Phenotypic manifestation of genetic risk for schizophrenia during adolescence in the general population

Hannah J. Jones, PhD[1,2]; Evie Stergiakouli, PhD[2]; Katherine E. Tansey, PhD[2]; Leon Hubbard, PhD[3]; Jon Heron, PhD[1]; Mary Cannon, MD, PhD[4]; Peter Holmans, PhD[3]; Glyn Lewis, PhD[5]; David E. J. Linden, D.Phil[3]; Peter B. Jones, PhD[6]; George Davey Smith, MD, DSc[2]; Michael C. O'Donovan, PhD, FRCPsych[3]; Michael J. Owen, PhD, FRCPsych[3]; James T. Walters, MRCPsych, PhD[3]; Stanley Zammit, MRCPsych, PhD[1,3]

[1]Centre for Academic Mental Health, University of Bristol, School of Social and Community Medicine, University of Bristol

[2]Medical Research Centre (MRC) Integrative Epidemiology Unit (IEU), University of Bristol, UK

[3]MRC Centre for Neuropsychiatric Genetics and Genomics, Institute of Psychological Medicine and Clinical Neurosciences, Cardiff University School of Medicine, Cardiff, UK

[4]Department of Psychiatry, Royal College of Surgeons in Ireland, Dublin, Ireland

[5]Division of Psychiatry, University College London, London, UK

[6]Department of Psychiatry, University of Cambridge, Cambridge, UK

Corresponding author: Hannah J. Jones, PhD; School of Social and Community Medicine, University of Bristol, Oakfield House, Oakfield Grove, Bristol, UK (Hannah.jones@bristol.ac.uk)

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Abstract

Importance: Schizophrenia is a highly heritable, polygenic condition characterized by a relatively diverse phenotype, and frequent comorbid conditions such as anxiety and depression. There is currently limited evidence on how high genetic risk for schizophrenia is manifest in the general population.

Objective: To investigate the extent to which genetic risk for schizophrenia is associated with different phenotypes during adolescence in a population-based birth cohort.

Design: Cohort study using the Avon Longitudinal Study of Parents and Children (ALSPAC)

Setting: General population

Participants: Adolescents (N 3676 to 5447 depending on outcome investigated)

Exposure: Polygenic risk scores (PRSs) for schizophrenia generated for individuals in ALSPAC using results of the second Psychiatric Genomics Consortium Schizophrenia genome-wide association study as a training set.

Main outcomes and measures: Logistic regression was used to assess associations between schizophrenia PRS and a) psychotic experiences (using PLIKSi at 12 and 18 years), b) negative symptoms (CAPE at 16.5 years), c) depressive disorder (DAWBA at 15.5 years) and d) anxiety disorder (DAWBA at 15.5 years) in adolescence.

Results: PRSs created using single nucleotide polymorphisms with a training set p value ≤ 0.05 were associated with negative symptoms (OR per SD increase in PRS = 1.21, 95% CI = 1.09, 1.36; R^2 = 0.007) and anxiety disorder (OR per SD increase in PRS = 1.17, 95% CI = 1.06, 1.29; R^2 = 0.005). No evidence was found of an association between schizophrenia PRS and psychotic experiences (OR per SD increase in PRS = 1.08, 95% CI = 0.98, 1.19; R^2 = 0.001) or depressive disorder (OR per SD increase in PRS = 1.02, 95% CI = 0.91, 1.13; R^2 = 0.00005). Results were mostly consistent across different training set p value thresholds and using different cut-offs and measures of the psychopathologies.

Conclusions: We demonstrate polygenic overlaps between common genetic polymorphisms associated with schizophrenia and both negative symptoms and anxiety disorder, but not with psychotic experiences or depression. As schizophrenia genetic risk is more commonly manifest as anxiety and negative symptoms during adolescence a greater focus on these phenotypes rather than on psychotic experiences might be required for prediction of transition in at-risk samples.

