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The contribution of psychiatric risk alleles to a general liability to psychopathology in early life

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Abstract.

Background. Psychiatric disorders show phenotypic as well as genetic overlaps. Factor analyses of child and adult psychopathology have found that phenotypic overlaps can be largely explained by a latent general factor that reflects general liability to psychopathology. We investigated whether shared genetic liability across disorders would be reflected in associations between multiple different psychiatric polygenic risk scores (PRS) and a 'general psychopathology' factor in childhood.

Methods. The sample was a UK, prospective, population-based cohort (ALSPAC), including data on psychopathology at ages 7 (N=8161) and 13 (N=7017) years. PRS were generated from large published genome-wide association studies.

Results. A general psychopathology factor was associated with both schizophrenia PRS and attention-deficit/hyperactivity disorder (ADHD) PRS, whereas there was no strong evidence of association for major depressive disorder (MDD) and autism spectrum disorder PRS. Schizophrenia and MDD PRS also showed association with a specific emotional problems factor and ADHD PRS were associated with a specific neurodevelopmental factor.

Conclusions. Our findings suggest that common variant genetic liability to schizophrenia and ADHD may contribute to shared genetic risks across childhood psychiatric diagnoses at least partly via association with a 'general psychopathology' factor, whereas genetic liability for MDD appears to contribute more specifically to an emotional factor in childhood.

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Introduction

Most psychiatric disorders originate early in development. Family and twin studies show that these disorders are heritable and many share genetic risk factors across diagnostic categories. For example, registry-based family and twin studies suggest that relatives of those with schizophrenia, mood disorders, autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) are at elevated risks for a broad range of psychopathology; not just for the same disorder as the affected probands (1, 2). Recent molecular genetic studies also provide evidence of common variant genetic overlaps between different psychiatric disorders (3-5); for example genetic correlations across schizophrenia, mood disorders, ASD and ADHD have been shown to range from 0.30 to 0.93 (6). Current psychiatric nosology does not take into account these complex patterns of shared inheritance across phenotypes (7).

While the genetic architecture of psychiatric disorders is complex, indicators of (common variant) genetic liability for psychiatric disorders including schizophrenia, depression, ASD and ADHD can be measured in individuals using polygenic risk scores (PRS) (8). Studies using this method also support the existence of shared genetic risks. For example, schizophrenia PRS are associated with increased liability to other disorders (including major depression, anxiety, ASD, and ADHD) and broader categories of psychiatric phenotypes (e.g. neurodevelopmental traits in childhood) (9, 10). Although it is now widely accepted that psychiatric disorder risk alleles are shared across disorders, how such risks have a shared impact on psychopathology remains unknown.

While different forms of psychopathology are considered as discrete categories for clinical purposes, it has long been known that different disorders show strong phenotypic (as well as genetic) overlaps. Factor analyses of child and adult psychopathology have observed that these phenotypic overlaps are largely explained by a latent general factor that reflects general liability to psychopathology (3, 11). Different disorders are distinguished by additional specific or unique factors. For example, factor analyses of psychiatric disorders in children have typically

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observed evidence for specific emotional (internalizing) and behavioral (externalizing) factors as well as a general psychopathology factor. In adulthood, recent studies have also highlighted the presence of a specific 'thought disorder' factor, as well as emotional, behavioral and general psychopathology factors (11). However, it is not clear where the DSM-5 neurodevelopmental disorders of ADHD and ASD fit: they have tended to either be excluded from these studies - or in the case of ADHD, often considered as an externalizing disorder (e.g. 3) - rather than modelled as a separate neurodevelopmental factor as would be predicted by DSM-5 classifications.

In this study, we set out to examine the structure of psychopathology in childhood and early adolescence in a population-based birth cohort, including broadly defined ASD and ADHD problems as well as emotional and behavioral difficulties that have been included in previous studies: we hypothesized that we would identify a neurodevelopmental factor as well as emotional and behavioral factors. We also aimed to examine associations between psychiatric risk alleles, indexed by PRS, and a 'general psychopathology' factor. We investigated psychiatric PRS derived from large, publicly available genome-wide association studies that have previously been shown to be associated with childhood psychopathology (12-15): schizophrenia, major depressive disorder (MDD), ASD and ADHD. We hypothesized that shared genetic liability across disorders would be reflected in associations between these multiple PRS and a general psychopathology factor, and that PRS would show additional "within phenotype" associations with specific factors: MDD PRS with an emotional factor; ASD and ADHD PRS with a neurodevelopmental factor. Given emerging evidence for developmental changes in the genetic architecture of psychopathology (16), we assessed associations at two time points (ages 7 and 13 years).

