Using genetics to examine a general liability to childhood psychopathology

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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 largely can be explained by a latent general "p" 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 age 7 (N=8161) years. PRS were generated from large published genome-wide association studies.

Outcomes. The general psychopathology factor was associated with both schizophrenia PRS and attention-deficit/hyperactivity disorder (ADHD) PRS, whereas there was no strong evidence of association with major depressive disorder and autism spectrum disorder PRS. Schizophrenia PRS was also associated with a specific "emotional" problems factor.

Interpretation. Our findings suggest that genetic liability to schizophrenia and ADHD may contribute to shared genetic risks across childhood psychiatric diagnoses at least partly via the 'general psychopathology' factor. However, the pattern of observations could not be explained by a general "p" factor on its own.

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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, attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD) and depression are at elevated risk for a broad range of psychopathology - not just for the same disorder as the affected probands.[1] Recent molecular genetic studies also provide evidence of common variant genetic overlaps between different psychiatric disorders; for example genetic correlations across schizophrenia, ADHD, ASD and mood disorders have been shown to range from 0·30 to 0·93.[2] Current psychiatric nosology does not take into account these complex patterns of shared inheritance across phenotypes.[1]

While the genetic architecture of psychiatric disorders is complex, indicators of (common variant) genetic liability for psychiatric disorders including schizophrenia, ADHD, ASD and depression can be measured in individuals using polygenic risk scores (PRS).[3] 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 ADHD, ASD, depression and anxiety) and broader categories of psychiatric phenotypes (e.g. neurodevelopmental traits in childhood).[4,5] 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 can be largely explained by a single, latent general factor that reflects general liability to psychopathology, known as the "p" factor.[6,7] In children, factor analyses show that different forms of psychopathology converge onto specific "emotional" (internalizing) and "behavioural" (externalizing) factors as well as a general "p" factor. However, such studies

typically have not included measures of ASD. In adulthood, recent studies have highlighted the presence of a specific "thought disorder" factor, as well as "emotional" and "behavioural" factors that aggregate into one general psychopathology dimension.[7] Indeed, it has been proposed recently that the general liability factor "p" could account for the relative lack of clinical and treatment specificity and shared risk factors across different forms of psychopathology.[7] However, this requires further empirical testing because there are some unique aspects to different types of psychopathology. For example, stimulant medication is effective for ADHD but not for anxiety disorder or ASD suggesting that there are also important biological differences between disorders.

In this study, we set out to examine associations between risk alleles for several different major psychiatric disorders, indexed by PRS, and the 'general psychopathology' factor. Unlike previous studies of psychopathology, we included ASD problems and hypothesised that we would identify a "neurodevelopmental" factor as well as "emotional" and "behavioural" factors. We investigated PRS for schizophrenia, ADHD, ASD and major depressive disorder (MDD), derived from large, publicly available genome-wide association studies, because these PRS have previously been shown to be associated with childhood as well as adult psychopathology.[8-11] First, we hypothesized that in childhood, all of these psychiatric genetic risk scores would be associated with the general "p" factor. Our second hypothesis was that PRS would show additional phenotype-specific associations; specifically, that we would observe associations between ASD and ADHD PRS with the specific "neurodevelopmental" factor and MDD PRS with the specific "emotional" factor.

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 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 enrolment 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.[12,13] 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. We focused on children, at age 7 years.

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.[14] Scores were standardized using Z-score transformation. Risk alleles were defined as those associated with case-status in recent large consortia analyses of schizophrenia (40,675 cases and 64,643 controls),[15] ADHD (19,099 cases and 34,194 controls),[16] ASD (18,381 cases and 27,969 controls)[17] and MDD (135,458 cases and 344,901 controls).[18] In the primary analyses we defined risk alleles as those associated at $p<0{\cdot}05$ as this threshold has previously been shown to maximally capture phenotypic variance for schizophrenia;[5] associations across a range of p-thresholds are shown in Supplementary Figure 1 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 68% of individuals (N=5518/8161) who also had phenotypic data at age 7. Sensitivity analyses were conducted using inverse probability weighting[19] to assess the impact of missing genetic data (see Supplementary Material).

