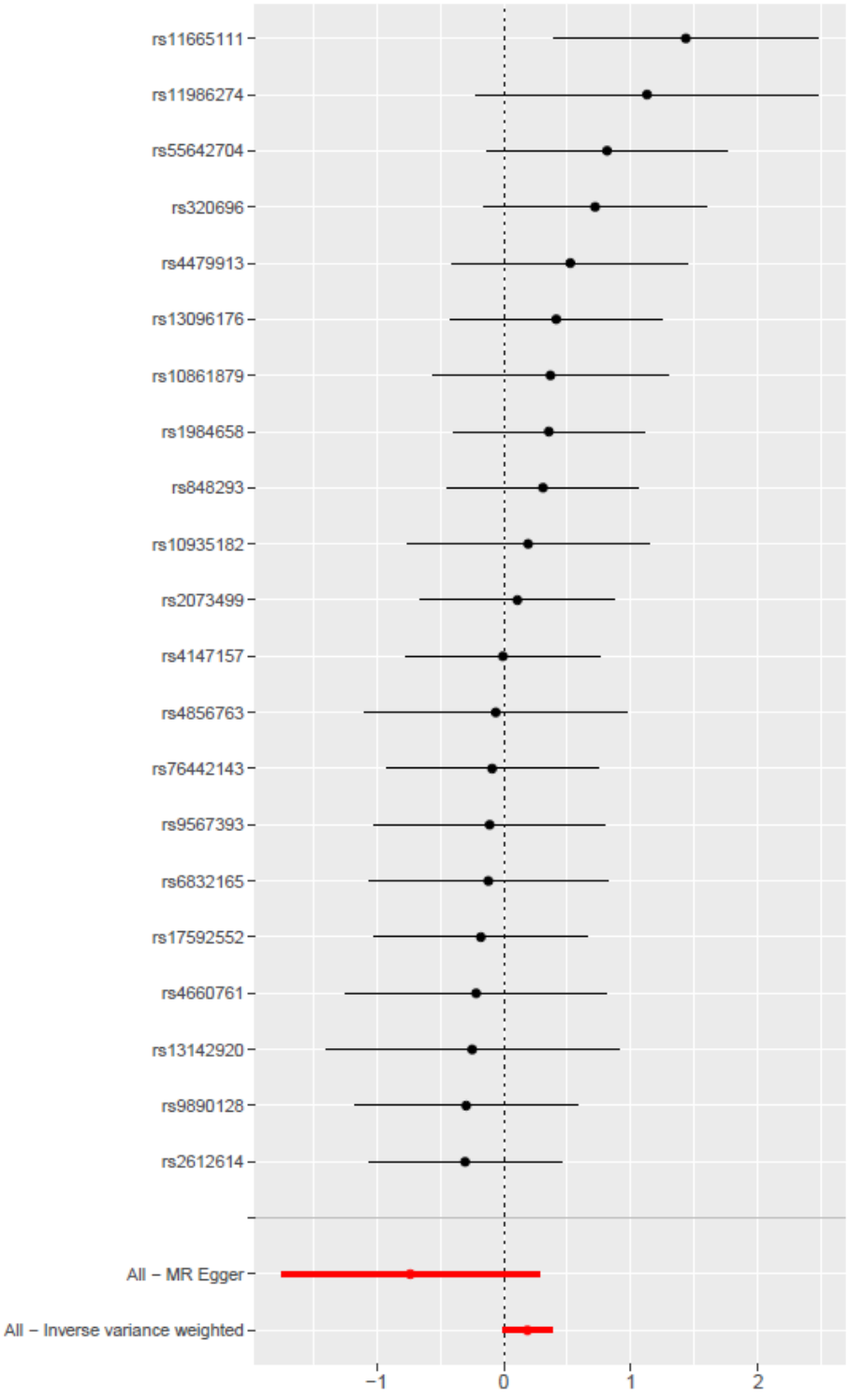

Figure 5-9: Single-SNP plot, SSD as exposure, poorer habitual visual acuity as outcome in East Asian ancestry sample

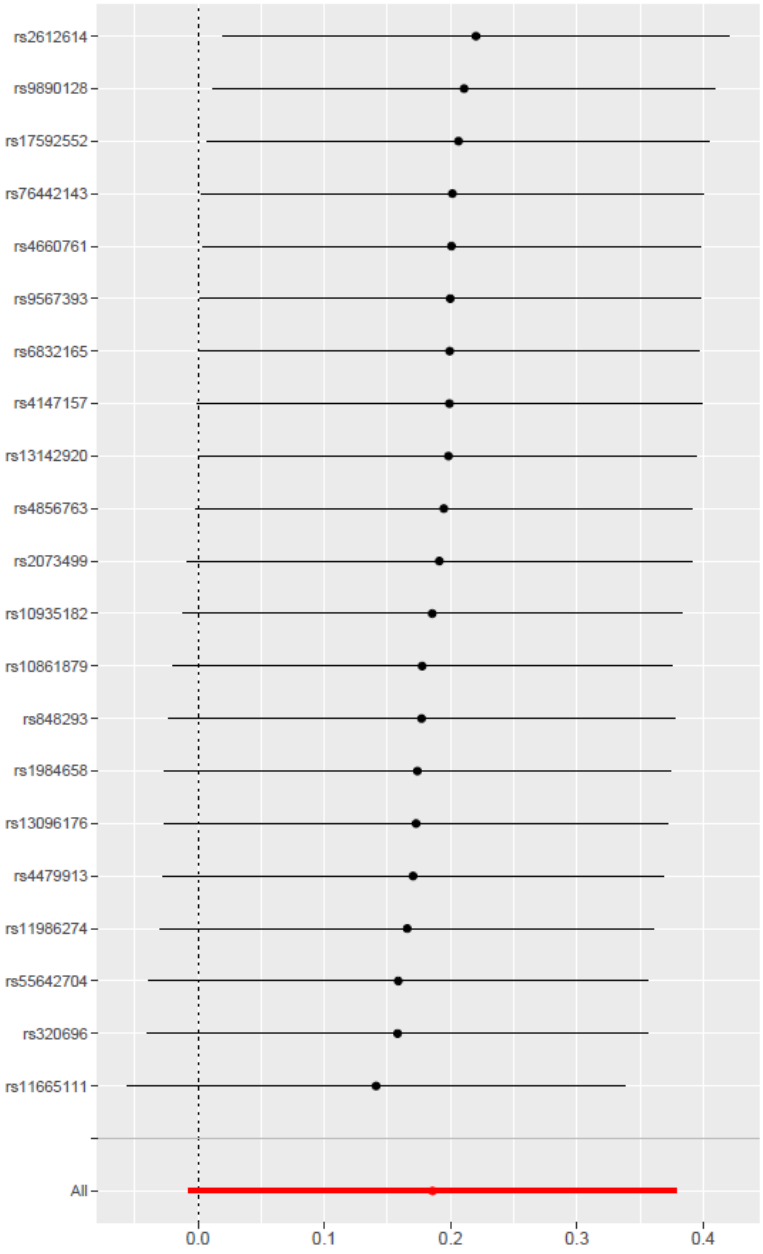

Figure 5-10: Leave-one-out plot: SSD as exposure, poorer habitual visual acuity as outcome in East Asian ancestry sample

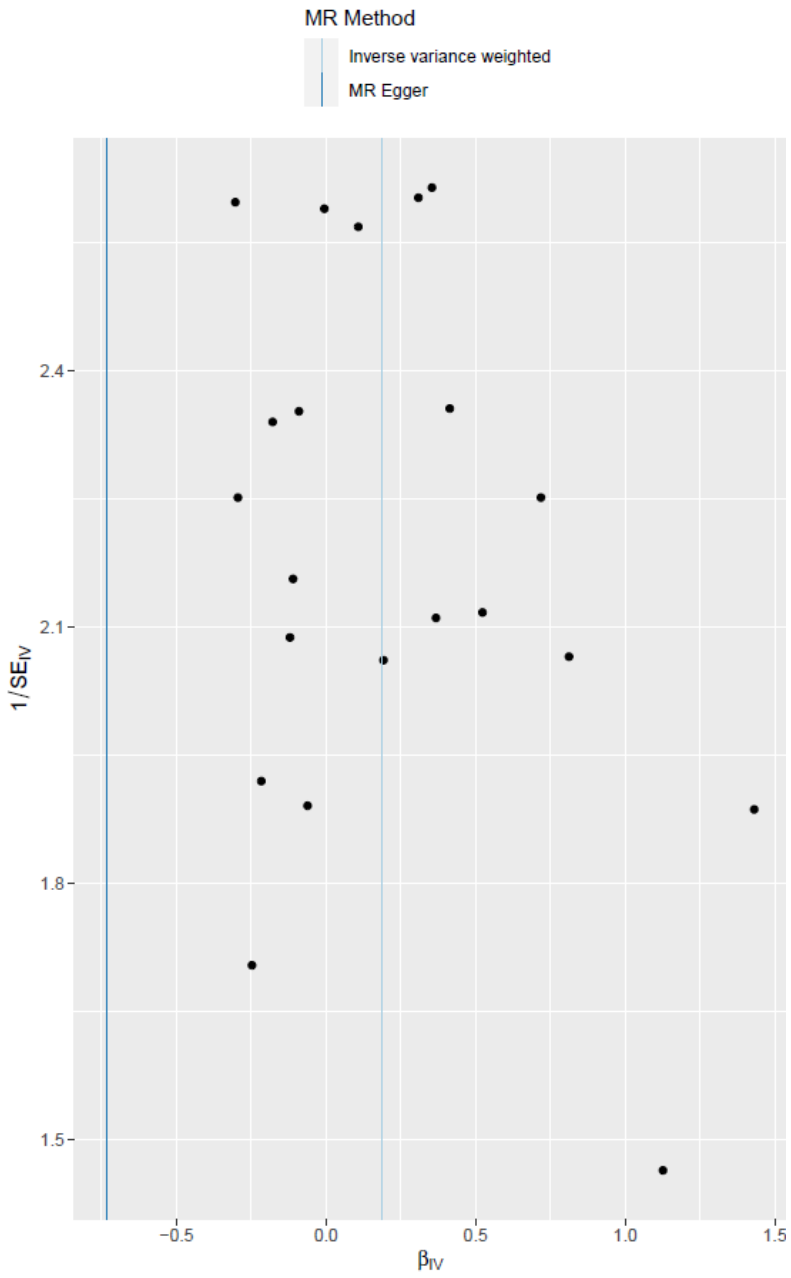

Figure 5-11: Funnel plot: SSD as exposure, poorer habitual visual acuity as outcome in East Asian ancestry sample

5.3.3 Hypothesis 2: Myopia is a causal risk factor for SSD – analyses using summary statistics from European samples

I found no evidence of a causal effect of myopia on SSD risk based on the association of the myopia genetic instruments with the outcome (SSD) (OR=1.00, 95% CI = 0.91 to 1.10, p=0.955). None of the sensitivity MR methods showed a significant causal association between-myopia and SSD. I

found evidence of heterogeneity between the SNPs' causal estimates based on Cochran's Q statistic (p<0.0001), consistent with no causal effect. The MR-Egger intercept did not suggest directional horizontal pleiotropy (p=0.624). The funnel plot was symmetrical, providing further evidence against bias introduced by pleiotropy.[333] Excluding SNPs using MR PRESSO did not change the results (corrected OR 0.98, p=0.526), and the MR PRESSO distortion test P-value was non-significant (0.256), suggesting minimal distortion of results by outlying SNPs. Single-SNP and leave-one-out plots did not show any evidence of association.

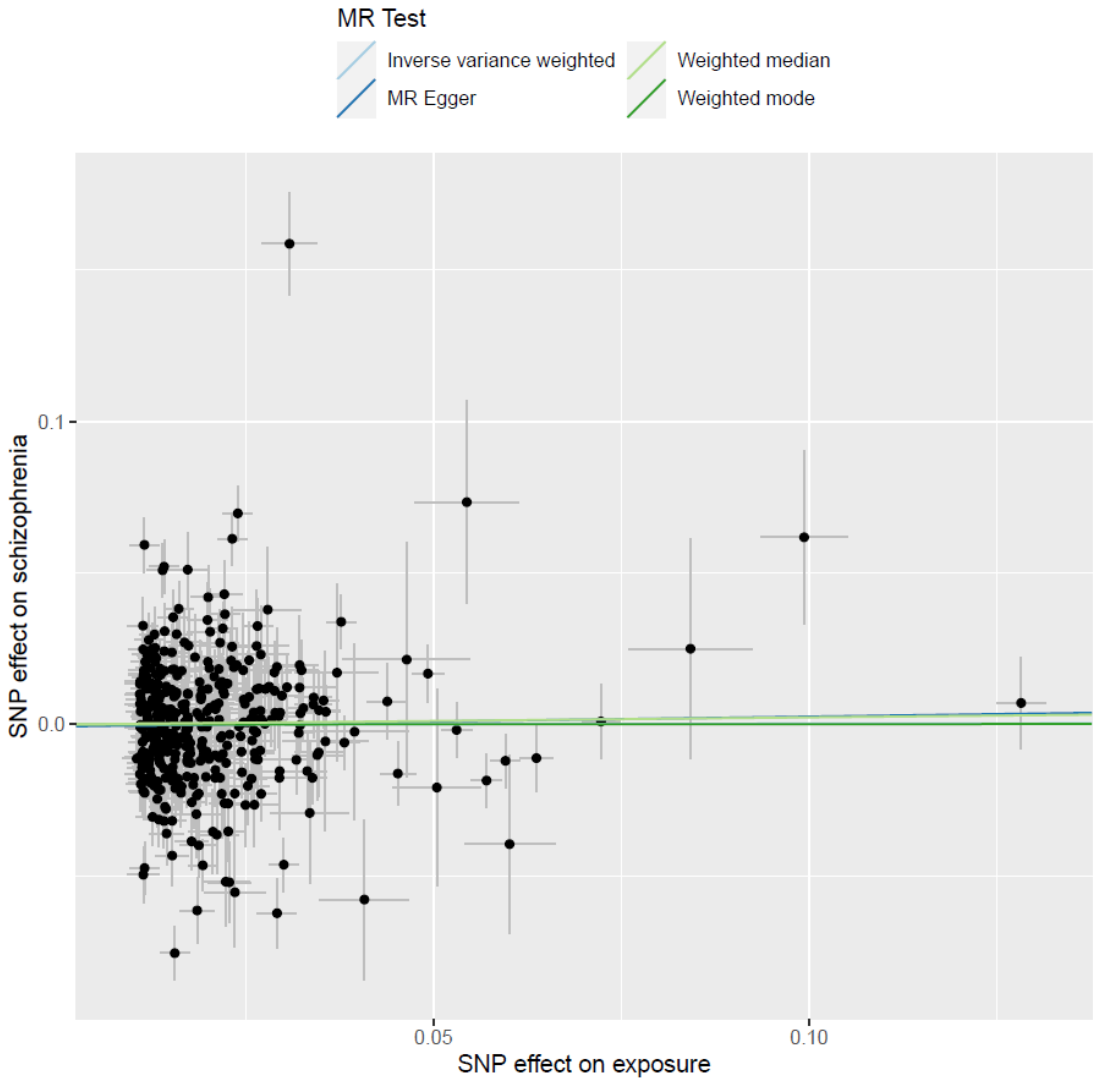

Figure 5-12: Myopia as exposure, SSD as outcome, European ancestry sample. MR= Mendelian Randomisation, SNP = Single Nucleotide Polymorphism

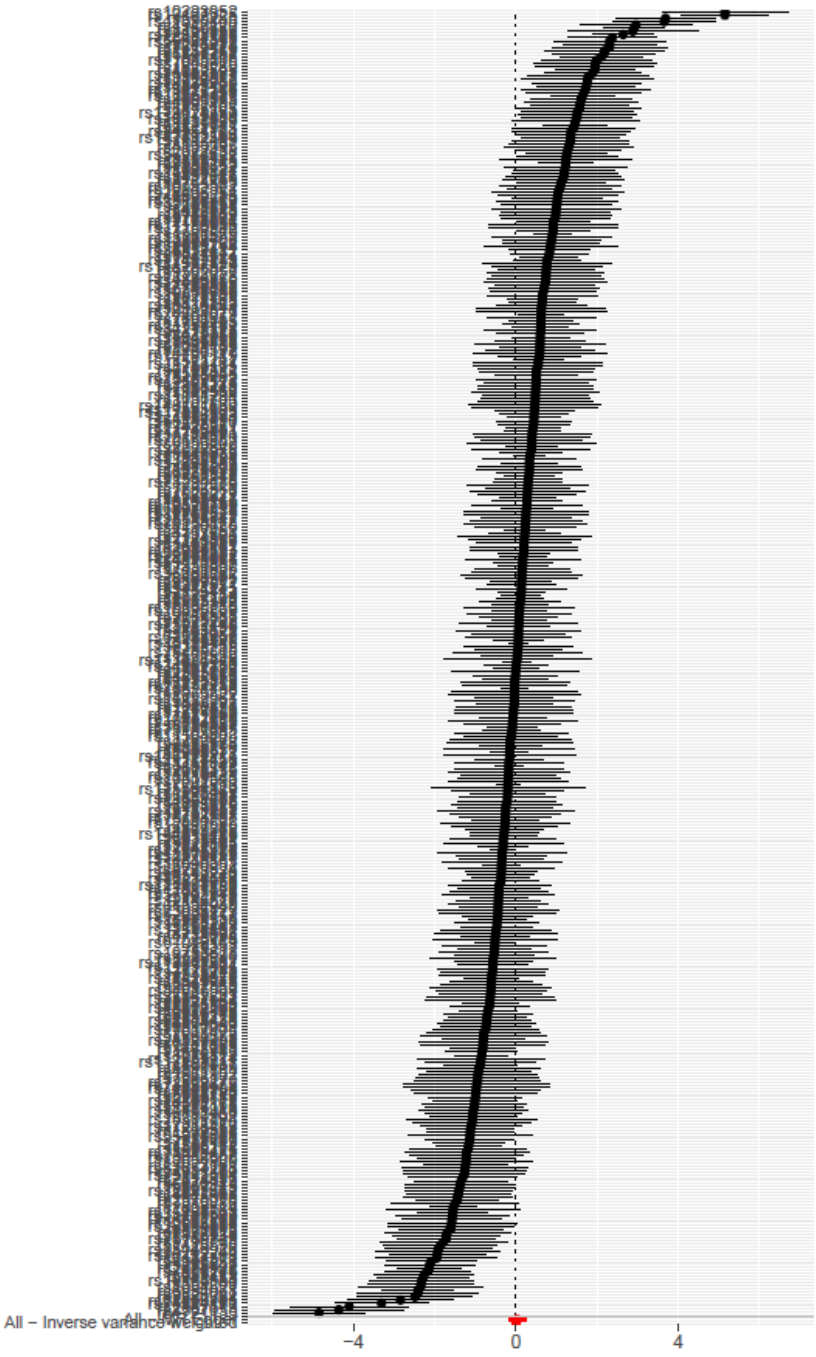

Figure 5-13: Single SNP Plot: Myopia as exposure, SSD as outcome in European ancestry sample.

