Schizophrenia risk alleles and neurodevelopmental outcomes in childhood: a population-based cohort study

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Summary
Background Schizophrenia typically onsets after puberty but is often preceded by observable childhood neurodevelopmental impairments. Whether these childhood antecedents index genetic liability is unknown. We used polygenic risk scores derived from a patient discovery sample as indicators of the genetic liability of schizophrenia. Our aim was to identify the early childhood manifestations of this liability in a UK population-based cohort.

Methods The study sample was the Avon Longitudinal Study of Parents and Children, a prospective population-based cohort study of 14701 children. Data were primarily analysed with regression-based analyses. Polygenic risk score were generated from a published Psychiatric Genomics Consortium genome-wide association study. Outcomes were childhood (age 4–9 years) dimensional measures in four developmental domains with 12 indicators: cognition and learning, social and communication, emotion and mood regulation, and behaviour (n=5100–6952).

Findings At age 7–9 years, schizophrenia polygenic risk scores showed associations with lower performance intelligence quotient (β –0·056, OR 1·13 [95% CI 1·04–1·23]), poorer social understanding (β –0·032, OR 1·08 [1·00–1·17]), worse language intelligibility and fluency (β –0·032, OR 1·10 [1·02–1·20]), more irritability (β 0·032, OR 1·07 [1·01–1·14]), and more headstart behaviour (β 0·031, OR 1·08 [1·02–1·15]). The schizophrenia polygenic risk scores also predicted social and behavioural impairments as early as age 4 years.

Interpretation Childhood cognitive, social, behavioural, and emotional impairments, implicated as antecedents to schizophrenia in high-risk, developmental studies, might represent early manifestations of genetic liability.

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Introduction Many mental disorders have prepubertal origins.1 Although schizophrenia typically onsets after puberty,2,3 studies in individuals at high risk, longitudinal studies, and retrospective studies have shown that the fully developed disorder is often preceded by impairments that manifest earlier in development.4 Childhood neurodevelopmental impairments involving cognition and learning, social and communication difficulties, emotion and mood dysregulation, and behavioural problems are known to predate the onset of schizophrenia,4,5 but it is not yet known whether these childhood antecedents index genetic liability for the disorder.4

Schizophrenia is highly heritable; although its genetic architecture is not fully resolved, a substantial amount of the genetic variance is explained by common risk alleles (minor allele frequency ≥1%).4 Composite polygenic risk scores, derived from these risk alleles, are now considered useful indices of genetic liability and provide biologically valid indicators of disease risk for research.5 Moreover, emerging evidence suggests that schizophrenia polygenic risk scores predict cognitive ability and postpubertal psychopathology including negative symptoms, but not psychotic-like symptoms, in the general population.4 Thus, before the typical age of illness onset, schizophrenia’s genetic liability might manifest as symptoms that do not resemble psychosis. Identification of the effect of risk alleles for schizophrenia on prepubertal developmental characteristics in population-based samples might help to identify and understand the early origins of this disorder and the initial manifestations of genetic liability.

We aimed to investigate the relationships between genetic risk for schizophrenia, as indexed by polygenic risk scores, and prepubertal developmental impairments assessed at ages 7–9 years in a large population-based cohort. We focused on developmental domains that have previously been implicated in the antecedent literature for schizophrenia:1–3 cognition and learning, social and communication, emotion and mood, and behaviour. We hypothesised that genetic liability for schizophrenia affects early childhood development across these domains (and that they thus represent trait liabilities) in a population-based birth cohort, the Avon Longitudinal Study of Parents and Children (ALSPAC). We also investigated whether associations extended to an earlier age (age 4 years). We hypothesised that polygenic risk scores for schizophrenia, a disorder considered by many as neurodevelopmental in origin, would affect all of the prepubertal domains that in high-risk samples have been reported to be antecedent features.1,4

Methods
Study design and patients The ALSPAC is a well-established prospective, longitudinal birth cohort study. The enrolled core sample

