Protocol: Association between visual acuity and subsequent psychotic-like experiences in the Avon Longitudinal Study of Parents and Children V.2

Natalie Shoham[1]

[1]University College London, University of London, Camden and Islington NHS Foundation Trust

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Natalie Shoham

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ABSTRACT

This is a protocol for a planned secondary analysis of longitudinal data, investigating whether there is an association between visual acuity and future psychotic symptoms in children.

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WHAT'S NEW

Exposure variable has been defined in greater detail

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Background and Rationale

Evidence exists for an association between visual acuity impairment and psychosis [1, 2]. The reasons for this are not fully understood [3]. Possible explanations include: that visual acuity impairment contributes to causing psychosis [4]; that the same neuropathological processes underlie both visual acuity impairment and psychosis [5]; that there is poorer access to eye care for people with psychotic illnesses [2]; or that confounding variables create an apparent association.It has been hypothesised that both perfect vision and complete congenital blindness could protect against schizophrenia in the 'Protection Against Schizophrenia' model [4, 6]. A longitudinal association between reduced visual acuity and subsequent hospitalisation due to schizophrenia has been robustly demonstrated in a sample of over 1 million men [7], whilst a similarly large 2009 study found the reverse association [8]. Improved understanding of the association between visual impairment and psychosis could ultimately improve the quality of care provided to people with both conditions.

Aims

1)To explore the relationship between visual impairment and subsequent psychotic symptoms in a large longitudinal birth cohort.

Hypotheses

1)In the ALSPAC birth cohort lower best corrected visual acuity scores at age 7 and 11 will be associated with higher odds of scoring positive on the Psychosis-like Symptoms Semi-structured Interview (PLIKSi) at age 13, 17, and 24.

Study Design and Plan

The Avon Longitudinal Study of Parents and Children (ALSPAC) is a longitudinal birth cohort of 14,500 families from the Avon area [9]. The cohort was enrolled between April 1991 and December 1992. Data from when the children were aged 24 have been released. We will employ secondary analysis of this pre-existing observational data set for this study.

Sample Size

The sample-size will be determined by the number of participants in the original ALSPAC study who have complete data for exposure and outcome variables.

Exposure Variables

The exposure variables will be best corrected visual acuity at ages 7 and age 11, visual acuity impairment category, between-eye difference in visual acuity, and wearing glasses.

Trained orthoptists carried out detailed visual assessments with children in the ALSPAC cohort, overseen by ophthalmologists, when children were aged 7 and 11.

Primary exposure Variables: Best Corrected Visual Acuity aged 7 and 11

Visual acuity was measured, with participants wearing their glasses if needed, using an Early Treatment of Diabetic Retinopathy Study (ETDRS) chart. Children wore their glasses unless they had not used the glasses for 6 months or more. Testing was performed monocularly only, using patches to occlude one eye. For children who did not know the alphabet, carers supported with matching cards. Children were encouraged to guess when unsure. The test was repeated using a pinhole. Best visual acuity was defined as whichever was the better measurement, with or without the pinhole. Children were moved to 0.5, 1, or 2 metres away from the chart if needed to allow them to read some of the letters.

We will use the best eye LogMAR score as a continuous exposure variable, with the unit change being 0.1 on the LogMAR scale.

Although a small number of children had visual acuity measured using Cardiff cards due to inability to cooperate with testing using the standard chart, we will not combine these results with the others due to evidence that they may not be fully compatible [10].

Wearing glasses

During the visual assessment, carers were also asked whether children wore glasses. We analysed this as a binary exposure variable (yes / no).

Visual Acuity Impairment Category

We will also test visual acuity impairment as a categorical variable with four categories: normal vision (LogMAR </= 0) without glasses; normal vision with glasses; visual acuity impairment (LogMAR > 0) without glasses; or visual impairment with glasses.

Between-Eye Visual Acuity Difference
Lastly, we will between-eye visual acuity difference as a continuous exposure variable.

Outcome Variables

Psychotic-Like Experiences
Psychotic-Like Experiences Interview (PLIKSi): The PLIKSi is a semi-structured interview designed to elicit psychotic symptoms in the general population. It includes core questions designed to detect positive symptoms of psychosis (hallucinations, delusions, and thought interference). Each item is rated as "suspected" or definite by interviewers, and symptoms occurring only in the context of partial sleep states or fever are excluded [11]. The PLIKSi was administered to participants at ages 13, 17, and 24, and has been validated in ALSPAC data [11]. The primary outcome measure will be suspected or definite symptoms suspected on PLIKSi at age 24. PLIKSi result at ages 13 and 17 will be tested separately. We will assess these as a binary variable dichotomised according to whether there are suspected or definite psychotic symptoms vs none.

Confounding Variables

The following variables have been measured in the ALSPAC dataset and will be considered a priori as putative confounders:

Basic Minimal Adjustment

1)Birth sex of child (male / female): there is some evidence that male gender might increase risk of psychosis [12]

2)Ethnicity of mother and mother's partner: people who are in an ethnic minority in their country of residence are also known to be at higher risk [13]

3)Categorical socioeconomic group of mother and mother's partner: being in a in lower socioeconomic group may increase the risk of psychosis [13] and lessen opportunity to access opticians.

Others

4)Age of mother and mother's partner in pregnancy and mother's partner's age in pregnancy as categorical variables: There is evidence that older paternal age is associated with schizophrenia, and maternal age is well-known to be associated with risk of chromosomal abnormalities which can increase risk of eyesight problems and mental illness [14]. Parental age <20 has also been associated with psychotic illness in offspring, which is why this variable will not be included as a continuous variable[14]. Categories will be <20, 21-29, 30-34, and 35+.

