Identifying Pediatric Mood Disorders From Transdiagnostic Polygenic Risk Scores: A Study of Children and Adolescents

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ABSTRACT

Objective: Mood disorders often co-occur with attention-deficit/hyperactive disorder (ADHD), disruptive behavior disorders (DBDs), and aggression. We aimed to determine if polygenic risk scores (PRSs) based on external genome-wide association studies (GWASs) of these disorders could improve genetic identification of mood disorders.

Methods: We combined 6 independent family studies that had genetic data and diagnoses for mood disorders that were made using different editions of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*). We identified mood disorders, either concurrently or in the future, in participants between 6 and 17 years of age using PRSs calculated using summary statistics of GWASs for ADHD, ADHD with DBD, major depressive disorder (MDD), bipolar disorder (BPD), and aggression to compute PRSs.

Results: In our sample of 485 youths, 356 (73%) developed a subthreshold or full mood disorder and 129 (27%) did not. The cross-validated mean areas under the receiver operating characteristic curve (AUCs) for the 7 models identifying participants with any mood disorder ranged from 0.552 in the base model of age and sex to 0.648 in the base model + all 5 PRSs. When included in the base model individually, the ADHD PRS (OR = 1.65, $P < .001$), Aggression PRS (OR = 1.27, $P = .02$), and MDD PRS (OR = 1.23, $P = .047$) were significantly associated with the development of any mood disorder.

Conclusions: Using PRSs for ADHD, MDD, BPD, DBDs, and aggression, we could modestly identify the presence of mood disorders. These findings extend evidence for transdiagnostic genetic components of psychiatric illness and demonstrate that PRSs calculated using traditional diagnostic boundaries can be useful within a transdiagnostic framework.

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Mental health problems, which have been shown to account for 45% of the global burden of disease in people between 10 and 25 years old, are complicated by low health care utilization.[1] One study[2] found that 66.9% of adolescents in need of health care services for psychiatric disorders received none. Many studies[3–5,6,7] have found that shorter duration of untreated disease is correlated with improved treatment response in mood disorders. Thus, better screening for these disorders would help get patients the care they need in the developmental period that gives the largest opportunity to improve outcomes.

In contrast to the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*) view of psychiatric disorders as distinct entities, several lines of evidence suggest that a transdiagnostic paradigm may be more appropriate. Several decades of research has shown that psychiatric comorbidity is pervasive for childhood disorders.[8,9] More recently, multiple groups have shown that many common genetic variants are shared among psychiatric disorders[10,11] and that these disorders share some brain variations documented by neuroimaging.[12] In parallel, many studies indicate that most psychiatric disorders fall along a continuum that is not discrete from the rest of the population.[10] These findings suggest that the discrete, categorical disorders of the *DSM* may be better represented as overlapping clusters of people expressing the extremes of multiple continuous traits. This notion suggests that transdiagnostic evidence may be useful when screening for disorders because, for example, subthreshold or biomarker manifestations of one disorder might be useful when diagnosing other disorders. Polygenic risk scores (PRSs) estimate risk by summing the effects of common genetic variants across the genome. For psychiatric conditions, such scores have not yet proven useful in clinical settings. Nevertheless, given the genetic correlations among many psychiatric disorders, a PRS from one disorder may be predictive of other genetically correlated disorders.[10] There are two reasons that PRSs from other disorders may be useful. First, it is well known that the reliability of a measure comprising correlated predictors is higher than the reliability of each individual predictor.[13] Thus, adding risk estimates calculated based on other disorders may result in better estimates of the true risk of psychopathology. A second point to consider is that the risk estimate derived from a comorbid disorder may be much more reliable than the risk estimate derived from the disorder that is the target of the

Clinical Points

- While comorbidities and genetic evidence suggest that a transdiagnostic framework for diagnosing psychiatric disorders may better reflect the underlying biology, there is a lack of research on transdiagnostic identification of psychiatric disorders.
- The current study combined 6 independent studies and found that models using polygenic risk scores calculated from multiple psychiatric disorders, age, and sex were significantly better at identifying the presence of any mood disorder compared to a model using just age and sex.
- Although promising, using polygenic risk scores to facilitate the diagnosis of psychiatric disorders is not yet possible due to low classification performance.

classification model. This occurs when the sample used to derive the PRS for the comorbid disorder is much larger than the sample used to derive PRS for the target disorder.

