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Role of Polygenic Risk Score in the Familial Transmission of Bipolar Disorder in Youth

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IMPORTANCE Establishing genetic contributions to the transmission of bipolar disorder (BD) from parents to offspring may inform the risk of developing this disorder and further serve to validate BD in youth.

OBJECTIVE To evaluate the specific association of BD polygenic risk scores (PRSs) on the familial transmission and validity of pediatric BD.

DESIGN, SETTING, AND PARTICIPANTS This community-based case-control longitudinal study (Pittsburgh Biological Offspring Study) included parents with BD I/II and their offspring and parents without BD (healthy or non-BD psychopathology) and their offspring. Participants were recruited between March 2001 and May 2007, and analysis took place from December 2020 to September 2021.

EXPOSURES PRSs for BD, major depressive disorder, schizophrenia, and attention-deficit/hyperactivity disorder.

MAIN OUTCOMES AND MEASURES Participants were prospectively evaluated using standardized interviews blind to parental diagnosis. DNA was extracted from saliva and genotyped. PRSs were constructed based on independent large-scale genome-wide association studies.

RESULTS A total of 156 parents with BD I/II and 180 parents without BD (mean [SD] age, 39.6 [7.9] years; 241 female [72%]) as well as 251 offspring of parents with BD and 158 offspring of parents without BD (mean [SD] age, 10.4 [4.7] years; 213 female [52%]) of European ancestry were analyzed. Participants were assessed a mean of 6.7 times during a mean (SD) of 13 (3.4) years of follow-up (84% retention). More offspring of parents with BD developed BD (58 [23.1%] vs 8 [5.1%]; $P < .001$) and depression (126 [50.2%] vs 52 [32.9%]; $P < .001$) compared with offspring of parents without BD. BD PRS was higher in both parents and offspring with BD than parents and offspring without BD (parents: odds ratio, 1.50; 95% CI, 1.19-1.89; $P < .001$; explained 4.8% of the phenotypic variance vs offspring: hazard ratio, 1.34; 95% CI, 1.03-1.7; $P = .02$; explained 5.0% of the phenotypic variance). BD PRS did not differ across BD subtypes. In a model combining parental and offspring BD PRS, the parental BD PRS association with offspring BD was fully mediated by offspring BD PRS (hazard ratio, 1.40; 95% CI, 1.05-1.86; $P = .02$). Parental BD had a stronger direct association than parental or offspring BD PRS with offspring BD risk (hazard ratio, 5.21; 95% CI, 1.86-14.62; $P = .002$), explaining 30% of the variance. Parental and offspring BD PRS explained 6% of the BD onset variance beyond parental diagnosis. There were no significant between-group differences in PRSs for major depressive disorder, schizophrenia, and attention-deficit/hyperactivity disorder in parents or offspring and they were not significantly associated with BD onset.

CONCLUSIONS AND RELEVANCE The findings of this study add to the extant clinical validation of BD in youth. Parental BD and offspring BD PRS independently associated with the risk of BD in offspring. Although this is promising, the association of BD PRS was relatively small and cannot be used alone to determine BD risk until further developments occur.

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Supplemental content

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Bipolar disorder (BD) is a familial illness that affects 2% to 3% of youth and is associated with functional impairment and increased risk for suicide and substance use, emphasizing the need for early identification and treatment.[1-3]

To identify who is at risk of BD, several family high-risk studies in youth have been carried out.[4-9] One of the largest and longest studies, the Pittsburgh Bipolar Offspring Study (BIOS),[10-12] found that offspring of parents with BD were at elevated, specific risk to develop BD compared with controls (22% vs 4%, respectively).[10,11] Parental early-onset BD and symptoms of depression/anxiety, mood lability, and subclinical mania were associated with higher risk of BD. However, these factors alone are insufficient to predict BD, highlighting the need to identify additional predictive factors (eg, biological).