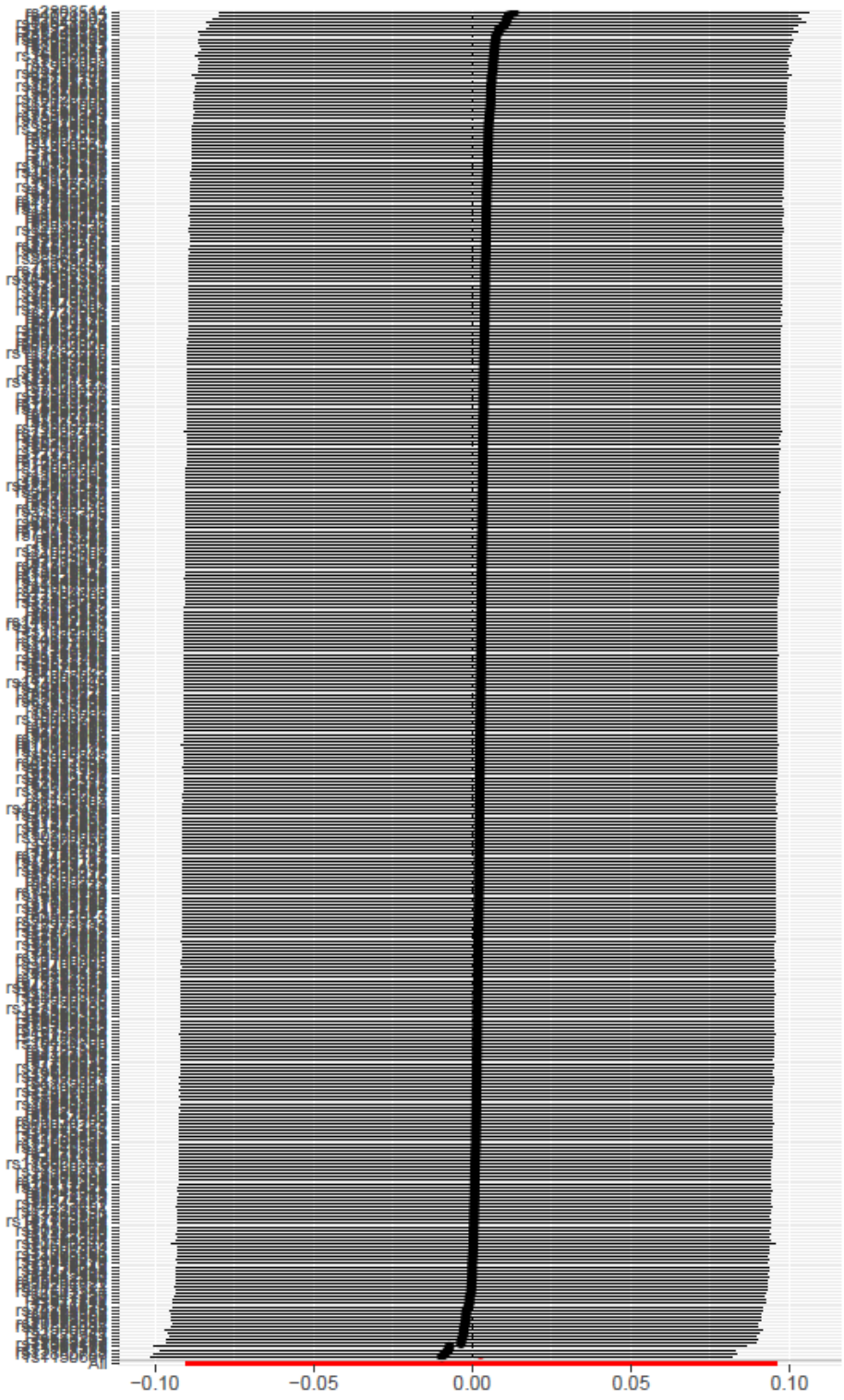

Figure 5-14: Leave-one-out plot: myopia as exposure, SSD as outcome in European ancestry sample

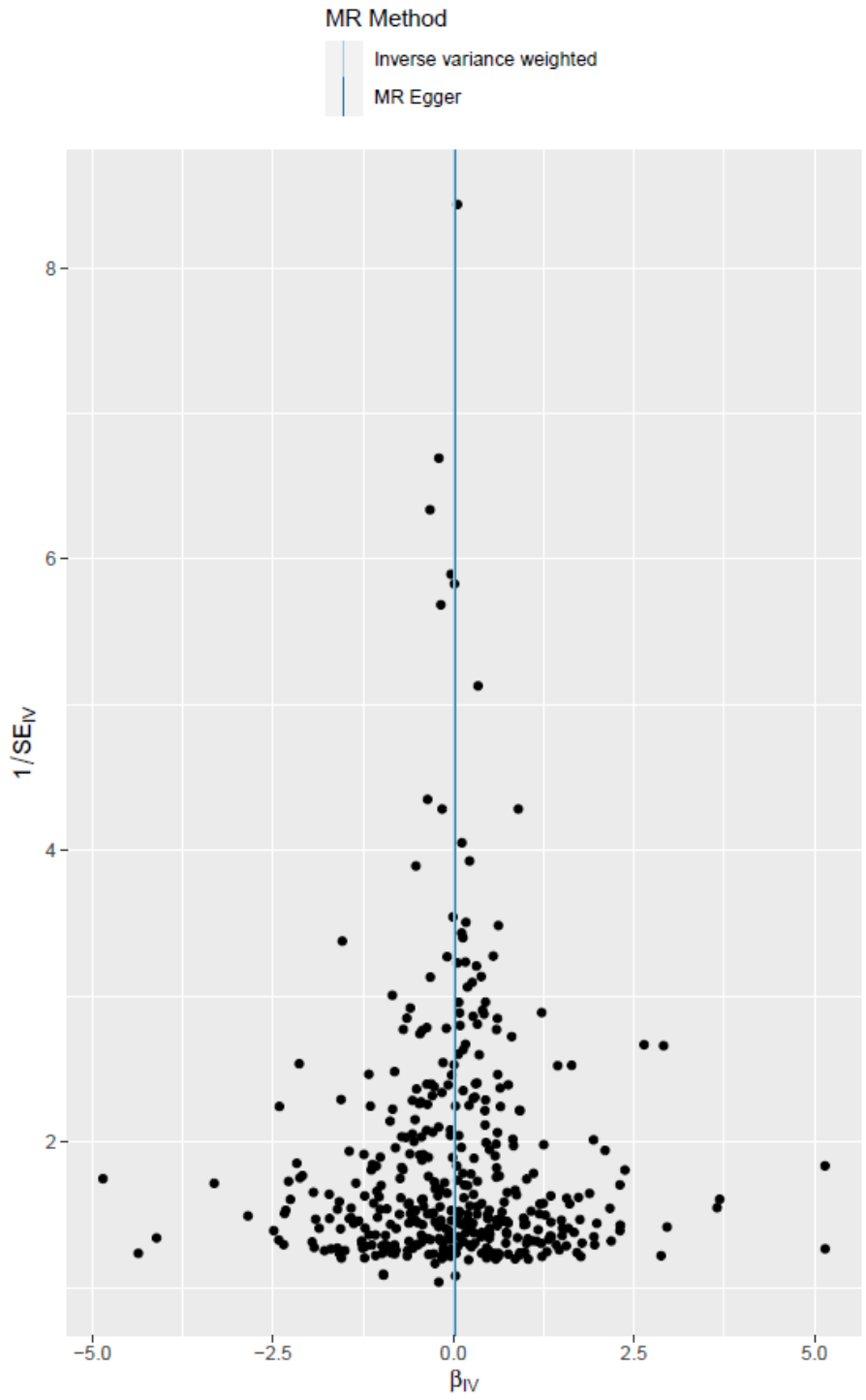

Figure 5-15: Funnel plot: myopia as exposure, SSD as outcome in European ancestry sample

5.3.4 Hypothesis 2: Severe myopia is a causal risk factor for SSD – analyses using summary statistics from East Asian samples

There was also no evidence of association between severe myopia as exposure and SSD as outcome in East Asian participant samples (OR 1.00, 95% CI 0.95 – 1.05, p=0.962), and the same was true in sensitivity analyses. Cochran's Q showed high heterogeneity (p=0.007). There was clear asymmetry of the funnel plot, but the MR Egger intercept did not suggest pleiotropy (p=0.146). Removing outlying SNPs using MR PRESSO also gave a non-significant result (corrected OR 0.97, p=0.269, distortion test P-value 0.639).

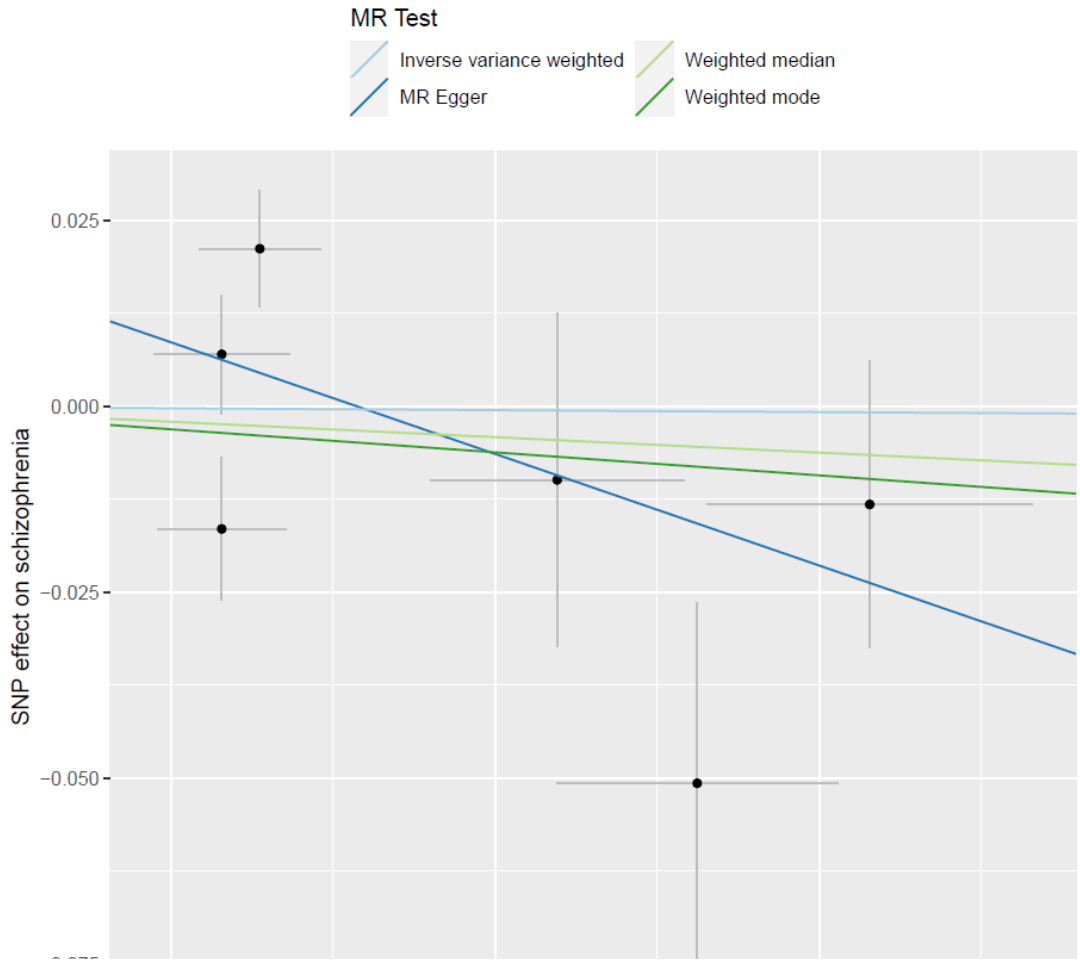

Figure 5-16: severe myopia as exposure, schizophrenia as outcome, East Asian ancestry sample. MR = Mendelian Randomisation, SNP = Single Nucleotide Polymorphism

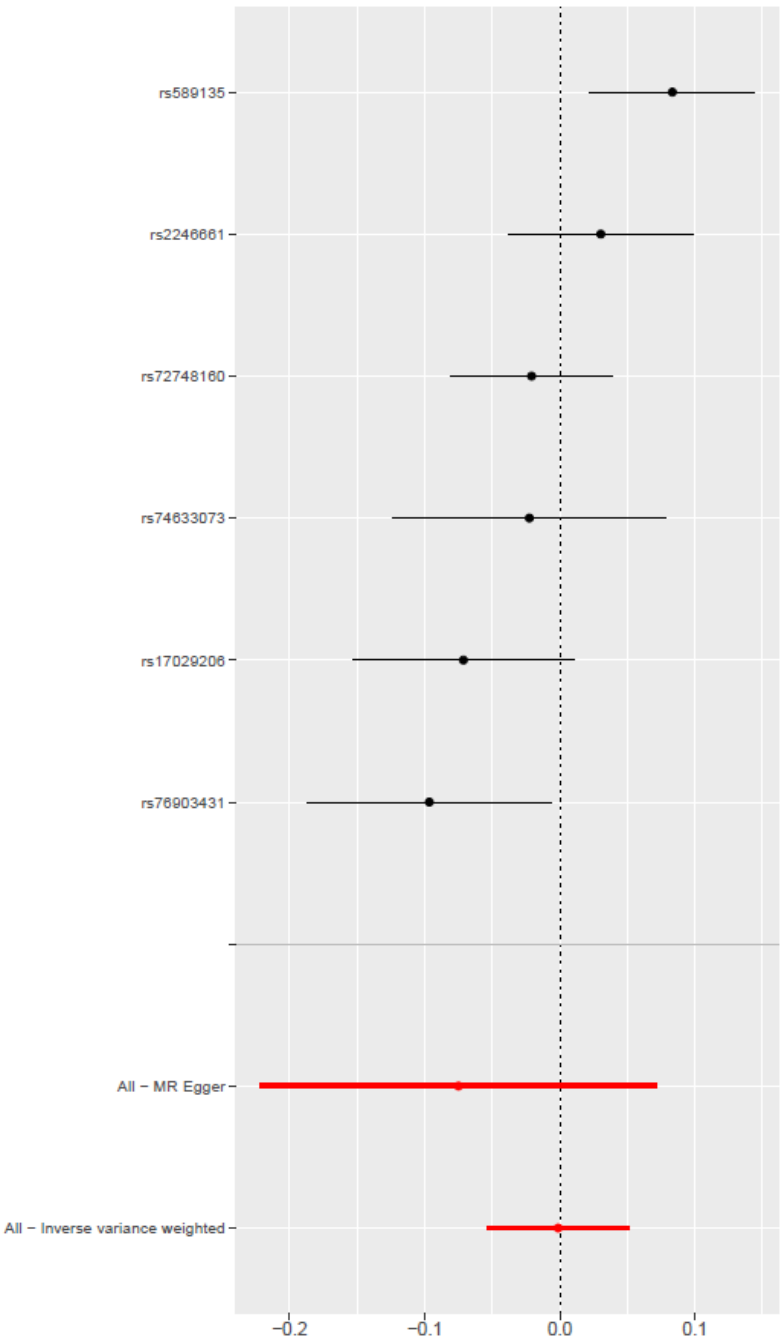

Figure 5-18 Single SNP plot: severe myopia as exposure, schizophrenia as outcome in East Asian ancestry sample

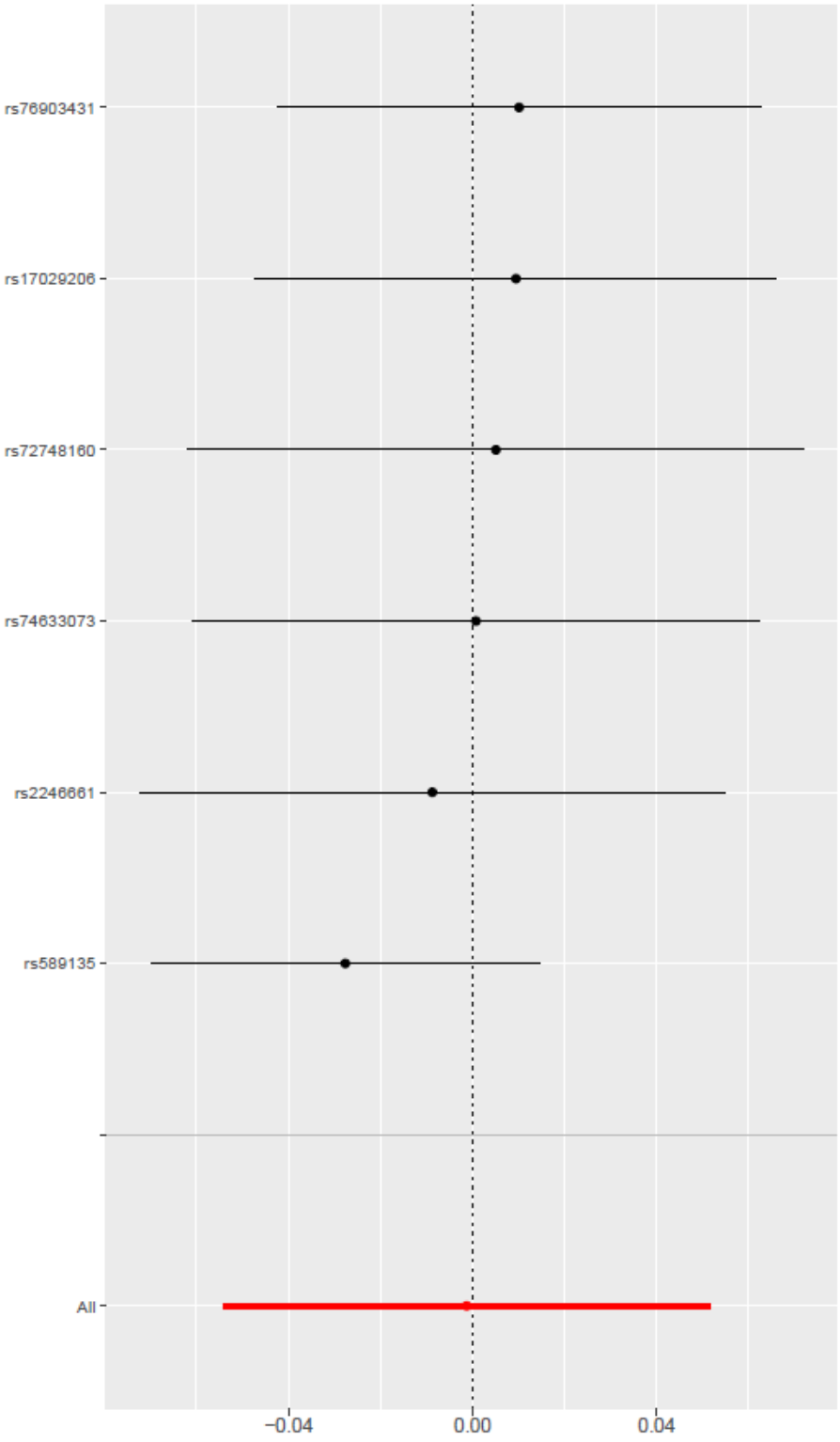

Figure 5-19: Leave-one-out plot: severe myopia as exposure, SSD as outcome in East Asian ancestry sample