Here, we use PRSs to identify the presence of mood disorders in children and adolescents. We know from prior clinical and epidemiologic studies that mood disorders frequently co-occur with attention-deficit/hyperactive disorder (ADHD),[14–16] disruptive behavior disorders (DBDs),[17,18] and aggression.[19] Moreover, genome-wide association studies (GWASs) have shown that these disorders share common genetic variants.[16,17,20,21]

Given these associations, and the lack of evidence for identification of mood disorders in children using PRSs derived from mood disorders alone,[22] we sought to capitalize on correlated associations to identify the presence of any mood disorders in a sample of well-characterized youth. Our analytic strategy aimed to determine if PRSs based on GWASs of bipolar disorder (BPD), major depressive disorder (MDD), ADHD, ADHD with DBDs, and aggression could improve upon the classification performance afforded by a mood disorder PRS alone.

METHODS

Sample

The sample was derived from 6 independent studies using identical assessment methodology. Studies 1[23] and 2[24] were prospectively controlled family studies of boys and girls 6 to 17 years of age with and without *DSM-III-R* ADHD and their first-degree relatives (boys: 140 ADHD probands with 454 first-degree relatives and 120 control probands with 368 first-degree relatives; girls: 140 ADHD and 122 controls); Study 3[25] was a prospective controlled family study of youth 10 to 18 years of age with and without *DSM-IV* pediatric bipolar I disorder (BPD-I) and their first-degree relatives (105 BPD-I probands with 320 first-degree relatives and 98 control probands with 288 first-degree relatives); Study 4[26] was a prospective family study of youth 6 to 17 years of age of both sexes with active symptoms of *DSM-IV* BPD-I and their first-degree relatives (239 BPD-I probands with 687 first-degree relatives); Study 5[27] was a cross-sectional family study of men and women 18 to 55 years of age with and without *DSM-IV* ADHD and their first-degree relatives (224 ADHD probands with 300 first-degree relatives and 146 control probands with 118 first-degree relatives); and Study 6[28] was a cross-sectional linkage study of families with 2 or more full biological siblings with a lifetime diagnosis of *DSM-IV* ADHD (271 families, 1,170 genotyped individuals). Subjects from the study of boys with ADHD were followed up after 1, 4, 10, and 16 years; subjects from the study of girls with ADHD were followed up after 5 and 11 years; and subjects from the BPD family study were followed up after 4, 5, and 6 years. Subjects from the other 3 studies had cross-sectional data only.

The pediatric ADHD studies (Studies 1 and 2) recruited subjects from pediatric and psychiatric clinics. The BPD studies and ADHD linkage study (Studies 3, 4, and 6) recruited subjects from referrals to the Clinical and Research Programs in Pediatric Psychopharmacology at the Massachusetts General Hospital (MGH) and through advertisements in the community. The ADHD linkage study (Study 6) also recruited subjects from pediatric clinics and private child psychiatry practices. The adult ADHD study (Study 5) recruited subjects from psychiatric clinics and advertisements in the community. Controls were recruited from pediatric clinics, advertisements to hospital personnel and community newspapers, and Internet postings. Potential subjects were excluded from all 6 studies if they had major sensorimotor handicaps, inadequate command of the English language, or a full-scale IQ < 70 (< 80 for the pediatric and adult ADHD studies) and from all studies except the adult ADHD study (ie, Studies 1, 2, 3, 4, and 6) if they were adopted or if their nuclear family was not available for study. Potential subjects were also excluded from all 4 ADHD studies (Studies 1, 2, 5, and 6) if they had psychosis, from the pediatric ADHD and BPD studies if they had autism, from the BPD studies if their BPD-I disorder was due solely to a medication reaction, and from the ADHD linkage study if they did not want to provide a blood sample. For all 6 studies, every subject 18 years and older provided written informed consent. Children and adolescents provided written assent to participate, and their parents provided written informed consent. The Partners Human Research Committee approved these studies.