BD is highly heritable, suggesting that genetic information may contribute to risk detection.[10-15] Large genome-wide association studies (GWAS) have identified many common genetic variants (single-nucleotide variations [SNVs]) associated with risk for BD. Each SNV accounts for a small proportion of variance in BD risk.[13,16-20] However, the polygenic risk score (PRS), reflecting the combined effects of many SNVs across the genome, is robustly associated with an individual's risk to develop the condition of interest.[17-20]

Studies in adults with BD show that the BD PRS is increased in adults with BD compared with controls,[21-28] their unaffected relatives,[23,24,29-31] and adults with depression who developed BD, had family history of BD, early onset, high depressive recurrence rates, or high BD familial burden.[31,32] BD PRS has been associated with attention-deficit/hyperactivity disorder (ADHD) and with higher scores in self-reported hypomanic symptoms during adulthood.[25]

To our knowledge, only 1 study has examined BD PRS in offspring of parents with BD. This study reported significantly higher BD PRS in offspring of parents with BD (aged 12-30 years) compared with controls.[24] However, this study was cross-sectional, did not report whether the offspring had BD, used a limited panel of SNVs in a mixed-ethnicity sample, and did not include PRSs for other psychiatric disorders. Consequently, the predictive validity and specificity of BD PRS in offspring of parents with BD remain unknown.

In this study, we evaluated whether parents with BD and their offspring had specifically increased BD PRS compared with PRSs for depression, schizophrenia, and ADHD. ADHD PRS was included owing to overlapping symptoms with BD and, although controversial, the reported cotransmission of BD and ADHD.[33] Also, for the first time in the literature to our knowledge, we examined pathways by which parental diagnosis of BD and parental BD PRS influenced the risk for offspring to develop BD.

Key Points

Question Is bipolar disorder (BD) polygenic risk score (PRS) specifically associated with the familial transmission of BD in youth?

Findings In this case-control study of 336 parents and 409 offspring, particularly those with mood disorders showed significantly and specifically higher BD PRS than those without BD. Parental and offspring BD PRS were associated with increased risk for offspring to develop BD, beyond the associations of parental BD diagnosis.

Meaning Specifically higher BD PRS in BD offspring may add to the clinical validation of BD in youth and increases the risk for BD; however, given the BD PRS's small association, it cannot be used alone to determine risk to develop BD.

Methods

The methods of Pittsburgh BIOS have been described in prior publications.[10,11] Briefly, biological parents with *DSM-IV*[34] BD I/II who had offspring aged 6 to 18 years were recruited, primarily through advertisements. Schizophrenia and IQ less than 70 were excluded. Community control parents, healthy or with non-BD disorders and without a spouse or first-degree relatives with BD, were recruited at random, group-matched by age, sex, and neighborhood. Participants were recruited from March 2001 to May 2007.

Parents with BD and a subgroup of biological coparents (31%) were assessed for lifetime (intake and follow-up) psychopathology using the Structured Clinical Interview for *DSM-IV*.[35] Family psychiatric history and psychiatric history of coparents who were not available for direct interview were obtained from the parent proband using the Family History Research Diagnostic Criteria.[36]

Offspring were recruited through their parents. Except for IQ less than 70, autism, or conditions that interfered with the evaluation, all offspring were included. Offspring's lifetime (intake and follow-up) disorders were ascertained by interviewing offspring and parents using the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version.[37] Offspring older than 19 years were assessed using the Structured Clinical Interview for *DSM-IV*. Specific BD-not otherwise specified (BD-NOS) criteria were used[38] (eFigure 1 in the Supplement). Socioeconomic status was determined using the Hollingshead scale.[39]

Follow-ups were performed every 2 years by trained interviewers who were blind to parents' diagnoses. A child psychiatrist, also blind to parental diagnosis, confirmed the diagnoses. The κ for diagnostic reliability for each disorder was 0.64 or higher.[10-12] The University of Pittsburgh's institutional review board approved the study, and written consent and/or assent was obtained from offspring and their parents.

Participants

For this study, only parents (probands) and biological coparents of European ancestry were included because the discovery GWAS samples included only individuals of this ancestry.[16-32,40-43] After quality control of genetic data (eFigure 2 in the Supplement), parents with BD I and II, parents without BD, and their offspring were included.

