Associations between psychiatric polygenic risk scores and general and specific psychopathology symptoms in childhood and adolescence between and within dizygotic twin pairs

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Background: Although polygenic risk scores (PRS) predict psychiatric problems, these associations might be attributable to indirect pathways including population stratification, assortative mating, or dynastic effects (mediation via parental environments). The goal of this study was to examine whether PRS-psychiatric symptom associations were attributable to indirect versus direct pathways. **Methods:** The sample consisted of 3,907 dizygotic (DZ) twin pairs. In childhood, their parents rated them on 98 symptoms. In adolescence (n = 2,393 DZ pairs), both the parents and the twins rated themselves on 20 symptoms. We extracted one general and seven specific factors from the childhood data, and one general and three specific factors from the adolescent data. We then regressed each general factor model onto ten psychiatric PRS simultaneously. We first conducted the regressions between individuals (β) and then within DZ twin pairs (β_w), which controls for indirect pathways. **Results:** In childhood, the PRS for ADHD predicted general psychopathology (β = 0.09, 95% CI: [0.06, 0.12]; β_w = 0.07 [0.01, 0.12]). Furthermore, the PRS for ADHD predicted specific inattention (β = 0.04 [0.00, 0.08]; β_w = 0.09 [0.01, 0.17]) and specific hyperactivity (β = 0.07 [0.04, 0.11]; β_w = 0.09 [0.01, 0.16]); the PRS for schizophrenia predicted specific learning (β = 0.08 [0.03, 0.13]; β_w = 0.19 [0.08, 0.30]) and specific inattention problems (β = 0.05 [0.01, 0.09]; β_w = 0.10 [0.02, 0.19]); and the PRS for neuroticism predicted specific anxiety (β = 0.06 [0.02, 0.10]; β_w = 0.06 [0.00, 0.12]). Overall, the PRS-general factor associations were similar between individuals and within twin pairs, whereas the PRS-specific factors associations amplified by 84% within pairs. **Conclusions:** This implies that PRS-psychiatric symptom associations did not appear attributable to indirect pathways such as population stratification, assortative mating, or mediation via parental environments. Rather, genetics appeared to directly influence symptomatology. **Keywords:** General factor of psychopathology; polygenic risk scores; genetic nurture; multi-polygenic score.

Introduction

Twin and molecular genetic studies show that mental health conditions have a partly genetic origin (Polderman et al., 2015; Watanabe et al., 2019), and that the extensive comorbidity among psychiatric phenomena is partly attributable to shared genetic factors (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019; Kendler et al., 2011). Nevertheless, an association between genetic factors and psychiatric phenomena might not necessarily imply a direct effect because the associations could be attributed to at least three non-direct mechanisms.

First, one possibility is that genetic associations might be mediated via general comorbidity, rather than directly influencing a specific psychiatric syndrome. Psychiatric comorbidity can be accounted for by a general factor of psychopathology, and family and twin studies indicate that it has a partly genetic origin (Caspi & Moffitt, 2018; Lahey, Krueger,

Rathouz, Waldman, & Zald, 2017). Furthermore, polygenic risk scores (PRS), which are weighted sums of thousands of alleles associated with a given psychiatric disorder, weakly but significantly predict general psychopathology (Allegrini et al., 2020; Brikell et al., 2018; Jones et al., 2018; Riglin et al., 2020). This implies that it is important to consider a general factor of psychopathology, in addition to specific syndromes, when exploring associations between genetics and psychiatric conditions. Such models, however, sometimes generate unreliable scale scores for the specific syndromes (Watts, Poore, & Waldman, 2019). A solution to this problem is to examine associations with the corresponding latent factors instead, as these are estimated as having perfect reliability.

Second, because PRS for psychiatric disorders are positively correlated, a bivariate association between a single PRS and a psychiatric condition might not necessarily be unique but rather attributable to PRS covariation (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2019; Watanabe et al., 2019). To isolate the unique effects of PRS on

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psychiatric conditions, it is useful to apply a multi-polygenic score approach (Krapohl et al., 2018).

Third, a genetic association might also be attributable to familial effects. That is, genetic associations can arise from confounding factors or indirect mechanisms including population stratification, dynastic effects, and assortative mating (Morris, Davies, Hemani, & Smith, 2020). Regarding population stratification, because phenotypes are often geographically patterned, spurious genotype–phenotype associations can arise if population structure is not properly accounted for (Novembre et al., 2008). Regarding dynastic effects, genetic associations can arise due to an indirect link between parental genotypes and children's characteristics that is not mediated via the children's own biology but rather by the family environment that covaries with parental genes (Kong et al., 2018). For example, the part of the parental genotype that children do not inherit nonetheless predicts children's educational attainment, and about half of the predictive power of the PRS for educational attainment appears attributable to passive gene–environment correlation (Cheesman, Hunjan, et al., 2020; Kong et al., 2018; Willoughby, McGue, Iacono, Rustichini, & Lee, 2019). Regarding assortative mating, non-random partner selection increases the likelihood of people having children with partners who are more genetically similar and thus induce genetic correlations between traits in offspring (Hartwig, Davies, & Smith, 2018). Because there is some degree of assortative mating for psychiatric disorders, the associations between genetics and psychiatric conditions might be biased (Nordsletten et al., 2016). One remedy to these issues is to estimate the genotype–phenotype associations within dizygotic (DZ) twin pairs, which vary in their genetic similarity due to random allele assignment during meiosis, while being perfectly matched for population stratification, dynastic effects, and assortative mating (Morris et al., 2020; Selzam et al., 2019). Therefore, any remaining within-pair association cannot be attributed to such potential familial effects. Selzam and colleagues demonstrated that whereas the prediction of a PRS for neuroticism on self-reported neuroticism decreased substantially within twin pairs, a PRS for ADHD predicted self-reported ADHD equally well within twin pairs (Selzam et al., 2019). However, if there is measurement error, the within-pair associations are underestimated more than the corresponding between-individual estimates (Frisell, Oberg, Kuja-Halkola, & Sjolander, 2012). Therefore, there is merit in analyzing (perfectly reliable) latent variables in within-pair analyses.