Methods and Materials

Sample

The Avon Longitudinal Study of Parents and Children (ALSPAC) is a well-established prospective, longitudinal birth cohort study. The enrolled core sample consisted of 14,541

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mothers living in Avon, England, who had expected delivery dates of between 1st April 1991 and 31st December 1992. Of these pregnancies 13,988 children were alive at 1 year. When the oldest children were approximately 7 years of age, the sample was augmented with eligible cases who had not joined the study originally, resulting in enrollment of 713 additional children. The resulting total sample size of children alive at 1 year was N=14,701. Genotype data were available for 8,365 children following quality control. Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. Full details of the study, measures and sample can be found elsewhere (17, 18). Please note that the study website contains details of all the data that is available through a fully searchable data dictionary (http://www.bris.ac.uk/alspac/researchers/data-access/data-dictionary). Where families included multiple births, we included the oldest sibling.

Polygenic risk scores

Polygenic risk scores (PRS) were generated as the weighted mean number of disorder risk alleles in approximate linkage equilibrium, derived from imputed autosomal SNPs using PRSice (19). Scores were standardized using Z-score transformation: results can therefore be interpreted as an increase per 1 standard deviation increase in PRS. Risk alleles were defined as those associated with case-status in recent large consortia analyses of schizophrenia (40,675 cases and 64,643 controls) (20) , MDD (135,458 cases and 344,901 controls) (21) , ASD (18,381 cases and 27,969 controls) (22), and ADHD (19,099 cases and 34,194 controls) (23). In the primary analyses we defined risk alleles as those associated at $p<0.05$ as this threshold has previously been shown to maximally capture phenotypic variance for schizophrenia (10); associations across a range of p-thresholds are shown in Supplementary Figure 2 in the online data supplement. Genotyping details as well as full methods for generating the PRS are presented in the Supplementary Material. PRS were available for 67% of individuals (N=6166/9179) with phenotypic data at age 7 and/or 13 years. Sensitivity analyses were conducted using inverse probability weighting (24) to assess the impact of missing genetic data (see Supplementary Material).

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Outcomes

Psychopathology was assessed using parent reports at the approximate ages of 7/8 and 13 years old. Emotional problems were assessed using the Development and Well-Being Assessment (DAWBA) (25) (individual item range 0-2) for depression (12 items), generalized anxiety (7 items), separation anxiety (10 items), social anxiety (6 items), specific phobia (7 items) and irritability (3 items) (in-line with the DSM-5 classification of disruptive mood dysregulation disorder as a mood disorder). Behavioral problems were assessed using the DAWBA for conduct disorder (7 items) and the two established behavioral components of oppositional defiant disorder: headstrong (4 items) and hurtful (2 items) behaviors. Neurodevelopmental problems were assessed using the DAWBA for activity/impulsivity (9 items) and inattention (9 items) for ADHD problems. Additionally, the Social and Communication Disorders Checklist (26) was used for social-communication problems related to ASD (12 items; individual item range 0-2). Prorated scores (the mean score multiplied by total possible number of items in the scale) were calculated for individuals with <30% missingness. Descriptive statistics and correlations between variables are given in Supplementary Tables 1 and 2.

Analysis

In-line with previous work, we first used confirmatory factor analysis to identify the best fitting model for psychopathology, comparing a correlated-factors model (specific factors only), a bifactor model (specific factors and a general psychopathology factor: correlations between factors fixed to zero) and a one factor model (a general psychopathology factor only) at each time point (see Supplementary Material for full details). Associations with PRS were examined in two steps: factors were fixed based on the best fitting model before associations with PRS were examined (i.e. PRS did not impact on the factor structure). Schizophrenia, MDD, ASD and ADHD PRS were included simultaneously (as were all factors within a given model) in a single test for each factor model. Analyses were conducted in Mplus using a maximum likelihood parameter estimator for which standard errors are robust to non-normality (MLR) (27).