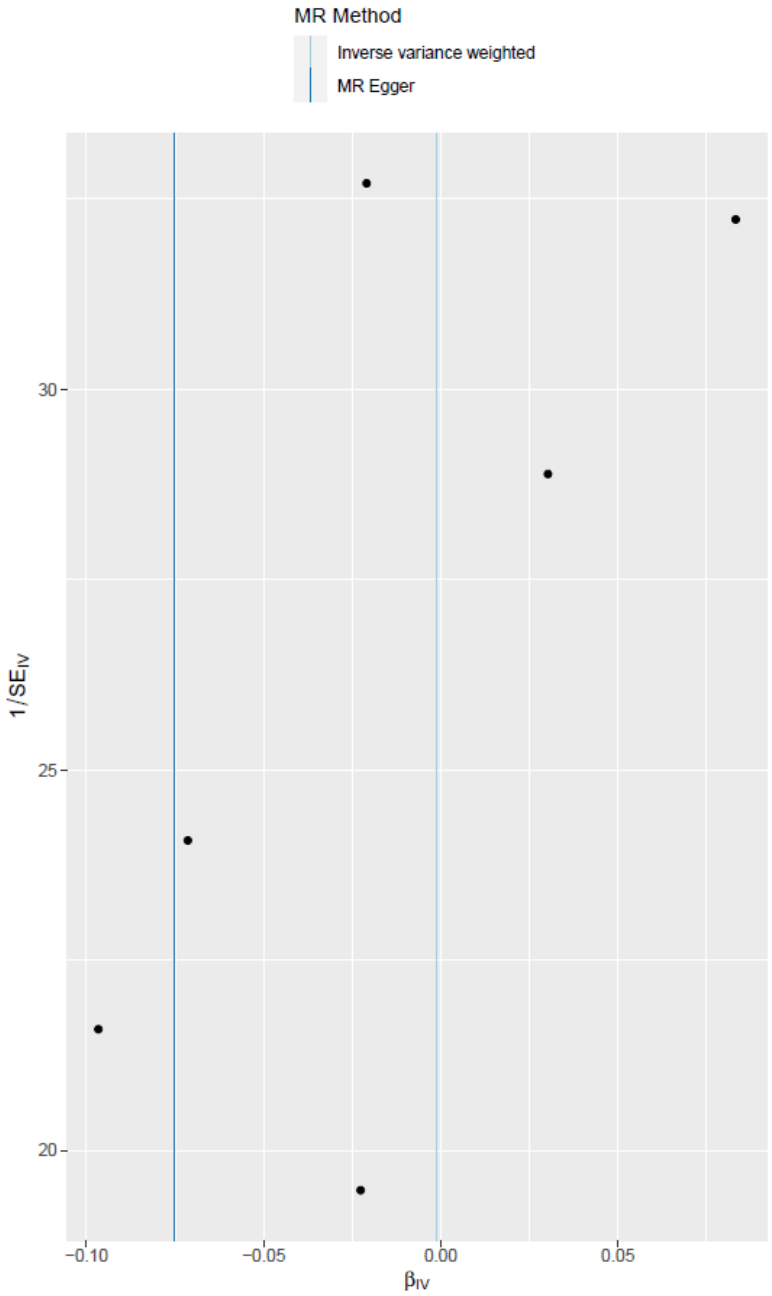

Figure 5-20: Funnel plot: Severe myopia as exposure, SSD as outcome in East Asian ancestry sample

5.3.5 Hypothesis 2: Poorer habitual visual acuity is a risk factor for SSD – analyses using summary statistics from European samples

Consistent with previous analyses, when using continuous logMAR score as the exposure phenotype in a sample of people with European ancestry I found no evidence of an association with SSD as the outcome (OR = 0.99, 95% CI

0.88 – 1.12, p=0.927). Sensitivity analyses did not find evidence of association and consistent with this, Cochran's Q showed high heterogeneity (p<0.0001). There was minor asymmetry of the funnel plot. The MR-Egger intercept showed no evidence of pleiotropy (p=0.808). Removing outlying SNPs using MR PRESSO did not alter results (corrected OR 1.01, p=0.839), and the distortion test was non-significant.

5.3.6 Hypothesis 2: Poorer habitual visual acuity is a risk factor for SSD – analyses using summary statistics from East Asian samples

I similarly found no association between poorer visual acuity and SSD as outcome in East Asian ancestry samples (OR = 0.98, 95% CI 0.95 – 1.01, p=0.179). The MR Egger intercept did not suggest directional horizontal pleiotropy (p=0.371), and Cochran's Q test was non-significant (p=0.418). There was minor asymmetry of the funnel plot. MR PRESSO did not identify outlying SNPs.

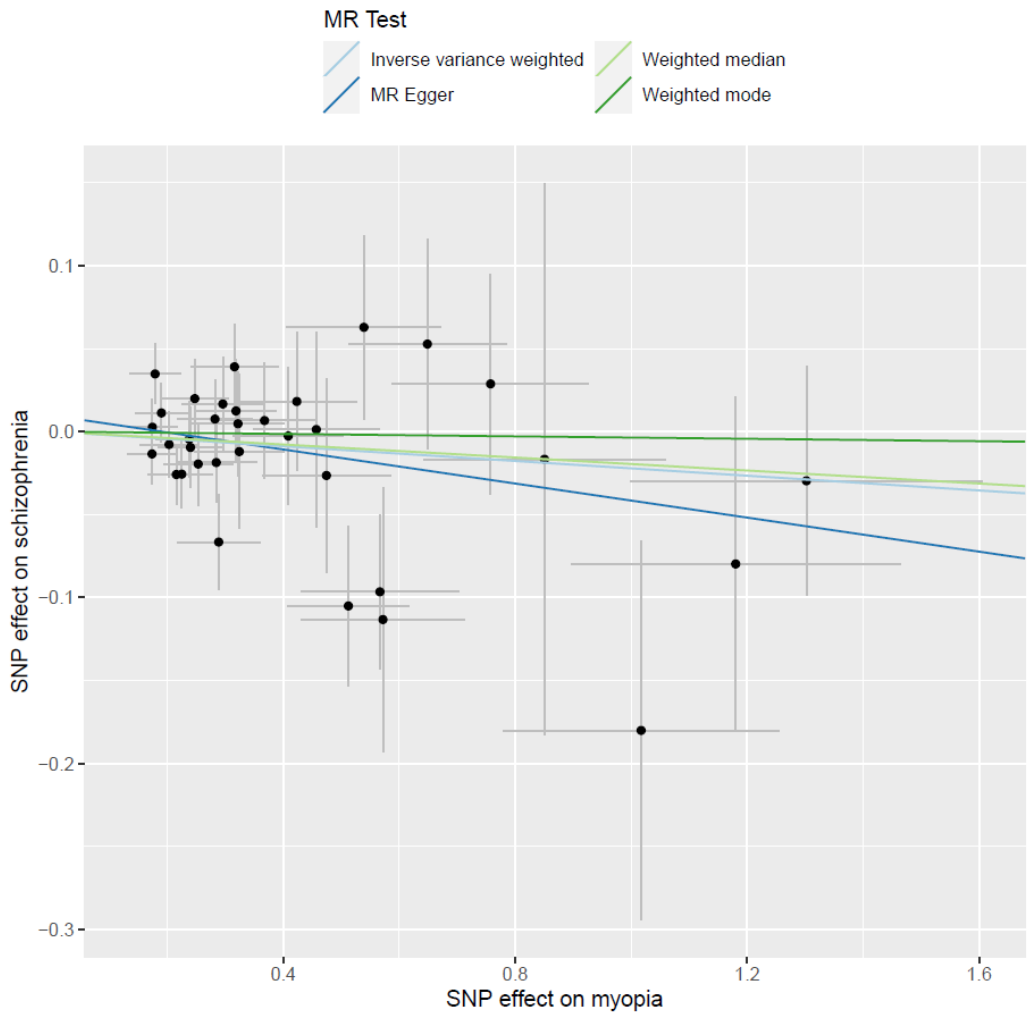

Figure 5-21: Habitual visual acuity (logMAR score) as exposure, SSD as outcome in East Asian ancestry sample. MR = Mendelian Randomisation, SNP = Single Nucleotide Polymorphism

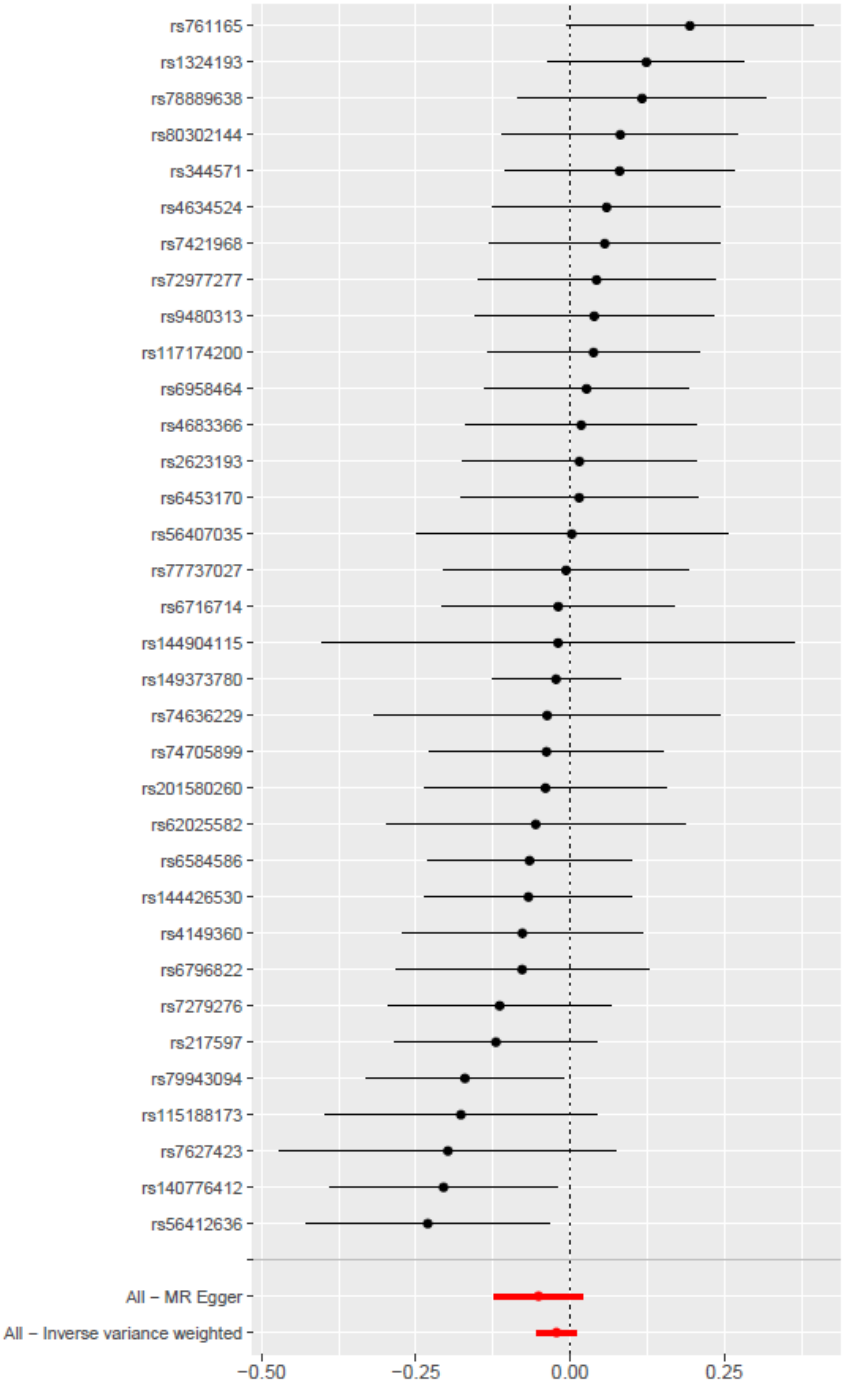

Figure 5-22: Single SNP Plot: habitual visual acuity as exposure, SSD as outcome in East Asian ancestry sample

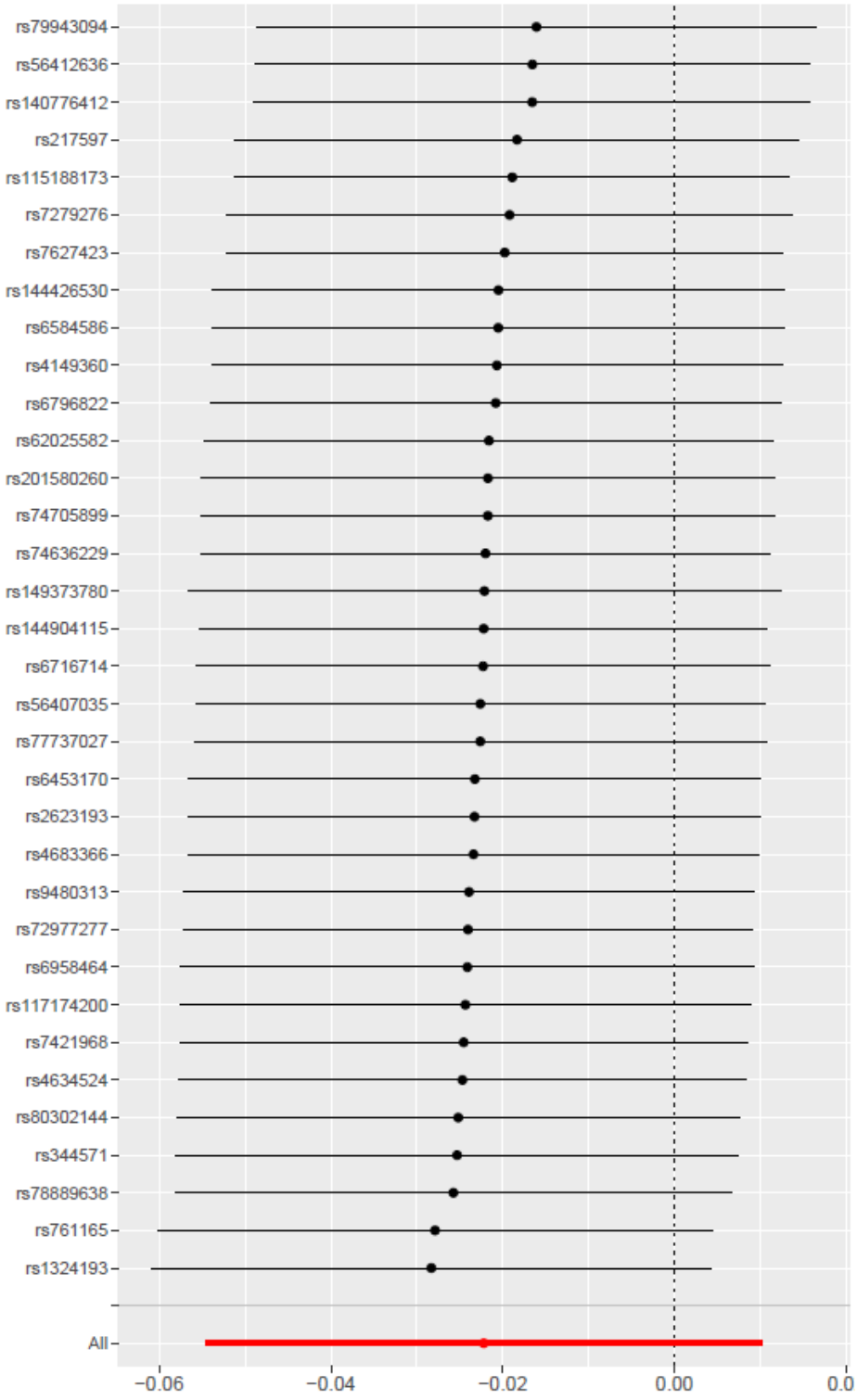

Figure 5-23: Leave-one-out plot: poorer habitual visual acuity as exposure, SSD as outcome in East Asian ancestry sample

5.3.7 Post-Hoc Analysis: SSD is a causal risk factor for non-correction of myopia

To assess whether non-correction of refractive error was a likely route to poorer visual acuity for people with SSD, I also assessed whether SSD was negatively associated with reporting glasses use for myopia. There was evidence of this (OR 0.95, 95% CI 0.920 – 0.974, p=0.0002). Sensitivity methods were consistent with this.

Table 5-1: Mendelian Randomisation: results from analyses to assess for evidence of a causal association between Schizophrenia Spectrum Disorder and Poorer Distance Visual Acuity

MR Method	Number of SNPs	Beta Coefficient [95% CI]	Standard Error	Odds Ratio [95% CI]	P-value
Myopia as exposure, SSD as outcome in European ancestry sample					
Inverse variance weighted	405	0.003 [-0.090 – 0.096]	0.048	1.003 [0.913 – 1.101]	0.955
MR Egger	405	0.033 [-0.177– 0.243]	0.107	1.034 [0.838 – 1.275]	0.757
Weighted median	405	0.001 [-0.124 – 0.126]	0.064	1.001 [0.883 – 1.135]	0.985
Weighted mode	405	0.023 [-0.070 – 0.117]	0.048	1.024 [0.932 – 1.124]	0.625
Myopia as exposure, SSD as outcome in East Asian ancestry sample					
Inverse variance weighted	6	-0.001 [-0.054 – 0.052]	0.027	0.999 [0.947 – 1.053]	0.962
MR Egger	6	-0.075 [-0.222 – 0.072]	0.075	0.928 [0.801 – 1.074]	0.373
Weighted median	6	-0.010 [-0.055 – 0.034]	0.023	0.990 [0.947 – 1.035]	0.648
Weighted mode	6	-0.015 [-0.096 – 0.065]	0.041	0.985 [0.909 – 1.067]	0.721
Poorer habitual visual acuity as exposure, SSD as outcome in European ancestry sample					
Inverse variance weighted	117	-0.006 [-0.125 – 0.114]	0.061	0.994 [0.882 – 1.121]	0.927
MR Egger	117	0.114 [-0.181 – 0.410]	0.151	1.121 [0.834 – 1.507]	0.450
Weighted median	117	0.032 [-0.105 – 0.169]	0.070	1.033 [0.900 – 1.184]	0.647
Weighted mode	117	0.191 [-0.239 – 0.621]	0.219	1.210 [0.787 – 1.861]	0.386
Poorer habitual visual acuity as exposure, SSD as outcome in East Asian ancestry sample					
Inverse variance weighted	34	-0.022 [-0.055 - 0.010]	0.017	0.976 [0.947 – 1.010]	0.179
MR Egger	34	-0.051 [-0.124 - 0.021]	0.037	0.950 [0.883 – 1.022]	0.176
Weighted median	34	-0.020 [-0.068 – 0.029]	0.025	0.980 [0.934 – 1.029]	0.426
Weighted mode	34	-0.004 [-0.088 – 0.081]	0.043	0.996 [0.916 – 1.084]	0.933
SSD as Exposure, poorer habitual visual acuity (logMAR score) as outcome in European ancestry sample					
Inverse variance weighted	355	0.024 [0.014 – 0.033]	0.005	-	<0.001

MR Egger	355	0.047 [0.007 – 0.087]	0.022	-	0.022
Weighted median	355	0.025 [0.012 – 0.038]	0.007	-	<0.001
Weighted mode	355	0.020 [-0.017 – 0.058]	0.019	-	0.290
SSD as exposure, poorer habitual visual acuity (logMAR) score as outcome in East Asian ancestry sample					
Inverse variance weighted	21	0.186 [-0.008 – 0.379]	0.099	-	0.060
MR Egger	21	-0.735 [-0.174 – 0.277]	0.516	-	0.171
Weighted median	21	0.0732 [-0.182 – 0.328]	0.130	-	0.574
Weighted mode	21	-0.081 [-0.533 – 0.371]	0.231	-	0.729
SSD as Exposure, myopia as outcome in European ancestry sample					
Inverse variance weighted	221	-0.055 [-0.084 - -0.026]	0.015	0.947 [0.920 – 0.974]	<0.001
MR Egger	221	-0.239 [-0.353 - -0.125]	0.058	0.787 [0.703 – 0.882]	<0.001
Weighted median	221	-0.094 [-0.127 - -0.062]	0.017	0.910 [0.880 – 0.940]	<0.001
Weighted mode	221	-0.144 [-0.222 - -0.066]	0.040	0.866 [0.801 – 0.936]	<0.001

5.3.8 Dental Caries

There was a negative association between SSD as exposure and dental caries recorded in hospital records as outcome using identical methods to those used to test hypothesis 2 (OR = 0.948, 95% CI 0.903 to 0.995, p=0.032). Sensitivity analyses showed consistent direction of effect.