The goal of this study was to examine the direct associations between PRS and psychiatric conditions. To accomplish this, we applied a multi-polygenic score approach to regress a latent (i.e., measurement error-free) general factor model based on parent-rated psychopathology in childhood, and self- and parent-rated psychopathology in adolescence, onto ten psychiatric PRS simultaneously. We first conducted the regressions between individuals, and then within DZ twin pairs.

Methods
Sample

As part of the Child and Adolescent Twin Study in Sweden (CATSS), parents of all twins born in Sweden since July 1992 were contacted annually when the twins turned 9 (born after July 1995) or 12 years old (born between July 1992 and July 1995) to participate in a study of well-being and development (response rate = 80%) (Anckarsater et al., 2011). We analyzed all DZ twins (N = 3,907 twin pairs) who were genotyped (birth year range: 1992, 2005; 52% male). A subset of these twins (n = 2,393 DZ pairs) were followed up at age 15 (birth year range: 1993, 2003; 49% male). This study received ethical approval from the Karolinska Institutet Ethical Review Board and all participants gave informed consent.

Measures

Exposures: Ten psychiatric PRS. Participants provided saliva DNA samples at study enrollment, which was analyzed using the Illumina PsychChip. Standard quality control and imputation procedures were performed (Brikell et al., 2018). We included PRS, which were computed at the end of 2018, for schizophrenia, bipolar disorder, major depressive disorder (MDD), neuroticism, anxiety disorder, post-traumatic stress disorder (PTSD), eating disorder, autism, attention-deficit/hyperactivity disorder (ADHD), and ADHD symptoms (see Table S1 for discovery sample sizes). We used PRS with a SNP-threshold of $P_T \leq 0.50$ for the main analysis, but we also re-ran the models using different *p*-value thresholds.

Outcomes

Parent-reported symptoms in childhood. When the twins turned 9 or 12 years old, their parents rated their symptomatology using the Autism-Tics, ADHD, and Other Comorbidities inventory (A-TAC), which consists of 96 items corresponding to DSM-IV childhood disorder symptoms. Questions assess lifetime symptoms in relation to same-age peers (Larson et al., 2010). We selected the 49 symptoms measuring inattention (IA), hyperactivity/impulsivity (H/I), learning difficulties (LD), autism (ASD), and conduct disorder (CD). For twins born after 1997, depression symptoms (DEP) were assessed using the Short Mood and Feelings Questionnaire, a 13-item questionnaire measuring child depressive symptoms experienced in the last 2 weeks (Angold et al., 1995), and anxiety symptoms were assessed using the Screen for Child Anxiety Related Emotional Disorders (SCARED), a 41-item questionnaire measuring symptoms experienced in the last three months across five domains including panic, generalized anxiety, separation anxiety, school anxiety, and social phobia (Hale, Raaijmakers, Muris, & Meeus, 2005). All items are displayed in Table S2. Symptoms were rated using three response categories: "no," "yes, to some extent," and "yes," which we recoded into two categories: "no" versus "yes, to some extent" or "yes" to facilitate estimation of tetrachoric correlations.

Parent- and self-reported symptoms in adolescence. When the twins turned 15 years old, the parents rated their children and the twins self-reported on the Strength and Difficulties Questionnaire (SDQ), a 25-item questionnaire capturing hyperactivity, conduct problems, emotional

symptoms, peer problems, and prosocial behavior (Goodman, 2001). We only modeled the four scales that pertained to problem behaviors (i.e., we excluded the prosocial scale). Table S3 displays all items. Symptoms were rated using three response categories ("not true," "somewhat true," and "certainly true"), such that we analyzed the polychoric correlations.

Statistical analyses

First, we fit a bifactor confirmatory factor analysis (CFA) model to the symptoms such that each item loaded on one general and seven specific factors in childhood (see Figure S1 for a graphical representation), and one general and four specific factors in adolescence (Holzinger & Swineford, 1937). The specific factors corresponded to the instrument scales (Holzinger & Swineford, 1937) (Tables S2 and S3). The general factor captures covariation shared among all symptoms, whereas the specific factors capture covariation unique to the symptom scales over and above the general factor. This separation between shared and specific variation is achieved by constraining the correlation between the general and specific factors at zero (however, we estimated correlations among the specific latent trait factors).