Background

Schizophrenia has a heritability of approximately 80% and genome-wide association studies (GWAS) provide strong evidence of multiple independent loci contributing to the aetiology of this disorder.[1]

The importance of studying the phenotypic manifestations of increased genetic liability for schizophrenia has long been recognised and originally involved small samples of individuals at high risk as indexed by having a family history.[2] Genetic advances now provide the opportunity to extend the power and generalizability of high-risk studies into the general population by examining individuals according to genetic risk. Whilst individual loci have small effects on risk, multi-locus approaches show that cumulatively, alleles on current GWAS platforms explain half to a third of the genetic risk for schizophrenia.[3,4] Furthermore, information from even moderately associated alleles can be collapsed into a single polygenic risk score (PRS) that can be used to explore shared genetic effects with other disorders and examine how genetic risk is manifest early during development in the general population.[5]

Schizophrenia is defined by the presence of psychotic experiences (hallucinations, delusions and thought disorder) and negative symptoms such as blunted affect and apathy, although cognitive deficits are also common as is comorbidity with other diagnoses, particularly affective and anxiety disorders.[6] Longitudinal studies show that anxiety, depression, and cognitive deficits often predate schizophrenia[7-11] indicating that these phenotypes might represent early expression of schizophrenia genetic risk. Whilst some degree of genetic overlap across psychiatric disorders is commonly found,[12-15] knowledge of how genetic risk is most commonly expressed at different stages of the life course could help understanding of aetiological mechanisms, identify individuals at highest-risk for developing schizophrenia, and inform targeted interventions.

Three previous studies have used a schizophrenia PRS generated from a GWAS training set capturing ≈3% of the proportion of risk variance[4] to examine associations with symptoms that characterise schizophrenia. In the first study, schizophrenia PRS was not associated with symptom dimensions

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characteristic of the disorder in either schizophrenia cases or controls.[16] Similarly, there was no association with positive symptom, cognitive and negative symptom dimensions in a general population sample of adolescents,[17] whilst we observed no strong evidence that schizophrenia PRS was associated with psychotic experiences at age 12 within a population-based birth cohort, the Avon Longitudinal Study of Parents and Children (ALSPAC).[18] Since then however, a larger GWAS has been completed which explains a substantially greater proportion of risk variance,[1] and thus provides greater power[19] to examine how genetic risk is manifest during development.

The aim of this study is to examine the psychopathology associated with early expression of genetic risk for schizophrenia, and more specifically, whether a schizophrenia PRS derived from the most recent GWAS is associated with i) psychotic experiences, ii) negative symptoms, iii) anxiety disorders, or iv) depression during adolescence in a large, population-based sample.

Methods

Participants

The sample comprised of young individuals within the ALSPAC cohort. The initial cohort consisted of 14,062 children born to women residing in the former Avon Health Authority area with an expected delivery date between April 1991 and December 1992 (www.alspac.bris.ac.uk, see http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary for all available data).[20,21] All subjects provided written informed consent and ethical approval for the study was obtained from the ALSPAC Law and Ethics Committee and the Local Research Ethics Committees.

Genetic Data

Genetic data were acquired from 9912 participants using the Illumina HumanHap550 quad genome-wide single nucleotide polymorphism (SNP) genotyping platform. Following quality control assessment, imputation and restricting to 1 young person per family, genetic data were available for 8230 individuals (see *eMethods* for more detail).

Measures

Psychotic experiences

The semi-structured Psychosis-Like Symptom Interview (PLIKSi)[22,23] was used to assess psychotic experiences (such as hallucinations, delusions or experiences of thought interference) at ages 12 and 18 years. To maximise the numbers within our sample, individuals were deemed as having a psychotic experience if rated as having one or more definite psychotic experiences at either age 12 or 18 years, compared to no or only suspected psychotic experiences at age 12 or 18 years. See *eMethods* for more detail on the PLIKSi, and on the other outcome measures used in this study.

Negative Symptoms

These were assessed using 10 questions based on items from the Community Assessment of Psychic Experiences (CAPE) self-report questionnaire[24] at age 16.5 years (see *eMethods* and *eTable 1*) which measures negative symptoms such as apathy, anergia and asociality. Each item was rated on a 4-point scale (0: never, 1: sometimes, 2: often, 3: always). A total score was constructed based on the sum of responses (minimum score: 0, maximum score: 30). A binary variable was created using a total score of 14 as a cut-off, chosen to approximately define the top decile (9.18%) of the sample.