Outcomes

Psychopathology was assessed using parent reports at the approximate age of 7/8 years old. Emotional problems were assessed using the Development and Well-Being Assessment (DAWBA)[20] (individual item range 0-2) for depression (12 items), generalized anxiety (7 items), separation anxiety (10 items), social anxiety (6 items) and specific phobia (7 items). Behavioural problems were assessed using the DAWBA for conduct disorder (7 items) and the three components of oppositional defiant disorder: irritability (3 items), headstrong (4 items) and hurtful (2 items) behaviours. 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[21] 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 Table 1.

Analysis

In-line with previous factor analysis work, we first used confirmatory factor analysis to fit bifactor models (including both general and specific factors, with correlations between factors fixed to zero) at each age. Model fit was assessed using a variety of indices including the comparative fit index (CFI, >0·95 considered good fit), Tucker-Lewis index (TFI, >0·95 considered good fit) and the root-mean-square error of approximation (RMSEA, <0·06 considered good fit).[22] Comparisons of model fit with different models are available from the first author. Omega reliability coefficients were calculated to assess model reliability.[23] 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 affect the factor structure). Schizophrenia, ADHD, ASD and MDD PRS were included simultaneously (as were all factors within a given model) in a single test at age 7 years. As the same measures were available on children at age 13 years, we assessed the developmental stability of observations by checking associations at this age (see Supplementary Table 2 for descriptive statistics and correlations

between variables at this age). Analyses were conducted in Mplus using a maximum likelihood parameter estimator for which standard errors are robust to non-normality (MLR).[24]

Results

A bifactor model including a general psychopathology factor "p" as well as three 'specific' "emotional", "behavioural" and "neurodevelopmental" factors – shown in Figure 1 and Table 1 - fit the data well (CFI=0·973, TFI=0·959, RMSEA=0·038).

Omega reliability coefficients, shown in Table 1, indicated that the inclusion of the specific factors explained additional variance (ω; compared to the general factor alone ω_H). These coefficients indicated that for ADHD and ASD problems, most of the variance was explained by the general "p" factor. In contrast, for anxiety/mood problems, most of the variance was explained by the specific "emotional" factor (variance explained was similar regardless of whether or not the general factor was partialled out: ω_{HS} compared to ω_S). Finally, for oppositional defiant problems, both the general "p" factor and specific "behavioural" factor captured variance.

Female sex was negatively associated with the general psychopathology "p" factor (β=-0·106, SE=0·014, p<0·001), positively associated with the "emotional" factor (β=0·117, SE=0·017, p<0·001), not strongly associated with the "behavioural" factor (β =0·028, SE=0·024, p=0·231) and negatively associated with the "neurodevelopmental" factor (β =-0·147, SE=0·018, p<0·001).

Genetic risk

Results of multivariable PRS association with the psychopathology factors are shown in Table 2. Schizophrenia and ADHD PRS were associated with the general psychopathology "p" factor, while ASD and MDD PRS were not.

Schizophrenia PRS were also associated with the specific "emotional" factor; MDD PRS was weakly associated with the "emotional" factor and ADHD PRS were negatively associated with the specific "emotional" factor.

There was no strong evidence of associations between ASD PRS and any of the factors.

Sensitivity analyses

Entering PRS in univariable (instead of multivariable) analyses revealed a similar pattern of results, with the exception that the association between MDD PRS and general psychopathology was stronger when the other PRS were not included in the model (age 7 β=0·041, SE=0·017, p=0·019, see Supplementary Table 3 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).

Developmental stability

The same bifactor model fit well at age 13 years (CFI=0·969, TFL=0·953, RMSEA=0·038). Correlations between the general "p" and specific factors at ages 7 and 13 suggested strong phenotypic stability in the factor structure of psychopathology between childhood and early adolescence (general psychopathology r=0·762, "emotional" factor r=0·828, "behavioural" factor r=0·871, "neurodevelopmental" factor r=0·907; see Supplementary Tables 4 and 5). The pattern of associations between neuropsychiatric PRS and the "p" factor and specific factors was the same at age 13 years as 7 years (Supplementary Table 6). Two exceptions were that the association between MDD PRS and the specific "emotional" factor was stronger in adolescence (β=0·056, SE=0·018, p=0·002) and that ADHD PRS were associated with the "neurodevelopmental" factor (β=0·061, SE=0·024, p=0·011) as well as the general "p" factor at age 13 years.