Table 5-2: Mendelian Randomisation results from comparison analysis assessing for a causal association between Schizophrenia spectrum disorder and dental caries

MR Method	Number of SNPs	Beta Coefficient [95% CI]	Standard Error	Odds Ratio [95% CI]	P-value
SSD as exposure, dental caries as outcome in European ancestry sample					
Inverse variance weighted	322	-0.053 [-0.102 – -0.005]	0.025	0.948 [0.903 – 0.995]	0.032
MR Egger	322	-0.321 [-0.520 – -0.122]	0.101	0.725 [0.595 – 0.885]	0.002
Weighted median	322	-0.070 [-0.141 – 0.000]	0.036	0.932 [0.869 – 1.000]	0.050
Weighted mode	322	-0.154 [-0.370 – 0.062]	0.110	0.857 [0.690 – 1.064]	0.162

5.3.9 Gene Function

As an association was found with the outcome of poorer visual acuity when SSD was the exposure in European ancestry samples, I used the *FUMA* and *enrichr* platforms to retrieve known functions of genes used in the instrument for this analysis. This identified that instrumental SNPs used to represent SSD were in genes with functions including neuronal differentiation, neurogenesis, myeloid cell differentiation, long-term synaptic depression and regulation of synaptic plasticity. Associated pathways suggested that these genes could have many actions including on long-term potentiation, the cholinergic synapse, glutamatergic synapse, and dopaminergic synapse, all of which could plausibly impact vision and visual processing as well as cognitive function in SSD. The top 50 associated pathways of genes are shown in the table below.

Table 5-3: Known functions and pathways of SSD instrument genes: Top 50 Pathways

Term	Adjusted P-value	Odds Ratio
GnRH secretion	0.025	5.480
Cortisol synthesis and secretion	0.357	4.027
Adherens junction	0.385	3.649
Aldosterone synthesis and secretion	0.385	2.966
Glyoxylate and dicarboxylate metabolism	0.385	5.116
Long-term potentiation	0.385	3.276
Cholinergic synapse	0.385	2.541
GnRH signaling pathway	0.385	2.712
Circadian entrainment	0.385	2.591
Phosphatidylinositol signaling system	0.385	2.591
Spinocerebellar ataxia	0.385	2.240
Arrhythmogenic right ventricular cardiomyopathy	0.385	2.813
cGMP-PKG signaling pathway	0.385	2.126
cAMP signaling pathway	0.385	1.965
Endometrial cancer	0.385	3.138
RNA degradation	0.385	2.736
Mannose type O-glycan biosynthesis	0.385	4.981
Protein export	0.385	4.981
Phospholipase D signaling pathway	0.385	2.159
Long-term depression	0.385	3.024
Parathyroid hormone synthesis, secretion and action	0.423	2.355
Cushing syndrome	0.423	2.055
Dopaminergic synapse	0.423	2.149
Axon guidance	0.423	1.939
Gap junction	0.423	2.435
Alzheimer disease	0.423	1.615
Rap1 signaling pathway	0.423	1.844
Estrogen signaling pathway	0.427	2.065
Glutamatergic synapse	0.427	2.178
Renal cell carcinoma	0.427	2.597
Cocaine addiction	0.439	2.953
Growth hormone synthesis, secretion and action	0.473	2.080
Huntington disease	0.512	1.600
Cell cycle	0.529	1.990
Adrenergic signaling in cardiomyocytes	0.529	1.875
Neuroactive ligand-receptor interaction	0.542	1.535
Oocyte meiosis	0.569	1.908
Selenocompound metabolism	0.569	4.421

MAPK signaling pathway	0.596	1.542
ErbB signaling pathway	0.615	2.076
Various types of N-glycan biosynthesis	0.615	2.765
Pathways of neurodegeneration	0.615	1.391
Taste transduction	0.615	2.050
Glycine, serine and threonine metabolism	0.615	2.690
Human T-cell leukemia virus 1 infection	0.615	1.592
GABAergic synapse	0.649	1.977
Hypertrophic cardiomyopathy	0.657	1.954
Dilated cardiomyopathy	0.736	1.824
Type II diabetes mellitus	0.736	2.314

5.4 Discussion

5.4.1 Main Findings

I found no evidence to support a causal role of myopia in the development of SSD. Not only was there no evidence, but the confidence intervals were narrow and did not include the estimated odds ratios found in my meta-analysis, or the longitudinal study of ALSPAC data. This would therefore appear to clearly refute the hypothesis that visual impairment in the form of myopia is a causal risk factor for SSD, although there may be caveats to this which I will discuss further below.

Conversely, I did find evidence that SSD is a casual risk factor for poorer visual acuity in people of European ancestry. To my knowledge, this has not previously been tested in longitudinal observational studies. I did not replicate this finding in analyses based on people of East Asian ancestry, which is likely due to the smaller samples used to generate summary statistics in this group and smaller number of SNPs identified giving lower power to detect an association. The point estimate in this analysis was however still consistent with an association.

The negative association with dental caries initially seemed to go against my hypothesis that the association was driven by neglect of overall healthcare in individuals with SSD, as I had anticipated a positive association driven by non-receipt of dental care. On reviewing this however, the negative association with an outcome based on healthcare records diagnosis might occur if people with SSD are less likely to receive healthcare attention and to have a diagnosis recorded, which would support reduced access to optical care as a plausible mechanism. The finding that SSD was associated with lower odds of using glasses for myopia further suggests that non-correction of refractive error is a mechanism contributing to the association.

I cannot exclude the possibility that the association was driven by shared actions of genes on the brain and the eye; particularly as the retina is an extension of the central nervous system, and our instrument SNPs are

associated with various neuronal functions.[23] 'Causation' in this case might therefore refer to SSD and poorer visual acuity sharing some genetic influence. Nevertheless, it might be expected that the associations I found in this study were bidirectional if this was the full explanation. It is possible however, that the neuropathology of SSD and related illnesses also affects the eye causing poorer visual acuity, and I will consider this in greater detail in the next chapter. A further possibility is that poorer visual processing in SSD leads to poorer performance on eyesight testing, without the structure or function of the eye itself being affected.

5.4.2 Strengths and Limitations

I tested the effect of myopia on SSD risk, and the converse, using a methodology not previously applied to this question. In doing so, I was able to exclude reverse causation in each analysis and reduce the influence of confounding from environmental variables. The SNPs I used in European samples were credible instruments due to their strong associations with the exposures in meta-analyses and replication samples, and numerous recognised biological pathways to the exposures.

There are however limitations to my methodology. As discussed, the inherent assumption in Mendelian Randomisation of no directional horizontal pleiotropy cannot be proven with absolute certainty. Although concern typically relates to false associations being driven by pleiotropy, particularly effects of SNPs on confounders, pleiotropy can also reduce detection of true positive associations.[295] This is relevant to the lack of association found when myopia or visual acuity was the exposure and SSD the outcome. An example of a possible negative confounder in the genetic relationship between myopia and SSD might be intelligence.[54] However, the large number of SNPs used in the analysis and the lack of evidence of pleiotropy in MR-Egger, weighted-median and weighted-mode analyses goes against this type of pleiotropy having nullified a true association. Pleiotropy could have affected the associations where SSD was the exposure and visual acuity the outcome, but again, sensitivity analyses were not suggestive of this, except in the smaller analysis

in East Asian participants where no statistical association was initially found. There was evidence of heterogeneity in the association between SSD as exposure and poorer logMAR score in Europeans, but as sensitivity analyses did not suggest directional pleiotropy, it seems likely that any horizontal pleiotropy contributing to this was balanced.

Sample overlap warrants mention, as it can bias results towards the null in two sample MR.[355] I have aimed to exclude this where possible, by using international rather than UK samples alongside the UK Biobank. Also, as SSD is a relatively rare condition, it is unlikely that many cases would be present in the other studies.

Weak instrument strength is another possible source of bias. Where instruments are weak predictors of the exposure phenotype, there is a higher chance that their influence on confounders will outweigh the association between exposure and outcome and drive the MR results.[356] The most robust way to avoid this appears to be to use large samples in identifying SNPs and to conduct multiple sensitivity analyses, which I have done as far as possible.[356] Although the high threshold of significance for each SNP reduces the likelihood that weak instrument bias has occurred in European samples, I could not avoid using small numbers of SNPs with a more lenient threshold in East Asian samples due to smaller available GWASs, and this remains a limitation of this study. It is also a likely reason why the association was seen in European ancestry but not East Asian ancestry samples, although this does not constitute weak instrument bias which refers to a false positive assocation.

I have used techniques which assume a linear relationship between exposure and outcome, which is not the assumption of the Protection against Schizophrenia (PaSZ) model. As most cases of myopia lead to mild, rather than severe visual impairment, I consider that the phenotypes used were primarily related only to the right-hand side of the curve, and that this approximation was therefore reasonable. I was however restricted to using severe myopia as the phenotype in one analysis using East Asian samples. The rationale for focussing the original GWAS on this phenotype was that high

myopia has a stronger genetic contribution than milder myopia, and so using this sample would yield more SNPs associated with myopia overall.[339] I have therefore used these SNPs as proxy instruments for myopia of any degree, as was the intention in the original GWAS.

There are other limitations regarding choice of phenotypes in this study. The studies included in the meta-analysis to detect genetic variants associated with myopia used a variety of phenotypic measures, and some of these were self-reported rather than objectively measured. Self-reported short-sightedness has however previously been shown to be a reliable indicator of measured myopia.[357]

Perhaps more importantly, I was unable to account for correction of myopia using aids when myopia was the exposure, and so cannot exclude modification of risk through correction. Indeed, people self-reporting myopia may be more likely to be using corrective aids than people who are unaware of their poor eyesight. This had potential to weaken any association.

I was also unable to account for age of onset of myopia, which would alter the dose of exposure received and whether it was received during central nervous system development, which may be important in this association, particularly as SSD is considered a neurodevelopmental disorder. This is perhaps the most likely mechanism by which a true association could have been missed in investigating the association between myopia as exposure and SSD as outcome and is one possible explanation for the discrepancy between the findings from this study and my longitudinal study of ALSPAC data described in the last chapter. There is some evidence that myopia-associated SNPs might affect the risk of onset differently at different ages.[336] The findings from participants of European ancestry showed a very conclusive null result however, and it might be expected that there would be at least some trend towards an association if myopia influenced SSD risk at any stage of life.

5.4.3 Comparison with other studies

I am unaware of any prior MR studies on this topic. As previously described, conventional cross-sectional studies investigating the relationship between visual impairment as exposure and psychosis as outcome report a positive association with reasonable consistency.[155] This can potentially be explained by psychotic illnesses causing visual impairment according to the results of my MR study. Since many of these studies treated visual impairment rather than psychosis as the exposure, this is presumably not the direction of effect which had been anticipated in all of them.

The three previous longitudinal studies of children which report a positive association between ocular dysfunction and subsequent psychotic illnesses or diagnoses, including my ALSPAC study, would seem to be at odds with the findings from my MR study.[224, 225, 358] This highlights the importance of not assuming, based on my results, that exposure to visual impairment during a critical phase of development does not have any causal relevance in psychosis. It is also possible that the findings in the small studies linking ocular dysfunction to SSD were driven by the non-acuity components of the ocular dysfunction measure. The findings in my ALSPAC study might also be evidence that the relationship between visual acuity impairment and psychotic illnesses differs from the relationship with psychotic illnesses. For example, depression rather than SSD could be the source of the psychotic experiences in the ALSPAC study.[81] Alternatively, the results in these previous studies might be artificially induced by confounding variables, poorer vision could result from a prolonged prodrome or lifelong state of susceptibility to psychosis.

I have already discussed that longitudinal studies of adolescents and older adults treating visual impairment as exposure and psychosis as outcome give mixed findings, with some reporting no association, some a positive, and some a negative association.[13, 14, 170, 216, 220] I consider that the positive association in some of these studies could be driven by shared underlying pathology of the central nervous system of the brain and visual acuity, which might include the

visual processing aspect inherent in measurement of visual acuity. Confounding is again an alternative explanation. In the case of the older adult studies, psychotic symptoms in the context of cognitive impairment, again distinct from SSD, could also be responsible for the association. I will consider the nature of the associations seen in older adult studies further in the next chapter.

Regarding the second hypothesis, that SSD is a risk factor for poorer visual acuity, I am unaware of any longitudinal studies investigating this. Several cross-sectional studies have reported on rates of uncorrected refractive errors and optician attendance in people with SSD and other psychotic illnesses. All found higher rates of refractive error, and lower self-reported recent optician attendance, than would be expected for the general population, consistent with my findings.[119, 125-127] This suggests non-correction of refractive error as a mechanism underlying the association in this MR study.

5.4.4 Conclusions

Since myopia is in most cases a cause of mild rather than severe visual impairment, my results are not necessarily inconsistent with more severe forms of visual impairment being a causal risk factor for psychotic experiences.[123] Other types of visual impairment, including retinal conditions, should also be considered. Investigating the relationship with age of onset of visual impairment might be especially important, given that the peak of SSD occurs in adolescence, and neurodevelopmental influences earlier in childhood may be crucial.[185]

My results do however suggest that common forms of mild visual acuity impairment across the lifespan are unlikely to be causally associated with SSD, and that perhaps other reasons for the associations seen between impaired visual acuity and subsequent psychosis in some longitudinal studies should be preferentially investigated.

I cannot conclude the exact pathway through which SSD might be a causal risk factor for visual impairment as suggested by these findings, but

hypothesize that reduced access to optical care, side effects from antipsychotic medications, common comorbidities of psychosis, and shared actions of genes on the developing brain and eye affecting shared neuropathology might all contribute. Regardless of the mechanism, my study again highlights the risk of lower visual acuity in people with SSD.

I have used the results from this MR study to develop three new research questions to investigate in the next study in the final two research chapters of this thesis. Firstly, since the results suggest that a typically mild form of visual impairment (myopia) is not causally associated with SSD specifically, I will not re-investigate this, but would like to find out whether poorer visual acuity is associated with psychotic symptoms more broadly in older adults. I will also aim to investigate whether the causal association between psychotic disorder and poorer subsequent visual acuity suggested by this MR study is replicated using classical methods in a large dataset. Lastly, although my data do not allow me to investigate associations with retinal conditions directly, I will test whether there is any evidence of an association between retinal structure measured by Optical Coherence Tomography (OCT) scans and psychotic symptoms in a large population sample.

Chapter 6 Associations between visual impairment and psychosis in the UK Biobank cohort: a study of working age and older adults

A version of this chapter has been published at:

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6.1 Introduction and Rationale for Key Decisions

My Mendelian Randomisation (MR) study from the previous chapter found no evidence that myopia was causally associated with subsequent SSD, contrary to my second hypothesis (that visual impairment is a causal risk factor for SSD). My MR study did support the first hypothesis, that SSD contributes causally to poorer visual acuity. Conversely, in chapter 4 I showed, using data from the Avon Longitudinal Study of Parents and Children (ALSPAC), [261, 262] that poorer visual acuity at age 11 was associated with psychotic experiences at ages 17 and 24, which, contrary to the MR findings, is supportive of hypothesis 2. One possible explanation for this discrepancy is that psychotic experiences are symptoms of, but not synonymous with SSD. They also occur in other mental and physical illnesses.[81] Therefore, even accepting the validity of the finding from the MR study that visual impairment (represented by myopia) does not contribute causally to SSD, there may still be a reason to investigate the association of visual impairment with subsequent psychotic experiences more broadly.

6.1.1 Psychotic Experiences in Older Adults

Unlike in younger adults, psychotic experiences in older people frequently occur in the context of cognitive impairment and can sometimes be a late-

stage symptom of dementia.[359] Delusional disorder is another variant of SSD that is more commonly diagnosed in older adults, with distinct features.[360] Further, SSD itself might have a neurodegenerative as well as neurodevelopmental aetiology, which could explain the increased rates of dementia diagnosis among people with SSD. [174] It cannot therefore be assumed that any relationship between visual impairment and psychosis or SSD will be consistent in younger and older adults, since the greater influence of neurodevelopmental or neurodegenerative processes respectively in these age groups might be influenced differently by visual impairment. Older adults have been frequently excluded from research [361] which might limit both potential to discover clinically relevant findings and generalisability of findings. Here, I will briefly review previous relevant research studies that influenced my study design in this chapter.

Three previous longitudinal studies of the association between visual impairment and psychotic experiences in older adults gave mixed findings.[170, 216, 220] A cohort study of over 3 million people followed from their 60th birthday found that a diagnosis of blindness or low vision was associated with a lower risk of subsequent Very-Late-Onset Schizophrenia-like Psychosis (VLOSLP). [170] By contrast, a second older adult cohort study found that vision problems in participants aged 65+ were associated with greater odds of subsequent paranoia. [216] This concords with the third study, which found a positive association between self-reported visual impairment and future auditory or visual hallucinations in two cohorts of people aged 65+. [220] Different exposure and outcome measures used in these three studies might explain the discrepancies. The measure of visual impairment used in the first, largest study (diagnosis of blindness and low vision in any medical records) was likely to detect only severe visual impairment, and as described in my thesis introduction, there is theoretical suggestion that moderate visual impairment could be more important in the association between visual impairment as exposure and psychosis as outcome. [136] The authors also suggested that survivor bias could have influenced their findings, leading to the apparent absence of association. [170] People who live long enough to be diagnosed with low vision or blindness in older age might have survived due to better overall

brain health. Alternatively, the measures of psychosis used in the second and third studies might have been overinclusive, leading to detection of associations between visual impairment and non-psychotic phenomena. For example, the second study based the outcome of paranoia on a positive response to either of the statements: “People were unfriendly”; or “I felt that people disliked me”. [216] These could arguably represent a range of experiences, including negative automatic thoughts in depression, which could have driven the apparent association. The third study used combined reporting of visual and auditory hallucinations as the outcome, so cases of Charles Bonnet syndrome could have contributed to the association. [123, 220] Another important consideration is that, similarly to my study of children, these discrepancies could also result from psychotic symptoms / experiences being distinct from psychotic illnesses. The pathway linking visual impairment and psychotic expereinces in older adults could incorporate dementia or depression, rather than schizophrenia and related illnesses, leading to different findings in this population.