Depressive Disorder and Anxiety Disorder

Depression and anxiety disorder outcomes were derived from the semi-structured Development and Well Being Assessment (DAWBA) interview at age 15.5 years, a valid instrument in community and clinical samples.[25] DSM-IV and ICD-10 diagnoses of depressive or any anxiety disorder were generated using a computerised diagnostic algorithm that predicts the likelihood of a clinical diagnostic rating (see http://www.DAWBA.com for more information).[26]

We defined individuals as having a depressive disorder or an anxiety disorder if they were categorised in the DAWBA band predicting a ≥ 15% probability of clinical diagnosis, a cut-off selected to approximately define the top deciles of the sample.

We conducted a series of sensitivity analyses using different phenotype-score cut-offs to define binary outcomes, and using different measures where available to test the robustness of our findings (see *eMethods*).

Polygenic Risk Score

Construction of PRSs follows the methodology described by the International Schizophrenia Consortium (ISC).[4] PRSs were constructed using results from the second Psychiatric Genomics Consortium (PGC) Schizophrenia GWAS (*eMethods*).[1]

Polygenic scores were calculated for each ALSPAC individual using the PLINK (v1.07)[27] 'score' command. Scores which sums the number of risk alleles present for each SNP (0, 1 or 2) weighted by the logarithm of its odds ratio (OR) for schizophrenia from the PGC.

Our primary analysis used scores generated using a list of SNPs with a GWAS training set *p* value threshold (p_T) ≤ 0.05, the threshold that maximally captures schizophrenia liability.[1] As the composition of a PRS is a balance between true and null effects,[28] scores generated using lists of SNPs meeting a series of *p* value thresholds and using all independent SNPs meeting genome-wide significance as reported by the PGC Schizophrenia GWAS [1] were used as sensitivity analyses.

Statistical analysis

Logistic regression was used to test association between outcomes and schizophrenia PRS. Results are presented as ORs and 95% confidence intervals (CIs) per standard deviation (SD) increase in PRS. Nonlinear associations between PRSs and outcomes were examined by inclusion of quadratic terms. We examined whether associations with our outcomes were independent by inclusion of all phenotypes within a multivariable model. To correct for multiple testing arising from using different p_T within our sensitivity analyses, permutation-adjusted *p* values were computed (*eMethods*).

To test whether the effect size of schizophrenia PRS was the same, or different, across phenotypes, we used bivariate probit regression to jointly model pairs of outcomes. We tested equality of regression parameters expressing the effect of schizophrenia PRS (p_T of 0.05) on each outcome using a likelihood ratio test to compare a model that allows effect estimates to differ with a model where

the PRS effect was constrained to be equal for both outcomes [29,30]. All statistical analyses were

performed using Stata (Version 13; StataCorp LP, College Station, TX, USA).

Results

Associations between schizophrenia polygenic score and psychopathology

The numbers of individuals who participated in the PLIKSi at age 12 and 18 years or completed questions relating to negative symptoms at age 16.5 years and depression and anxiety at age 15.5 years are shown in Table 1.

There was no strong evidence that individuals who had a higher PRS, and thus increased genetic risk for schizophrenia, had an increased risk of developing psychotic experiences (OR per SD increase in PRS = 1.08, 95% CI = 0.98, 1.19; permutation-adjusted p = 0.142; Nagelkerke R^2 = 0.001) (Figure 1a & *eTable 2*).

We observed strong evidence of association between schizophrenia PRS and negative symptom score at age 16.5 (OR = 1.21, 95% CI = 1.08, 1.36; permutation-adjusted p = 0.001; R^2 = 0.007) (Figure 1b & *eTable 2*). There was also strong evidence that individuals with a higher schizophrenia PRS were at an increased risk of anxiety disorder at age 15.5 years (OR per SD increase in polygenic score = 1.17, 95% CI 1.06, 1.29; permutation-adjusted p = 0.0017; R^2 = 0.005) (Figure 1d & *eTable 2*). There was no strong evidence of association between PRS and depressive disorder at age 15.5 years (OR per SD increase in polygenic score = 1.02, 95% CI 0.91, 1.13; permutation-adjusted p = 0.770; R^2 = 0.00005) (Figure 1c & *eTable 2*).