References
Evidence before this study  
We searched PubMed for articles published from Aug 24, 2011, to Aug 24, 2016 for the terms (“schizophrenia” OR “psychosis” OR “psychotic”) AND (“child” or “adolescent”) AND (“antencedents” OR “genetic” OR “polygenic risk scores”) AND (“review”); no language restrictions were imposed. We identified two reviews of childhood antecedents to adult mental health, including schizophrenia. Follow-up studies in participants at high risk, retrospective studies, and population studies have reported that although schizophrenia onset typically occurs after puberty, illness is often preceded by observable childhood neurodevelopmental impairments that can also be viewed as traits in the general population. The genetic liability of schizophrenia, as indexed by polygenic risk scores, contributes to postpubertal mental health problems.

Consisted of 14,541 mothers living in Avon, UK, who had expected delivery dates of between April 1, 1991, and Dec 31, 1992. Of these pregnancies 13,988 children were alive at 1 year. When the oldest children were approximately 7 years of age, an attempt was made to bolster the initial sample with eligible cases who had not joined the study originally, resulting in an additional 713 children being enrolled. The resulting total sample size of children who were alive at 1 year was 14,701.

Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. After quality control, genotype data were available for 8,365 children. Phenotype data were available for between 5,100 and 6,952 individuals depending on the measures. Full details of the study, measures, and samples can be found elsewhere.

Polygenic risk scores  
Genotyping details, as well as full methods for generating the polygenic risk scores, are given in the appendix. In brief, polygenic risk scores were generated as the weighted mean number of disorder risk alleles in approximate linkage equilibrium ($R^2 < 0.25$), defined in previously published genome-wide association studies, with standard procedures. In ALSPAC, these were derived from dosage data of 1813 imputed autosomal single nucleotide polymorphisms (appendix). Risk alleles were identified as those associated with case-status in the Psychiatric Genetic Consortium analyses (35,476 patients and 46,839 controls) at a threshold of p<0.05, as this threshold maximally captures phenotypic variance for this disorder. Associations across a range of p value thresholds are shown in the appendix.

Outcomes  
Primary outcome variables were assessed at ages 7–9 years. Descriptive information, including correlations between variables, is included in the appendix. The cognition and learning variables were inattention, reading ability, verbal intelligence quotient (IQ), and performance IQ. Inattention was assessed with nine ADHD items from the parent-rated Development and Well-Being Assessment (DAWBA), a structured diagnostic assessment widely used in child mental health surveys (individual items ranged from none to two). Reading ability was measured with the Wechsler Objective Reading Dimensions and verbal and performance IQ with the Wechsler Intelligence Scale for Children; these were standardised with a Z-score transformation.

The social and communication variables were social understanding, language intelligibility and fluency, and pragmatic language. Social understanding was measured by four items from the Social and Communication Disorders Checklist (possible range none to eight; reverse scored—higher scores indicate greater social understanding). Measures of intelligibility and fluency, and pragmatic language were derived from the Children’s Communication Checklist, and comprised 11 and 38 items respectively (possible ranges 16–38 and 86–162).

Emotion and mood regulation included irritability and anxiety, which were assessed with the DAWBA. Irritability included temper tantrums, being touchy or easily annoyed, and being angry and resentful, while anxiety was composed by summing six generalised anxiety items.

For behaviour, measures were headstrong behaviour, aggression, and activity and impulsiveness, all measured by DAWBA items. Headstrong items included arguing with adults, ignoring rules or refusing to do as told, doing things to annoy other people on purpose and blaming others for his or her own mistakes or bad behaviour. Aggression included starting fights and bullying or threatening people. Activity and impulsiveness were measured by nine attention deficit hyperactivity disorder items.

Polygenic risk scores for schizophrenia are associated with higher levels of neurodevelopmental and mental health problems in the general population from early childhood to adult life. The genetic liability for schizophrenia might manifest as symptoms that do not resemble psychosis.

Implications of all the available evidence  
Polygenic risk scores for schizophrenia are associated with higher levels of neurodevelopmental and mental health problems in the general population from early childhood to adult life. The genetic liability for schizophrenia might manifest as symptoms that do not resemble psychosis.

Research in context  

See Online for appendix
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