Discussion

In this study we first set out to examine the hypothesis that PRS for different psychiatric disorders would be associated with a general childhood psychopathology "p" factor that captures the main forms of psychopathology including ASD problems. This has not previously been tested. As expected, given previous factor analysis studies, a bifactor model fit the data well. This included the general "p" factor and specific "emotional" and "behavioural" factors. Uniquely, we also included ASD symptoms and additionally observed a third "neurodevelopmental" factor that captured variance for ADHD and ASD problems although here, most of the variance for these problems was captured by the general "p" factor. Our first hypothesis was partially but not entirely supported: schizophrenia and ADHD PRS were associated with a general psychopathology "p" factor at age 7 years but associations were not observed for ASD and MDD PRS. This suggests that there is a more complex explanation to the structure of psychopathology and its aetiology than a single unifying dimension. Our second hypothesis was that neuropsychiatric PRS would contribute additionally to specific latent factors. Schizophrenia PRS were associated with the specific "emotional" factor and MDD PRS were weakly associated (this association was more prominent at age 13 years). We also observed that ADHD PRS were negatively associated with the "emotional" factor.

Results for each set of neuropsychiatric PRS are discussed next. For schizophrenia PRS, results supported our hypothesis that its association with different forms of psychopathology in early life (age 7 years) are mainly but not entirely explained by its contribution to a latent general psychopathology factor. Several studies have now reported associations between schizophrenia PRS and psychopathology as well as IQ and social traits from early childhood onwards.[4,8,25] Our findings suggest that these associations may be driven mainly by a general liability to psychopathology. Recent work in this sample that focused on psychosis-related and emotional problems, suggests the same to be true for associations between schizophrenia PRS and other forms of psychopathology (i.e. psychotic experiences, depression and anxiety) in later adolescence.[26] This is consistent with previous suggestions that risk factors for rarer forms of

psychopathology, such as schizophrenia, are also associated with (non-specific) risk for common psychopathology via a single general "p" factor.[27] However, the general "p" factor on its own was an insufficient explanation for the pattern of results as we also observed association between schizophrenia PRS and the specific "emotional" factor.

For MDD genetic liability we observed evidence of specificity - MDD PRS were not associated with the general "p" factor. However, sensitivity analyses suggested that on their own, MDD PRS are associated with the general "p" factor but this attenuated in the multivariable analyses. These observations suggest that MDD PRS do contribute but effects are not independent of the other psychiatric disorder PRS. Interestingly, MDD PRS were independently weakly associated with the specific "emotional" factor at age 7 years. The test of developmental stability suggested that developmental change is likely important as the association was more robust 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.[25] Again this suggests that for depression and MDD PRS, developmental change is likely to be important.

We also observed that ADHD PRS were associated with the general psychopathology "p" factor as well as with the specific "neurodevelopmental" factor at age 13 - consistent with another population-based study that investigated ADHD PRS. That study of Swedish children aged 9-12 years observed associations between ADHD PRS and a latent general "p" factor encompassing emotional, behavioural and neurodevelopmental problems but was also associated with specific ADHD hyperactive/impulsive problems – although they did not investigate a specific "neurodevelopmental" facor.[10] The findings taken together suggest that while ADHD genetic liability contributes to child psychopathology via a general liability or "p" factor, there is also additional specificity in its associations with ADHD/neurodevelopmental problems. Unexpectedly, we found a negative association between ADHD PRS and the specific "emotional" factor at age 7 – similar findings were observed for social phobia in previous work[10] although it is not clear why. It may be that genetic liability for ADHD is so strongly captured by the general "p" factor that the overlap with emotional symptoms is explained by this general factor and the

remaining loading becomes negative. Another possibility is that the genetic and clinical overlap between ADHD and emotional problems (depression, anxiety) changes after mid-late adolescence.

