

# 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 ( $\beta -0.056$ , OR 1.13 [95% CI 1.04–1.23]), poorer social understanding ( $\beta -0.032$ , OR 1.08 [1.00–1.17]), worse language intelligibility and fluency ( $\beta -0.032$ , OR 1.10 [1.02–1.20]), more irritability ( $\beta 0.032$ , OR 1.07 [1.01–1.14]), and more headstrong behaviour ( $\beta 0.031$ , 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.<sup>1</sup> Although schizophrenia typically onsets after puberty,<sup>1,2</sup> 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.<sup>1</sup> 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,<sup>1–3</sup> but it is not yet known whether these childhood antecedents index genetic liability for the disorder.<sup>1</sup>

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  $\geq 1\%$ ).<sup>4</sup> 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.<sup>5,6</sup> 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.<sup>7</sup> 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:<sup>1–3</sup> 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.<sup>1–3</sup>

## Methods

### Study design and patients

The ALSPAC is a well-established prospective, longitudinal birth cohort study. The enrolled core sample

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**Research in context****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 (“antecedents” 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.

**Added value of this study**

This study suggests that the genetic liability to schizophrenia, indexed by genetic risk scores that were generated from a sample of adults with the disorder, affects childhood neurodevelopment, emotional problems, and behaviour in the general population as early as age 4 years.

**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.

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 8365 children. Phenotype data were available for between 5100 and 6952 individuals depending on the measures. Full details of the study, measures, and samples can be found elsewhere.<sup>8–10</sup> (appendix).

See Online for appendix

**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.<sup>6</sup> In ALSPAC, these were derived from dosage data of 1 813 169 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)<sup>4,11</sup> at a threshold of  $p < 0.05$ , as this threshold maximally captures phenotypic variance for this disorder.<sup>4</sup> 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),<sup>12</sup> 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<sup>13</sup> and verbal and performance IQ with the Wechsler Intelligence Scale for Children;<sup>14</sup> 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<sup>15,16</sup> (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,<sup>17</sup> 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,<sup>18</sup> 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.<sup>18</sup> Aggression included starting fights and bullying or threatening people. Activity and impulsiveness were measured by nine attention deficit hyperactivity disorder items.

DAWBA data were not collected before age 7 years but related questionnaire measures were available for children at age 4 years. The Strengths and Difficulties Questionnaire<sup>19</sup> is a brief, widely used questionnaire designed to assess different domains of children's mental health. It was completed by parents when children were aged 4 years. Strengths and Difficulties Questionnaire data were also available at age 7 years and are shown in the appendix to allow comparison across ages with the same measure. The subscales (each comprising five items, individual items range none to two) included prosocial behaviour (eg, considerate of other people's feelings), emotional problems (eg, many worries), and conduct (behaviour) problems (eg, often lies or cheats). The conduct problems subscale includes an irritability item (temper tantrums), which was analysed separately because this item has been found to be an indicator of emotion or mood dysregulation.<sup>18</sup> All descriptive information and associations with primary measures are available in the appendix.

### Statistical analysis

Initial univariate regression analyses involved one predictor (polygenic risk scores for schizophrenia) and multiple dimensional outcomes (12 phenotypic measures within the four domains). We used a false discovery rate<sup>20</sup> to correct for multiple testing in our primary analyses with R (version 3.0.0). Given that our phenotypic measures are correlated, traditional methods of correcting for multiple testing, such as the Bonferroni method, would be too conservative.<sup>21</sup> Analyses were done in Mplus (version 7) with a robust maximum likelihood parameter estimator and full information maximum likelihood estimation.<sup>22</sup> We also generated odds ratios for dichotomised versions of the outcome indicators ( $\geq$  one symptom for DAWBA and bottom 10% for reading, IQ, and social and communication variables, in line with previous work<sup>7</sup>; appendix).

We considered the possibility of potential confounders (ie, child sex and social class); the sample is ancestrally homogeneous (appendix).

### Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. LR and AT had full access to all the data in the study and had final responsibility for the decision to submit for publication.

### Results

Univariate associations for phenotypes at ages 7–9 years are shown in table 1. In the cognition and learning domain, we observed an association of polygenic risk scores for schizophrenia with lower performance IQ, but not with inattention, reading, or verbal IQ. Within the social and communication domain, we observed associations with poorer social understanding and lower language intelligibility and fluency, but not with

pragmatic language. Within the emotion and mood regulation domain, we observed an association between schizophrenia polygenic risk scores and irritability, but not with anxiety. Within the behaviour domain, we noted an association specifically with headstrong behaviour, but not with aggression or activity and impulsivity. These associations with schizophrenia polygenic risk scores were significant after correcting for multiple testing and false discovery rate adjusted p values (table 1).