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Results

A correlated factors model suggested that three 'specific' emotional, behavioral and neurodevelopmental factors (Figure 1a and Table 1) fit the data well, but the addition of a general psychopathology factor in the bifactor model (Figure 1b and Table 1) showed improvement in model fit (see Supplementary Material for full details and explanation of model fitting). Associations for both models are reported to assess the impact of including a general psychopathology factor.

Within the correlated factors model, female sex was positively associated with the emotional factor (age 7: β=0.024, SE=0.01 , p=0.014; age 13: β =0.108, SE=0.011, p<0.001) and negatively associated with the behavioral (age 7: β =-0.042, SE=0.007, p<0.001; age 13: β =-0.008, SE=0.009, p=0.337) and neurodevelopmental (age 7: β =-0.085, SE=0.007, p<0.001; age 13: β =-0.066, SE=0.008, p<0.001) factors.

Within the bifactor model, female sex was negatively associated with the general psychopathology factor (age 7: β=-0.053, SE=0.009, p<0.001; age 13: β =-0.038, SE=0.010, p<0.001), positively associated with the emotional (age 7: β=0.057, SE=0.011, p<0.001; age 13: β =0.144, SE=0.011, p<0.001) and behavioral (age 7: β =0.013, SE=0.016, p=0.430; age 13: β =0.054, SE=0.014, p<0.001) factors and negatively associated with the neurodevelopmental factor (age 7: β =-0.075, SE=0.011, p<0.001; age 13: β =-0.067, SE=0.011, p<0.001).

Correlations between factors at ages 7 and 13 suggested strong phenotypic stability in the factor structure of psychopathology between childhood and early adolescence (bifactor: general psychopathology r=0.763, emotional factor r=0.771, behavioral factor r=0.817, neurodevelopmental factor r=0.711; see Supplementary Table 6).

Genetic risk

Results of multivariable PRS associations with the psychopathology factors are shown in Table 2. At both ages the general psychopathology factor (bifactor model) was associated with both

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schizophrenia PRS and ADHD PRS, whereas there was no strong evidence for associations with MDD and ASD PRS.

In the correlated factors model, schizophrenia PRS were associated with all three specific factors at age 7. In the bifactor model – with the inclusion of a general factor – there was no strong evidence of associations between schizophrenia PRS with the specific factors, with the exception of the emotional factor. At age 13 the same pattern was found for behavioral and neurodevelopmental problems, but there was no strong evidence of associations with emotional problems.

MDD PRS were specifically associated with emotional problems both in the correlated factors models and the bifactor model. There was no strong evidence of associations between ASD PRS and any of the factors at either age. Finally, ADHD PRS were specifically associated with behavioral and neurodevelopmental problems in the correlated factors models at both ages. With the inclusion of a general factor in the bifactor model, there was no strong evidence of association with the specific factors, with the exception of neurodevelopmental problems.

Sensitivity analyses

Entering PRS in univariable (instead of multivariable) analyses revealed a similar pattern of results, with the exception that there was also some evidence of association between MDD PRS and general psychopathology when the other PRS were not included in the model (age 7 β=0.041, SE=0.017, p=0.017; age 13 β=0.031, SE=0.017, p=0.067, see Supplementary Table 7 for full results). Associations for schizophrenia, ASD and ADHD PRS were consistent regardless of whether or not the other PRS were controlled for.

Using inverse probability weighting to assess the impact of missing genetic data revealed a similar pattern of results (see Supplementary Material).

Discussion

In this study we set out to examine the structure of psychopathology in childhood and early adolescence and to investigate the contribution of psychiatric risk alleles to underlying latent

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psychopathology factors. In line with previous work, we identified a general psychopathology factor underlying all forms of psychopathology (3, 11, 28). Our models also included emotional, behavioral and neurodevelopmental problems, supporting the DSM-5 classification in distinguishing a neurodevelopmental factor from both emotional and behavioral factors.

This study examined the hypothesis that shared genetic liability across disorders would be reflected in associations between multiple disorder PRS and a general psychopathology factor. This hypothesis was partially supported: schizophrenia and ADHD PRS were associated with a general psychopathology factor in childhood but MDD and ASD PRS were not. Results for each PRS are discussed in detail below.