There was no strong evidence to support non-linear effects of polygenic risk on any of the phenotypes examined. Results per decile of PRS for training set p-threshold of 0.05 are presented in *eTable 3*. Associations with negative symptoms and anxiety disorder were independent, persisting when testing all phenotypes within a multivariable model (*eTables 4-7*).

Common and specific associations with schizophrenia polygenic score

Tetrachoric correlations between each psychopathology are shown in *eTable 8*. The results of the bivariate analyses, examining whether schizophrenia PRS (p_T = 0.05) effect sizes are similar or different across phenotypes, are summarised in Table 2. We observed some evidence that the strong associations between schizophrenia PRS and both negative symptoms and anxiety are different to that of PRS on depression (p=0.020 & p=0.020 respectively), with weaker evidence that they are different from effects of PRS on psychotic experiences (p=0.141 & p=0.105). There was no strong evidence that the association between PRS effect and negative symptoms differed from that on anxiety (p=0.917).

Sensitivity analyses

Our results were unchanged when using different cut-off values or different measurement tools to assess our outcomes (see *eFigures 1-5*), when adjusting for parental self-reported history of schizophrenia or depression or when excluding individuals with a psychotic disorder at age 18. Results were also consistent across all training set p-thresholds for all outcomes with exception of psychotic experiences where there was weak evidence that increased genetic risk was associated with a decreased risk of psychotic experiences at lower training set p-thresholds ($p_T \leq 1 \times 10^{-7}$; OR per SD increase in polygenic score = 0.90, 95% CI 0.81, 0.99; permutation-adjusted p = 0.037, R^2 = 0.002) (Figure 1a & *eTable 2)*.

Discussion

In this study we examined how increased genetic risk for schizophrenia is manifest phenotypically during adolescence in the general population. We found no strong evidence of association with occurrence of psychotic experiences or depressive disorder. However, there was strong evidence that negative symptoms and anxiety disorders were more common in adolescents with higher genetic risk, and that these were independent of each other.

Whilst it may seem surprising that schizophrenia genetic risk is not associated with psychotic experiences in adolescence, these findings are consistent with previous studies that have examined this relationship.[17,18] The estimates of association and strength of evidence in this study are very similar to those from a previous study using ALSPAC even though power here is substantially greater given the use of a much larger training set to generate the risk-scoring algorithm.

At p-thresholds that maximally capture schizophrenia liability, psychotic experiences were more common in those with higher genetic risk, albeit the confidence intervals included the null. At the most stringent p-thresholds however, there was weak evidence that genetic risk was associated with reduced psychotic experiences. This could be due to random error, or could result from attrition bias. Missing data is likely greater for those who develop a psychotic disorder and for those at high genetic risk. It is possible therefore that psychotic experiences are under-represented in high compared to low genetic risk participants included in these analyses, akin to the apparently protective effect of smoking on Alzheimer's disease seen using risk rather than rate models of analysis.[31] It is not clear though why this would only be observed at p-thresholds that explain less of the variance for schizophrenia.

There are a number of potential explanations for our findings of strong evidence of association between schizophrenia genetic risk and negative symptoms and anxiety disorder, but not with psychotic experiences in the general population. First, it is possible that genetic risk for schizophrenia is expressed heterotypically during adolescence as anxiety and negative symptoms,

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and that psychotic experiences develop later during development. For the minority of individuals who go on to develop schizophrenia, anxiety and negative symptoms would represent prodromal symptoms of the disorder. This implies that hallucinations and paranoid beliefs arising during adolescence might be explained to a greater degree by non-genetic effects such as childhood trauma[32,33] or cannabis use[34] than by genetic risk for schizophrenia in comparison to psychotic experiences arising later in life. The association between schizophrenia genetic risk and psychotic experiences might therefore get stronger with increasing age akin to that seen for general cognitive ability.[35]

It is highly plausible that anxiety and negative symptoms occur as early manifestations of genetic risk for schizophrenia, and we might speculate on possible mechanisms. For example, disturbed biological processes secondary to genetic variation might result in subtle alterations in prediction error processing and attributional salience that might lead to anxiety prior to onset of clear-cut psychotic phenomena.[36,37] Whilst this might arise from processes primarily affecting mesolimbic pathways, prefrontal cortical abnormalities might lead to subtle cognitive deficits and impairment of motivational drive and emotion that are observed as negative symptoms. Schizophrenia genetic risk is also associated with impaired childhood performance IQ in this cohort (under review), though it is not known whether variants acting primarily through different brain pathways are differentially related to these phenotypes.