ASD PRS were not associated with the general "p" factor or the neurodevelopmental factor. Previous studies have found associations between ASD PRS and for social-communication problems related to ASD (one of our indices of neurodevelopmental problems)[9] but our findings suggest that ASD common variants (at least as far as can be estimated using currently available GWAS discovery sample sizes) do not contribute to a broader (latent) liability for "neurodevelopmental" problems or general childhood psychopathology. This is somewhat surprising given that family and twin studies, the latest ASD patient GWAS (genome-wide association study) and studies of rare genetic mutations all suggest considerable genetic overlap between ASD and ADHD diagnoses.[28] We speculate that this could in part be due to the relatively small ASD discovery GWAS and the typically weaker associations with trait measures than diagnoses. In addition, genetic findings for ASD PRS do not parallel observations for many other neuropsychiatric PRS (e.g. ADHD, schizophrenia). For example, unlike ADHD PRS, they predict higher IQ in population-based samples.[17]

Our findings examining neuropsychiatric PRS provide evidence in favour of a general liability to childhood psychopathology but also suggest that this unidimensional approach is probably insufficient on its own for explaining variance and associations of PRS with psychopathology. Indeed, we observed much of the variance in neurodevelopmental and early behavioural problems was captured by a general psychopathology factor and that most of the associations between neuropsychiatric PRS and child psychopathology in this sample were driven by association with the general "p" factor. However, based on our study, we cannot dismiss specificity. This was particularly the case for emotional problems, for which a specific factor accounted for the majority of the variance in these phenotypes, and for which MDD PRS showed some evidence of association. This suggests there may not be just a single liability to psychiatric problems. The findings are consistent with recent papers that highlight the possibility that

much of the (genetic) risk for psychopathology is captured by a general liability to psychiatric disorders.[7,29] The previous two studies that also investigated neuropsychiatric PRS focused either on ADHD PRS or on psychosis-related and emotional PRS and did not simultaneously test the same range of psychiatric PRS. Considering the contribution of schizophrenia, MDD as well as ADHD and ASD PRS together is important given that most adult psychiatric disorders have their roots in childhood and there is strong etiological overlap between ADHD, ASD and the typically later (late adolescence/adult) onset disorders of schizophrenia and MDD.

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.[30] 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 had to restrict our measures to parent-rated problems given the young age of the children - this is typical practice. Finally, it is also important to note that PRS currently only explain a small proportion of genetic liability to psychiatric disorders[5] 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.[6]

Conclusion

Our results suggest that schizophrenia and ADHD PRS contribute to shared genetic risks across psychiatric diagnostic categories from an early age (age 7 years) at least partly via association with a 'general psychopathology' factor but that variance in psychopathology and its links with neuropsychiatric risk alleles appear to be explained additionally by "specific" factors. Our conclusion from these findings is that a unidimensional view of all psychopathology is a helpful but insufficient explanation on its own; there is also specificity and this requires further empirical testing.

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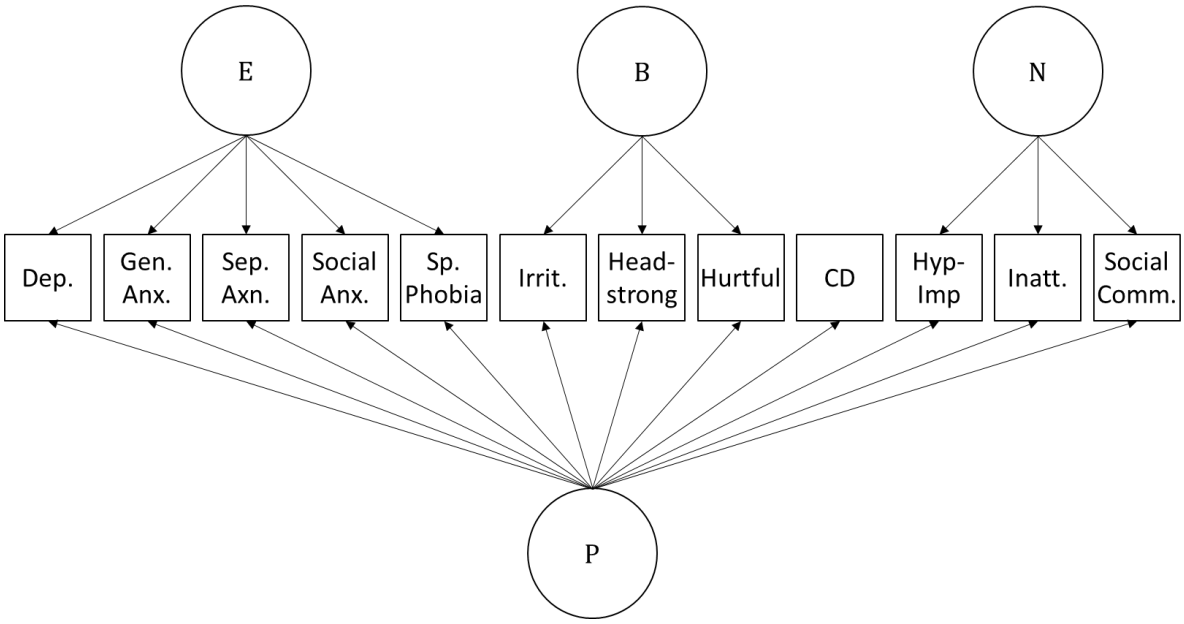
Conflict of Interest Disclosures: None.