To circumvent potentially anomalous loading patterns, we used the bifactor-(S-1) approach, whereby one specific factor serves as a reference symptom group for the general factor (Eid, Geiser, Koch, & Heene, 2017). In other words, the items related to a particular symptom cluster do not form a specific factor. We used the autism language subscale from the A-TAC (thus, the resulting autism factor consisted of 11 items measuring problems with social interaction and inflexibility), and the conduct scale from the SDQ, to serve as bifactor reference symptom groups in childhood and adolescence, respectively.

Second, to analyze the associations with the PRS between individuals, we regressed the latent bifactor model on all ten PRS simultaneously (i.e., akin to a multi-polygenic score approach) within a Structural Equation Modeling (SEM) framework, with sex, birth year, and the first six principal components (to account for measured population stratification) included as covariates, as outlined below in equation (1)

$$\text{latent factor}_i = \beta * \text{PRS}_{ki} + \gamma * \text{PCs} + \omega * \text{covariates}, \quad (1)$$

where the latent factors were estimated in the aforementioned bifactor models, i equals individuals and k equals PRS 1 through 10. Thus, β measures the unique associations between individuals, controlling for correlations among PRS, but without adjusting for unmeasured factors shared by twin pairs.

Third, to analyze the PRS associations within twin pairs while adjusting for the correlations among PRS, we regressed the latent bifactor model on all ten PRS simultaneously (i.e., akin to a multi-polygenic score approach) using a marginal between-within model (Sjolander, 2019), as outlined below in equation (2)

$$\text{latent factor}_i = \beta_w * \text{PRS}_{ij} + \beta_b * -\text{PRS}_j, \quad (2)$$

where j indicates twin pairs. By including PRS twin pair means, this model estimates associations within pairs (β_w), thereby controlling for all unmeasured factors that make twins within pairs similar to each another (including population stratification, dynastic effects, and assortative mating), while also adjusting for overlap among the ten PRS. To account for the non-independence of twin data, we clustered on the twin pair and used the sandwich estimator to estimate unbiased standard errors. Analyses were carried out using the Mplus software using the mean- and variance adjusted weighted least square estimator (Muthén & Muthén, 1998-2015).

Fourth, to estimate potential indirect effects, we computed the mean of the ten absolute betas for each factor, and then compared the differences from the between-individual and within-pair estimates, $-|\beta_w|/-|\beta|$ where a value less than unity would indicate indirect effects, and a value close to unity would indicate direct genetic effects. We compared the aggregate effects because we lacked statistical power to compare each of the between/within associations.

Sensitivity analyses

First, we split the specific anxiety factor into its five predetermined subscales to examine if the results remained similar when based on more fine-grained anxiety measures. Second, we re-ran the models using different PRS p-value thresholds. Third, we re-ran the regressions using a confirmatory correlated factors model as the outcome, which was similar to the bi-factor model but without a general factor. Fourth, we also estimated the association between the PRSs and the observed scale scores. Fifth, to protect against potential CFA misspecifications, we additionally conducted an exploratory factor analysis (EFA) of the symptoms. Sixth, although we circumvented issues related to unreliability by regressing the latent (measurement error free) factors onto the PRS, we also used Item Response Theory to estimate test information (i.e., reliability conditional on latent scores) of the factor scale scores and then converted these into classic reliability estimates to improve interpretability (O'Connor, 2018). Seventh, we also regressed the latent bifactor model on education and intelligence PRS to compare against the psychiatric PRS.

Results
Bifactor measurement models in childhood and adolescence

The bifactor CFA model in childhood, which consisted of one general and seven specific factors, fit the data relatively well (root mean square error of approximation [RMSEA] = 0.016; confirmatory fit index [CFI] = 0.936; Tucker-Lewis index [TLI] = 0.933; χ^2_{4542} = 13,502.168; $p < .001$). Likewise, the bifactor CFA model in adolescence, which consisted of one general and four specific factors, also fit relatively well (RMSEA = 0.054; CFI = 0.930; TLI = 0.912; χ^2_{304} = 4419.290; $p < .001$). The general factor in childhood captured broad psychopathology (standardized mean loading = 0.49; range −0.03, 0.80; the few loadings close to zero captured shyness; Table S2), as did both the parent- (standardized mean absolute loading = 0.51) and self-reported general factors in adolescence (standardized mean absolute loading = 0.40; Table S3). The loadings on the specific factors were of comparable magnitude in both childhood and adolescence.

Latent bifactor models regressed on all ten PRS simultaneously

Between individuals. Between individuals, as displayed in Figure 1 (Table S4 displays all regression betas and corresponding standard errors), the parent-rated general psychopathology factor in childhood was significantly predicted by the PRS for ADHD (β = 0.09, 95% CI: [0.06, 0.12]) and ADHD symptoms (β = 0.04 [0.01, 0.07]). Similar results

emerged in adolescence (Figure 2 and Table S5). Furthermore, in adolescence, the PRS for neuroticism predicted both parent- (β = 0.06 [0.03, 0.10]) and self-rated (β = 0.05 [0.01, 0.08]) general psychopathology.

With regard to the specific factors in childhood, between individuals, the PRS for ADHD predicted specific inattention (β = 0.04 [0.00, 0.08]) and impulsivity (β = 0.07 [0.04, 0.11]); the neuroticism PRS (β = 0.06 [0.02, 0.10]) and anxiety disorders PRS (β = 0.05 [0.02, 0.09]) predicted specific anxiety; the PRS for schizophrenia predicted specific learning problems (β = 0.08 [0.03, 0.13]), inattention (β = 0.05 [0.01, 0.09]), and autism symptoms (β = 0.06 [0.01, 0.11]); and the PRS for PTSD predicted specific conduct problems (β = 0.06 [0.02, 0.10]).