6.1.2 Optical Coherence Tomography in the Study of Schizophrenia

Multiple studies have used Optical Coherence Tomography (OCT) to test for retinal differences between people with schizophrenia and controls.[362] Relative to healthy controls, reductions in macular volume, and macular, ganglion cell-inner plexiform layer, and retinal nerve fibre layer thickness are reported in schizophrenia.[76] Several systematic reviews of these studies exist, showing generally consistent findings.[23, 76, 362] A frequently given explanation for the alterations is that cerebral neuropathology seen in schizophrenia, potentially including neuronal cell loss, is reflected in the retina, an extension of the central nervous system. As published studies have used a case-control design, it has been difficult to elucidate when in the course of schizophrenia the retinal changes might occur. Some studies of first-episode schizophrenia have not found these changes, suggesting that they begin only after illness is established. [362-364]

Limitations of existing OCT studies have been well-described in the literature. [76] These include small sample sizes in many published studies, and being also largely unable to adjust for the effects of potential confounding variables, including socioeconomic variables.

A further uncertainty is the extent to which retinal neural layer thinning corresponds to poorer visual acuity. Recent evidence has shown associations between retinal thinning and poorer visual acuity in ophthalmic and neurologic populations, although no such study has been done in the general population to my knowledge. [365-367]

As well as potentially being a manifestation of more advanced schizophrenia, retinal alterations can occur as part of ocular disease processes, for example in Age-related Macular Degeneration and diabetic retinopathy. [368, 369] Therefore, retinal changes would be expected theoretically to correpsond to poorer visual acuity, and might be another route by which schizophrenia and related illnesses could causal risk factors for poorer vision.

6.1.3 Aims

In this chapter, I investigate the temporal association between visual acuity and psychotic experiences in a sample of adults including older adults. I also move beyond using visual acuity or myopia alone as a measure of eyesight and investigate associations with the structure of the retina. I conducted the largest study assessing whether retinal thinning is associated with psychotic symptoms. I also aimed to assess the extent to which thinning of retinal structures was associated with the poorer visual acuity typically seen in groups of people with SSD.

6.1.4 Hypotheses

1) Poorer visual acuity and retinal neural thinning will be associated with psychotic experiences measured subsequently. This would be consistent with poorer vision being a potential causal risk factor for psychotic experiences, or

being part of a psychosis prodrome, or with a shared central nervous system pathology causing both.

2) Retinal neural thinning as assessed using OCT will be cross-sectionally associated with poorer visual acuity in this general population sample. This would suggest that neural cell loss might account for a degree of visual acuity impairment seen in schizophrenia and related disorders, and therefore that neurodegeneration as an inherent part of psychotic illnesses could be responsible for the eyesight damage suggested by my MR study.

6.1.5 Choice of Sample

I chose to use the UK Biobank cohort[328] due to its very large sample size of approximately 500,000, and inclusion of older adults. Other reasons included the availability of hospital-linked diagnoses, mental health questionnaires, and OCT measures within the same sample. Further detail on the UK Biobank cohort is given below.

6.1.6 Choice of Study Design

I planned to conduct a cohort study with the aim of establishing the temporality of the association between visual impairment and psychotic experiences. I had initially planned to use a bidirectional cohort study design, but this was not possible, as is outlined further in the next chapter.

6.2 Methods

6.2.1 Sample

The UK Biobank cohort includes over half a million participants from around the UK who were originally recruited at the age of 40-69 in 2006-2010.[328] Its aim was to facilitate identification of causes of diseases of middle and older age.[328] Five million participants who lived within approximtely 10 miles of an assessment centre were identified through NHS records and invited by post to attend one of 22 assessment centres around the UK.[370] The response rate was 5.5%.[371] Participants contribute to a large biomedical database by regularly

donating biological samples and answering questionnaires. The North West Multi-Centre Research Ethics committee provided ethical approval for the UK Biobank. Further details are available at https://www.ukUK Biobank.ac.uk/.

6.2.2 Aim 1: To test the hypothesis that poorer visual acuity, and thinner retinal structures on OCT scan will be associated with subsequent psychotic experiences.

6.2.2.1 Outcome Variable

An online questionnaire on symptoms and experiences of mental illness was added into the UK Biobank in 2016. The questionnaire was developed based on existing validated measures in consultation with a reference panel.[372] One subsection asked about 'psychotic and unusual experiences' and included questions designed to elicit four psychotic-like experiences: believing in an unreal conspiracy against the self; believing in unreal communications or signs; hearing an unreal voice; or seeing an unreal vision. The questions are included in appendix C. These were completed by 157,315 participants. Participants were asked whether they had ever had these experiences, and if so at what age they first had the experience. I classed psychotic experiences as positive if participants reported any symptoms except for seeing an unreal vision, to avoid categorising cases of Charles Bonnet Syndrome as psychosis. I also classed psychotic experiences as positive only if the age at which the participant reported the experiences began was older than their age at vision testing.

6.2.2.2 Exposure Variables

Ocular testing was added into the UK Biobank baseline assessment in 2009 and undertaken by 117,907 participants. My primary exposure variable was visual acuity, in line with internationally recognised classifications of visual impairment.[373] Habitual distance visual acuity was tested separately in each eye using any corrective aids that participants were presently prescribed, to give a 'real-world' measurement. Participants read letters on a screen from 4 metres, or 1 metre if they were unable to see any letters. The test ended when they were unable to read 2+ letters. [374] Standard scoring was used to

determine a Logarithm of Minimal Angle of Resolution (LogMAR) score,[374] with 0 being roughly equivalent to a 6/6 or 20/20 reading on a Snellen chart; positive numbers indicating vision worse than this; and negative numbers indicating vision better than this.

67,321 participants underwent OCT imaging between 2009 and 2010 using a “spectral domain” OCT device, which has an axial resolution of </=6µm and a transverse resolution of approximately 15µm. [375] Automated software was used to analyse the images; this has been described in detail elsewhere.[375] To my knowledge, the UK Biobank is the largest sample where OCT measures are available, due to this novel use of automation for interpretation.

I tested as secondary exposure variables macular thickness and retinal pigment epithelial (RPE) layer thickness measurements in micrometres derived from OCT scans. Thinning of the macula, the region associated with highest visual acuity, has been specifically implicated in schizophrenia and related illnesses in case-control studies. [362] The RPE is a highly metabolically active layer at the back of the eye which plays a crucial supportive and regulatory role in sustaining the retinal nerve cell layer. [376] Degeneration of the RPE is implicated in causing retinal conditions with potential to induce sight loss, including Age-related Macular Degeneration. [376] A thinner RPE might therefore be considered a proxy for risk of Age-related Macular Degneration and other retinal conditions.

6.2.2.3 Confounders

Few participants with a prior diagnosis of schizophrenia and related disorders (based on linked hospital records) had completed the follow-up questionnaire, and among those who had, none reported psychotic experiences at follow up. No baseline measure of the outcome was available. I adjusted models for two separate scores: one derived from the Patient Health Questionnaire 2 (PHQ2);[377] 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.[378] I intended to account for baseline depression and anxiety symptoms which are known to be associated with psychotic symptoms.[81]

I also adjusted for two variables that were related to both the exposure and outcome: continuous age in years as reported by participant at recruitment; and sex, reported as binary (male / female). In a separate model I adjusted for three vascular risk factors: Body Mass Index (BMI) as a continuous measure, taken at baseline; diabetes as a binary variable self-reported by participants at baseline; and self-reported smoking status as a categorical variable (past smoker / current smoker / never smoker). These are all risk factors both for retinal thinning (and therefore reduced visual acuity) and neurodegenerative states such as dementia, which could be a cause of psychotic experiences in this sample.[76, 209]

In final, fully adjusted models I included three additional baseline variables associated with Socioeconomic Status (SES): Townsend deprivation score, average household income before tax, and age of leaving full time education. The Townsend score is a continuous score designed to measure relative deprivation by 'Lower-level Super Output Areas' (small areas).[379] In 2011 it ranged from -6.36 to 2.87.[379] Average household income before tax was categorised as <£18,000 / £18,000 to £30,999 / £31,000 to £51,999 / £52,000+. Age of leaving full time education was a discrete variable, reported by participants, in years. Lower SES might be associated with non-correction of refractive errors due to lower income and is also consistently associated with psychosis.

6.2.3 Aim 2: To test whether OCT measures are associated with visual acuity

I also tested whether the baseline OCT measures described above (as exposures) were cross-sectionally associated with same-eye baseline logMAR scores as an outcome.

6.2.4 Statistical Analyses

I ran all analyses in STATA/MP versions 16 and 17. [214, 380] As the primary outcome was binary (psychotic experiences) I used logistic regression. I ran models unadjusted; adjusted for age and sex; adjusted for age, sex, and vascular risk factors; and adjusted for age, sex, vascular risk factors and socioeconomic variables. To test whether OCT measures were associated with visual acuity, I used linear regression. I ran these models both unadjusted and adjusted for age and sex.

6.2.4.1 Missing Data

Missing data are substantial in the UK Biobank, reducing the power to detect an association and potentially introducing bias. I therefore used multiple imputation through chained equations to increase sample size and reduce the risk of bias as my primary analysis, on the basis that multiple imputation should give less biased results than complete case analysis provided data are missing in relation to observed variables.[381] I used multiple auxiliary variables to improve prediction of the missing variables. These were: housing score; employment score; 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; frequency of feeling loved as a child; disability status; frequency of feeling tired in past two weeks; and frequency of drinking alcohol.

I used the command *mi impute chained* in STATA version 17[380] to generate 20 imputations, and combined imputations for analysis using Rubin's rules. [300] This process uses a 'burn-in' of 10 cycles. I imputed normally-distributed continuous variables using linear regression; non-normally distributed continuous variables using predictive mean matching with 10 nearest neighbours; binary variables using logistic regression; and ordinal categorical variables using ordered logistic regression. I only included participants with an observed left eye logMAR score (the ocular measure with least missing data) and who had no date of death recorded prior to 2017 in these analyses.

As a sensitivity analysis and for comparison, I also report analyses using only participants with all necessary analytic data; the complete case sample. I report multiply imputed data results including only participants with complete data for each exposure in the appendix D.

6.3 Results

Table 6-1: 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	2,968 (2.6)	898 (1.8)	2,031 (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)	7,409 (15.2)	14,059 (21.3)
£18,000 - £30,999	24,746 (21.3)	9,809 (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)	4,680 (9.6)	6,787 (10.3)
Diabetes	6,789 (5.9)	2,189 (4.5)	4,494 (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 1,219 (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 8,248 (7.1); anxiety score 5,466 (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)

116,012 participants with an observed left eye logMAR score constituted the baseline sample for analyses of multiply imputed data (Table 6-1: Demographics of sample with observed left eye visual acuity according to visual impairment status in 2009. In this 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%). Otherwise, groups with and without visual impairment were broadly similar. After excluding participants who died during follow-up, 113,044 participants remained in the multiply imputed cohort analysis.

Table 6-2: Characteristics of complete case and multiply imputed samples

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)	9,350 (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)	9,632 (56.9)
Average household income before tax		
<£18,000	17,639 (22.2)	3,221 (19.0)
£18,000 - £30,999	19,266 (24.2)	4,761 (28.1)
£31,000 - £51,999	19,913 (25.0)	4,869 (28.8)
£52,000+	22,794 (28.6)	4,065 (24.0)
Smoking Status		
Never	53,918 (56.5)	8,959 (53.0)
Past	31,815 (33.4)	6,558 (38.8)
Current	9,650 (10.1)	1,399 (8.3)
Diabetes	5,676 (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)

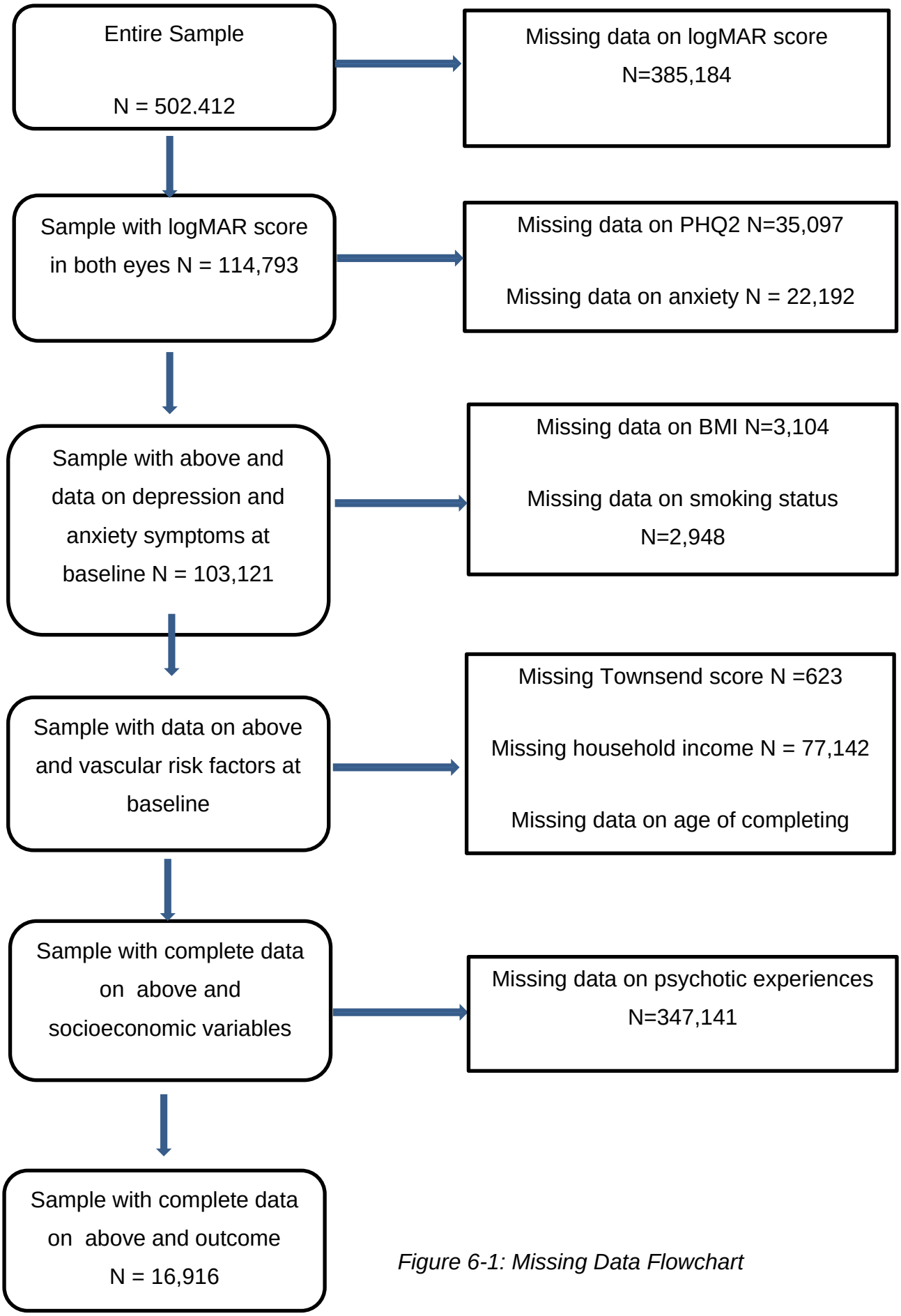

Figure 6-1: Missing Data Flowchart

The complete case sample were less likely to have had an SSD diagnosis (<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%) Full details can be seen in Table 6-2: Characteristics of complete case and multiply imputed samples

6.3.1 Aim 1: To test the hypothesis that poorer visual acuity, and thinner retinal structures on OCT scan will be associated with subsequent psychotic experiences.

Table 6-3: 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 6-4: Odds of reporting psychotic experiences at follow-up according to baseline retinal thickness measures

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=9,962	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=9,962	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

People with poorer baseline logMAR score in either eye had higher odds of psychotic experiences at follow-up including following adjustment for age, sex, and vascular risk factors (AOR per 0.1-point increase in logMAR score 1.08, 95% CI 1.03 – 1.13, p=0.003; and 1.05, 95% CI 1.02-1.09 p=0.004, in right and left eye respectively) (Table 6-3: Odds of Reporting Psychotic Symptoms at Follow-up According to Visual Acuity at Baseline. The association was attenuated but still seen following adjustment for SES (right eye AOR 1.06, 95% CI 1.01 – 1.11, p=0.020; and similar though with weaker statistical evidence in the left eye; AOR 1.04, 95% CI 1.00-1.08, p=0.037). 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 in complete case data 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.

I found no evidence of any association between OCT measures and subsequent psychotic experiences in any analyses (Table 6-4: Odds of reporting psychotic experiences at follow-up according to

6.3.2 Aim 2: To test whether OCT measures are associated with visual acuity

As expected, 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 (Table 6-5: Change in LogMAR score in same eye according to OCT Measures in Complete Case Data.

Confidence intervals were similar across multiply imputed and complete case data.

Table 6-5: Change in LogMAR score in same eye according to OCT Measures in Complete Case Data

Exposure	Model 1 Unadjusted mean change in logMAR score per micrometre [95%CI]	P-Value	Model 2 Adjusted mean change in logMAR score per micrometre [95%CI]	P-Value
Multiply Imputed Data				
Right macular thickness N=113,044	-0.0002 [-0.0003 - -0.0002]	<0.001	-0.0001 [-0.0002 - -0.0001]	<0.001
Left macular thickness - per µm N=113,044	-0.0002 [0.0003 - -0.0001]	<0.001	-0.0001 [-0.0002 - -0.0001]	<0.001
Overall right retinal pigment epithelium thickness - per µm N=113,044	0.0001 [0.0001 – 0.0001	<0.001	0.0001 [0.0000 – 0.0001]	<0.001
Overall left retinal pigment epithelium thickness - per µm N=113,044	0.0001 [0.0000 – 0.0001]	0.013	0.0001 [0.0000 – 0.0001]	0.010
Complete Case Data				
Right macular thickness N=10,022	-0.0004 [-0.0006 - -0.0003]	<0.001	-0.0003 [-0.0005 - -0.0002]	<0.001
Left macular thickness N=9,962	-0.0001 [-0.0003 - 0.0000]	0.058	-0.0001 [-0.0002 - -0.0001]	0.275
Overall right retinal pigment epithelium thickness N=10,022	0.0002 [0.00002 – 0.0003]	0.024	0.0002 [0.0000 – 0.0003]	0.020
Overall left retinal pigment epithelium thickness N=9,962	0.0002 [0.0001 – 0.0004]	0.001	0.0002 [0.0001 – 0.0004]	0.001

Adjusted: Adjusted for age and sex.