References

1. Doherty JL, Owen MJ. Genomic insights into the overlap between psychiatric disorders: implications for research and clinical practice. *Genome Med* 2014; **6**(4): 29.
2. Schork AJ, Won H, Appadurai V, et al. A genome-wide association study for shared risk across major psychiatric disorders in a nation-wide birth cohort implicates fetal neurodevelopment as a key mediator. *bioRxiv* 2017.
3. Sullivan PF, Agrawal A, Bulik CM, et al. Psychiatric Genomics: An Update and an Agenda. *Am J Psychiatry* 2018; **175**(1): 15-27.
4. Riglin L, Collishaw S, Richards A, et al. Schizophrenia risk alleles and neurodevelopmental outcomes in childhood: a population-based cohort study. *Lancet Psychiatry* 2017; **4**(1): 57-62.
5. Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights from 108 schizophrenia-associated genetic loci. *Nature* 2014; **511**(7510): 421-7.
6. Lahey BB, Van Hulle CA, Singh AL, Waldman ID, Rathouz PJ. Higher-order genetic and environmental structure of prevalent forms of child and adolescent psychopathology. *Arch Gen Psychiatry* 2011; **68**(2): 181-9.
7. Caspi A, Moffitt TE. All for One and One for All: Mental Disorders in One Dimension. *Am J Psychiatry* 2018; **175**(9): 831-44.
8. Poletti M, Raballo A. Polygenic Risk Score and the (neuro)developmental ontogenesis of the schizophrenia spectrum vulnerability phenotypes. *Schizophr Res* 2018.
9. St Pourcain B, Robinson EB, Anttila V, et al. ASD and schizophrenia show distinct developmental profiles in common genetic overlap with population-based social communication difficulties. *Mol Psychiatry* 2018; **23**(2): 263-70.
10. Brikell I, Larsson H, Lu Y, et al. The contribution of common genetic risk variants for ADHD to a general factor of childhood psychopathology. *Mol Psychiatry* 2018.
11. Rice F, Riglin L, Thapar AK, et al. Characterizing developmental trajectories and the role of neuropsychiatric genetic risk variants in early-onset depression. *JAMA Psychiatry* 2018.
12. Boyd A, Golding J, Macleod J, et al. Cohort Profile: the 'children of the 90s'--the index offspring of the Avon Longitudinal Study of Parents and Children. *International journal of epidemiology* 2013; **42**(1): 111-27.
13. Fraser A, Macdonald-Wallis C, Tilling K, et al. Cohort Profile: the Avon Longitudinal Study of Parents and Children: ALSPAC mothers cohort. *International journal of epidemiology* 2013; **42**(1): 97-110.
14. Euesden J, Lewis CM, O'Reilly PF. PRSice: Polygenic Risk Score software. *Bioinformatics* 2015; **31**(9): 1466-8.
15. Pardinas AF, Holmans P, Pocklington AJ, et al. Common schizophrenia alleles are enriched in mutation-intolerant genes and in regions under strong background selection. *Nat Genet* 2018; **50**(3): 381-9.
16. Demontis D, Walters RK, Martin J, et al. Discovery Of The First Genome-Wide Significant Risk Loci For ADHD. *bioRxiv* 2017.
17. Grove J, Ripke S, Als TD, et al. Common risk variants identified in autism spectrum disorder. *bioRxiv* 2017.
18. Wray NR, Ripke S, Mattheisen M, et al. Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. *Nat Genet* 2018; **50**(5): 668-81.
19. Seaman SR, White IR. Review of inverse probability weighting for dealing with missing data. *Stat Methods Med Res* 2013; **22**(3): 278-95.
20. Goodman R, Ford T, Richards H, Gatward R, Meltzer H. The Development and Well-Being Assessment: description and initial validation of an integrated assessment of child and adolescent psychopathology. *J Child Psychol Psychiatry* 2000; **41**(5): 645-55.
21. Skuse DH, Mandy WP, Scourfield J. Measuring autistic traits: heritability, reliability and validity of the Social and Communication Disorders Checklist. *Br J Psychiatry* 2005; **187**(6): 568-72.