When we controlled for social class and sex, associations with schizophrenia polygenic risk scores remained for performance IQ, intelligibility and fluency, and headstrong behaviour, but not for social understanding or irritability (appendix).

Effect sizes were in keeping with previous findings for polygenic risk scores in epidemiological research;<sup>7,23</sup> adopting the approach used by Kendler,<sup>24</sup> we estimated that individuals in the top 2.5% for schizophrenia polygenic risk scores would have a roughly 12–26% increased risk of high versus low scores for the different phenotypes.

Table 2 shows the results of secondary analyses that examined associations between polygenic risk scores for schizophrenia and Strengths and Difficulties Questionnaire outcomes at age 4 years. Associations with schizophrenia polygenic risk scores were found for social difficulties and behaviour problems, but not for emotion and mood regulation. At age 7 years, findings for the Strengths and Difficulties Questionnaire subscales were similar to those for the DAWBA data, with associations

	Continuous outcomes				Dichotomised outcomes*	
	$\beta$	Standard error	False discovery rate adjusted p value	R <sup>2</sup>	OR	(95% CI)
<b>Cognition and learning</b>						
Inattention	0.012	0.013	0.46	<0.001	1.01	(0.96–1.07)
Reading	-0.017	0.013	0.26	<0.001	1.04	(0.96–1.14)
Verbal IQ	-0.020	0.013	0.24	<0.001	1.05	(0.96–1.15)
Performance IQ	-0.056	0.013	0.00034	0.003	1.13	(1.04–1.23)
<b>Social and communication</b>						
Social understanding	-0.032	0.013	0.043	0.001	1.08	(1.00–1.17)
Intelligibility and fluency	-0.032	0.013	0.043	0.001	1.10	(1.02–1.20)
Pragmatic language	-0.003	0.013	0.82	<0.001	0.97	(0.89–1.06)
<b>Emotion and mood regulation</b>						
Irritability	0.032	0.013	0.043	0.001	1.07	(1.01–1.14)
Anxiety	0.022	0.014	0.22	0.001	1.02	(0.97–1.08)
<b>Behaviour</b>						
Headstrong	0.031	0.013	0.043	0.001	1.08	(1.02–1.15)
Aggression	0.016	0.013	0.28	<0.001	1.06	(0.98–1.16)
Activity and impulsivity	0.004	0.013	0.82	<0.001	1.01	(0.96–1.06)

OR=odds ratio. IQ=intelligence quotient. \*One or more than one symptom for DAWBA, bottom 10% of distribution for reading, IQ, and social and communication variables.

Table 1: Associations between schizophrenia polygenic risk scores and phenotypic variables at age 7–9 years

	Continuous outcomes				Dichotomised outcomes*	
	$\beta$	Standard error	p value	R <sup>2</sup>	OR	(95% CI)
<b>Social and communication</b>						
Prosocial behaviour	-0.031	0.013	0.012	0.001	1.05	(0.97-1.15)
<b>Emotion and mood regulation</b>						
Emotional problems	0.021	0.013	0.12	<0.001	1.01	(0.93-1.10)
Irritability	0.021	0.013	0.11	<0.001	1.04	(0.96-1.11)
<b>Behaviour</b>						
Conduct problems	0.026	0.013	0.046	0.001	1.08	(0.99-1.18)

\*Bottom 10% of distribution for prosocial behaviour; top 10% for emotional problems, irritability, and conduct problems.

**Table 2: Associations between schizophrenia polygenic risk scores and Strengths and Difficulties Questionnaire subscales at age 4 years**

observed for social difficulties, emotion and mood regulation, and behaviour problems (appendix).

## Discussion

This study showed that schizophrenia polygenic risk scores is associated with prepubertal performance IQ, social and communication difficulties, emotion and mood dysregulation, and behaviour problems in a population-based sample of children.

Cognitive, language, and social impairments as well as emotional and behavioural difficulties have been documented in children who developed schizophrenia in high-risk follow-up, case-control, and retrospective studies.<sup>13</sup> However, most children who show such deficits do not later develop schizophrenia, and whether these factors are indicators of genetic liability has been questioned.<sup>1</sup> Our work suggests that prepubertal lower performance IQ, poorer social understanding, language intelligibility and fluency, irritability, and headstrong behaviour, might be early manifestations of schizophrenia genetic liability. These findings require further testing. Our results highlight that schizophrenia polygenic risk scores contribute to traits that are observable in the general population from a very early age, many years before the onset of any adult forms of psychopathology. Given that the prevalence of schizophrenia in the general population is low, the findings suggest that these prepubertal features represent indices of liability rather than an illness prodrome.