6.4 Discussion

6.4.1 Main Findings

Whilst I found that poorer visual acuity was associated with broadly defined subsequent psychotic symptoms, this association was only present in multiply imputed data, presumably due to the larger sample size. The effect was small, and therefore the clinical significance is uncertain. Rather than being causal, this finding may indicate that impaired visual processing is part of a psychosis / neurodegenerative prodrome which adversely affects acuity testing.[35] In keeping with this, I found no evidence that reduced thickness of retinal structures was associated with subsequently measured psychotic experiences, which might be expected if visual impairment at the level of the eye itself was implicated.

Poorer visual acuity was correlated with lower macular thickness as expected, but with increased thickness of the retinal pigment epithelium. After consultation with an expert (Professor Steven Silverstein), I concluded that the latter could reflect RPE layer oedema in eye disease.[382] In terms of my PhD hypothesis 1 (that psychotic illnesses are a causal risk factor for visual impairment), this suggests a further mechanism by which SSDs may predispose to visual impairment; through retinal deterioration seen in later stages of the illness, which I will discuss further in the next chapter.

6.4.2 Strengths and Limitations

This is the first study, to my knowledge, to investigate associations between OCT scan results and psychotic experiences in a sample of 1000s of participants. There are however limitations.

Firstly, there was no measure of the outcome, psychotic experiences, at baseline. This is arguably the most crucial limitation because psychotic symptoms might have existed prior to the exposure, limiting inferences about temporality. I have made some attempt to address this by incorporating the age at which participants reported their psychotic experiences first began, but

this retrospective self-reporting does not compensate for the lack of contemporaneous measurement at the time of eyesight testing. I was however able to adjust for baseline anxiety and depression symptoms, which are associated with psychotic experiences.

The number of participants with complete data for all relevant variables represent a very small proportion of the entire sample. Fewer still reported psychotic experiences occurring newly during follow-up (n=109), so most of my sample comprised participants without psychosis. This reduced power to detect associations with potential for type 2 error. 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. The fact that very few participants with a psychotic illness diagnosis from linked hospital records answered the follow-up questions is suggestive of this. I sought to overcome these limitations using multiple imputation. Although the Missing At Random (MAR) assumption cannot be proven, I 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.[381]

I had initially intended to create 100 imputations due to an extremely high proportion of missing data (96.7% total sample; 85.5% participants who had visual acuity measured in both eyes). The computationally intensive nature of imputing such a large dataset limited the number of imputations that I could generate, however.

The UK Biobank sample is not representative of the UK population. It had a low response rate of just 5.5%.[383] 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.[384] This can adversely affect the validity of associations found in the UK Biobank.[383, 385, 386] Consistency of my findings with some previous research is reassuring is this regard, but caution should be applied when generalising findings.

As with all observational studies, I cannot exclude a possible influence of residual and unmeasured confounding on results. Recruitment occurred at age 40+, meaning I could not account for potential confounding variables from earlier in life, such as birth trauma or in utero infection. I could not include ethnicity due to small numbers in most categories.

I discounted visual hallucinations to avoid confounding by severe eye disease and Charles Bonnet Syndrome. In so doing, I likely excluded people with psychotic experiences not driven by severe eye disease, as for example, visual hallucinations may affect 20-30% of people with schizophrenia;[387] therefore my 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.

Another limitation is that there was no information available on whether the outcome psychotic experiences occurred in the context of sleep or fever states, so I was unable to exclude psychotic experiences that might be part of short-term delirium or non-pathological sleep states as I did with the ALSPAC study in chapter 4.

6.4.3 Comparison with other Literature

My finding in support of hypothesis 2; that poorer visual acuity precedes psychotic experiences, may contradict my MR study findings that mild visual impairment (in the form of myopia) does not cause schizophrenia. Nevertheless, some studies of children and adolescents did find this association between visual acuity and subsequent psychotic disorders and experiences, including my ALSPAC study from chapter 4.[13, 358] As I have mentioned previously, this could simply be because psychotic experiences and schizophrenia-spectrum disorders are overlapping but separate phenomena. A polygenic risk score for schizophrenia does not predict psychotic experiences in the ALSPAC cohort, [388] suggesting that the experiences I measured there were mainly non-pathological, or manifestations of depression and anxiety disorders, rather than indicative of psychotic illness.[389] In both the

current chapter and the ALSPAC study, it could be that visual impairment predisposes to psychotic experiences via these mechanisms rather than through psychotic disorder. Given that the UK Biobank cohort includes older adults, the association could also be mediated by cognitive impairment or dementia in this sample. I have also discussed that another likely candidate explanation for the association I found in the ALSPAC study is underlying central nervous system disturbance, which could cause visual impairment and psychosis to co-occur. In this case, my finding in this chapter would suggest that this mechanism applies during the neurodegenerative as well as the neurodevelopmental phase of life.

Clearly, my finding of an association between visual impairment and subsequent psychotic symptoms is consistent with the two previous longitudinal studies of visual impairment and psychosis in older adults which a positive association,[216, 220] but inconsistent with the study which found a negative association.[390] I note that this concords with the possibility that visual impairment is a risk factor for psychotic experiences but not disorders, given that the division in findings between these studies falls along these lines. One of these studies adjusted for the outcome at baseline, [216] and still gave results consistent with mine. Both studies of symptoms had samples with an older average age than mine and one had a high proportion of participants with dementia, which is supportive of my interpretation that neurodegeneration is a route by which the association could occur. A further consideration is that the previous studies had greater power to detect an association, due to a larger number of people reporting the outcome in complete case analyses.

I did not find an association between thickness of retinal structures and subsequently measured psychotic experiences in this sample that is typically seen in case control studies of schizophrenia.[23, 76] This might be because these changes are specific to SSDs. 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.[362-364] 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[391] 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.[392] This sequence of changes is consistent with what is observed in other diseases.[393-395]

6.4.4 Conclusions

My findings are consistent with visual impairment acting as a risk factor for psychotic experiences in adults including older adults, but the effect was small and I consider this to be more likely to reflect shared central nervous system dysfunction than a causal relationship since there was no association with retinal thickness. The absence of the latter association is 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.[226] Further studies are needed which exclude the presence of the outcome at first measurement of the exposure, and which test for possible mediators of the association such as depression and dementia.[165] I do not consider that there is sufficient evidence from this study to suggest that visual impairment is a target for prevention of psychotic experiences.

Chapter 7 Associations between visual impairment and psychosis in the UK Biobank cohort: a nested case control study of adults

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7.1 Introduction and Rationale for Key Decisions

Originally for my thesis, I had planned to look at the bidirectional associations between visual impairment and psychosis in a cohort study in the UK Biobank cohort, to test hypothesis 1 (psychotic illnesses are a causal risk factor for visual impairment) in addition to hypothesis 2. This is especially pertinent given that my systematic review in chapter 3 identified an absence of longitudinal cohort studies investigating psychotic illness as exposure and visual impairment as outcome. On reviewing the available variables in the UK Biobank data however, it was not possible to design a suitable cohort study for this question since the outcome was only measured at the baseline of the study; the same time as the exposure and all putative confounding variables; many of which could therefore have resulted from the outcome. In view of this, I decided to conduct a nested case-control study, using a binary measure of visual impairment / no visual impairment as the outcome. This represents an advance on previous research, since only one case control study identified in the systematic review was rated as at low risk of bias, and this used a far smaller sample size than the UK Biobank (just 60 participants in total). [226] This previous study also excluded people with myopia requiring lens strength greater than 2 Dioptres for correction. Many prior case control studies had similar limitations in terms of relatively small sample sizes, excluding people with myopia above a certain level, or choosing cases and controls from

selected populations, for example an eye clinic or psychiatric facilities.[190, 230] Most also treated psychotic illness, rather than visual impairment, as the outcome. The UK Biobank has the advantage of being a general population sample, where cases and controls were selected using identical methods from the same population. It also did not exclude anyone based on level of visual impairment. My aim therefore, was to test whether people with a degree of visual impairment in the UK Biobank sample had a higher odds of having been diagnosed with a diagnosis of schizophrenia or a related psychotic illness prior to eyesight measurement, which would provide further evidence in support of my hypothesis that psychotic illness is a risk factor for visual impairment.

7.2 Methods

7.2.1 Study Population

The study population was the UK Biobank sample, which I have described in the previous chapter.

7.2.2 Outcome

A subset of UK Biobank participants had their visual acuity tested at baseline, as described in the previous chapter. I defined cases (with visual impairment) as participants who had logMAR score >0 in either eye, and controls as participants who had logMAR score </=0 in both eyes (considered 'normal' vision).

7.2.3 Exposure

My exposure variable was an International Classification of Diseases 10 (ICD10) diagnosis code F20-29 (Schizophrenia-Spectrum Disorder - SSD), derived from Hospital Episode Statistics (HES) data from linked hospital records. I chose this for consistency with other research that used SSD as a measure of related psychotic illnesses [92]. I 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. I also coded several participants as positive because they had an equivalent ICD9 diagnosis.

7.2.4 Putative Confounding Variables

I adjusted for two variables that were related to both exposure and outcome and could not be mediators of the association between them. These were reported by participant at baseline: continuous age in years; and sex (male / female) [76].

In a separate model I further adjusted for several variables self-reported by participants at baseline that were intended to capture aspects of socioeconomic status. These were: age of completing full time education; annual household income as a categorical variable (<£18,000, £18,000 - £30,999, £31,000 - £51,999, and £52,000+); and Townsend deprivation score. These are all described in the previous chapter. My rationale was that these variables are all plausible confounders of an association between psychosis and visual impairment. As they may also be mediators to some extent however, I wanted to assess their effect separately from the other variables.

7.2.5 Statistical Analysis

I used logistic regression to model the association between prior diagnosis of SSD as exposure and visual impairment as the outcome. I conducted primary analyses using the multiply imputed dataset described in the previous chapter to reduce bias introduced by missing data and enhance the sample size. I restricted all analyses to participants who had had a left eye logMAR score measured, meaning that the multiply imputed sample was the same sample as in the previous chapter.

7.3 Results

7.3.1 Baseline characteristics of Complete Case Sample and Sample with Missing Data in Imputed Analyses

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. Full details of the differences between the complete case sample and multiply imputed sample can be seen in Table 7-1: Comparison of Complete Case Sample and Sample with Missing Data in Multiply Imputed Analyses

Table 7-1: Comparison of Complete Case Sample and Sample with Missing Data in Multiply Imputed Analyses

	Sample with missing data in Imputed Analyses N [%]	**Complete Case Sample N [%]**
Total	55,834 [48.1]	N=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	4,614 [11.9]	17,146 [28.5]
£18,000 - £30,999	7,403 [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 7-2: 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, average household income before tax, and age at leaving full time education

7.3.2 Main Findings

Using the multiply imputed dataset (N=116,012), I 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) (Table 7-2: Odds of Prior Schizophrenia-Spectrum Disorder Diagnosis in Group with Visual Impairment compared to Group Without). 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, I 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). I noted that the confidence intervals overlapped with those from multiply imputed data, suggesting that the findings between the two analyses were not incompatible.

I show results for participants with and without missing outcome data in appendix E.

7.4 Discussion

7.4.1 Main Findings

Main Findings

In line with my hypothesis that schizophrenia-spectrum disorders will be associated with visual impairment, I found that individuals with any degree of visual impairment (cases) had higher odds of a preceding SSD diagnosis than controls with no visual impairment in primary analyses. The association could occur through suboptimal correction of refractive errors, degenerative neuronal alterations in the retina (as may be found in the brain in schizophrenia[23]), or other factors typically over-represented in people with SSD such as diabetes, hypertension, obesity, smoking, or antipsychotic medications.[76] Adjusting for socioeconomic status attenuated the association, in keeping with SES being part-mediator, part-confounder in this relationship.

7.4.2 Strengths and Limitations

Strengths of this study included the use of a large population-based sample, and the ability to use multiple imputation to reduce bias and sample size loss introduced by missing data. A further strength was the use of linked hospital records to determine exposure status, which avoids recall bias; and the use of an objective measure of the outcome.

My case control study was also subject to multiple limitations. Although confidence intervals for estimates overlapped between complete case and multiply imputed data, the association was not strongly statistically evidenced in complete case data. This could be due to the smaller number of people with an SSD diagnosis that had complete data for all confounding variables, reducing power to detect an association. Nevertheless, the difference in sample size between the complete case and multiply imputed datasets was

driven entirely by missing data in the SES variables. The discrepancy between results therefore suggests that differences in socioeconomic status were predictive of ongoing participation in the UK Biobank study, as well as being associated with SSD diagnosis, and so perhaps drove attrition bias influencing findings in complete case data.

Although the SSD diagnoses were recorded in linked hospital records before visual acuity testing took place, it is not possible to know whether the visual impairment preceded the exposure. There are also multiple putative confounding variables which were not measured in this dataset, such as birth trauma, and in utero infections, and as with all observational studies, I could not exclude the possibility of residual or unmeasured confounding. Further, I could not adjust for vascular risk factors since these were measured contemporaneously with the outcome; or ethnicity due to small numbers in most categories.

To conduct a case control study, I needed to dichotomise the outcome data, which meant that much of the detail in this continuous variable was lost. As with the study described in the previous chapter, selection bias in the UK Biobank sample poses a degree of threat to the validity of associations in the UK Biobank and means that generalisation of results to other samples warrants caution.[371] Again, I was able to generate fewer imputations than would have been ideal, given the large volume of missing data. The limitations regarding assumptions of multiple imputation also apply to this chapter.

The use of corrected visual acuity as an outcome measure might also have led to an underestimate of associations, unless the only relevant mechanism of association is through non-correction of refractive error.

7.4.3 Comparison with Previous Literature

My finding concords with the cross-sectional studies showing that people with SSD have poorer visual acuity on average than people without. [119, 125-127] 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 drop in functioning or available funds making optical care less accessible. My results are also compatible with the findings from my Mendelian Randomisation study that schizophrenia and related disorders are causally associated with poorer eyesight.

7.4.4 Conclusions

My findings would appear to support the hypothesis that people with a schizophrenia-spectrum disorder diagnosis are at greater risk of future visual impairment. I have discussed potential mechanisms in previous chapters, but reference here retinal neural atrophy as a progressive aspect of CNS changes in schizophrenia given the association between retinal thickness and visual acuity evidenced in the previous chapter. 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.[165]

Chapter 8 Discussion

I will begin this chapter by summarising the main findings from my thesis, and how I addressed gaps in the evidence relating to the association between visual impairment and psychosis, as per my aims in chapter 2. Next, I will discuss overarching limitations of my research findings, how these could have influenced results, and implications for the interpretation of results. I will then discuss my findings in the context of other research pertaining to visual impairment and psychosis. I will finish by considering the potential implications of my findings for research, clinical practice, and healthcare policy.

8.1 Summary of Main Findings

In Chapter 3, I reported a systematic review and meta-analysis aiming to collate all published studies reporting on the existence and strength of an association between visual acuity impairment, defined either as low measured visual acuity, diagnosis of blindness or low vision in medical records, or self/informant-report of subjectively poor vision; and psychosis, defined as diagnosed psychotic illness, or reported symptoms. Thirty-one studies were included in the narrative review, and 12 in the meta-analysis. According to the GRADE criteria, there was grade D (troublingly inconsistent) evidence of an association between measured visual acuity impairment as exposure and schizophrenia as an outcome in longitudinal studies. There was also grade D evidence for an association between visual impairment and psychosis in case-control studies. I found grade B evidence (consistent evidence from observational studies) for an association between visual impairment and psychosis in cross-sectional studies. This applied to studies of both younger and older adults, and psychotic diagnoses and symptoms. Across 12 cross-sectional studies that could be meta-analysed, the pooled odds ratio for the association when visual impairment was the exposure was 1.76 (95% CI 1.34-2.31), and when psychosis was the exposure was 1.85 (95% CI 1.17 – 2.92). Study heterogeneity was high, however. Another crucial finding was that there were no

longitudinal studies investigating psychosis as exposure and visual impairment as outcome. It was not possible to infer a direction of effect from the results of the systematic review.

From the systematic review, I found that the only age group where longitudinal studies gave consistent findings that visual impairment as exposure was associated with psychosis was children. This may be suggestive that exposure to visual impairment during a critical developmental phase is relevant to the development of psychotic illness. Nevertheless, this finding was derived from just two small studies, and both combined visual acuity with other measures of ocular function in the exposure variable. Therefore, to disentangle visual acuity from these other aspects, I carried out a larger study testing the association between childhood visual acuity, and other aspects of ocular function separately, and adolescent psychotic symptoms. In this study I used a cohort of 6,686 children from the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort. In addition to using a larger sample than the previous two studies of children, I was able to adjust for multiple putative confounding variables. I found that best corrected visual acuity aged 11 was associated with psychotic symptoms aged 17 and 24 (Adjusted Odds Ratio per 0.1-point worse logMAR score 1.23, 95% CI 1.06 – 1.42). Requiring glasses aged 11 was also associated with this outcome (AOR 1.63, 95% CI 1.21 – 2.19). Contrary to my hypothesis, other measures of ocular function were not associated with adolescent psychotic symptoms in this sample. Evidence for an association with best corrected visual acuity aged 7 was weaker. Overall, these findings support a temporal association between visual acuity impairment in childhood and psychotic symptoms in adolescence but cannot be used to conclusively determine whether this association is causal, or the result of shared disturbance to the developing central nervous system affecting the brain and the eye, or another form of confounding.

To address these limitations of classical observational studies in testing causal associations, I conducted a two-sample Mendelian Randomisation (MR) study in chapter 5. This was bidirectional: testing evidence for myopia as a causal risk factor for schizophrenia; and schizophrenia as a causal risk factor for poorer habitual visual acuity. I found no evidence in support of myopia as a causal risk

factor for schizophrenia but did find evidence that schizophrenia was causally associated with poorer visual acuity, at least in samples comprising participants with European ancestry. The latter finding was robust to multiple sensitivity analyses. This suggests that my previous findings that visual acuity impairment is associated with subsequent psychosis in children and adolescents are either: not causal; relevant only at a specific neurodevelopmental phase of life; or apply to psychotic experiences more broadly but not to schizophrenia.

I considered how findings regarding visual impairment and psychosis might differ between older and younger adults, and how findings from retinal imaging studies might correlate with findings regarding visual acuity in psychotic illnesses. This led to my study using UK Biobank data in chapter 6. Here, I found an association between poorer visual acuity and psychotic symptoms reported subsequently, but not between thinner retinal structures and the outcome. I also found in this study that, as expected, reduced macular thickness and volume were associated with poorer visual acuity. From this I concluded that retinal alterations are a plausible mechanism by which psychotic illnesses could cause visual impairment.

I considered it important to replicate the MR study findings using a traditional epidemiological method. Although it was not possible to conduct a cohort study using the UK Biobank data, I was able to conduct a nested case-control study comparing adults who had a degree of visual impairment to those who did not. Here I showed that the group who had visual impairment had higher odds of having been diagnosed with Schizophrenia-Spectrum Disorder, which was consistent with the findings from the MR study.

8.2 Broad Limitations of Studies

As with all research studies, the findings in my thesis must be considered in light of limitations which could lead to potential threats to their validity. In this section, I focus on four key threats to the validity of epidemiological studies: chance; bias; confounding; and reverse causality, and how these could impact my findings.