22. Hu LT, Bentler PM. Cutoff Criteria for Fit Indexes in Covariance Structure Analysis: Conventional Criteria Versus New Alternatives. *Struct Equ Modeling* 1999; **6**(1): 1-55.
23. Rodriguez A, Reise SP, Haviland MG. Applying bifactor statistical indices in the evaluation of psychological measures. *Journal of Personality Assessment* 2016; **98**(3): 223-37.
24. Muthén LK, Muthén BO. Mplus User's Guide. Seventh ed. Los Angeles, CA: Muthén & Muthén; 1998-2012.
25. Riglin L, Collishaw S, Richards A, et al. The impact of schizophrenia and mood disorder risk alleles on emotional problems: investigating change from childhood to middle age. *Psychol Med* 2018; **48**(13): 2153-8.
26. Jones HJ, Heron J, Hammerton G, et al. Investigating the genetic architecture of general and specific psychopathology in adolescence. *Translational psychiatry* 2018; **8**(1): 145.
27. Lahey BB, Krueger RF, Rathouz PJ, Waldman ID, Zald DH. A hierarchical causal taxonomy of psychopathology across the life span. *Psychol Bull* 2017; **143**(2): 142-86.
28. Rommelse NN, Franke B, Geurts HM, Hartman CA, Buitelaar JK. Shared heritability of attention-deficit/hyperactivity disorder and autism spectrum disorder. *Eur Child Adolesc Psychiatry* 2010; **19**(3): 281-95.
29. Selzam S, Coleman JRI, Caspi A, Moffitt TE, Plomin R. A polygenic p factor for major psychiatric disorders. *Translational psychiatry* 2018; **8**(1): 205.
30. Taylor AE, Jones HJ, Sallis H, et al. Exploring the association of genetic factors with participation in the Avon Longitudinal Study of Parents and Children. *International journal of epidemiology* 2018; **47**(4): 1207-16.

Figure 1. Bifactor model



E=emotional, B=behavioural, 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 omega reliability coefficients

	P	E	B	N
Factor loadings				
Depression	0·292	0·311		
Generalized anxiety	0·230	0·566		
Separation Anxiety	0·296	0·500		
Social anxiety	0·206	0·402		
Specific phobia	0·158	0·447		
Irritability	0·731		0·416	
Headstrong	0·824		0·374	
Hurtful	0·622		0·351	
Conduct disorder	0·557			
Hyperactivity-impulsivity	0·697			0·535
Inattention	0·608			0·564
Social-communication	0·795			0·199
Omega reliability coefficients				
Omega (ω)	0·944			
Omega hierarchical (ω_H)	0·554			
Omega subscale (ω_S)		0·933	0·947	0·894
Omega hierarchical subscale (ω_{HS})		0·897	0·420	0·054

P = general psychopathology, E=emotional, B=behavioural, N=neurodevelopmental

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

	Schizophrenia PRS			ADHD PRS			ASD PRS			MDD PRS			
	β	SE	p	β	SE	p	β	SE	p	β	SE	p	Total R^2
General psychopathology	0·042	0·018	0·016	0·087	0·019	<0·001	0·002	0·018	0·912	0·026	0·017	0·144	0·011
Emotional problems	0·040	0·019	0·035	-0·046	0·020	0·021	0·007	0·019	0·713	0·035	0·019	0·073	0·005
Behavioural problems	0·015	0·028	0·577	-0·050	0·034	0·143	-0·022	0·029	0·444	-0·017	0·028	0·539	0·004
Neurodevelopmental problems	-0·002	0·022	0·539	0·041	0·025	0·109	-0·021	0·023	0·362	-0·002	0·022	0·912	0·002

ADHD=attention-deficit/hyperactivity disorder, ASD=autism spectrum disorder, MDD=major depressive disorder, PRS=polygenic risk score.

Betas represent a 1 standard deviation increase in factor score per 1 standard deviation increase in PRS.