Genetic Overlap Between Schizophrenia and Developmental Psychopathology: Longitudinal and Multivariate Polygenic Risk Prediction of Common Psychiatric Traits During Development

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Background: Several nonpsychotic psychiatric disorders in childhood and adolescence can precede the onset of schizophrenia, but the etiology of this relationship remains unclear. We investigated to what extent the association between schizophrenia and psychiatric disorders in childhood is explained by correlated genetic risk factors. *Methods:* Polygenic risk scores (PRS), reflecting an individual's genetic risk for schizophrenia, were constructed for 2588 children from the Netherlands Twin Register (NTR) and 6127 from the Avon Longitudinal Study of Parents And Children (ALSPAC). The associations between schizophrenia PRS and measures of anxiety, depression, attention deficit hyperactivity disorder (ADHD), and oppositional defiant disorder/conduct disorder (ODD/CD) were estimated at age 7, 10, 12/13, and 15 years in the 2 cohorts. *Results* were then meta-analyzed, and a meta-regression analysis was performed to test differences in effects sizes over, age and disorders. *Results:* Schizophrenia PRS were associated with childhood and adolescent psychopathology. Meta-regression analysis showed differences in the associations over disorders, with the strongest association with childhood and adolescent depression and a weaker association for ODD/CD at age 7. The associations increased with age and this increase was steepest for ADHD and ODD/CD. Genetic correlations varied between 0.10 and 0.25. *Conclusion:* By optimally using longitudinal data across diagnoses in a multivariate meta-analysis this study sheds light on the development of childhood disorders into severe adult psychiatric disorders. The results are consistent with a common genetic etiology of schizophrenia and developmental psychopathology as well as with a stronger shared genetic etiology between schizophrenia and adolescent onset psychopathology.

Key words: developmental psychiatry/schizophrenia prodrome/genetic epidemiology

Introduction

The onset of schizophrenia generally occurs during adolescence or early adulthood,[1] but it is well established that nonpsychotic psychiatric symptoms can be present in the period before the first psychotic episode. The prodromal phase is characterized by neurodevelopmental deficits,[2–4] cognitive learning and memory problems,[5] and elevated psychiatric symptoms.[6] Well before the prodromal phase, psychiatric symptoms or disorders are more prevalent in individuals who later develop schizophrenia, as becomes apparent from longitudinal population-based cohorts,[7,8] retrospective assessments of schizophrenia cases,[9] and from studies on populations at risk for developing schizophrenia.[10] Both externalizing symptoms or disorders, including attention deficit hyperactivity disorder, conduct disorder, aggression, and antisocial behavior,[11,12] and internalizing symptoms or disorders, including anxiety and depression, are associated with a higher risk of schizophrenia.[7,8,11,13–16] In sum, these studies indicate that the onset of schizophrenia can be preceded by a broad range of childhood and adolescent psychopathology.

The early detection of schizophrenia can improve outcomes,[8] and preventive treatment for individuals at risk for schizophrenia can reduce the risk of psychosis.[17,18] Insight into the risk factors associated with the predictors of schizophrenia may facilitate early detection. Here, we focused on the role of genetic risk factors. Schizophrenia is highly heritability (approximately 80%[19]) and molecular genetic and twin and family studies generally found evidence for a genetic association between childhood and adult psychopathologies,[20–27] with one exception.[28] Consequently, we hypothesized that genetic risk factors for schizophrenia are associated with childhood and adolescent psychopathology. We further expected this association to become stronger from childhood into adolescence, since the prevalence rates of prodromal symptoms and of psychiatric disorders genetically correlated to schizophrenia (ie, major depression and bipolar disorder) show a marked increase during adolescence.[1] Previous molecular genetics studies[27,28] have also related schizophrenia to psychopathology in childhood or adolescence, but never considered how the genetics associations with psychopathology developed from childhood into adolescence.

We tested these hypotheses with a novel approach which involves the meta-analysis of multiple polygenic risk score (PRS) analyses of the genetic associations between schizophrenia and longitudinal psychopathology measures. The PRS were based on the most recent schizophrenia GWA meta-analysis[29] that yielded 108 genome wide associations, which provides an excellent starting point to investigate the genetic overlap between schizophrenia and other traits (for a review of PRS analyses see: refs.[30–32]). The schizophrenia PRS were used to predict DSM-IV[33] based measures of anxiety, depression, attention deficit hyperactivity disorder (ADHD) and oppositional deviant disorder and conduct disorder (ODD/CD) assessed at ages 7, 10, 12/13, and 15 years, in 2 large cohorts. The 192 univariate PRS predictions were subjected to a multivariate meta-analysis, and a meta-regression analysis. The multivariate meta-regression framework provided the opportunity to test for differences in the association between schizophrenia PRS and childhood psychopathology across cohorts, disorders and over age.