Genotyping and Polygenic Scores

The methods regarding DNA extraction, genotyping, and PRSs are shown in eMethods 1 in the Supplement. Genotypes were

Table 1. Demographic and Clinical Characteristics of Parents With Behavior Disorders vs Parents Without Behavior Disorders[a]

Characteristic	Behavior disorder, No. (%)		Test statistic	*P* value
	Yes	No		
No.	156	180	NA	NA
Age, mean (SD), y				
At intake	39.3 (7.7)	39.9 (8.0)	$t = 0.68$	.50
At last follow-up	44.8 (8.3)	45.2 (8.0)	$t = 0.45$	.70
Male	36 (23.1)	59 (32.8)	$\chi^2 = 3.88$	.05
Female	120 (76.9)	121 (67.2)	$\chi^2 = 3.88$	.05
SES, mean (SD)	13.6 (34.5)	12.2 (42.0)	$t = 4.77$	<.001
Married at intake	83 (53.2)	123 (68.3)	$\chi^2 = 8.06$	.005
Psychosocial functioning and lifetime psychiatric disorders				
Functioning (GAF), mean (SD)	60.6 (12.5)	82.57 (10.8)	$t = 17.29$	<.001
Any major depressive episodes	148 (94.9)	70 (38.9)	$\chi^2 = 114.95$	<.001
Any anxiety disorder	124 (79.5)	56 (31.1)	$\chi^2 = 78.63$	<.001
Psychosis	29 (18.6)	1 (0.6)	$\chi^2 = 33.43$	<.001
ADHD	40 (25.6)	7 (3.9)	$\chi^2 = 32.87$	<.001
DBD	56 (35.9)	9 (5.0)	$\chi^2 = 51.13$	<.001
SUD	104 (66.7	46 (25.6)	$\chi^2 = 57.15$	<.001

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; DBD, disruptive behavior disorder (oppositional defiant and conduct disorders); GAF, Global Assessment of Functioning Scale; NA, not applicable; SES, socioeconomic status; SUD, substance use disorder.

[a] Parents include the proband parents and biological coparents.

pruned using clumping to obtain an independent set of SNVs in linkage equilibrium with $r^2 < 0.1$ within any 500-kb window. The PRSs were constructed using PRSice-2[44] and the results of meta-analyses of GWAS of BD, schizophrenia, major depressive disorder (MDD), and ADHD using the *P* value threshold that maximally captured variance in the discovery GWAS sample (BD = .20, MDD = .05, schizophrenia = .05, ADHD = .50).[16,40-42,45] When constructing the PRS, the contribution of each allele was weighted by the effect size of its association with each phenotype in the reference sample GWAS.

Analysis

Between-group demographic/clinical differences were analyzed using *t* and χ^2 tests and mixed linear/generalized linear models (random intercept for familial clustering). Associations with multiple categorical outcomes were tested with multinomial logistic regression. Survival analyses modeling the onset of depressive disorders treated BD onset as a competing risk outcome because a BD diagnosis precludes depressive diagnoses; all other survival analyses implemented Cox proportional hazards regression (frailty models accounting for familial clustering; proportional hazards assumption verified via Schoenfeld residuals test) and/or Kaplan-Meier estimation. Associations were estimated as odds ratios (OR) in logistic regressions and hazard ratios (HR) in Cox regressions. Effect sizes were standardized to report the association per 1-SD increase in the PRS. Intercorrelation between PRSs was low (all Pearson $r \leq 0.25$), which enabled the use of multiple regression to estimate and test multiple PRS effects in the same model to try and separate the marginal effects of each. Because genetic analyses can be skewed by population stratification, we used PLINK2 to perform principal component analysis,[46] and all genetic analyses controlled for population structure indexed with 10 principal components of linkage disequilibrium-pruned genetic variants as well as sex. Mediation models implemented robust standard errors to account for familial clustering, tested indirect effects using bootstrap standard errors, and estimated total association as the sum of the direct association and indirect association for each submodel. Percent of variation statistics were estimated using Nagelkerke pseudo R^2 in logistic regressions[47] and the coefficient of explained randomness in Cox regressions.[48] Further details are included in eMethods 2 in the Supplement. Analysis took place from December 2020 to September 2021.

Results

A total of 156 parents with BD (including 2 coparents with BD) (BD I: 115; BD II: 41) and 180 parents (including 90 coparents) without BD were included (**Table 1**). Offspring included 251 offspring of parents with BD and 158 offspring of parents without BD with a mean (SD) age at intake of 10 (4.7) years (**Table 2**). Offspring were assessed a mean of 6.7 times over 13 years (mean [SD] age at last follow-up, 23 [5.6] years; retention at last follow-up: offspring of parents with BD, 83%; offspring of parents without BD, 86%).

Parents

At intake, compared with parents without BD, parents with BD had lower socioeconomic status, were less likely to be married (Table 1), and had lower overall functioning during follow-up and more lifetime (intake plus follow-up) anxiety disorders, major depressive episodes, psychosis, ADHD, disruptive behavior disorders, and substance use disorder.

