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Protocol: Association between visual acuity and subsequent psychotic-like experiences in the Avon Longitudinal Study of Parents and Children V.1

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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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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 Avon Longitudinal Study of Parents and Children (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 age 7 and age 11.
Visual acuity was measured with participants wearing their glasses or contact lenses using LogMAR testing and will be dichotomized into no visual impairment (LogMAR0 or less), or visual impairment (LogMAR > 0). We will also test it as a continuous measure, with the unit change 0.1 on the LogMAR scale.

Outcome Variables

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 [10]. The PLIKSi has been validated in ALSPAC data [10]. The primary outcome measures will be suspected or definite symptoms suspected on PLIKSi at age 13, 17, and 24 separately. We will assess this as a binary variable dichotomised according to whether there are suspected or definite psychotic symptoms vs none. The PLIKSi is typically used as a binary measure [11].

Confounding Variables

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

1)Birth sex (male / female) ethnicity of mother and partner, and categorical socioeconomic group (highest of mother / partner – as an ordinal variable) in pregnancy will be included in the models as minimal adjustment. There is some evidence that male gender might increase risk of psychosis [12], and people who are in an ethnic minority in their country of residence or in lower socioeconomic groups are also known to be at higher risk [13], and may be less likely to be able to access opticians.

2)Age of mother 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+.

3)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. If this is not possible, we will use Apgar score at 5 minutes categorized as <7 or 7+ [17] as a proxy.

4)IQ: Intellectual disability is a risk factor for psychosis [18] as well as being associated with visual impairment [19]. IQ aged 8 will be analysed as a categorical variable, <70 or 70+.

5)Higher educational level is known to predispose to myopia [20], 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. Parental educational level will be used as a categorical variable.

6)Hearing impairment: Hearing impairment co-occurs with visual impairment in certain genetic conditions and birth complications

[21]. It is also a risk factor for psychosis, and therefore may confound the association [22]. Presence of significant hearing impairment at age 7 will be analysed as a binary variable. (normal hearing vs any impairment).

7)Polygenic Risk Score (PRS) for schizophrenia[23], PRS for Bipolar affective disorder [23]; to mitigate against the possibility that an association between myopia and psychosis is purely due to shared genetic vulnerability. This will be a continuous variable.

8)Parity: There is evidence that higher parity increases risk of psychosis [14] but being first-born increases risk of myopia [24], leading to a possibility of negative confounding by birth order. This will be included as a continuous variable.

9)Mother's daily vitamin D intake in pregnancy. Vitamin D deficiency has been shown to be associated with both myopia and schizophrenia [25, 26]. This will be included as a continuous variable.

10)Mother's diagnoses by pregnancy: diabetes,hypertension:
There has been some evidence linking diabetes in pregnancy with hallucinatory experiences in offspring[27], and in mouse models diabetes disrupts ocular development [28]. Similarly maternal hypertension is a risk factor for psychosis [14] and myopia [24]. These will be assessed as binary variables (present / absent).

11)Conditions during pregnancy: rubella influenza herpes. There is evidence that in-utero exposure to infection can increase the risk of both psychosis and ocular pathology [29, 3031]. Again, these will be assessed as binary variables (present / absent).

12)Mother used alcohol in 1-3 months of pregnancy, maternal smoking in first 3 months of pregnancy, and mother's recreational drug use in pregnancy. There is evidence that maternal use of alcohol and tobacco during pregnancy increases the risk of psychosis and ocular pathology in offspring[3233], and recreational drug use has been linked with ocular and cerebral changes [34]. 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 [35]. Tobacco use will be a binary variable (yes / no). Drug use will also be binary; reported use of any recreational drug vs none.

13)Parental history of mental illness by time child aged 11: depression, schizophrenia. Family history of psychotic illness has been found to be associated with ocular abnormalities from a young age, and is a well-known risk factor for psychotic illness [36]. These variables will be dichotomised as present / absent.

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 sensitivity analyses, we will also explore different components of the PLIKSi individually, and whether any association remains when only 'definite' symptoms are considered.

Statistical Test
We will use the statistical package STATA SE 16 [37] to analyse the results. We will use univariable (unadjusted) and multivariable (adjusted) 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 [38].

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 [39]. 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 [11]. 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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