5)Requirement for resuscitation at birth: This is a marker of birth hypoxia. There is clear evidence that birth hypoxia can cause both visual impairment and psychosis [15, 16]. We will assess this as a dichotomous variable, i.e. resuscitation at birth or no resuscitation at birth, as it is expected that the need for resuscitation rather than the method used will be the confounder.

6)IQ: Intellectual disability is a risk factor for psychosis [17] as well as being associated with visual impairment [18]. IQ aged 8 will be analysed as a continuous variable.

7)Higher educational level is known to predispose to myopia [19], and might also be a protective factor against psychosis [12], so could plausibly lead to negative confounding of the relationship between visual impairment and psychosis.Parental educational level will used as a proxy as this has been measured before the exposure, unlike participant educational level. This will be a categorical variable.

8)Hearing impairment: Hearing impairment co-occurs with visual impairment in certain genetic conditions and birth complications [20]. It is also a risk factor for psychosis, and therefore may confound the association [21]. Presence of significant hearing impairment at age 7 will be analysed as a binary variable (normal hearing vs any impairment).

9)Standardised Polygenic Risk Scores (PRS) for schizophrenia and bipolar affective disorder will be tested [22]; to mitigate against the possibility that an association between myopia and psychosis is purely due to shared genetic vulnerability. These will be a continuous variables.

10)Parity: There is evidence that higher parity increases risk of psychosis [14] but being first-born increases risk of myopia [23], leading to a possibility of negative confounding by birth order. This will be included as a continuous variable.

11)Mother's daily vitamin D intake in pregnancy: vitamin D deficiency has been shown to be associated with both myopia and schizophrenia [24, 25]. This will be included as a continuous variable.

12)Maternal diagnosis of diabetes or hypertension reported during pregnancy: there has been some evidence linking diabetes in pregnancy with hallucinatory experiences in offspring[26], and in mouse models diabetes disrupts ocular development [27]. Similarly maternal hypertension is a risk factor for psychosis [14] and myopia [23]. These will be assessed as binary variables (present / absent).

13)Infection during pregnancy: there is evidence that in-utero exposure to infection can increase the risk of both psychosis and ocular pathology [28, 2930]. Again, this will be assessed as a binary variable (present / absent).

14)Mother used alcohol in 1-3 months of pregnancy , maternal smoking in first 3 months of pregnancy, and maternal use of recreational drugs in pregnancy: There is evidence that maternal use of alcohol and tobacco during pregnancy increases the risk of psychosis and ocular pathology in offspring[3132], and recreational drug use has been linked with ocular and cerebral changes [33]. Alcohol use will be a categorical variable: none; < 1 glass per week; or > 1 glass per week, due to low numbers in higher categories and limited evidence that drinking < 1 unit per week in pregnancy is harmful [34]. Tobacco use will be a binary variable (yes / no). Drug use will also be binary; reported use of any recreational drug vs none.

15)Parental history of depression: these variables will be dichotomised as present / absent. Parent depression could plausibly be associated with neglect of children's eyesight and shared genetic vulnerability to mental illness.

16)Parental history of sight problems at time of pregnancy. This is to aim to mitiagte against the possiblity of shared genetic liablity to myopia and psuychosis accounting for any association.

The above putative confounding variables will be included in final models if there is evidence of attenuation of the effect size. Variables will not be included as confounders if their introduction leads to significant problems with sparsity or missing data. Where this is a problem, we will consider testing the association in the subset who do have this information available as a sensitivity analysis.

Sensitivity Analysis

As a sensitivity analysis, we will also explore different components of the PLIKSi individually.

Statistical Test

We will use the statistical package STATA SE 16 [35] to analyse the results. We will use univariable (unadjusted) and multivariable (adjusted) multilevel logistic regression models to assess for an association between these variables. Odds ratios, 95% confidence intervals, and p-values will be reported.

Missing Data

If there is evidence that data is missing at random then we will use multiple imputation to assess and report on the likely effects of the missing data [36].

Anticipated Strengths and Limitations

Strengths of the proposed study include use of one of the largest, most detailed birth cohorts available to seek longitudinal evidence of an association between visual impairment and psychosis beginning in childhood [9]. To our knowledge this would be the first study to test an association using a childhood exposure of this type, and the first longitudinal study to test this association including female participants.

Limitations include the potential for attrition bias. There is likely to be a significant amount of missing data given that ALSPAC is a longitudinal cohort study. Previous studies have found that only half of the cohort had complete data necessary for analysis [37]. It is plausible that people who develop psychotic illnesses are less likely to remain in the study, which might lead to weakening of any genuine association. Missing data may introduce similar bias into the results, though the planned use of multiple imputation aims to address this.

A further limitation is the inability to link ALSPAC to hospital records in this study. The PLIKSi is designed to measure psychotic-like experiences, rather than psychotic illnesses, which are of greater clinical relevance. In keeping with this the PLIKSi has shown poor correlation with polygenic risk scores for schizophrenia, showing that psychotic-like experiences do not entirely overlap with propensity to develop psychotic illness [38]. The use of self-reported schizophrenia diagnosis as a secondary outcome measure is intended to strengthen validity of findings.

Residual and unmeasured confounding remains a possibility given that the exposure in this study cannot be allocated at random.

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