Higher BD PRS was significantly associated with BD diagnosis (OR, 1.50; 95% CI, 1.19-1.89; $P < .001$), explaining 4.8% of the phenotypic variance (BD vs no BD) (**Figure 1**A). Controlling for demographic/clinical differences and family history of

Table 2. Demographic and Clinical Characteristics of Offspring of Parents With Bipolar Disorder and Offspring of Parents Without Bipolar Disorder

Characteristic	Offspring of parents, No. (%)		Test statistic	*P* value
	With BD	Without BD		
No.	251	158	NA	NA
Age, mean (SD), y				
At intake	11.1 (3.9)	10.7 (3.8)	$t = 0.98$	.33
At last assessment	23.5 (6.1)	22.9 (5.4)	$t = 1.01$	.30
Male	119 (47.4)	77 (48.7)	$\chi^2 = 0.07$	.80
Female	132 (52.6)	81 (51.3)	$\chi^2 = 0.07$	.79
SES, mean (SD)	36.7 (14.2)	42.9 (12.6)	$t = 4.54$	<.001
Maternal age at offspring's birth, mean (SD), y	28.1 (5.8)	29.5 (5.3)	$t = 2.48$	.01
Psychosocial functioning and lifetime psychiatric disorders				
Functioning (CGAS), mean (SD)	75.5 (12.8)	82.3 (10.9)	$t = 5.78$	<.001
Bipolar disorder	23.1 (58)	5.1 (8)	$\chi^2 = 23.33$	<.001
I	7.2 (18)	0.6 (1)		
II	4.8 (12)	1.9 (3)		
Not otherwise specified	11.2 (28)	2.5 (4)		
Bipolar disorder onset age (among offspring with diagnoses), y	12.39 (5.47)	19.04 (6.02)	$t = 22.62$[a]	<.001
Any depressive disorder	126 (50.2)	52 (32.9)	$\chi^2 = 11.9$	<.001
Any anxiety disorder	146 (58.2)	47 (29.8)	$\chi^2 = 31.43$	<.001
Psychosis	4 (1.6)	1 (0.6)	FET	.65
ADHD	72 (28.7)	25 (15.8)	$\chi^2 = 8.87$	.003
DBD	65 (25.9)	16 (10.1)	$\chi^2 = 15.18$	<.001
SUD	81 (32.3)	26 (16.5)	$\chi^2 = 12.55$	<.001
Parental psychiatric disorder history				
Any depressive episodes	242 (96.4)	68 (43.0)	$\chi^2 = 150.58$	<.001
Any anxiety disorder	205 (81.7)	55 (34.8)	$\chi^2 = 91.95$	<.001
Psychosis	42 (16.7)	0 (0.0)	$\chi^2 = 29.46$	<.001
ADHD	62 (24.7)	8 (5.0)	$\chi^2 = 26.36$	<.001
DBD	85 (33.9)	4 (2.5)	$\chi^2 = 55.91$	<.001
SUD	164 (65.3)	56 (35.4)	$\chi^2 = 34.86$	<.001

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; DBD, disruptive behavior disorder (oppositional defiant and conduct disorders); CGAS, Children's Global Assessment Scale; FET, Fisher exact test; NA, not applicable; SES, socioeconomic status; SUD, substance use disorder.

[a] Kaplan-Meier log-rank χ^2 test (includes right-censored cases) is reported.

BD did not change the results. Increased BD PRS was independently associated with BD I (OR, 1.44; 95% CI, 1.13-1.85; *P* = .004) and BD II (OR, 1.68; 95% CI, 1.19-2.36; *P* = .003) vs no BD. There were no significant differences in BD PRS between BD I and II; thus, they were combined for all comparisons. There were no significant associations between BD PRS and age at BD onset as a continuous or a dichotomous measure (older/younger than 18 years).