With regard to the specific factors in adolescence, the PRS for ADHD predicted parent-reported specific hyperactivity (β = 0.06 [0.01, 0.10]) and self-reported specific emotional symptoms (β = −0.04 [−0.07, −0.01]); the PRS for eating disorders predicted self-rated specific hyperactivity (β = 0.04 [0.00, 0.08]) and parent-rated specific emotional symptoms (β = −0.05 [−0.09, −0.01]); the PRS for schizophrenia predicted self-rated specific hyperactivity (β = −0.07 [−0.11, −0.03]); and the PRS for neuroticism predicted parent-reported specific emotional symptoms (β = 0.05 [0.01, 0.09]).

Within twin pairs.   Within twin pairs (Figures 1 and 2 and Tables S4 and S5), the PRS for ADHD remained significantly associated with the general factor in childhood (β_w = 0.07 [0.01, 0.12]) and adolescence (parent-rated β_w = 0.15 [0.08, 0.22]; self-rated β_w = 0.09 [0.02, 0.15]). However, in adolescence, twins with higher scores on the PRS for neuroticism were no longer rated significantly higher on the general factor than their co-twins (parent-rated β_w = 0.03 [−0.04, 0.10]; self-rated β_w = −0.01 [−0.07, 0.06]).

With regard to the specific factors in childhood, the PRS for ADHD continued to predict specific inattention (β_w = 0.09 [0.01, 0.17]) and impulsivity (β_w = 0.09 [0.01, 0.16]) within twin pairs; the PRS for schizophrenia continued to predict specific learning (β_w = 0.19 [0.08, 0.30]) and inattention problems (β_w = 0.10 [0.02, 0.19]) within pairs; the PRS for MDD (β_w = 0.07 [0.01, 0.13]) and autism (β_w = −0.08 [−0.15, −0.02]) predicted specific anxiety within pairs; and the PRS for PTSD predicted specific learning problems (β_w = −0.11 [−0.20, −0.02]) within pairs.

With regard to the specific factors in adolescence, the PRS for eating disorders predicted parent-rated specific peer problems (β_w = −0.16 [−0.24, −0.09]) and self-reported specific hyperactivity (β_w = 0.10 [0.03, 0.17]) within twin pairs; the PRS for PTSD predicted self-rated specific emotional problems
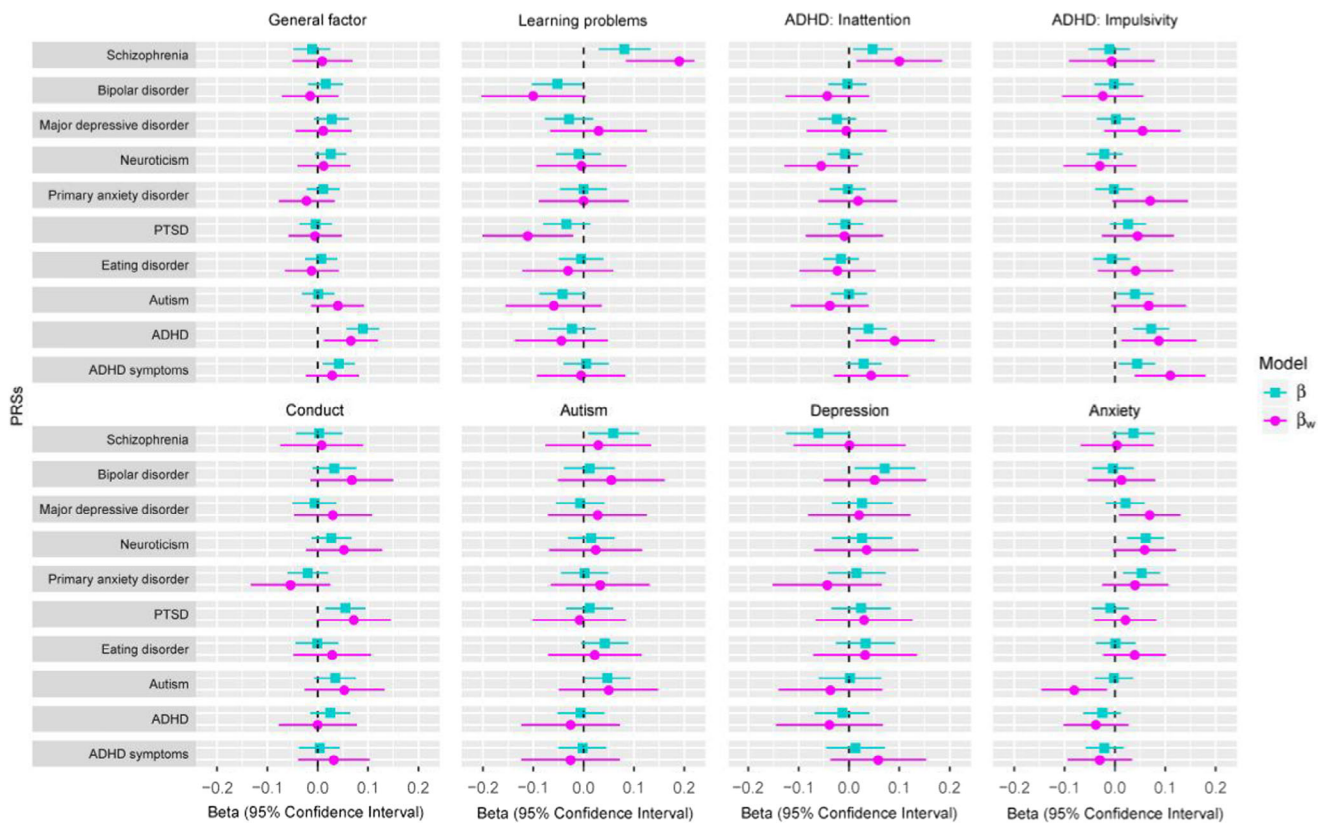