Second, it is possible that genetic risk for schizophrenia is expressed during adolescence as increased psychotic experiences as well as anxiety and negative symptoms, but that psychotic experiences are observed with greater measurement error; thus associations would be relatively underpowered for this phenotype. Use of a semi-structured interview and similar estimates using questionnaires suggests this is an unlikely explanation, but cannot be excluded.

Third, it is possible that genetic variants identified as showing association with schizophrenia in the GWA studies only weakly index risk for hallucinations and delusions, and more strongly reflect risk for other characteristics of the disorder such as negative symptoms that index severity or chronicity

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of illness, and which might be selected for in clinically-ascertained samples. Similarly, such ascertainment might be biased towards those with multiple morbidities, for example co-morbid anxiety disorders. Studies that have examined symptom dimensions within schizophrenia[38] and in the general population[39,40] show that heritability of negative and disorganised symptoms is greater than that of positive symptoms, and that schizophrenia polygenic risk is more strongly associated with negative and disorganised symptoms than positive symptoms.[41]

Whilst evidence exists of genetic overlap between schizophrenia and major depressive disorder in adults[12,42] we found no evidence to support this in our study. It is possible that measures of depression in this study capture more transient disorders in adolescence that obscures a genetic overlap between schizophrenia and a more persistent, chronic form of depression.

Our results indicate that anxiety and negative symptoms are likely to be the best markers of high schizophrenia genetic risk in population-based samples, however we note that the variance of these phenotypes explained by schizophrenia genetic risk is small (0.5%-0.7%) and that the negative symptoms measure used in the general population might not fully capture negative symptoms seen in schizophrenia. Our findings have potentially important implications for studies of at-risk samples where current approaches for informing prediction of transition rely heavily on psychotic experiences. Our results are consistent with an evolving literature describing anxiety as a common symptom during the prodromal stage of psychosis.[43-45]

Our study has a number of strengths. First, we used the most recent schizophrenia GWAS from the PGC,[1] the largest schizophrenia dataset available as a training set, thus minimising measurement error. Second, we used a large, well characterised, relatively homogenous population-based sample for examining psychosis-related phenotypes during adolescence, a key period of development that closely predates the start of the peak in incidence of schizophrenia. Third, we used a semi-structured interview to determine the presence of psychotic experiences, as is used clinically. We also used multiple measures of depression and anxiety at different ages during adolescence, and different cut-

offs of these and measures of psychotic experiences and negative symptoms as sensitivity analyses to test the robustness of our findings.

There are also a number of limitations of our study. First, despite the use of one of the largest population-based birth cohorts worldwide with the required data, our sample may not be adequately powered to identify small-sized effects of cumulative genetic risk on the phenotypes examined,[19] especially given potential differences in heritability across the phenotypes.[14,39,40] Given that our sample is too small to estimate heritability of the phenotypes accurately, it is at present difficult to determine whether the absence of significant polygenic association between a phenotype and genetic risk for schizophrenia reflects an absence of genetic correlation, or inadequate power. Second, missing data in the cohort could potentially lead to bias in our estimates. Whilst it is possible that selective missingness has led to over-estimates of association it seems unlikely that this has occurred for some of our phenotypes but not others. A further limitation is that rare genetic variants are not captured by GWAS, and therefore we are only able to examine the effect of common variants (as captured by current GWA studies) on adolescent phenotype expression.