Methods

Subjects

The Netherlands Twin Register (NTR) (www.tweelingenregister.org) follows newborn and adult twins. In the Young NTR (YNTR), twins are registered by their parents and followed from birth onwards. Until age 12, parents complete surveys to report on their twins. From age 14 onwards, information is collected by means of self-report.[34] In the current study, maternal ratings of childhood psychopathology collected at age 7, 10, and 12 years were analyzed as well as self-report data collected between ages 14–16 years. The number of genotyped children with scores available varied between 1223 and 2588 depending on age group (supplementary table S1). Informed consent was obtained from all participants. The study was approved by the Central Ethics Committee on Research Involving Human Subjects of the VU University Medical Centre, Amsterdam, an Institutional Review Board certified by the US Office of Human Research Protections (IRB number IRB-2991 under Federal-wide Assurance-3703; IRB/institute codes, NTR 03-180).

The Avon Longitudinal Study of Parents And Children (ALSPAC) (www.bristol.ac.uk/alspac/) consists of mothers and their children, born between 1990 and 1991 in the Avon area in southwest England, UK.[35] The ALSPAC cohort includes maternal ratings of psychopathology at age 7, 10, 13, and 15 and self-ratings at 15 years. The number of genotyped children at each age group varied between 4445 and 6127 (supplementary table S1). Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. The study website contains details of all data available through a fully searchable data dictionary (www.bris.ac.uk/alspac/researchers/data-access/data-dictionary).

Measures

In the NTR, psychopathology was measured with DSM-IV based symptom scales[36] of the age appropriate versions of the Achenbach System of Empirically Based Assessment (ASEBA). For ages 7 to 12, maternal Child Behavior Checklist (CBCL) ratings of the anxiety disorder scale (anxiety), the affective disorder scale (depression), the attention deficit hyperactivity disorder scale (ADHD), and a combined oppositional deviant disorder and conduct disorder (ODD/CD) scale were analyzed. From age 14 onwards, self-ratings of these scales were analyzed.

In ALSPAC, psychopathology was assessed using the development and wellbeing assessment (DAWBA), which measures the presence of symptoms required for a DSM-IV diagnosis.[37] Disorders comparable to the ASEBA scales were included in the analyses: any anxiety disorder (anxiety), major depression (depression), attention deficit hyperactivity disorder (ADHD), and combined oppositional deviant disorder and conduct disorder (ODD/CD).[38] Any anxiety disorder included generalized anxiety disorder, specific phobia, social phobia (at age 7, 10, 13, and 15), separation anxiety disorder (at age 7, 10, and 13), and panic disorder and agoraphobia (at age 15). At ages 7, 10, and 13 all ratings were maternal ratings. At age 15, ADHD and CD/ODD were rated by mothers, and anxiety and depression were self-ratings. The DAWBA yields a diagnosis, but also a more finely grained indicator of disease risk, the DAWBA band. DAWBA band scores, which range from 0 to 5, correspond to probabilities of less than 0.01%, 0.5%, 3%, 15%, 50%, and more than 70% of satisfying DSM-IV diagnostic criteria.

Genotyping

Genotyping and genotype quality control were performed in accordance with common standards to (for a detailed description see supplementary note 1).

Polygenic Risk Scores

PRS were calculated by summing the number of risk alleles across all genetic loci (coded as 0,1,2), weighted by the schizophrenia risk conferred by each locus. The risk conferred by each locus was based on the results from the most recent genome-wide association meta-analysis for schizophrenia (PGC-SCZ2, available online: http://www.med.unc.edu/pgc/downloads).[29] For all participants, we calculated PRS using LDpred,[39] a method which accounts for correlations between adjacent genetic loci, and adjusts the effect size for each locus in a Linkage Disequilibrium (LD) block to avoid inflation due to LD. LDpred further uses an expectation for the per locus risk, which is based on the expected degree of polygenicity in a trait, ie, in the case of low polygenicity, a small proportion of the SNPs, eg, 1%, explains the total genetic variation and the per locus effect is high, whereas in the case of high polygenicity a large proportion of the SNP, eg, 50% explains the genetic variation and the per locus effect is low. Since it is of interest to know the proportion of the genome that exerts an influence on a trait, we computed 6 PRS at 6 different priors for the proportion of SNPs with a casual effect (0.01, 0.05, 0.1, 0.25, 0.5, and 1) and investigated at which prior the predictions were most optimal. Setting a prior on the polygenicity determines for how many loci LDpred expects the effect size to be zero. The discovery markers were not pruned and neither were markers a priori eliminated based on thresholds. Instead, the effect of all markers, the LD between markers and the prior expectation of the degree of polygenicity were leveraged to obtain optimal weights for all markers. For each prior a set of weights was obtained, which was converted in a polygenic score for each subject. The inclusion criteria for SNPs were minor allele frequency above 5% and high imputation quality ($R^2 > .9$). The PRS were scaled to unit variance and mean centered within cohort.