Figure 1 Associations between 10 PRS and bifactor model in the childhood sample. Between models were adjusted for overlap among ten PRS, birth year, sex, and six principal components. Within models were adjusted for overlap among ten PRS, unmeasured confounds shared within dizygotic twin pairs, and sex. Reported betas are standardized
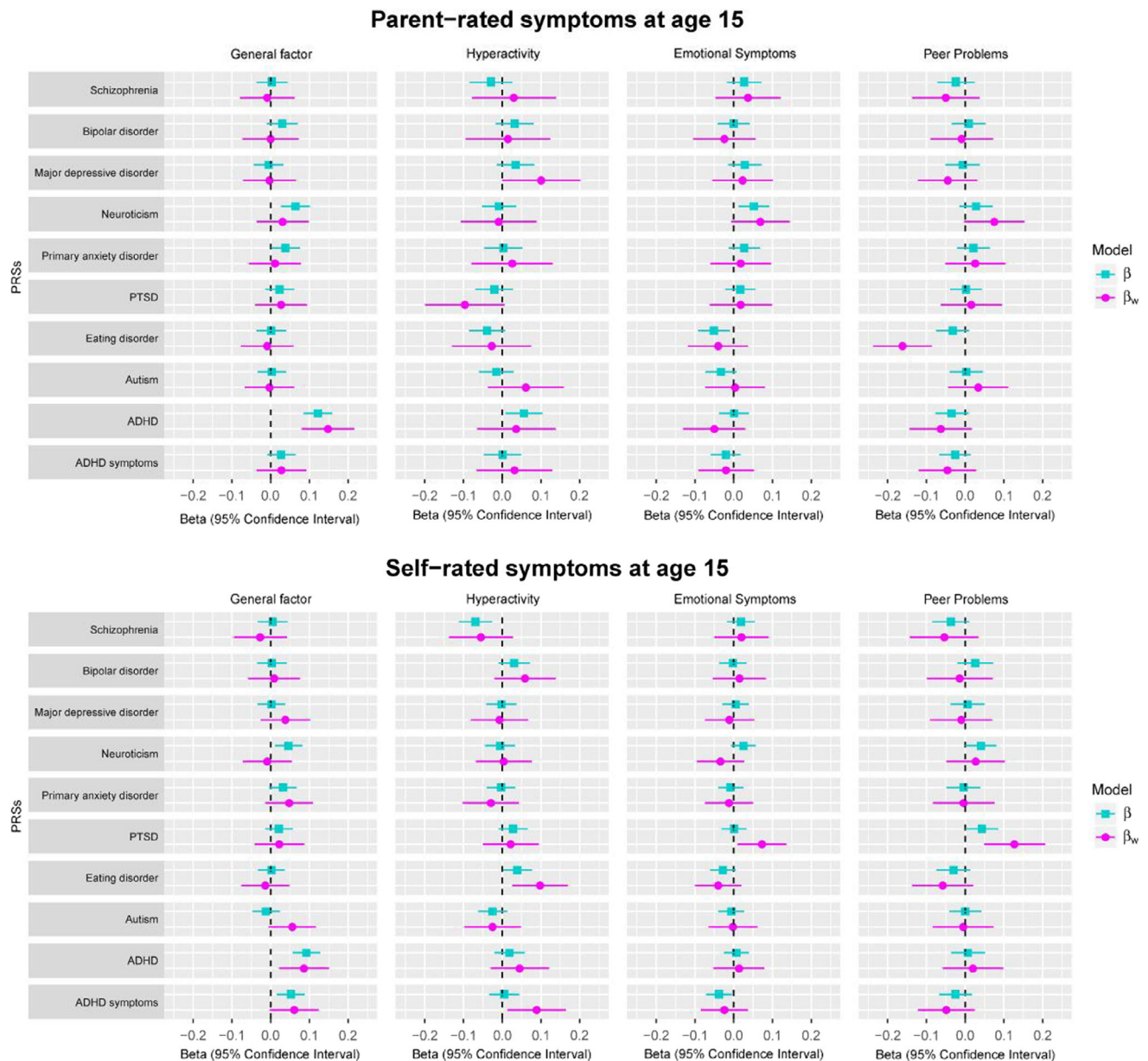
Figure 2 Associations between ten PRS and bifactor model in the adolescent sample for the parent-reported and self-reported data. Between models were adjusted for overlap among ten PRS, birth year, sex, and six principal components. Within models were adjusted for overlap among ten PRS, unmeasured confounds shared within dizygotic twin pairs, and sex. Reported betas are standardized

(β_w = 0.07 [0.01, 0.14]) and peer problems (β_w = 0.13 [0.05, 0.21]); and the PRS for ADHD symptoms predicted self-rated specific hyperactivity (β_w = 0.09 [0.01, 0.16]; Figure 2 and Table S5).