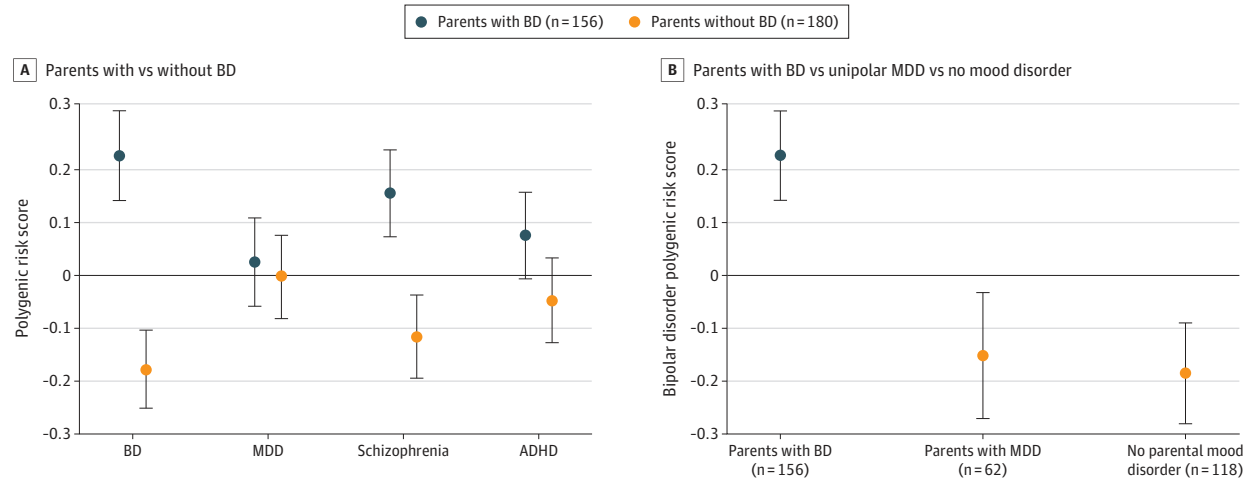
The schizophrenia PRS was also significantly higher in parents with vs without BD (OR = 1.30; 95% CI, 1.05-1.62; *P* = .02) (Figure 1A) but became nonsignificant after adjusting for confounders (mainly socioeconomic status). Further, after running the models only with BD PRS and then only with schizophrenia PRS, we ran a model with both BD PRS and schizophrenia PRS in the same model, comparing the forward and reverse models. Results indicated that when modeling BD risk with BD PRS and schizophrenia PRS as predictors in the same multiple logistic regression model, the schizophrenia PRS association was nonsignificant (OR, 1.20; 95% CI, 0.96-1.51; *P* = .10), whereas the BD PRS remained significant (OR, 1.44; 95% CI, 1.14-1.83; *P* = .003). After adjusting for confounders, the results were similar. There was an insufficient number of parents with psychosis to evaluate whether the high scores in the schizophrenia PRS were associated with these parents. There were no significant between-group differences in the PRSs for MDD or for ADHD.

To evaluate whether higher BD PRS was specific for BD and not for mood disorders in general, parents with BD were compared with 62 parents with unipolar MDD and 118 parents without BD or MDD (Figure 1B). BD PRS was significantly higher in parents with BD than those with unipolar MDD (OR, 1.47; 95% CI, 1.07-2.01; *P* = .02) or without MDD (OR, = 1.52; 95% CI, 1.17-1.97; *P* = .002). There were no BD PRS differences between parents with or without MDD.

Offspring

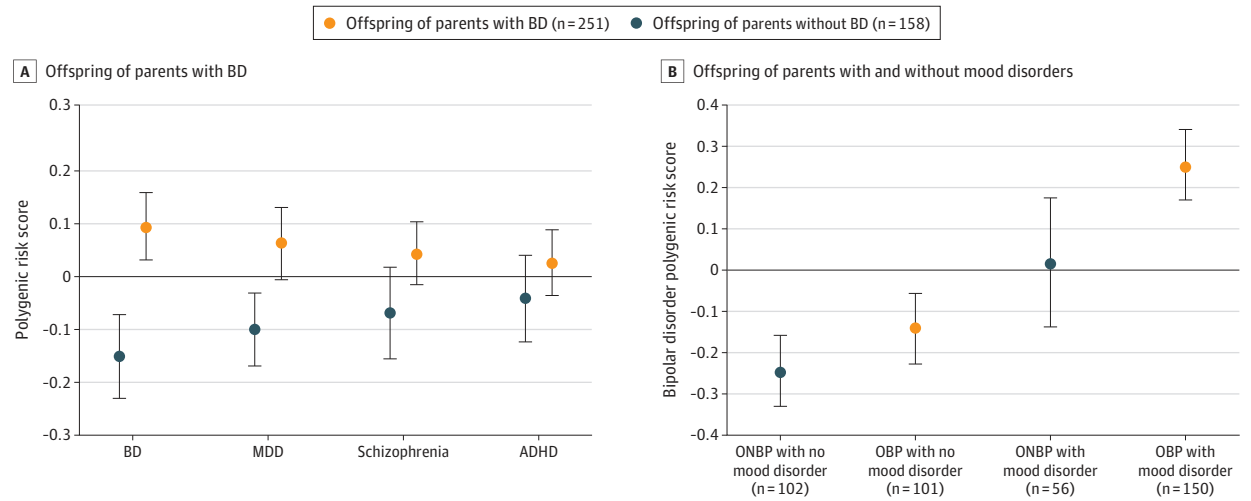
Offspring of parents with BD had significantly lower socioeconomic status and overall functioning, their mothers were younger at offspring birth, and they had more lifetime depression, anxiety, ADHD, disruptive behavior disorders, and substance use disorder than offspring of parents without BD (Table 2). More offspring of parents with BD developed BD (BD