Statistical Analyses

In NTR and in ALSPAC, 96 (4 age bins × 4 disorders × 6 polygenic scores) regression analyses were performed to analyze the prediction of the psychopathology measures by the schizophrenia PRS. Psychopathology measures were scaled to unit variance. As the NTR contained related individuals, the linear regression was performed using a generalized estimation equation with exchangeable background correlations within family, and robust standard errors. This procedure adequately corrects for the presence of related individuals in the sample.[40] In the ALSPAC sample, an ordered logistic regression was performed since the DAWBA bands are ordered categorical variables. The ordered logistic regression in ALSPAC was transformed to a scale where the underlying latent variable has variance 1. This results in comparable betas in the 2 cohorts, as in both samples a 1 SD increase in the schizophrenia PRS results in a 1 SD increase in the (latent) phenotype. The expression of the effect sizes on a common scale enabled a meta-analysis of regression coefficients from the 96 NTR and 96 ALSPAC analyses. Meta-analyses were performed in the metaphor R-package.[41] In contrast to most meta-analyses, the outcome variables were correlated since within the NTR and ALSPAC the same individuals were repeatedly assessed. The PRS were also correlated since they were based on a common set of effect sizes, and only differ in the degree of polygenicity assumed in their construction. These correlations result in dependencies between the parameters to be meta-analyzed. We accounted for this in the meta-analysis by specifying the error covariance matrix as the observed correlations between traits and PRS (see supplementary note 1 for type 1 error simulation and sensitivity analysis).

In a meta-analysis, we tested whether the effect sizes obtained from the 192 univariate PRS analyses departed from zero. We subsequently used a meta-regression to model differences in the effect sizes of the association between PRS and childhood psychopathology as a function of cohort, age, prior, and disorder. To clarify, by adding the variable age to the meta-regression model, it is tested whether the observed effect sizes differ over the 4 age groups, ie, become smaller or larger with age. Cohort was coded 1 for ALSPAC and 0 for NTR. Age was coded in years over 7 (age 7 was coded as 0). We considered 4 meta-regression models, which include an increasing number of predictors (table 1). The most comprehensive model included cohort, age, prior, prior^2, disorder, age × disorder, age^2, age^2 × disorder. To guard against over fitting, which is a risk in meta-regression,[42] we performed 1000 parametric resamples of the data and performed the model selection on each resample (supplementary note 1). We report the proportion of resamples in which each model is selected based on the Akaike's Information Criterion (AIC). To check whether the presence of undetected random effects influenced the fixed effects meta-regression, we performed 2 additional random effects meta-regression analyses as a robustness check (supplementary note 1).

To summarize our methodology, first, regression analyses were performed to estimate the effect sizes for the associations between schizophrenia PRS and each disorder at each age at multiple SNP priors across the 2 studies. Subsequently, these results were analyzed in a multivariate meta-analytic model. In this model, we tested whether schizophrenia PRS are associated with childhood psychopathology and whether the magnitude of this association depends on factors such as age or disorder. This meta-analysis resulted in a best-fitting model describing

Table 1. Model Fit Criteria for the Meta-Regression Models

Predictors	LL	df	LRT	P Value LRT	AIC	Residual Heterogeneity (QE)	P Value QE	Parametric Resample
Model 1 Cohort	602.6325	2			−1200.476	274.2758	<.0001	0%
Model 2 Cohort age, prior, prior², disorder	616.8587	8	28.4087	<.0001	−1216.885	245.867	.0016	0.50%
Model 3 Cohort age, prior, prior², disorder, age × disorder	626.5272	11	19.3732	.0002	−1230.258	226.4939	.0122	22.40%
Model 4 Cohort age, prior, prior², disorder, age × disorder, age², age² × disorder	631.0907	15	9.0458	.06	−1231.304	217.448	.0207	77.10%

Note: QE is the test statistic associated with the residual variation in a meta regression. This table contains the predictors, likelihood ratio test (LRT), Akaike's Information Criterion (AIC) and residual heterogeneity for the 4 meta-regression models considered. The LRT tests the relative performance of adjacent models, ie, model 2 is tested against model 1, model 3 is tested against model 2, and model 4 is tested against model 3. The test of residual heterogeneity considers whether the residual variance in the effects observed in the original studies, after conditioning on the predictors, still deviates from zero. Parametric resample reports on the percentage of resampled datasets in which each model fitted best according to the AIC.

the relationship between childhood psychopathology and schizophrenia PRS.