Comparing associations between individuals versus within twin pairs

As displayed in Figure 3, in the aggregate, the PRS-general factor within-pair associations were 1.05 times larger than the corresponding between-individual associations, indicating that the genetic effects on broad comorbidity appeared largely direct. Furthermore, the PRS-specific factors associations were on average 1.84 times larger within twin pairs compared to between individuals.

Sensitivity analyses

First, the more fine-grained subscales of the anxiety measure were associated with the PRS for neuroticism, MDD, and anxiety, similar to the original analyses when they were combined into a single specific anxiety factor (Table S6 displays the factor loadings; regressions betas and mean of absolute betas are displayed in Figures S2 and S3, respectively).

Second, regardless of PRS p-value thresholds, the PRS-general and specific factor associations remained similar to the main analyses (Figures S4 and S5).

Third, when predicting the correlated factors model (Tables S7 and S8 displays the factor loadings and factor intercorrelations, respectively), the
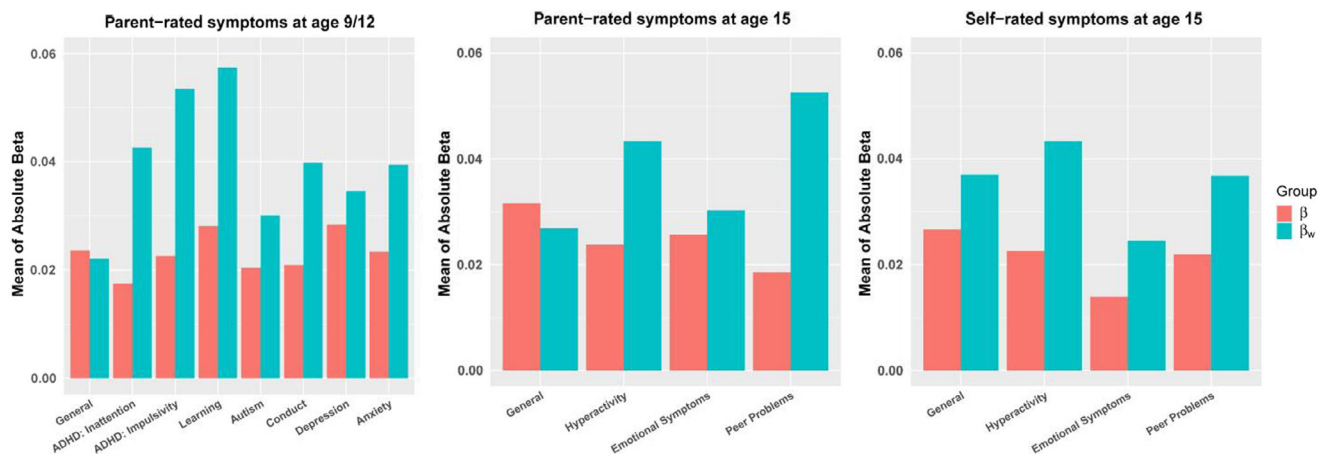
Figure 3 Mean of absolute beta of 10 PRSs in the bifactor model in the childhood sample, and the adolescent sample for the parent-reported and self-reported data

associations were similar to the specific factors in the bifactor model, except that the PRS for ADHD tended to additionally predict specific factors other than inattention and impulsivity, likely because these partly captured general variation (Figure S6). Furthermore, in the correlated factors model, the aggregate within-pair associations were more similar to that of the between-individual associations (the associations were 1.31 times larger within twin pairs; Figure S7), presumably because these factors represented a blend between the general and specific variation, regardless of PRS p-value threshold (Figure S8).

Fourth, for the scale score analyses, the pattern of results was largely similar to when we predicted a correlated factors model, except that the associations tended to be slightly smaller in magnitude (Figures S9 and S10).

Fifth, we additionally conducted an EFA on the symptoms to protect against potential CFA misspecifications. We extracted three factors in both childhood (RMSEA = 0.012; CFI = 0.956; Table S9) and adolescence (RMSEA = 0.026; CFI = 0.960; Table S10) and then applied a bifactor rotation to facilitate identification of one general and two specific factors akin to internalizing and externalizing problems. We then regressed these latent bifactor models onto the PRS. As displayed in Figures S11 and S12, the results were similar to the main analyses in that the PRS for neuroticism significantly predicted the general factor between individuals but not within pairs. Furthermore, the PRS for ADHD remained significantly associated with the general factor within twin pairs, akin to the main CFA analyses.

Sixth, as displayed in Figure S13, the reliability of the scale scores was highest for individuals scoring about a 1.5 standard deviations above the latent trait means, which is desirable for items designed to measure mental health problems. Peak reliability ranged from close to unity (general factor) to just below 0.80 (learning problems), largely as a function of scale length. Note, however, that we circumvented

these unreliability issues by estimating the associations at the latent (i.e., measurement error free) level.