Figure 1. Comparison of Parental BD, MDD, Schizophrenia, and ADHD PRS



Plots depict standardized group means and standard errors. A, BD PRS: OR, 1.50; $P < .001$; schizophrenia PRS: OR, 1.30; $P = .02$. B, BD vs MDD: OR = 1.47; $P = .02$; BD vs no mood disorder: OR, 1.52; $P = .002$. ADHD indicates attention-deficit/hyperactivity disorder; BD, bipolar disorder; MDD, major depressive disorder; OR, odds ratio; PRS, polygenic risk score.

Figure 2. Comparison of Offspring BD, MDD, Schizophrenia, and ADHD Polygenic Risk Scores



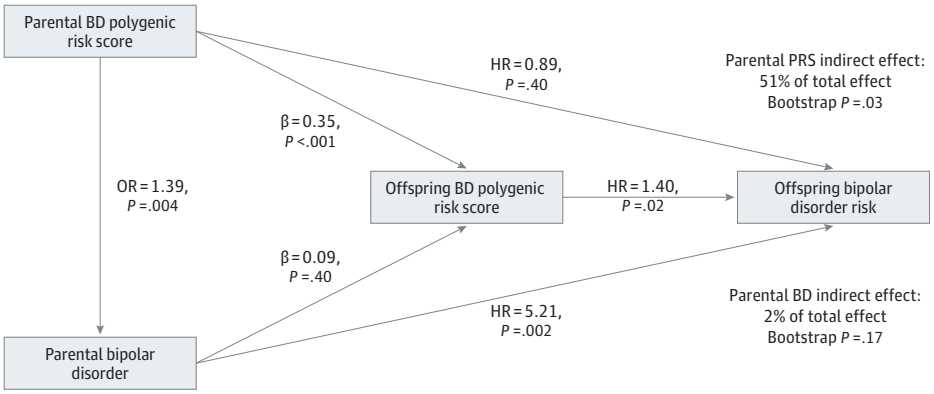
Plots depict standardized means and standard errors. A, Significant contrast: BD PRS $P = .02$. B, Significant contrasts: OBP with mood disorder vs ONBP with no mood disorder ($P < .001$), OBP with mood disorder vs OBP with no mood disorder ($P = .003$). ADHD indicates attention-deficit/hyperactivity disorder; BD, bipolar disorder; MDD, major depressive disorder; OBP, offspring of parents with bipolar disorder; ONBP, offspring of parents without bipolar disorder; PRS, polygenic risk score.

I: 18; BD II: 12; BD-NOS: 28) than offspring of parents without BD (BD I: 1; BD II: 3; BD-NOS: 4).

After adjusting for within-family correlations, there were no significant between-group differences in PRSs for MDD, schizophrenia, and ADHD. In contrast, offspring of parents with BD showed significantly higher BD PRS ($F = 5.67$, $P = .02$) (**Figure 2**A). There were no statistical differences in BD PRS between BD I/II and BD-NOS and between offspring of parents with BD with depression vs BD.

There were too few offspring of parents without BD with BD (n = 8) to analyze statistically. Thus, subsequent offspring analyses grouped offspring by mood vs no mood disorder (Figure 2B). Offspring of parents with BD with mood disorders had significantly higher mean BD PRSs than offspring of parents without BD with no mood disorders (Cohen $d = .51$, $P < .001$) and offspring of parents with BD with no mood disorders (Cohen $d = .51$, $P = .003$) and marginally higher mean BD PRS than offspring of parents without BD with a mood disorder (Cohen $d = .51$, $P = .06$). Offspring of parents with BD with no mood disorders and offspring of parents without BD and without mood disorders did not significantly differ. Thus, BD PRS differences between offspring of parents with BD and

Figure 3. Mediation Path Analysis for Estimation of Offspring BD Risk



BD indicates bipolar disorder; HR, hazard ratio; OR, odds ratio.

without BD were driven by offspring of parents with BD or depression.