The regression coefficients and the variance explained by the PRS are expected to be small, as their effect is determined largely by the ratio of the discovery sample size to the number of independent genetic effects. The number of independent genetic effects on schizophrenia has been show to be large (up to ~70% of the regions in the human genome could affect schizophrenia[43]). By accounting for the sample size in the discovery study and the number of expected, independent genetic loci, regression coefficients as obtained in PRS analyses can be transformed to genetic correlations between traits.[44] We calculated the genetic correlations between schizophrenia and childhood psychopathology based on the best fitting meta-regression model. Since this calculation relies on assumptions regarding the variance explained by the SNPs and the number of independent SNPs influencing the disorders, we also present the results of the calculations while making different assumptions on the variance explained by all SNPs.

Results

The descriptive statistics of the psychopathology measures revealed the expected sex differences of adolescent girls scoring higher on internalizing disorders than boys and boys scoring generally higher than girls on ADHD and ODD/CD (supplementary tables S1–S2 and supplementary note 1). Consequently, sex was included as a covariate in the PRS analyses.

Meta-analysis of the associations between all schizophrenia PRS and all childhood psychopathology measures revealed a significant positive association (estimate = 0.0182, SE = 0.005, Z = 3.66, P = .0002). This meta-analysis accounted for the dependence between outcomes.

Given the association between childhood psychopathology and schizophrenia PRS, we continued with meta-regression analyses. Model fit statistics, and comparative model fit statistics for the 4 meta-analytic models are presented in table 1. The model in which the effect sizes of the associations between childhood psychopathology and schizophrenia PRS were predicted by age, prior, prior², disorder, and age × disorder (ie, a different relationship between disorder and schizophrenia PRS over age) outperformed the basic model which only allowed for differences in effect sizes between cohorts. Inclusion of nonlinear age effects did not yield an improvement in fit. Likelihood-ratio testing and AIC suggested that model 3 provided the best balance between parsimony and model complexity. In 77.1% of parametric resamples, model 4 provided the best fit to the data according to the AIC, in 99.5% of the resampled datasets either model 3 or 4 provided the best fit. The increased complexity in model 4 by the addition of nonlinear age effects yielded little extra information.

Because fixed effects meta-regression can yield false positive results if random effects are ignored, we further performed random effects meta-regressions as a robustness check. The random effects meta-regression did not substantially change the parameter estimates nor the conclusions drawn based on the meta-regression (supplementary note 1). Further sensitivity analyses showed that the model selection and model parameters were robust to considerable misspecification of the error covariance matrix (supplementary note 1).

Continuing with meta-regression model 3, we tested the degree of polygenicity of the association between schizophrenia and childhood psychopathology by varying the covariate values for prior and prior^2 while keeping the other covariates fixed at their inverse variance weighted means. The prediction accuracy as a function of prior peaked between the prior values of 0.50 and 1, suggesting the optimal prior can be found in this range (supplementary figure S1). This result suggests that the relationship between childhood psychopathology and schizophrenia is highly polygenic in nature, ie, a large portion of the genome is involved in the relationship between schizophrenia and childhood psychopathology. The forest plot (figure 1), which contains both the empirical and model

predicted estimates for the PRS predictions (for PRS prior = 0.50), reveals that the meta-regression predictions were close to the observed PRS regression coefficients.