Seventh, as displayed in Figures S14 and S15, the associations between the PRS for intelligence and education, and the latent bifactor psychopathology models, remained largely the same between individuals and within twin pairs. One possibility is that the previously uncovered dynastic effect of the education PRS is primarily related to observed educational outcomes (Cheesman, Hunjan, et al., 2020; Kong et al., 2018; Willoughby et al., 2019).

Discussion

Although the effect sizes were small, some PRS significantly predicted general and specific psychopathology symptoms in childhood and adolescence. Furthermore, overall, the associations did not attenuate within twin pairs, indicating that population stratification, assortative mating, or mediation via parental environments did not appear relevant.

Associations between PRS and general and specific psychopathology

Between individuals, the PRS for neuroticism predicted general psychopathology in adolescence, akin to past research showing that neuroticism is both phenotypically and genetically associated with nonspecific variation, and that neuroticism predicts a wide range of mental health problems (Class et al., 2019; Lahey, 2009; Tackett et al., 2013; Widiger & Oltmanns, 2017). Within twin pairs, these associations tended to the null, potentially highlighting the role of indirect pathways. The PRS for MDD and neuroticism also tended to predict specific anxiety problems within twin pairs in childhood. This is consistent with past multivariate studies indicating that internalizing problems appear to consist of both general distress, including problems such as depression and generalized anxiety, as well as more specific problems, such as various phobias (Krueger, 1999).

Between and within twin pairs, the PRS for ADHD and ADHD symptoms predicted specific inattention and impulsivity. Furthermore, these ADHD PRS also predicted general psychopathology, replicating a previous study (Riglin et al., 2020). Because the associations with the general psychopathology factor remained significant within twin pairs, it indicates that impulsivity and inattention might be a central part of broad impairment and distress in childhood and adolescence. This observation aligns with the hypothesis that impulsive responses to emotional urges might capture an important aspect of general psychopathology (Carver, Johnson, & Timpano, 2017).

Three PRS were associated with the outcomes in somewhat surprising ways. First, within twin pairs, the schizophrenia PRS predicted both specific learning problems and inattention in childhood, dovetailing with a large study showing that children with ADHD were close to three times more likely than their unaffected siblings to be diagnosed with a psychotic disorder in adulthood (Bjorkenstam, Pierce, Bjorkenstam, Dalman, & Kosidou, 2020). One speculation is that the polygenic risk for schizophrenia might materialize in childhood as intrusive thoughts that impair attention and learning, or perhaps both are influenced by disrupted executive functions. Second, within twin pairs, the PTSD PRS protected against learning problems in childhood but increased risk of self-rated emotional and peer problems in adolescence. Past research has demonstrated that internalizing problems, after adjusting for general psychopathology, is positively associated with scholastic performance (Lahey et al., 2015), which perhaps might be partly attributable to genetics for PTSD. Third, within twin pairs, the eating disorder PRS was negatively associated with parent-rated peer problems and positively associated with self-rated hyperactivity in adolescence. One speculation is that eating disorders and hyperactivity share traits related to restlessness and energy, which parents might perceive as sociability in adolescence. Nevertheless, we reiterate that these observations were surprising and that our speculations remain tentative until replicated.

Comparing associations between individuals versus within twin pairs

The aggregate PRS-general factor associations remained similar between individuals and within twin pairs, indicative of direct genetic effects. In contrast, in the aggregate, the associations with the specific factors amplified within twin pairs. This might simply be attributable to sampling variation; however, should this pattern replicate when based on larger GWAS discovery and sibling samples, one possibility might be that parents implicitly contrasted their children against one another, rather than against same-aged peers (Carey, 1986). We

explored this hypothesis by examining the self-reported symptoms at age 15, as adolescent twins might be less likely to contrast themselves against their co-twins. Because a similar pattern of results emerged when the twins self-reported on their mental health in adolescence, the stronger within-pair associations might not be attributable to contrast rating effects. Likewise, in a recent study of middle-aged sibling pairs, who might also be less prone to contrast themselves against one another, a PRS for externalizing problems predicted several risky behaviors more strongly within pairs (Linnér et al., 2020).

An alternate possibility is that the direct and indirect genetic factors might be negatively associated, which surprisingly was observed between parent and offspring genetics for childhood depressive symptoms in Norwegian trios (Cheesman, Eilertsen, et al., 2020). The authors cautiously speculated that the parental genetics that indirectly increased offspring depression also protected against (i.e., was negatively associated with) the same phenomenon via sensitivity and empathy. Although the sensitivity hypothesis might not necessarily apply to the externalizing and neurodevelopmental symptoms in our study, a negative covariance between parental and offspring genetics is consistent with observing stronger within-pair associations.

Implications

Whereas previous research has found evidence of dynastic effects (i.e., mediation via parental environments) for the association between PRS for education and school-related outcomes (Cheesman, Hunjan, et al., 2020; Kong et al., 2018), the overall pattern of results in this study indicated that the psychiatric PRS directly influenced the children and adolescents' symptomatology. As has been noted by others, one possibility is that variables with a higher proportion of shared environmental effects (such as education) are more susceptible to dynastic intergenerational transmission than variables that tend to display higher heritabilities and lower shared environmental effects (such as psychiatric symptomatology) (Selzam et al., 2019; Willoughby et al., 2019). This might imply that alleles identified in psychiatric GWAS have a higher chance of uncovering biological pathways, compared to those from GWAS of education.