Higher BD PRS was significantly associated with higher BD risk (standardized HR, 1.34; 95% CI, 1.03-1.75; P = .02). BD PRS explained 5.0% of phenotypic variance (BD vs no BD). Within the offspring who developed BD, there were no significant BD PRS associations with BD age of onset (standardized HR, 0.91; 95% CI, 0.74-1.13; P = .40) or significant differences in BD PRS between offspring with BD onset by age 18 years (54 [82%]) vs later (12 [18%]) (F = 0.21, P = .70). Controlling for between-group demographic/clinical differences and family history of BD in the offspring models above did not change the findings.

Parental Transmission of BD

As expected, parental BD PRS was significantly associated with parental BD (standardized OR, 1.39; 95% CI, 1.11-1.73; P = .004) and offspring BD PRS with offspring BD (HR, 1.40; 95% CI, 1.05-1.86; P = .02) (**Figure 3**). Parental BD diagnosis was a strong direct predictor of offspring BD risk (HR, 5.21; 95% CI, 1.86-14.6; P = .002), with no significant indirect association via offspring BD PRS (bootstrap indirect effect P = .17). The parental BD PRS association with offspring BD risk was fully mediated (no significant direct association) by a significant indirect association via offspring BD PRS (P = .03, accounting for 51% of the total association of parental BD PRS with offspring BD risk, consistent with mendelian predictions). Specifically, each 1-SD increase in parental BD PRS was associated with an increase in offspring BD PRS by an estimated 0.35 SDs (standardized β, 0.35; 95% CI, 0.26-0.44; P < .001), and each 1-SD increase in offspring BD PRS increased hazard of BD onset by an estimated 40% (HR, 1.40; 95% CI, 1.05-1.86; P = .02). In the combined path model, parent/offspring model, parental BD accounted for 30% of the BD risk variation, whereas parental and offspring BD PRS combined model accounted for 6% of offspring variance risk.

Fitting the same path model for risk of depression as the outcome variable, both the direct association of offspring BD PRS (HR, 1.26; 95% CI, 0.98-1.63; P = .06) and indirect association of parental BD PRS via the mediator (offspring BD PRS; bootstrap indirect effect P = .07) were nonsignificant (eFigure 3 in the Supplement).

Discussion

In this study, we found that parents with BD had higher BD PRS than parents without BD and a subset of parents with unipolar MDD. Also, offspring of parents with BD, particularly those with mood disorders, showed higher BD PRS than offspring of parents without BD. BD PRS explained a similar proportion of variance of outcome (lifetime BD diagnosis) in parents and offspring (4.8% and 5.0%, respectively). For parents and offspring, there were no significant between-group differences in PRSs for MDD, schizophrenia, or ADHD.

As expected, in a model combining parental and offspring BD PRS, parental BD PRS association with offspring BD risk was fully mediated by the offspring BD PRS. While parental BD had a stronger association than BD PRS, it was still significant beyond the association with parental BD diagnosis. Offspring BD PRS was not significantly associated with depressive disorders.

Replicating studies among adults with BD,[19-28] higher BD PRS was significantly associated with BD in parents. We found no significant differences between BD I and II, while the few studies published have reported inconsistent findings.[21,23,26] Also, comparable with other publications,[21,22,26,28,29,31,32,49] parents with BD showed higher schizophrenia PRS than parents without BD, a finding that may be explained by pleiotropy[50] or other factors because this comparison was no longer significant after adjusting for confounders, mainly socioeconomic status. Similar to another adult study, the schizophrenia PRS was no longer significant after including the BD PRS in the model.[32] Because there was a subgroup of parents with unipolar MDD, we further compared this group with parents with BD and found that parents with BD had significantly higher BD PRS than parents with MDD. The above findings together with the lack of differences in MDD PRS and ADHD provide support for a degree of specificity of BD PRS.