Figure 2 shows, based on model 3, the associations between schizophrenia PRS and childhood psychopathology as a function of age, age x disorder, while keeping all other predictors (ie, cohort, prior and prior^2) fixed at their respective inverse variance weighed mean value. The associations increased with age, confirming our hypothesis that the genetic relationship between schizophrenia and developmental psychopathology is stronger in adolescence than in early childhood. Post-hoc inspection of the parameters obtained from 3 (table 2) further indicate that the association with schizophrenia at age 7 was highest and significant for depression (0.0262, $Z = 2.227$, $P < .03$). The effect sizes were lower for ODD/CD compared to depression ($Z = -2.49$, $P < .02$). The predictions for ADHD ($Z = -1.61$, $P < .11$) and anxiety ($Z = -.38$, $P = .70$) did not differ with depression. The increase in association with schizophrenia with age was significant for depression ($Z = 2.93$, $P < .003$) and even stronger in ADHD ($Z = 4.18$, $P < .001$) and ODD/CD ($Z = 2.17$, $P < .03$) compared to depression. The increase was of
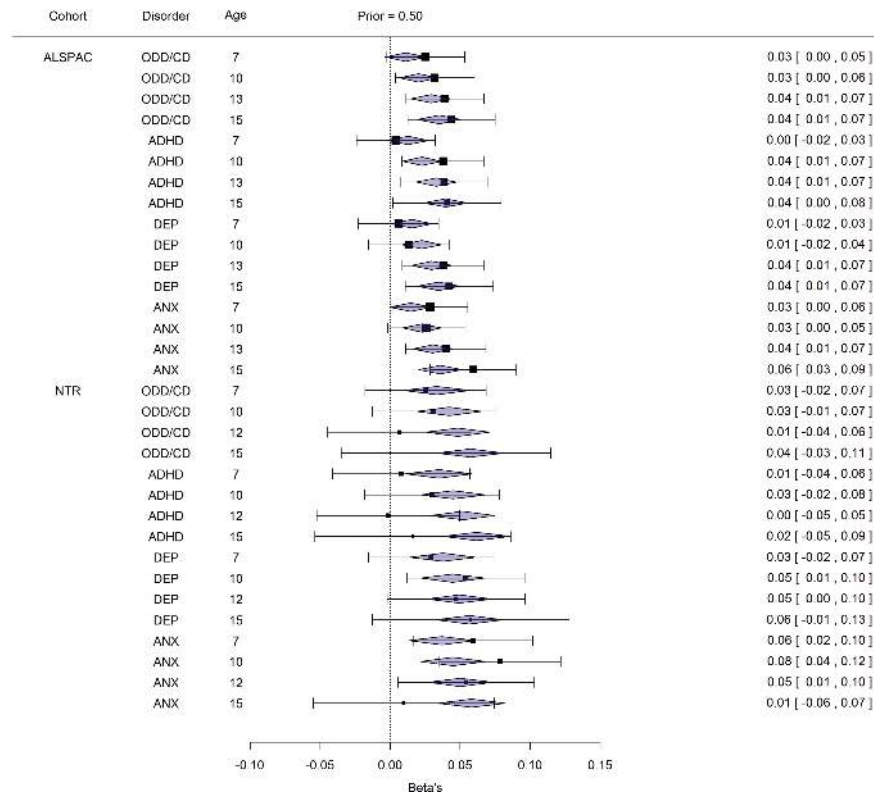
Fig. 1. A forest plot of the observed associations between schizophrenia polygenic risk score (PRS) (obtained at prior proportion of causal SNPs = 0.50) and of the model predicted associations. The blue polygons indicate the association as predicted from the meta-regression model, while the black square indicates the association as observed in the empirical data. The whiskers indicate the 95% confidence regions around the empirical PRS associations. The results are ordered by increasing age for each disorder, with in the top halve the results in the ALSPAC cohort and in the bottom halve the results for the NTR cohort.
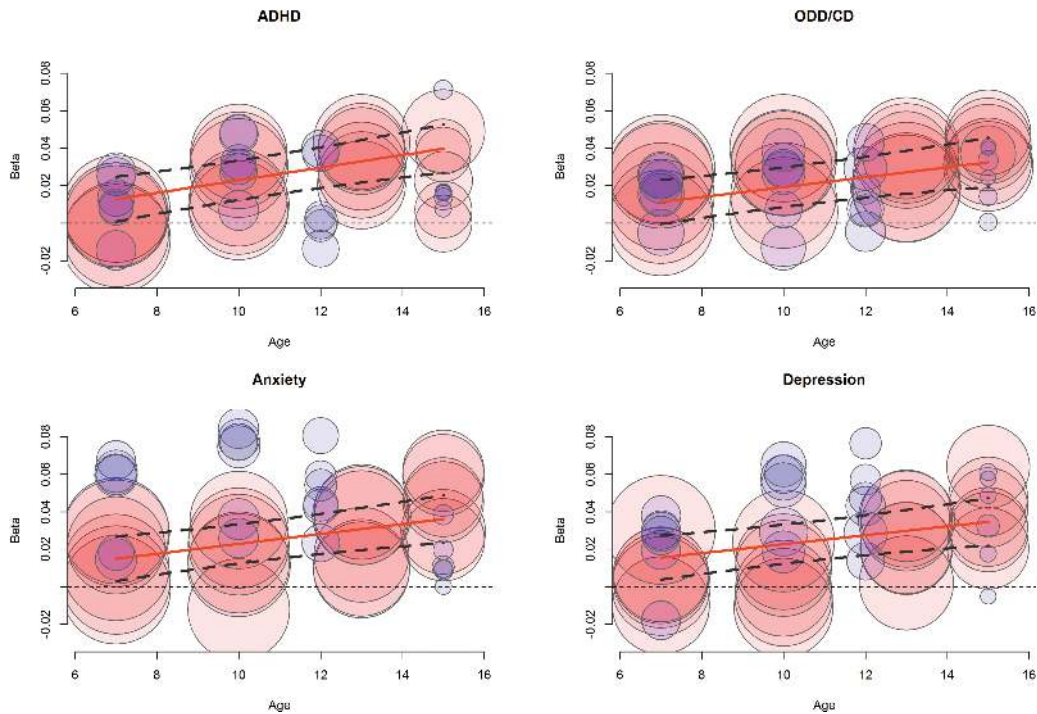
Fig. 2. Bubble plot showing the effect of age on the association between schizophrenia polygenic risk score (PRS) and childhood psychopathology, split per disorder. Circles indicate the observed effect sizes in the univariate regression analyses (ALSPAC in red, NTR in blue). The size of the circles is proportional to the inverse of the variance, and thus larger circles reflect more accurate estimates. The solid line reflects the meta-regression fitted effect size and the dashed lines indicate the upper and lower 95% CI around the meta-regression line.