Regarding the specific developmental domains, we found evidence of association with schizophrenia genetic risk scores for performance IQ. Earlier measures of cognitive ability were not available, although genetic overlap between schizophrenia and prepubertal performance IQ specifically has been identified by previous work.<sup>25</sup> Our work extends these findings by suggesting that links are not generalised to other aspects of cognition and learning including inattention, reading, and verbal IQ (that are predicted by attention deficit hyperactivity disorder polygenic risk scores

despite genetic discovery samples of this disorder being much smaller and thus less well powered than those for schizophrenia).<sup>23</sup>

Schizophrenia genetic risk was also associated with social and communication difficulties as early as age 4 years. Social impairments and communication skills have received less attention in the published literature than cognitive features as possible early antecedents of mental disorders. Interestingly, some of these social and communication difficulties could be regarded as similar to negative symptoms of schizophrenia that show postpubertal associations with schizophrenia polygenic risk scores.<sup>7</sup> Our findings suggest that these domains of development that affect early socialisation, such as prosocial behaviour, might also be manifestations of genetic liability to schizophrenia.

While emotional problems in childhood are most commonly considered precursors to mood disorders, a recent review<sup>26</sup> suggests that schizophrenia spectrum disorders are preceded by emotional problems in middle childhood (ages 6–12 years) and recent evidence suggests an association between the schizophrenia genetic risk score and postpubertal anxiety disorder at age 16 years in the general population.<sup>7</sup> Our findings were mixed for emotional problems; associations were observed for irritability but not for our diagnostic measure of generalised anxiety symptoms.

Associations between schizophrenia polygenic risk scores and behavioural problems were also noted as early as age 4 years. While behavioural problems are often considered largely environmentally driven, our findings are consistent with a neurodevelopmental component to early-onset behavioural problems,<sup>27</sup> which for some might index genetic liability to adult-onset mental disorders.

Our study has some limitations. First, although our four developmental domains were conceptually selected a priori on the basis of the scientific literature,<sup>1-3</sup> our analysis involved multiple testing. We attempted to adjust for these tests, but we cannot rule out false-positive findings and replication is advisable for any genetic finding. Additionally, our outcome variables are intercorrelated and the genetic correlation between the different childhood traits we have identified as associated with schizophrenia polygenic risk scores should be tested.<sup>28</sup>

Another limitation is that DAWBA, cognition, and language data were not available for children before the age of 7 years. Correlations between primary and secondary (Strengths and Difficulties Questionnaire) measures in ALSPAC were modest, and the extent to which these reflect the same underlying construct is unclear. Thus, the questionnaire findings do not represent a replication. Furthermore, after correction for multiple testing, although the associations between social understanding, intelligibility and fluency, irritability and headstrong behaviour, and the polygenic risk score for

schizophrenia were statistically significant, they represent only weak evidence of an association with the outcome.

However, we provide novel evidence that some prepubertal features implicated as antecedents to schizophrenia index genetic liability and highlight the importance of research into these features at a very early age in high-risk longitudinal samples.<sup>1-3</sup>

Another limitation is that our target sample is a longitudinal birth cohort study, which inevitably is associated with issues of non-random attrition. This bias probably resulted in a retained sample with a lower schizophrenic polygenic risk score and fewer developmental impairments, which might have resulted in underestimated associations between polygenic risk scores and prepubertal characteristics. Finally, although polygenic risk scores provide a useful indicator of genetic liability,<sup>24</sup> they are not a recommended method for an explanation of a substantial amount of phenotypic variance of population traits that might be only weakly correlated with a risk of the disorder. Indeed, the polygenic risk scores for schizophrenia explain only a small amount of the variance in childhood neurodevelopment in our analyses. Some associations did not remain when controlling for social class and sex, although schizophrenia polygenic risk scores were not associated with social class (appendix). The effect sizes of our associations are small but typical for this kind of work with polygenic risk scores.<sup>7,23</sup>

The present study indicates that early manifestations of schizophrenia genetic liability, including cognitive, social, behavioural and emotional impairments, might be present in children as early as age 4 years. An important research goal is to distinguish between early manifestations of liability that reflect pleiotropy and those that represent developmental impairments that are causally associated with schizophrenia. Intervention studies are likely to be useful for this task. Pleiotropic effects might provide insight into cross-diagnostic nosology and transdiagnostic processes,<sup>29</sup> while causal factors might inform interventions that promote resilience to future impairment.<sup>30</sup>

#### Contributors

AT, MCO'D, SC, and BM contributed to the initial study design. All authors contributed to the manuscript writing, literature search, and final approval of the manuscript. LR, AKT, and AR contributed to data analyses. All authors contributed to data interpretation.

#### Declaration of interests

All authors report no competing interests.

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