Replicating past studies, some PRS predicted both general and specific psychopathologies, which highlights that PRS derived from genetic differences between cases and controls contain not only disorder-specific but also general psychopathology variation (Jones et al., 2018; Riglin et al., 2020). To the extent the goal is to identify genetic markers with direct effects on comorbidity, it might be beneficial to further examine the genetic architecture behind ADHD, as this was the only PRS that remained

significantly associated with the general psychopathology factor within twin pairs.

To the extent the goal is to identify disorder-specific enriched pathways, it might be beneficial to isolate variation attributable to broad comorbidity using a multivariate method, such as Genomic SEM bifactor models or conditional GWAS analysis (Byrne et al., 2020; Grotzinger et al., 2019). Furthermore, if the larger within-pair associations with the specific factors are not attributable to sampling variation, within-sibling pair GWAS might be more suitable for investigating the genetic architecture of specific psychiatric conditions. Future research might also benefit from analyzing trios to examine the covariance between parental and offspring genetics (Morris et al., 2020; Young et al., 2018).

Limitations

First, a salient weakness is that effect sizes were small and the standard errors were relatively large, particularly within twin pairs. Also, we lacked statistical power to compare each of the between/within associations, such that we only examined the overall aggregate trends. On a related note, if the null hypothesis is true that all PRS-phenotype associations are zero in the population, our results are vulnerable to type I errors. Therefore, replication in independent samples remains important. Second, the GWAS discovery samples varied in size, likely contributing to variability in their accuracy. Third, the within-twin pair analyses control for passive gene-environment correlation, but not for active or evocative gene-environment correlations that likely become increasingly important as children grow into adults (Plomin, DeFries, & Loehlin, 1977). Likewise, within-twin pair analyses fail to account for whether the twins directly influence each other.

Conclusion

Genetics appeared primarily directly associated with psychopathology symptoms in childhood and adolescence. However, the pattern might vary for general and specific conditions.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article:

Table S1. Discovery sample sizes of the 10 PRSs.
Table S2. Standardized factor loadings from the confirmatory bifactor model in the childhood sample.
Table S3. Standardized factor loadings from the confirmatory bifactor model in the adolescent sample.
Table S4. Parent-rated childhood psychopathology regressed on all ten PRS simultaneously between twins (Model: Between), and all ten PRS simultaneously within twins (Model: Within).
Table S5. Self and parent-rated adolescent psychopathology regressed on all ten PRS simultaneously between twins (Model: Between), and all ten PRS simultaneously within twins (Model: Within).
Table S6. Standardized factor loadings from the confirmatory bifactor model with anxiety subscales in the childhood sample.
Table S7. Standardized factor loadings from the correlated factors model in the childhood sample.
Table S8. Factor intercorrelations from the correlated factors model in the childhood sample.
Table S9. Standardized factor loadings from the exploratory factor model in the childhood sample.
Table S10. Standardized factor loadings from the exploratory factor model in the adolescent sample.
Figure S1. Bifactor model of the childhood sample.
Figure S2. Associations between ten PRS and latent bifactor model with anxiety subscales in the childhood sample.
Figure S3. Mean of absolute beta of 10 PRSs in the bifactor model with anxiety subscales in the childhood sample.
Figure S4. Mean of absolute beta of 10 PRSs in the bifactor model by different PRS *p*-value thresholds in the childhood sample.
Figure S5. Mean of absolute beta of 10 PRSs in bifactor model by different PRS *p*-value thresholds in the adolescent sample for the parent-reported and self-reported data.
Figure S6. Associations between PRS and the latent correlated factors model in the childhood sample.
Figure S7. Mean of absolute beta of 10 PRSs in the correlated factors model in the childhood sample.
Figure S8. Mean of absolute beta of 10 PRSs in the correlated factors model by different PRS *p*-value thresholds in the childhood sample.
Figure S9. Associations between ten PRS and observed sum score scales of the symptoms in the childhood sample.
Figure S10. Associations between ten PRS and observed sum score scales of the symptoms in the adolescent sample.
Figure S11. Associations between ten PRS and latent exploratory factors with a bifactor rotation in the childhood sample.
Figure S12. Associations between ten PRS and latent exploratory factors with a bifactor rotation in the adolescent sample.
Figure S13. Item response theory conditional reliability of the bifactor model (childhood sample).
Figure S14. Associations between education and intelligence PRS and latent bifactor model in the childhood sample.
Figure S15. Associations between education and intelligence PRS and latent bifactor model in the adolescent sample.

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Key points

- Although genetics predict psychiatric problems, these associations might be attributable to indirect pathways including population stratification, assortative mating, or dynastic effects (mediation via parental environments).
- To control for potential indirect pathways, we examined whether dizygotic twins who had higher scores on a given polygenic risk score (PRS) also were rated as having more psychiatric symptoms, compared to their siblings.
- Results showed that PRS-psychiatric symptom associations did not attenuate within twin pairs.
- This implies that PRS-psychiatric symptom associations did not appear attributable to indirect pathways such as population stratification, assortative mating, or mediation via parental environments; rather, genetics appeared to directly influence symptomatology.

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