Like a prior cross-sectional high-risk study,[24] BD PRS was higher in offspring of parents with BD than offspring of parents without BD. There were no between-group differences in the groups for PRSs for MDD, schizophrenia, and ADHD, again

providing further evidence for the specificity of the association between BD PRS and offspring of parents with BD.

Offspring of parents with BD who developed depressive disorders showed comparable BD PRS as offspring with BD suggesting that, at least in youth, BD PRS is associated with mood disorders in general and not only BD. These results are not surprising given that approximately half of the offspring were younger than 21 years at the last follow-up; thus, they had not yet passed through the period of highest risk to develop BD.[1-3] These offspring are particularly at risk to develop BD because most of their parents had early-onset BD.[1,3,11,49] Moreover, in adults with unipolar MDD, particularly those with family history of BD, BD PRS was specifically associated with conversion to BD.[49]

Because BD is a highly heritable illness,[1-3,13,14] it is expected that genetic factors contribute to the increased risk of BD that is seen among offspring of parents with BD. In fact, we found that the association of parental BD PRS with offspring BD risk was mediated by the offspring BD PRS beyond the associations of parental diagnosis of BD. To our knowledge, only one other study compared the associations of BD PRS and parental history of BD with risk to develop BD in adults with MDD.[49] Mirroring our results, the associations of parental BD were much stronger than the BD PRS; here, we add to the literature the finding that BD PRS and parental BD made independent contributions to offspring risk. Both the current study and most priors PRS studies indicate small associations of PRS.[17-20] These findings are explained, at least partly, by the limited number of SNVs included in PRS,[17-20] can perhaps be addressed by increasing the sample size of the discovery samples used for GWAS, and as a result the number of SNVs to be included in the PRS. In addition, other factors may account for the small associations of the PRS; for example, existing PRS analyses do not consider the complex interactions among SNVs, the associations of other categories of genetic variants (eg, copy number variants), and environmental factors.[17-20]

Importantly, for the first time in the pediatric BD literature to our knowledge, this study contributes to the validation of the diagnosis of BD in youth by adding a biological criterion to existing clinical criteria (eg, longitudinal course and family history) necessary to validate the existence of any disorder.[1,3,51] In fact, offspring showed the same magnitude of genetic risk alleles as their parents with BD, multiple other large-scale studies of adults with BD[20-28,32] and the original BD GWAS meta-analysis (4.6%).[16] Also, BD PRS in parents were associated with the onset of BD in offspring, controlling for BD PRS in the offspring fully accounted for the increased risk associated with parental genotypes (suggested that it was same risk alleles passed on from parent to offspring), and offspring BD PRS predicted offspring BD even after accounting for parental BD diagnosis in the model, suggesting that the pediatric BD may have similar underlying genetic risk structure to adult BD.

Finally, there were no differences in the BD PRS between offspring with BD I/II and BD-NOS, giving biological evidence in support of the diagnosis of BD-NOS, a BD subtype that increases the risk to develop BD I/II and is as strongly associated with family history of BD, suicidality, and substance use disorder as are BD I/II.[1,3,38,52,53]

Limitations

The following limitations need to be considered. Although BIOS is the largest existing high-risk BD study in youth, the sample size of offspring with BD was relatively small. Thus, results that depended on failure to detect differences between subgroups need to be taken cautiously. Also, the discovery GWAS samples predominantly included individuals of European ancestry,[17-20] precluding generalization of the results to other groups.

Conclusions

In conclusion, using PRSs for BD, MDD, schizophrenia, and ADHD in a sample of parents with vs without BD and their offspring, this study demonstrated that BD PRS is specifically elevated among parents with BD and among offspring of parents with BD with mood disorders. The BD PRS was associated with increased risk of offspring BD, above and beyond the association of parental BD diagnosis. These results and the finding that BD PRS was associated with similar risk variance to develop BD between adults and offspring with vs without BD and the existing BD PRS literature provide biological evidence for pediatric BD. Although promising, given the small associations, BD PRS is not yet suitable for clinical use to determine individual risk of BD. However, as suggested by the literature, when the methods to derive the PRS improve and the discovery samples become larger, BD PRS has the potential to be useful to predict BD in at-risk populations, inform differential diagnosis (eg, with ADHD or unipolar MDD) and response to treatment, and use in research studies of at-risk youth and youth with BD.[17-20] The genetic data used in this study will be reanalyzed once additional associations between SNVs and BD are identified and when methods to include other types of genetic variants and environmental factors into the PRS become available.[17-20]

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