Table 2. Parameter Estimates and Test Statistics for Meta-Regression Model 3

| Parameter	Estimate	SE	z Value	P Value	ci.lb	ci.ub
Intercept	0.0262	0.0115	2.2716	**.0231**	0.0036	0.0487
Age	0.0024	0.0008	2.9275	**.0034***	0.0008	0.004
Prior	0.0354	0.0155	2.284	**.0224**	0.005	0.0657
Prior²	−0.0253	0.0109	−2.331	**.0198**	−0.0466	−0.004
Cohort	−0.0221	0.0124	−1.7856	.0742	−0.0464	0.0022
Anxiety	−0.0006	0.0016	−0.3771	.7061	−0.0039	0.0026
ODD/CD	−0.0042	0.0017	−2.4959	**.0126**	−0.0076	−0.0009
ADHD	−0.0027	0.0017	−1.6058	.1083	−0.006	0.0006
Age × anxiety	0.0003	0.0003	0.9681	.333	−0.0003	0.0008
Age × ODD/CD	0.0006	0.0003	2.1763	**.0295**	0.0001	0.0012
Age × ADHD	0.001	0.0002	4.1855	**<.0001***	0.0005	0.0014

Note: ci.lb, lower bound of 95% CI; ci.ub, upper bound of 95% CI; ADHD, attention deficit hyperactivity disorder; ODD/CD, oppositional defiant disorder/conduct disorder. Depression serves as a reference disorder. Therefore the intercept and age effect reflect the expected association between schizophrenia and depression at age 7 and the yearly increase in the expected association. Bold is nominally significant at .05.
*Significant when adjusted for the fact we consider 11 parameters.

similar magnitude for anxiety compared to depression ($Z = 0.97$, $P = .30$).

Finally, based on the relationship between the outcomes of PRS analyses and genetic correlations as described by Dudbridge,[44] we computed the expected genetic correlation between developmental psychopathology and schizophrenia as a function of age and split over disorders based on the betas obtained in the meta-regression (for details see: supplementary note 1). We assumed that