For schizophrenia PRS, results supported our hypothesis that shared genetic risks – in this case between schizophrenia and childhood emotional, behavioral and neurodevelopmental problems - are at least partly explained by genetic risk for general psychopathology. Several studies have now reported associations between schizophrenia PRS and psychopathology as well as IQ and social traits from early childhood onwards (9, 12, 16, 29, 30). Our findings suggest that schizophrenia genetic liability may be associated with these childhood impairments via a general liability to psychopathology. This is consistent with previous suggestions that risk for rarer forms of psychopathology, including schizophrenia, is also associated with (non-specific) risk for common psychopathology dimensions via the general factor (31). Beyond this general factor, there was evidence for association between schizophrenia PRS and childhood emotional problems at age 7 years but this was not found at age 13 years.

We also found ADHD PRS to be associated with the general psychopathology factor as well as with the specific neurodevelopmental factor - consistent with another population-based study that found associations between ADHD PRS and a latent factor encompassing emotional, behavioral and neurodevelopmental problems in Swedish children aged 9-12 years (15). This suggests that while shared genetic overlap between ADHD and some forms of psychopathology may be due to association with a general liability, there is also some specificity in associations with neurodevelopmental problems.

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ASD PRS, in contrast to expectations, were not associated with the general factor or the neurodevelopmental factor. Previous work in the same sample has found associations between ASD PRS and social-communication (one of our indices of neurodevelopmental problems) at age 7 years (13, 32) but our findings suggest that ASD common variants (at least based on currently available GWAS discovery sample sizes) do not predict a common liability to a broader (latent) measure of neurodevelopmental problems. This is somewhat surprising given that family and twin studies, the latest GWAS (genome-wide association study) of patient samples and studies of rare genetic mutations all suggest considerable genetic overlap between ASD and ADHD diagnoses (33). We speculate that this is likely in part due to the still relatively small ASD discovery GWAS and the typically weaker associations with trait measures than diagnoses. Finally, MDD PRS were not associated with the general factor - sensitivity analyses provided some evidence of association but this attenuated in the multivariable analyses, suggesting that this effect was not independent of the other psychiatric disorder PRS. MDD PRS were independently associated with an emotional problems factor, particularly at age 13 years. Previous work in another UK cohort found MDD PRS to be associated with emotional problems in adulthood but not in childhood (16). The findings in this cohort might differ because we investigated latent factors and included more anxiety measures or because we used a more powerful (larger) MDD discovery sample.

Our findings should be considered in light of a number of limitations. First, the sample is a longitudinal birth cohort study that suffers from non-random attrition, whereby children with higher PRS and higher levels of psychopathology are more likely to drop out of the study (34, 35). Second, our models were statistically driven - although theoretically informed - and are therefore dependent on the properties of the measures that are included in the models; while our bifactor model was the best fitting model that we tested, this does not mean that this is the best possible model. We restricted our measures to parent-rated problems given the ages of the children and to avoid changes in instrument and rater across age. Finally, it is also important to note that PRS currently only explain a small proportion of genetic liability to psychiatric

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disorders (10) and that environmental risk factors and shared symptoms (as well as other non-common, non-additive genetic factors not captured by existing PRS) will also contribute to phenotypic overlaps (3).

Conclusion

Our results suggest that at both ages 7 and 13 years schizophrenia and ADHD PRS may contribute to shared genetic risks across psychiatric diagnostic categories at least partly via association with a 'general psychopathology' factor, whereas genetic liability for MDD appears to contribute to a specific emotional factor in childhood, indexing depression and anxiety disorder symptoms.

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Conflict of Interest Disclosures: None.