8.2.1 Chance

The possibility that results have occurred due to chance, rather than genuine associations, almost universally applies to research studies, as they can rarely be carried out on entire populations.[396] Explicitly specifying a clear hypothesis or hypotheses prior to conducting any analysis strengthens causal inference. Specifying advance hypotheses provides some reassurance that results have been presented in line with planned analyses, and not 'cherry-picked' due to having small P-values, for example.[397] For each study in my thesis, I developed an advance protocol. For the systematic review, I published this on PROSPERO ahead of carrying out the study,[197] and for the longitudinal study presented in chapter 4 I published the advance protocol on *protocols.io*.[258] At times, I updated protocols based on findings from a previous study or following further discussion with supervisors; in particular, I updated the protocol for my study in Chapters 6 and 7 based on the results from the MR study, after the initial version of the protocol had been published on *Open Science Framework.*[398] This decision was explicitly based on results from the prior study however, and not analysis of the data in the UK Biobank. I made further significant amendments to this protocol after discovering that the numbers of people with severe ocular conditions in the UK Biobank was too small to investigate these as I had planned, and again after Optical Coherence Tomography (OCT) data was released newly from the UK Biobank, providing a novel opportunity to use this data. These changes were pragmatic based on updated knowledge of data availability, and again not based on prior analyses.

One traditional metric by which evidence against findings being caused entirely by chance can be assessed is the P-value.[397] The P-value can be described as a measure of how well data conform to a chosen statistical model containing a variety of assumptions, of which one is that the null hypothesis is true.[397] A practice which has been criticised is reporting binary 'significant' and 'non-significant' results based on such an arbitrary cut-off. To overcome this, I reported exact P-values throughout this thesis, except where P-values are very small ($p<0.001$), to allow a more nuanced description of the compatibility of data with the model tested.[397] I have also reported Confidence Intervals alongside P-values. These represent a theoretical range within which the estimate would be found 95% of the time if repeat samples were drawn from the same population.[399] Whilst these are subject to some of the same limitations as P-values, they have the advantage of quantifying a range within which the true effect size may lie and provide information on the precision of the estimation,, and are increasingly preferred in research.[400] In presenting confidence intervals, I have given more information about the range of likely values of effect estimates.

Chance findings are also more likely in smaller studies, due to lower precision of estimation. I have used larger samples wherever possible throughout my research. Although some studies in the systematic review have small sample sizes, pooling these increased the overall sample size. The ALSPAC sample, with over 14,500 initial recruits, constitutes a large sample, particularly for the level of detail that has been collected. In the MR study, I have searched for the largest available GWAS studies reporting usable summary statistics in all analyses. The UK Biobank, with over half a million participants, constitutes a very large sample, even though I was unable to use the full cohort.

8.2.2 Bias

Bias is a lack of validity or error in the measurement of association between exposure and outcome resulting from systematic problems at any stage of research design, as opposed to resulting from chance fluctuation.[401] In systematic reviews, an important potential

source of bias is unequal publication of results between studies; for example depending on positive or negative findings, and smaller and larger sample sizes.[401] I have tried to assess the extent to which this has influenced results in my systematic review by performing two recognised tests for this; visual inspection of the funnel plot and Egger's test.[402] Importantly, publication bias is not the only possible cause of funnel plot asymmetry, which can also result from heterogeneity due to different methodologies between studies, and might reasonably be termed 'small study effects'. Any form of this could introduce bias, typically inflating effect estimates.[402] As I found a small degree of asymmetry in my funnel plot, it seems possible that bias resulting from small studies (two, in particular) exaggerated effects in my meta-analysis. The fact that the Egger test was not supportive of this does provide some reassurance, as does the fact that nearly all studies found some evidence of a positive association. Language bias can also affect reviews; as studies with positive findings have been noted to be somewhat more likely to be published in English.[401] The effect of this on summary estimates has however also been found to be small.[401] By searching systematically rather than in a narrative fashion, I was able to minimise bias from other sources in the systematic review.[401]

Selection bias may have affected my longitudinal ALSPAC study in chapter 4, though I took several steps to reduce this possibility. Selection bias, where participants differed systematically from non-participants in the intended sample, may take several forms.[403] Targeting one specific area with a slightly higher than average socioeconomic status may have led to selection bias at the design stage, and limited generalisability of results to the rest of the UK. The ALSPAC sample was also at risk of specific forms of selection bias: response bias, where participants who agreed to participate once invited differed systematically from those who declined, and attrition bias, where participants who remained in the study differed from participants who dropped out.[403] Attrition bias in particular has a high chance of having affected my results, as I consider it likely that young people who developed psychotic illnesses would have been less able to continue in the study or to complete all requested assessments, due to the symptoms and distress caused by illness. This would likely serve to weaken the apparent association with the exposure. Simulation in ALSPAC data shows that even

in the presence of substantial selection bias, associations found are still valid, however.[404] Further, as outlined in the relevant chapter, I used statistical methods intended to minimise the resultant bias from missing data (multiple imputation).

Bias in Mendelian Randomisation could result from a weak instrument. As previously discussed, this would bias results towards the null in two-sample MR, since the weaker the instrument, the more likely pleiotropic effects are to outweigh its effect on the exposure.[356] The stringent threshold used for each instrument SNP in primary analyses has however mitigated against this to some extent. In the presence of significant sample overlap, the bias introduced in two-sample MR can be in the direction of effect instead; but I have explained in chapter 5 why substantial sample overlap is unlikely.[355] Assortative mating is another possible source of bias in two-sample MR, and one which I have not discussed previously.[405] This occurs when genetic variants in an analysis are correlated because people with a particular phenotype are more likely to choose people with a phenotype (the same, or another) as partners, and it can create spurious associations.[405] To my knowledge, there is no consensus yet as to how best to mitigate against this form of bias. Reassurance can to some extent be taken from the fact that the association between visual acuity and schizophrenia was only found in one direction, and I would have expected to find it bidirectionally if it resulted from assortative mating.

Selection and response bias are of greater concern in my studies using UK Biobank data than those using ALSPAC data. There was a particularly low response rate in the UK Biobank (5.5%) and a recognised healthy volunteer effect making the sample systematically different to the UK population overall.[386] For this reason, it is widely acknowledged that caution must be used generalising associations found in the UK Biobank.[385] People with established psychotic illnesses were probably less likely to participate in this study, reducing power to detect associations. There is suggestion in published literature that the healthy volunteer bias in this sample might be severe enough not only to affect generalisability to the UK population, but also to invalidate associations.[385] Attrition bias could have weakened associations seen in my UK Biobank studies, as it is likely that people with psychotic illness, or other illnesses causing psychotic experiences, may be more likely to drop out. I used multiple imputation once more, but the highly resource intensive

computing power needed to impute this large dataset meant that the number of imputations I was able to reasonably generate was lower than ideal given the volume of missing data. However, I checked that the results did not markedly alter as more imputations were added. Some reassurance comes from the fact that the associations I found were consistent with studies using different samples.

8.2.3 Confounding

Confounding is a further threat to validity which almost universally affects observational studies testing causal hypotheses. Despite attempts to account for it in analyses, confounding can both be unmeasured (when levels of a confounding variable are simply unknown in research participants) and residual (when the confounding variable has been measured sub-optimally). A good example of a variable in which residual confounding can occur is socioeconomic status, since this is a complex multifaceted concept, typically adjusted for using a single measure which is arguably too blunt an instrument to capture the nuance.[312] This is highly relevant to my thesis, since lower socioeconomic status is a plausible confounder which might lead to both poorer eyesight (perhaps due to difficulty meeting costs of correction of myopia) and schizophrenia. In chapters 4, 6 and 7 I have attempted to adjust for socioeconomic status but cannot have eliminated its influence altogether for the above reasons.

In the ALSPAC study, I identified other variables which had been measured in the dataset and for which I wanted to adjust, but could not, due to unavailability or a high proportion of missing data in those variables. Examples were birth trauma, polygenic risk score for schizophrenia, and IQ prior to age 7. The possibility therefore remains that the association I identified was in fact due to these or other unmeasured confounding variables.

One significant advantage of the MR study in chapter 5 is that by design, MR reduces the influence of confounders on results by simulating the randomisation in a randomised trial. I was also able to reduce the influence from genetic confounders by excluding instrumental variants that were in linkage disequilibrium with one another. Unfortunately, I was unable to exclude the influence of

confounding on results entirely, due to the possibility that a proportion of instrumental genetic variants acted on the outcome phenotypes via confounders of the association between exposure and outcome. For example, myopia has been shown to be markedly pleiotropic with intelligence, which is negatively associated with schizophrenia.[406] Hypothetically, if a substantial proportion of the instrument SNPs in the myopia instrument lowered schizophrenia risk by increasing intelligence, then this could have artificially caused the low estimate. This could be testable in future MR studies using mediation analyses. However, the robustness of findings to a range of sensitivity analyses does provide evidence against this being the reason for the findings in most of my MR analyses.

Confounding in my study using UK Biobank data in chapters 6 and 7 warrants consideration. There were several additional putative confounding variables that I would ideally have adjusted for, including ethnicity in both studies, and vascular risk factors in the case-control study. This was not possible due to these variables being measured contemporaneously with the outcome in the case control study, or to small numbers in most categories in the case of ethnicity. Data on important putative confounding variables from earlier in life was also absent from this dataset. Some influence of confounding on results from the UK Biobank study is therefore likely, and findings from this study require replication following adjustment for a broader range of variables.

8.2.4 Reverse Causation

The group of studies giving the most consistent findings in the systematic review were cross-sectional, meaning that the temporal relationship between exposure and outcome was unknown, and making it impossible to draw conclusions about the direction of effect. My studies described in chapters 4 and 6 are longitudinal, so I have been able to comment on the temporal associations between exposure and outcome here. Nevertheless, I have been unable to fully exclude the possibility that participants had the outcome (psychotic experiences) at the time that the exposure (visual acuity) was measured in chapter 4. Therefore, it is possible that participants with perceptual distortions (as an example) from a young age were less able to visually process the acuity chart and this

that caused poorer scores, rather than the assumed converse relationship. It is also possible that poorer visual processing and resultant poorer acuity could form part of a psychosis prodrome. The same is true of my UK Biobank study from chapter 6.

I have however been able to eliminate reverse causation as an explanation for findings in the Mendelian Randomisation study in chapter 5, as it is not possible that genetic variants, allocated randomly during meiosis and conception, could result from the outcomes of either poorer visual acuity or schizophrenia.

8.3 Findings in relation to Bradford Hill Criteria

In this section, I will consider my findings in relation to each hypothesis concerning the nature of the association between visual impairment and psychosis described in the introduction.

Causality cannot be concluded with certainty from any of the work that I have produced in this thesis. As I aimed to test two causal hypotheses however, I will consider how my findings support or go against the existence of a causal association between visual impairment and psychosis. I will do this by outlining how my findings fit with Bradford-Hill's criteria for assessing the likelihood of causality in epidemiological research.[1]

Bradford Hill Criteria for Assessing Likelihood that an Association is Causal in Epidemiology

Strength of the Association: For an association to be causal, it must be strong enough to be clinically significant.

Consistency of the Evidence: Findings of association should be consistent across different settings and study designs.

Specificity: The relationship between exposure and disease outcome should be specific to that exposure and outcome

Temporal Sequence: The exposure must occur prior to the outcome

Biological Gradient: The greater the exposure, the greater to chance of the outcome (sometimes called ‘dose response’)

Biological Rationale: The possibility that exposure causes outcome should be plausible in terms of current biological knowledge

Coherence: A relationship is more likely to be causal if it is consistent with what is already known about the disease or disorder

Experimental Evidence: The relationship is more likely to be causal if the association can be produced under experimental conditions, such as in a Randomised Controlled Trial (RCT)

8.3.1 Findings in relation to hypothesis 1: Psychotic illnesses are a causal risk factor for visual impairment

Anticipating that there would be an association between visual impairment and psychosis based on previous literature, I considered the hypothesis that the association would be driven by psychotic illnesses causing visual impairment. At the most basic level, I tested whether the conditions visual impairment and psychosis were associated using the systematic review and meta-analysis, and the strength and consistency of their association. I found that they are associated cross-sectionally. A stronger effect size means that the association is less likely to be nullified once the influence of confounders is eliminated. Although there is no agreed cut-off for this, the pooled odds ratio of 1.76 (95% CI 1.34-2.31) or 1.85 (95% CI 1.17 – 2.92) is similar in magnitude to other established risk factors for psychosis. This criterion therefore may be met.

The association was seen with consistency across different populations and settings. The second criterion, that the association must be consistent, is therefore also satisfied by the results of the systematic review.

The third criterion, specificity of the association, is clearly not satisfied based on pre-existing literature. Schizophrenia and other psychotic illnesses are complex multifactorial phenomena and have known associations with a multitude of risk factors. Visual impairment is also clearly associated with other physical and psychiatric conditions, such as diabetes, and depression.[133, 281] It has been argued that the criterion of specificity is somewhat outdated, as we increasingly understand many conditions to be multifactorial, and therefore specificity is not always considered pivotal in inferring causality.[1]

The next criterion, temporality, is however crucial.[1] One variable can only cause another if it precedes it. This has proven particularly difficult to demonstrate where the exposure is psychotic illness, due to a lack of studies which follow affected people over time and test their eyesight. I have however been able to overcome this in the Mendelian Randomisation study by using genetic variants

associated with schizophrenia as proxy exposures. The results of the MR study therefore imply that schizophrenia as an exposure is temporally associated with poorer visual acuity.

Biological gradient, also known as a dose-response relationship, is the next criterion, and one which has been noted to be difficult to evidence in the context of neuropsychiatric conditions.[1] I hypothesized that psychotic illness, a binary phenomenon, rather than psychotic symptoms would be casually related to the outcome of visual impairment, which has meant that I was unable to assess for a biological gradient. This could potentially be done in future research, for example by using duration of illness as the 'dose'.

The criterion of biological rationale must be satisfied through theory and contextualising research. I have argued that there are multiple plausible mechanisms through which psychotic illnesses might cause greater visual impairment; namely, antipsychotic medications, comorbidities, poorer access to optical care. This criterion therefore appears to be met, though there is a degree of subjectivity in whether these explanations are considered plausible, and whether these proposed mediators truly lie on the causal pathway. Another pathway might be neurodegeneration occurring in schizophrenia and related illnesses affecting the retina or visual processing areas of the brain directly.

Whether the suggestion that psychotic illnesses are causally associated with visual impairment is consistent with current knowledge of the disorders (coherence) also contains a degree of subjectivity. I would argue that in view our understanding that psychotic illnesses are associated with poorer general physical health,[105] the requirement for coherence is met.

Experimental evidence is the most compelling argument for causation.[1] In the purest scientific terms, this would require inducing psychotic illnesses in a controlled manner, to find out whether doing so led to visual impairment. Clearly, ethical and practical considerations preclude this. The closest to this I could achieve in my thesis was to conduct the Mendelian Randomisation study to

simulate a randomised controlled trial. Since findings from this were suggestive of a causal association, I would conclude that the requirement for experimental evidence is partially satisfied.

Regarding the criterion of analogous association, I tested to see whether a similar association was found between schizophrenia and related disorders, and dental caries in chapter 5.[1] The negative association was supportive of non-receipt of optimal healthcare contributing to an association with poorer visual acuity. I have not tested for similar analogous associations in the other studies in my PhD, although arguably previous research as done this. Known associations between schizophrenia and poorer diabetes control,[407] or later diagnosis of cancer,[408] are possible examples.

Considering the above, I would conclude that my findings overall support the possible existence of a causal effect of psychotic illnesses on visual impairment, albeit a possibly indirect one. The most important criteria in establishing a causal relationship: consistent association, temporality, biological plausibility, and experimental evidence, have all been met or partially met in my findings. Caution is needed in interpretation of the word 'cause' here however, since the association might still result from shared actions of genes on the developing brain or eye, or from neuropathology that is inherent in schizophrenia, and these might not fit with traditional notions of causation.

8.3.2 How my findings regarding hypothesis 1 relate to previous literature

There are several previous studies of which I am aware that directly test the hypothesis that people with psychotic illnesses have poorer visual acuity due to lower rates of correction of refractive error. These were outlined in the introduction and again in the relevant chapters. The largest, a Finnish study by Viertio and colleagues, investigated whether visual acuity was poorer in people with schizophrenia compared with the general population using a nationally representative sample of 6,663 participants.[119] This found that schizophrenia was associated with fivefold odds of having distance acuity impairment (OR 5.04, 95% CI 1.89–13.48) after adjusting

for age and sex, and further that only 44% of people with schizophrenia had accessed eyesight tests within the past five years, compared to 70% of the general population.[119] A second, small UK study did not use a comparator group but surveyed people using psychiatric services due to serious mental illnesses, and found a similarly low rate of uptake of optical screening.[127] A similar Australian study found that around 70% of inpatients with schizophrenia had untreated visual acuity problems.[126] This was similar to a study in Hong Kong, which estimated rates at 75%.[124] A study in China found lower rates, but also used more stringent cut-offs.[125] My findings that psychotic illnesses are likely to be a causal risk factor for visual impairment are therefore supported by the findings from these studies, which further imply that non-correction of refractive error is one important mechanism.

8.3.3 Findings in relation to hypothesis 2: Visual impairment may be a causal risk factor for psychosis

According to the Protection against Schizophrenia (PaSZ) model, the presence of both lifelong perfect and absent vision might be protective against schizophrenia, with aberrant visual input at any stage in life being a risk factor. I was unable to test the premise that congenital blindness is protective, due to the very large samples which would be required for this. I have however been able to test an extension of the PaSZ model which infers that less severe, or shorter duration of visual impairment than congenital blindness is a causal risk factor for psychosis.

The findings regarding the strength and consistency of the association between visual impairment and psychosis in the cross-sectional studies from the systematic review would support my second hypothesis as equally as my first. The evidence from the longitudinal studies is however more important, as temporality of the association is also tested in these. Since these found varied and sometimes contradictory results, I cannot say that there was consistent evidence of an association between visual impairment as exposure and psychosis as outcome in the systematic review. I did however find consistent evidence of a temporal association in children, though

this related to ocular dysfunction generally, rather than poorer acuity specifically. Due to the mixed findings across studies, I could not conclude that this criterion was satisfied in other age groups.

The criterion of specificity has been argued to be relevant regarding congenital blindness being protective, since there are very few medical conditions proposed to protect against schizophrenia, with the possible exception of rheumatoid arthritis.[121] This criterion cannot be said to apply to visual impairment as a risk factor however. If anything, the association of schizophrenia with a vast array of physical health conditions seems to reinforce that association alone is not enough to suggest causality in this area of research.[118]

I was able to demonstrate a temporal relationship between visual impairment as exposure and psychotic experiences as outcome, to some extent, in the longitudinal study of children described in chapter 4 and the study of adults in chapter 6. However, although I was able to show that the exposure was associated with the outcome when measured subsequently, I was unable to exclude presence of the outcome at baseline, meaning that this criterion is not conclusively satisfied.