15% of the variance in childhood psychopathology is captured by the genetic markers used to compute the scores,[23,45,46] that 35% of variance in the schizophrenia liability is explained by the markers included in the score,[24,47] and that 200 000 independent genetic effects are captured by the markers included in the PRS. Given these assumptions genetic correlations increased from around 0.10 at age 7 and around 0.25 at age 16, differences in genetic correlations with schizophrenia between disorders were
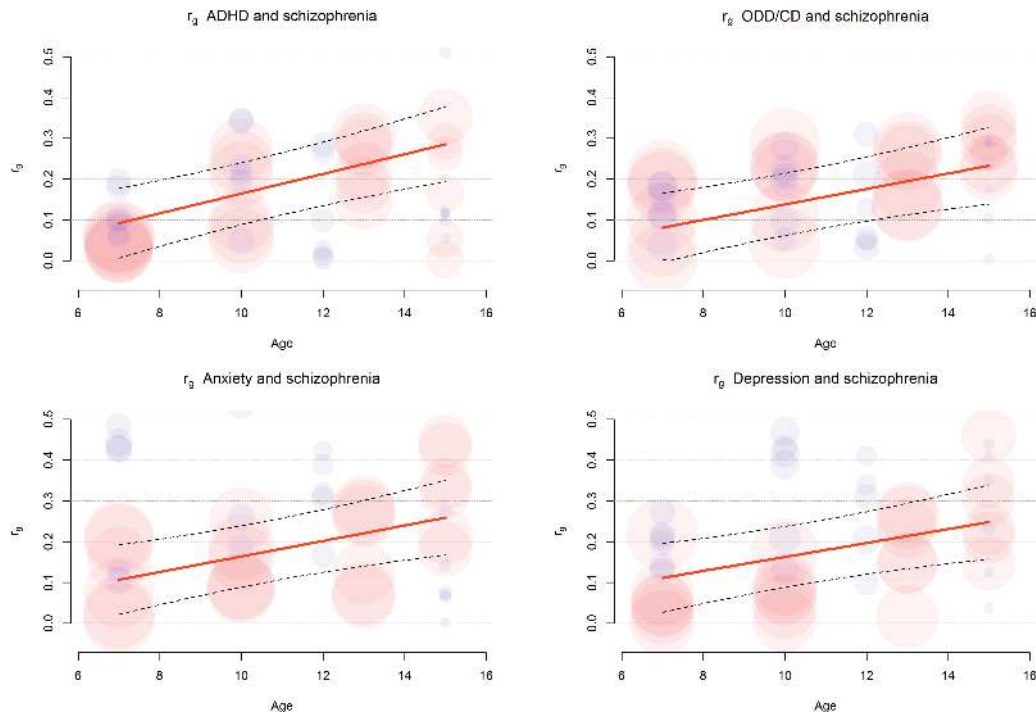
Fig. 3. Bubble plot of the approximated genetic correlations between schizophrenia and childhood psychopathology per disorder. We assume the variance in childhood psychopathology explained by all markers used to construct the polygenic risk score (PRS) is 15% and constant over disorders and age. We further assume the PRS captures 200 000 independent genetic effects. Circles indicate the transformed observed regression coefficients to genetic correlations (ALSPAC in red, NTR in blue). The size of the circles is proportional to the inverse of the variance, and thus larger circles reflect more accurate estimates. The solid line reflects the genetic correlation and the dashed lines indicate the upper and lower 95% CI around the genetic correlation, quantifying the uncertainty in the meta-regression.

modest (figure 3). The influence of assuming lower (10%) or higher (20%) true variance explained by all measured genetic markers in childhood psychopathology on the estimated genetic correlation is quantified in supplementary figures S2 and S3.

Discussion

We investigated whether associations between schizophrenia PRS and childhood psychopathology were explained by shared genetic risk factors. Our meta-analysis revealed a significant association between genetic schizophrenia risk and childhood psychopathology. Further meta-regression analysis revealed that the genetic overlap between schizophrenia PRS and childhood psychopathology became stronger with age. The associations differed between disorders, with a weaker association for ODD/CD at age 7, and a stronger age related increase for ADHD and ODD/CD. We further found evidence for a high degree of polygenicity in the relationship between schizophrenia PRS and childhood psychopathology, as was evident from the increase in effect with an increase in the prior used in computing the PRS.

The variance explained by the PRS was small. This was expected since the predictive accuracy of a PRS is not only a function of the genetic correlation between the trait investigated in the discovery GWAS and the target

sample, but also is a function of the sample size in the discovery and the number of genetic markers studied.[44] This is illustrated by other studies analyzing PRS who reported similarly small effect sizes, ie, explained variance ranging from 0.001 to 0.03.[30] More interpretable units of the magnitude of the associations are the genetic correlations derived from the betas. These ranged from 0.1 to 0.25, depending on the age of measurement and the assumptions in the formulae. These correlations indicate a modest but robust genetic association between schizophrenia and childhood psychopathology. This is an important finding in the search for factors influencing the persistence of symptoms from childhood into adulthood and the development into severe mental illness. The genetic correlations between schizophrenia and childhood psychopathology seem to be lower than the correlations between adult psychiatric disorders (MDD-SCZ $r = .43$,[24] $r = .51$,[48] bipolar disorder-SCZ; $r = .68$[24]). This is probably not surprising given that, around 50% of the children with psychiatric disorders are disorder free in adulthood[49] so the association with schizophrenia to begin with was already smaller than for adult disorders.

Strengths of our study were the substantial sample sizes of the discovery and target samples. The schizophrenia PRS were based on a large discovery set, a GWAS which revealed 108 genome wide significant loci,[29] The target samples varied between 5354 and 8253 at different ages,

which is substantially higher than the required number of ~2000 subjects generally indicated as sufficient for PRS analysis.[30] Innovative strengths of our analyses were the explicit modeling of all univariate analysis results in the meta-regression approach which accounted for the covariance between disorders and ages, correction for cohort specific effects and the simultaneous consideration of multiple risk scores trained at different priors.