Our results highlight the need for GWAS consortia of schizophrenia to include detailed phenotyping data to examine to what extent current GWA findings relate to specific phenotypes, and to identify genetic variants and pathways that are symptom domain specific rather than examining presence of disorder per se. Furthermore, large population-based longitudinal studies with robust measures of these phenotypic constructs are required to determine how schizophrenia genetic risk is expressed from childhood through adulthood to study if this changes with age, to examine potential mediators and moderators of risk, and determine usefulness of genetic risk scores for prediction of transition to psychosis. A better understanding of how genetic risk for schizophrenia manifests during development could inform early recognition of problems in those at greatest risk, and potentially inform targeted interventions.

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Acknowledgments

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Figure legends

Figure 1. Associations between A) psychotic experiences, B) negative symptoms, C) depressive disorder and D) anxiety disorder and polygenic scores for schizophrenia generated using lists of SNPs meeting a series of p value thresholds (P_T). Odds ratio per standard deviation (SD) change in polygenic risk score are shown with upper and lower 95% confidence intervals. Grey bars: $\log_{10}$ number of SNPs used to create polygenic risk scores. Genome-wide significant (5e-08) P_T = polygenic score created from 111 genome wide significant schizophrenia SNPs as reported by PGC.[1]

Tables

Table 1. Number of individuals (all and those genotyped only) with outcome measure (psychotic experiences, negative symptoms, depression and anxiety)

Age (years)	Data source	Outcome measure	Outcome measure type	N participants	N (%) with outcome	N genotyped	N (%) with outcome
12 18 12 & 18†	PLIKSi	Psychotic Experiences	Binary (yes/no)	6,792 4,718 7,452	383 (5.64) 229 (4.85) 575 (7.72)	5,103 3,486 5,444	280 (5.49) 168 (4.82) 419 (7.70)
16.5	CAPE	Negative Symptoms	Binary (score </≥ 14)	5,095	467 (9.17)	3,673	337 (9.18)
15.5	DAWBA	Depression	Binary (</≥ 15% band)	5,365	498 (9.28)	4,106	373 (9.08)
15.5	DAWBA	Anxiety	Binary (</≥ 15% band)	5,367	596 (11.10)	4,107	444 (10.81)

† Individuals who completed at least 1 interview session at age 12 and/or 18

Table 2. Effects of schizophrenia polygenic risk score (per SD; discovery sample p-threshold = 0.05) on psychopathology[a], and examination of whether psychopathology-specific effects differ from a common effect

| Phenotype 1 | Phenotype 2 | n | Phenotype specific effect | | Common effect | |
| | | | Phenotype 1 | Phenotype 2 | | |
			OR (LCI,UCI)	OR (LCI,UCI)	OR (LCI,UCI)	P[b]
Psychotic experiences	Negative symptoms	3288	1.037 (0.934, 1.150)	1.146 (1.039, 1.263)	1.094 (1.015, 1.179)	0.141
	Depressive disorder	3965	1.059 (0.966, 1.161)	1.024 (0.939, 1.118)	1.041 (0.972, 1.114)	0.575
	Anxiety disorder	3966	1.053 (0.960, 1.154)	1.157 (1.064, 1.258)	1.109 (1.038, 1.186)	0.105
Negative symptoms	**Depressive disorder**	**2872**	**1.171 (1.055, 1.301)**	**0.994 (0.895, 1.105)**	**1.080 (0.998, 1.168)**	**0.020**
	Anxiety disorder	2873	1.169 (1.053, 1.298)	1.161 (1.052, 1.282)	1.165 (1.078, 1.258)	0.917
Depressive disorder	**Anxiety disorder**	**4106**	**1.008 (0.925, 1.098)**	**1.135 (1.045, 1.232)**	**1.073 (1.004, 1.148)**	**0.020**

Note: OR, Odds Ratio; LCI, L95% CI; UCI, U95% CI (see *eMethods* for details of how ORs were derived)

[a] Complete case data, bivariate model estimation

[b] P value calculated from likelihood ratio tests comparing a model assuming psychopathology-specific effect versus a common effect model where exposure effect is constrained to be the same across phenotypes. A p-value of 0.5 for example would provide little evidence that the association between polygenic score and Phenotype 1 was different to that for the association between polygenic score and Phenotype 2. A p-value of 0.01 for example would provide strong evidence that there was a difference.