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Figure 1A. Correlated factors model

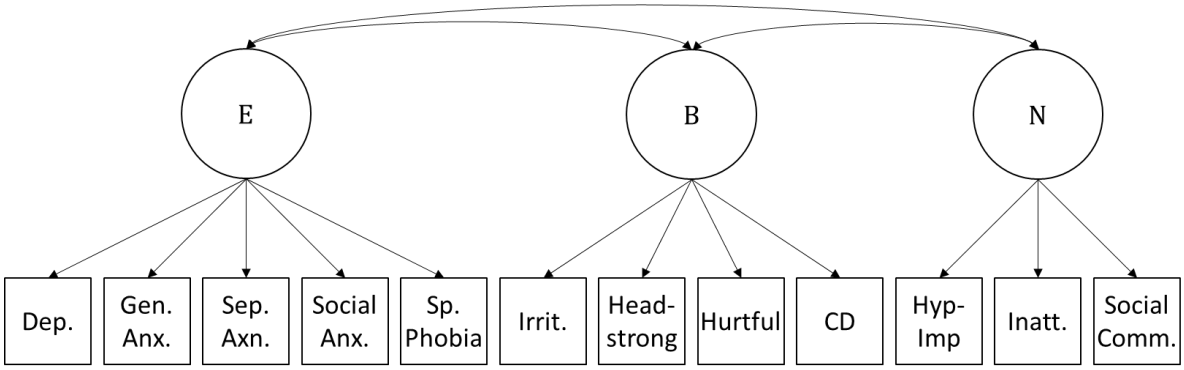
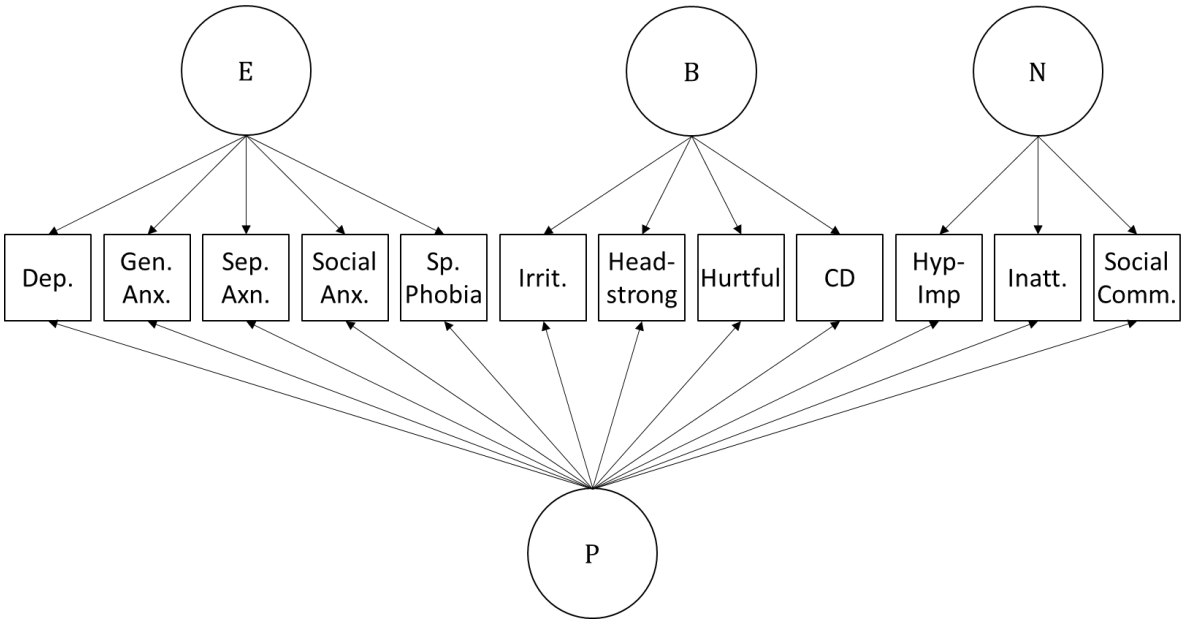


Figure 1B. Bifactor model



E=emotional, B=behavioral, N=neurodevelopmental, P = general psychopathology, Dep=depression, Gen=Generalized, Anx=anxiety, Sep=separation, Sp=Specific, Irrit=irritability, CD=conduct disorder, Hyp-imp=Hyperactivity/impulsivity, Inatten=Inattentive, Comm=communication.