We note that the heterogeneity in assessments that also required slightly different regression methods in the NTR and ALSPAC may have biased the results downwards, beyond the point where the effect can be mitigated by transformations and covariates. Heterogeneity in phenotypes is often mentioned in genetic studies as a reason for few or no significant findings and, although both measures used in this study were based on ratings that are consistently related to clinical DSM-IV diagnoses,[36,37,50] combining these measures has probably increased heterogeneity. It follows that it would be preferable for cohorts to use the same measurement instruments. This does not withstand the fact that to get to large enough sample sizes, it is preferable to combine the data collected in different cohorts. This is supported by studies that show that different measures of a phenotype are associated with the same risk factors. Genetic factors for clinically diagnosed ADHD, eg, overlap with genetic factors influencing continuous ADHD measures assessed in the general population.[51–53] These results suggest that combining several measures is an appropriate way to increase sample size and thus statistical power. Moreover, in the current study, we mitigated the effects of heterogeneity induced by the different instruments by performing a meta-regression analyses which provided the opportunity to test and control for between cohort mean differences in the effect of PRS on outcome. In this way, the current study strikes the optimal balance between the risk of bias and maximizing statistical power.

Another limitation that concerns longitudinal studies is the dropout over the years. We analyzed whether the schizophrenia PRS predicted non-participation and observed significant associations between schizophrenia PRS and non-participation at age 15 in both cohorts and at all ages in ALSPAC (supplementary table S3). We further observed that non-participation was related to a higher score on psychopathology scales at an earlier age in ALSPAC, especially for ODD/CD and ADHD at age 13 and 15. In NTR nonparticipation at age 15 was related to ODD/CD and depression at age 12 (supplementary table S4). As those with higher PRS and higher psychopathology scores at earlier ages are more likely to drop out, we expect that the dropout introduces downward bias in the estimated relationship between schizophrenia and childhood psychopathology. Thus, the magnitude of genetic associations may be underestimated. Note that only longitudinal analyses can provide insight into the influence of dropout on the estimate genetic relationship between traits, while in univariate studies a failure to participate results in the absence of genetic data and thus the influence of failure to participate cannot be quantified. For more comprehensive genetically informed dropout analysis of the ALSPAC data see: ref.[54]

Results from previous research focusing on the genetic overlap between schizophrenia and (childhood) psychopathology are largely in line with ours.[24–28,48] Three differences are noteworthy. Another study in the ALSPAC sample focused on psychiatric symptoms at age 15 and found that schizophrenia PRS predicted anxiety disorder and negative symptoms, but not depressive disorder and psychotic experiences. The difference with the current results for depression may be explained by improvements in the method used to compute the polygenic scores and in the definition of the phenotype.[27] Two studies by the Psychiatric Genomics Consortium Cross Disorder Group detected strong correlations between major depressive disorder, bipolar disorder and schizophrenia, but no genetic correlation between ADHD and schizophrenia.[24,25] The latter is probably explained by the smaller sample size for ADHD at the time, as is confirmed by recent analyses which detected a significant association between ADHD and schizophrenia.[55] Finally, a study analyzing the association between schizophrenia and attention problems and impulsivity, anxiety and a general tendency for psychopathology yielded no significant associations.[28] Yet, the direction of the effects was positive (ie, higher schizophrenia risk predicted higher scores). As that study comprised PRS for 13 traits as well as 50 outcome variables, the multiple-testing burden was considerably higher than in the current study resulting in lower power to detect an effect. Overall, the evidence so far suggests the presence of a positive genetic correlation between schizophrenia and psychopathology in childhood.

These previous studies[24–28] also analyzed multiple outcomes, but our study provides additional insights into differences of genetic effects across diagnostic boundaries and over ages by adopting a longitudinal and multivariate approach. Our findings suggest that there are sets of SNPs broadly influencing psychopathology across ages in the general population, and that there are sets of SNPs of which the effect is either limited to or increases in puberty. This signifies that age-sensitive genome-wide meta-analysis of repeated measures, in either case-control or population based samples could well identify genetic variants. Some of these genetic variants will increase an individual's vulnerability for psychopathology and may be associated with persistence of symptoms from childhood into adolescence and adulthood, while other variants can be identified that have an age or disorder dependent effect on psychopathology. Identifying not only which variants influence psychopathology but also at what age can aid to focus translational studies on developmental processes.

To conclude, our study shows how genetic risk factors for schizophrenia are of increasing importance during

1204

childhood and adolescence and demonstrate the value of longitudinal studies across diagnostic boundaries to increase our insight into the etiology of severe psychiatric disorders.

Supplementary Material

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