Given the proposed bell shape of the PaSZ model, the traditional linear dose response relationship between exposure and outcome might not apply in this relationship. Theoretically, it still applies up until the highest-risk level of visual capacity at the peak of the distribution, but it is unknown at what level of visual capacity this occurs. The implication of congenital blindness, but not later-life blindness or other visual impairment contributing causally to psychosis, seems to be that any dose response-relationship only ceases to be relevant in very severe visual impairment. My studies in chapters 4 and 6 both showed that the odds of psychotic experiences increased with each 0.1-point worsening of visual acuity on the logMAR scale, which would be supportive of a dose-response relationship, but I did not test non-linear models.

The detailed biological rationale for the PaSZ model is elegantly described,[121, 136] but this is less well understood than the simpler mechanisms proposed in hypothesis 1. There is also limited literature describing this theoretical causal mechanism.

Similarly difficult is concluding whether a causal association between visual impairment as exposure and psychosis as outcome is consistent with existing knowledge of these disorders. Life stressors and traumas are known risk factors for psychotic illness, and development of a visual impairment could clearly constitute a stressor. However, the proposal in the PaSZ model is that aberrant vision or visual processing have relevance to the development of schizophrenia through a range of neurological mechanisms, as described in the introduction, and the consistency of this relatively novel theory with existing knowledge is more difficult to judge.

Regarding hypothesis 2, the closest study to an experimental design, the MR study, did not support a causal association. In fact, the results refuted that myopia, at least, is a causal risk factor for schizophrenia.

An analogy could perhaps be drawn with hearing impairment, which is a recognised risk factor for psychotic illnesses and cognitive disorders which might result in psychotic symptoms.[153, 209] The analogy is however suboptimal, since congenital deafness is not proposed to be a protective factor, unlike congenital blindness.

Overall, I conclude that I have not sufficient found evidence to take the stance that visual impairment is causally associated with the outcome of psychosis, either illnesses or symptoms, in this PhD due to the lack of consistent temporal evidence in the systematic review, the experimental evidence in the MR study countering this, and the existence of alternative explanations for the longitudinal associations found in chapters 4 and 6. I also cannot conclude with certainty that visual impairment is not a causal risk factor for psychosis, for reasons outlined in the next section.

8.3.4 How my findings regarding hypothesis 2 relate to previous literature

My conclusion that I have not found evidence that visual impairment is a causal risk factor for psychosis appears to contradict previous longitudinal studies investigating visual impairment as exposure and psychosis as outcome which found a positive association between the two. There are several possible explanations for these discrepancies. The positive findings in two studies of adolescents (including my own), two of children, and three of older adults (again including chapter 6), might have resulted either from shared neuropathology or confounding given the results of my MR study.[13, 216, 220, 224, 225] An alternative explanation for the discrepancy with the positive findings in the studies of children, however, is that visual impairment could have causal relevance in the development of psychosis, but only during a critical period of neurodevelopment in childhood. The distinction between psychotic illnesses and psychotic experiences or symptoms might also explain the discrepancy. Perhaps, visual impairment is causally associated with psychotic experiences through the route of common mental illness, rather than schizophrenia, which would not have been captured in my MR study. Alternatively, perhaps the visual impairment seen at baseline in the previous cohort studies was in fact the result of a long psychosis prodrome, despite attempts to exclude this.

The negative association seen in the other previous study of adolescents and the remaining previous study of older adults are difficult to explain, but seem most likely to result from differences in the way exposure and outcome status was ascertained in these studies, since both appear to have captured severe visual impairment specifically.[14, 170] If severe visual impairment actually protects against psychotic disorder; one possible implication of the PaSZ model, then this may still be compatible with mild visual impairment having no effect as found in my MR study, but further research would be needed before concluding this.

8.3.5 Findings in relation to alternative hypothesis: Visual impairment may share underlying neuropathology with psychosis

This hypothesis has been relevant throughout my PhD although I did not aim to directly test it. The consistent association seen between visual impairment and psychosis in cross-sectional studies in the systematic review is equally consistent with this hypothesis as hypothesis 1. Unlike hypothesis 2, the mixed findings in longitudinal studies do not provide evidence against this hypothesis since it makes no claim regarding the temporal association between the variables.

For the same reason, my finding in chapter 4, that visual impairment in childhood is associated with psychotic experiences in adulthood is consistent with shared underlying disturbance to the developing central nervous system. The same applies, regarding a neurodegenerative perspective, to the findings in older adults in chapter 6. The results from the MR study might also be explained through this hypothesis if shared genetic aetiology underlies both visual impairment and psychosis. In this case, the fact that I only found the association in one of the two directions in this study would suggest that it might be biological pathways typically associated with schizophrenia, rather than myopia, which underlie such shared aetiology.

In reality, there is not insubstantial overlap between my first hypothesis (that psychotic illness is a causal risk factor for visual impairment) and the alternative hypothesis of shared underlying neuropathology between the two conditions, since schizophrenia and related disorders might 'cause' visual impairment through their inherent neuropathology. The studies referenced throughout this thesis which show retinal thinning and altered retinal function and vasculature, or altered visual processing in schizophrenia, are supportive of this mechanism.

8.4 Implications of Findings

In this section, I will discuss some potential implications of my findings, focussing on clinical practice, policy, and research. Great caution is required in making causal inferences from observational research, but I have aimed to make use of the best available methodology to provide evidence in support of or against each relationship being causal. Even where I have concluded that causality is likely, it must be borne in mind that both visual impairment and psychosis are highly multifactorial conditions, and it is likely rare that a single causal risk factor alone could result in the outcome condition.

8.4.1 Implications from testing hypothesis 1

The most important finding from my research appears to be that people with psychotic illnesses are at greater risk of poorer visual acuity. It is beyond the scope of my PhD to determine the exact mechanisms by which psychotic illnesses might predispose to or cause visual impairment. Based on the low rates of glasses use identified in several studies, I would suggest that non-correction of refractive error is one candidate mechanism underlying the proposed causal association, although there are others and the association is probably multifactorial.

8.4.1.1 Visual screening for people with psychotic illnesses

Regardless of the mechanisms underlying the association, it highlights a need to support people with psychotic illnesses to access appropriate optical care at the same levels as the general population. Public Health England describes health inequalities as 'unavoidable and unfair differences in health status and determinants between groups of people due to demographic, socioeconomic, geographical and other factors', and has a focus on reducing these inequalities for people with mental illnesses.[409] This is crucial as this group already faces disadvantage in terms of opportunities for employment, wealth, and access to wider healthcare.[409] Calls to reduce health inequalities for people with serious mental illness frequently focus on cardiovascular comorbidities,[410] but there is a

case for improving vision as it is important to quality of life and as outlined in my introduction, marked visual impairment introduces other barriers to optimal healthcare. Arguably, people with psychotic illnesses might warrant targeted testing of eyesight, as is already recommended in some countries.[110] The UK annual physical health check, where several physical parameters are measured, might be an ideal opportunity for this.[4] The current National Institute for Clinical Excellence guidelines for schizophrenia and psychosis do not reference visual impairment or eye care, except to acknowledge blurred vision as a possible side effect of antipsychotic medications and to once mention an optician as a possible healthcare contact.[411] The 2016 Five Year Forward View for Mental Health report by the UK government's mental health taskforce specified that: *NHS England should also lead work to ensure that by 2020/21, 280,000 more people living with severe mental illness have their physical health needs met by increasing early detection and expanding access to evidence-based physical care assessment and intervention.*[412] Performance of these checks is incentivised by the Quality Outcomes Framework in England.[413] Again, eye care is not referenced. For visual screening to be widely offered, it is likely these guidelines would need to be updated. In addition, coordinated efforts to encourage adherence would likely be needed, since there is evidence that without this, uptake of the current guidelines is lower than 20%.[414]

8.4.1.2 How this complements existing policy

I referenced the NHS long-term plan in my impact statement.[2] Aims of the long-term plan include reducing inequalities in health, expanding mental health service provision, and improving secondary prevention to minimise complications of established chronic illness. Arguably, improving eyesight screening and correction for people with serious mental illnesses is in line with all three of these aims. The plan also discusses widening access to digital appointments. Since the Freiburg eye test is computerised and freely available online, it may be possible for staff to use this to support patients who do not attend in person.[415] A further key facet of the long-term plan is establishment of Integrated Community Services which bring together primary and secondary healthcare teams, including mental healthcare teams, so that patients can access everything they need in one place.[2] Since 2022 these have been legal entities with statutory basis, and they have obligations both to reduce inequalities and to use resources sustainably and efficiently.[3]

Each includes an Integrated Care Board responsible for planning funding, which must set out a five year plan outlining how they will meet the needs to of the population, and must include a panel member with expertise in mental health.[3] Primary care networks, which cover a smaller number of patients and are led by general practice staff, have also been established to facilitate sharing of information between different healthcare services and facilitate easier access to healthcare.[416] Optical care could be considered in this.

Screening people with psychotic illnesses for eyesight problems is also in line with the recent global Right to Sight initiative, which aimed to reduce the burden of avoidable visual impairment, defined as cataract and uncorrected refractive error, worldwide by 25% by 2019.[5] The lack of success shows that more assertive, approaches may be needed in future, which could include proactive screening of at-risk groups.

8.4.1.3 Practicalities of Implementation

As described in my introduction optician services have traditionally been private and separate from other healthcare services in the UK, but the focus on joined-up care to accommodate the increasingly complex health needs of individuals could be complemented by easier and more routine referral pathways from mental health services or primary care into opticians for people with psychotic illnesses. The reverse could also be considered; pathways for high street opticians to refer people into primary care and mental health services for suspected psychotic illnesses, since my findings imply that opticians might be likely to come into contact with these individuals.

There are potential barriers to implementation of this however, including limited staff time, competing demands, costs, and particularly, unclear pathways for further optical care once an abnormality has been detected. Future research would need to investigate the effectiveness acceptability, cost-effectiveness, and quality-of-life implications of such an intervention. I will discuss this further in the next section. If these suggestions were assessed with encouraging results, then it might be feasible to add eyesight checks, such as

basic Snellen chart testing, into guidelines and policy documents that determine best practice for annual physical health checks. The practical barriers to implementation would still however need to be overcome. There is cause for optimism however, as the Royal College of Psychiatrists' report on integrating mental health services in line with the NHS long-term plan notes a growing number of psychiatrists, and impetus to improve the physical health of people with serious mental illnesses.[417]

8.4.1.4 Further Implications for Clinicians

Even if widespread visual screening for people with psychotic illnesses is not conducted, awareness of the potential for visual impairment in serious mental illness could still be improved amongst clinicians including GPs and psychiatrists. This might allow targeted interventions for affected patients. Improved awareness could be achieved relatively easily by adding the simple fact that people with serious mental illnesses are at increased risk of poorer vision into the exam syllabus for psychiatrists.[418]

8.4.1.5 Further Implications for National Health Service Policy

Perhaps the NHS could fund free eyesight testing for people with serious mental illness by an optician, as it does for people over 60, children, people on low incomes or people with or predisposed to eye disease.[419] Public health messaging about eye care for the whole population could also be reviewed. Routine attendance for eye examinations might lead not only to refractive error, but also to more serious eye diseases being identified and treated.[420] It has been argued that currently, attending for eye tests is approached in a reactive, rather than preventative manner by most people, but this might lead to eye diseases being identified after they have progressed and are less treatable.[420]

8.4.1.6 Further Implications for non-government organisations

Organisations that advocate for the rights of visually impaired people, such as the Royal National Institute for the Blind, may be able to use the findings from this thesis to enable them to consider how to best support people with serious mental illnesses who may be

at heightened risk for visual impairment. Organisations which exist to support and advocate for people with mental illnesses, for example MIND, or the Royal College of Psychiatrists, could include information about how to access eye tests and when appropriate free visual aids in information for patients and carers.[421, 422] Further, organisations such as The Kings Fund, which aim to improve healthcare policy, could also consider advocating for improving access to visual testing and treatment in their information regarding reducing healthcare inequalities for people with serious mental illness.[423]

8.4.2 Implications from Testing Hypothesis 2

A second key finding from my thesis is that according to genetic evidence, myopia is not causally implicated in the development of schizophrenia. Whilst it cannot be assumed that this generalises to other forms of visual impairment, particularly more severe forms of visual impairment, it does suggest that future research in this area should consider other non-causal explanations for the association between visual impairment as exposure and psychosis as outcome. I found no convincing evidence in my PhD that impaired visual acuity is a candidate target for prevention of psychosis. This is however still compatible with Cognitive Remediation Therapy that targets visual processing having potential benefit in treating negative symptoms of psychosis.

8.5 Future Research Questions

Here, I make suggestions for further research questions in this field. Perhaps the most important question arising from my findings is: what are the mechanisms by which psychotic illnesses act as causal risk factors for poorer eyesight? Improved understanding of this has potential to improve efforts at preventing or correcting visual impairment in this group. There are also several other questions that would need to be answered before recommending that eyesight testing is incorporated into the annual physical health check for people with serious mental illness. Examples are: 1) How severe is visual impairment that typically affects people with psychotic illnesses; 2) What is the impact upon quality of life of visual impairment in people with psychotic illness; 3) Does visual acuity testing

at the annual physical health check improve ocular or other health outcomes for people with serious mental illnesses; 4) Are people with serious mental illnesses supportive of eyesight testing at the annual physical health check; 5) Is adding eyesight testing to the annual physical health check cost effective, and; 6) How extensive is the inequality in access to eyesight testing and visual impairment prevention for people with psychotic illnesses?

To answer these, I propose several possible avenues. Qualitative work, such as one-to-one interviews and focus groups with people affected by psychotic illnesses and their carers, could be beneficial in terms of understanding the importance of eye care to members of this group, and whether they feel that assertive eye care intervention would be a helpful addition to the healthcare they receive. In particular, people with known visual impairments alongside psychotic illnesses could be included in focus groups. Healthcare professionals, such as psychiatrists and nurses who carry out the annual physical health check, should also be consulted. This might help to answer questions 2 and 4 above regarding importance and acceptability of screening.

To determine the severity of visual impairment, a cohort of people with psychotic illness diagnosis could be invited to participate in a pilot of eyesight testing. Although cross-sectional samples of inpatients have participated in this screening,[126, 127] people living in the community should be included for representativeness, and longitudinal work could assess the impact of testing. This sample could be recruited through routine appointments in a community mental health team, perhaps in a cluster Randomised Controlled Trial. The nature of the testing and subsequent signposting for individuals found to have suboptimal visual acuity could be co-produced perhaps with members of the focus groups. A cost effectiveness analysis could be conducted using the same data.

Another question for future research is that of generalisability, since the cohorts I have used in my research mainly consisted of White participants or participants with European ancestry due to data availability. In recognition of the need for improved inclusivity, more recent genetic cohorts have targeted different ancestry groups, for example people with South Asian ancestry.[424] As more is

understood about genes associated with schizophrenia and visual impairment, this information could be used to replicate my MR findings and ensure that they apply to some of the people who might be most affected by this association.

To answer the question as to the extent of inequalities in access to eyecare that affect people with psychotic illnesses, access to large datasets including both optical and primary healthcare records would be needed. This may require linkage of usually disparate data sources to perform a large cross-sectional or cohort study. Similar studies have been conducted into uptake of eyesight tests by area using data from free eyesight test claim forms.[419, 420] The authors of these studies proposed that these forms should be digitised to make them more accessible for research, and that private eye test data should be included. If this were done it could be possible, in principle, to carry out an equivalent study to assess differences in uptake according to presence of mental illness.

Regarding hypothesis 2, I have not been able to answer the question as to whether visual impairment might contribute causally to psychotic symptoms in a broader context than schizophrenia and related disorders; for example through dementia or common mental illness. This is another potential topic for future research and could perhaps be addressed through longitudinal analysis of large cohorts of older adults including people with cognitive impairment. Mendelian randomisation with different types of visual impairment, such as age-related macular degeneration, lends itself to addressing the question of whether typically more severe forms of visual impairment than myopia are a causal risk factor for schizophrenia and related illnesses.

The alternative hypothesis may be testable through imaging studies, which have already been described in detail.[76] In the field of retinal imaging, other key questions for future research include: at what stage of psychotic illness does retinal thinning occur?; can retinal alterations be used for diagnostic or prognostic purposes in psychotic illnesses; and do retinal alterations mirror cerebral neuropathology in schizophrenia and related illnesses? The former are testable through well-designed cohort studies of at-risk groups, and the latter might inform development of new treatments, as a distal target of this research. Improved genome-wide association

study data and understanding of functional genomics might also lead to identification of shared genetic mechanisms to psychosis and poorer eyesight which support the alternative hypothesis.[425]

8.6 Conclusions

I tested two key hypotheses in this PhD thesis; firstly, that psychotic illnesses are causally associated with the outcome of visual impairment and secondly, that visual impairments are causally associated with the outcome of psychosis. I found evidence in support of the first hypothesis. I found insufficient evidence in support of the second hypothesis to imply a causal relationship, but also could not conclusively discount this across age groups and types of the exposure and outcome. Much of the evidence I have found is also supportive of shared neuropathology between psychotic illnesses and visual impairments, in line with my alternative hypothesis which was not directly tested. The key clinical implication from my PhD is that people with psychotic illnesses appear to be at increased risk of visual impairment, which could adversely impact quality of life in an already disadvantaged population. Therefore, strategies to improve eye care for people with psychotic illnesses should be considered.

Chapter 9 References

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9.1 Appendix D: Chapter 5 Supplementary Table: Odds of Reporting Psychotic Symptoms at Follow-up According to Eyesight Variables at Baseline, Excluding Participants with Missing Exposure Data

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=113,026	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 – 1.12]	0.021
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
Right macular thickness - per µm N=64,370	1.00 [0.99 – 1.00]	0.621	1.00 [0.99 – 1.00]	0.567	1.00 [0.99 – 1.00]	0.631	1.00 [0.99 – 1.00]	0.759
Left macular thickness - per µm N=63,951	1.00 [0.99 – 1.00]	0.886	1.00 [0.99 – 1.00]	0.822	1.00 [0.99 – 1.01]	0.973	1.00 [1.00 – 1.01]	0.835
Overall right retinal pigment epithelium thickness - per µm N=64,370	1.00 [1.00 – 1.00]	0.389	1.00 [1.00 – 1.00]	0.494	1.00 [1.00 – 1.00]	0.529	1.00 [1.00 – 1.00]	0.691
Overall left retinal pigment epithelium thickness - per µm N=63,951	1.00 [1.00 – 1.00]	0.303	1.00 [1.00 – 1.00]	0.344	1.00 [1.00 – 1.00]	0.395	1.00 [1.00 – 1.00]	0.571

Model 2: Adjusted for baseline anxiety and depression score, 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

9.2 Appendix E: Chapter 7 Supplementary Table: Results from Nested Case Control Study: Odds of Prior Schizophrenia-Spectrum Disorder Diagnosis in Group with Visual Impairment compared to Group Without, Excluding Participants with Missing Outcome Data

	Model 1: Unadjusted **Odds Ratio [95% CI]**	**P-Value**	**Model 2: Adjusted for age and sex**	**P-Value**	**Model 3: Adjusted for age, sex, socioeconomic status and age at leaving full time education**	**P-Value**
Multiply imputed dataset **N=114,793**	1.50 [1.12 – 2.01]	0.006	1.86 [1.38 – 2.51]	<0.001	1.41 [1.04 – 1.91]	0.025
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