Table 1. Factor loadings and correlations

	Age 7							Age 11						
	Correlated factors model			Bifactor model				Correlated factors model			Bifactor model			
Factor loadings	E	B	N	E	B	N	P	E	B	N	E	B	N	P
Depression	0.441			0.311			0.292	0.499			0.303			0.394
Generalized anxiety	0.583			0.565			0.229	0.630			0.663			0.219
Separation anxiety	0.599			0.500			0.296	0.535			0.435			0.270
Social anxiety	0.449			0.402			0.206	0.455			0.362			0.248
Specific phobia	0.446			0.448			0.157	0.446			0.498			0.105
Irritability		0.824			0.412		0.734		0.871			0.445		0.760
Headstrong		0.915			0.366		0.827		0.924			0.447		0.803
Hurtful		0.708			0.340		0.627		0.702			0.349		0.610
Conduct disorder		0.512			-0.013		0.560		0.553			0.075		0.579
Hyperactivity/impulsivity			0.857			0.540	0.694			0.761			0.620	0.633
Inattention			0.787			0.566	0.605			0.758			0.410	0.650
Social-communication			0.801			0.207	0.791			0.801			0.109	0.804
Factor correlations	E	B	N	E	B	N	P	E	B	N	E	B	N	P
Emotional	1			1				1			1			
Behavioral	0.424	1		0	1			0.391	1		0	1		
Neurodevelopmental	0.413	0.766	1	0	0	1		0.455	0.795	1	0	0	1	
General psychopathology				0	0	0	1				0	0	0	1

E=emotional, B=behavioral, N=neurodevelopmental, P=general psychopathology. Factor correlations fixed to zero in the bifactor model.

Table 2. Multivariable associations between genetic risk and the factor models model

	Schizophrenia PRS			MDD PRS			ASD PRS			ADHD PRS			
Age 7 years (N=5518)	β	SE	p	β	SE	p	β	SE	p	β	SE	p	Total R^2
Correlated factor model													
Emotional problems	0.055	0.017	0.001	0.038	0.017	0.025	0.004	0.017	0.822	-0.003	0.018	0.851	0.005
Behavioral problems	0.042	0.014	0.003	0.016	0.014	0.255	-0.010	0.014	0.478	0.061	0.014	<0.001	0.006
Neurodevelopmental problems	0.038	0.015	0.009	0.019	0.015	0.184	-0.006	0.014	0.677	0.089	0.015	<0.001	0.010
Bifactor model													
Emotional problems	0.042	0.019	0.025	0.032	0.019	0.092	0.006	0.019	0.744	-0.050	0.020	0.011	0.005
Behavioral problems	0.019	0.028	0.492	-0.018	0.028	0.511	-0.018	0.029	0.531	-0.059	0.030	0.051	0.005
Neurodevelopmental problems	0.000	0.022	0.987	-0.002	0.021	0.916	-0.018	0.022	0.414	0.037	0.023	0.098	0.001
General psychopathology	0.041	0.017	0.017	0.025	0.017	0.134	0.000	0.018	0.995	0.088	0.018	<0.001	0.011
Age 13 years (N= 4987)	β	SE	p	β	SE	p	β	SE	p	β	SE	p	R^2
Correlated factor model													
Emotional problems	0.013	0.017	0.456	0.056	0.017	0.001	0.013	0.017	0.459	0.029	0.017	0.092	0.005
Behavioral problems	0.033	0.014	0.024	0.009	0.014	0.535	-0.011	0.014	0.432	0.077	0.015	<0.001	0.007
Neurodevelopmental problems	0.056	0.016	<0.001	0.009	0.015	0.564	-0.018	0.016	0.240	0.103	0.016	<0.001	0.014
Bifactor model													
Emotional problems	-0.022	0.018	0.237	0.053	0.018	0.003	0.018	0.019	0.322	-0.016	0.019	0.398	0.004
Behavioral problems	-0.050	0.024	0.035	-0.008	0.024	0.744	0.003	0.026	0.911	-0.003	0.027	0.899	0.003
Neurodevelopmental problems	-0.021	0.022	0.349	-0.014	0.021	0.519	-0.012	0.022	0.591	0.063	0.023	0.005	0.004
General psychopathology	0.065	0.017	<0.001	0.015	0.017	0.371	-0.015	0.017	0.395	0.086	0.018	<0.001	0.012

MDD=major depressive disorder, ASD=autism spectrum disorder, ADHD=attention-deficit/hyperactivity disorder, PRS=polygenic risk score.
Betas represent a 1 standard deviation increase in factor score per 1 standard deviation increase in PRS.