For the current study, we restricted our sample to subjects who were 6 to 17 years of age, had genetic data available, and had diagnosis information for BPD and MDD. Based on these criteria, our sample consisted of 485 subjects, including 112 subjects from the study of boys with ADHD (Study 1), 144 subjects from the study of girls with ADHD (Study 2), 21 subjects from the controlled BPD study (Study 3), 80 subjects from the BPD family study (Study 4), 10 subjects from the adult ADHD study (Study 5), and 117 subjects from the ADHD linkage study (Study 6). There was also 1 subject with genetic data included from an "unselected" clinic population referred for psychiatric care at MGH for which there were no exclusion criteria and for whom we received approval from the Partners Human Research Committee to review,

analyze, and report on anonymously. Details about sample assessments, psychiatric diagnoses, and polygenic risk scoring can be found in Supplementary Appendix 1.[16,17,29–33]

Statistical Analysis

First, we stratified patients by lifetime development of any subthreshold or full mood disorder (MDD or BPD) and compared them on sociodemographic characteristics using *t* tests, ordered logistic regression, and Pearson χ^2 tests. We included subthreshold cases based on a meta-analysis[34] that showed evidence for the validity of subthreshold cases. Participants were classified as having a subthreshold mood disorder if they did not meet full criteria, had 3 or more symptoms, and had a duration of symptoms of at least 1 week to qualify as an episode. For subjects from the pediatric ADHD studies and the BPD family study, we defined lifetime history of any mood disorder as positive if the subject met subthreshold or full diagnostic criteria for MDD or BPD at any assessment (baseline or follow-up visits). For subjects with cross-sectional data from the adult ADHD study, ADHD linkage study, and controlled BPD study, we defined lifetime history of any mood disorder as positive if the subject met subthreshold or full diagnostic criteria for MDD or BPD at the time of assessment. Next, we examined the classification performance of 7 models to identify any mood disorder versus no mood disorder. We started by using multiple logistic regression to test a model that identified any mood disorder from age, sex, and the first 10 principal components from a principal components analysis, which reduces the dimensionality of the genetic data to explain as much variance as possible. If the ancestry of our subjects differed between cases and controls, the principal components would be predictive and control for differing ancestries between samples.[35] However, none of the principal components were significantly predictive; therefore, the principal components were excluded from other models to minimize overfitting and overestimation of performance that could be caused by overparameterization. We used a logistic regression model that included age and sex to identify any mood disorder as the base model. We then added each PRS to the base model individually (ie, base model + BPD PRS, base model + MDD PRS, base model + ADHD PRS, base model + ADHD with DBD PRS, base model + aggression PRS) to test the classification performance of each PRS. Finally, we tested a model that included all 5 PRSs plus the base model. We assessed the classification performance of the models using receiver operating characteristic (ROC) curve analysis with 10× cross-validation and summarized the results using mean area-under-the-curve (AUC) statistics across the 10 folds. In our 10× cross-validation protocol, we randomly split subjects into 10 folds, and each fold was iteratively held out of model fitting to measure the classification performance in that fold on a model fit using the other 9 folds. All AUCs we report are based only on the classification performance in the withheld folds during cross-validation. AUC represents the probability that a randomly selected case/control pair are accurately classified. AUCs from different models were compared using the DeLong test[36] for comparing AUCs. Our test for equality of AUC statistics used a single AUC based on cross-validated probabilities for each model. We also performed 2 sensitivity analyses; the first restricted the sample to White patients, and the second identified full mood disorders only. All analyses were 2-tailed and performed at the .05 α level using Stata (Version 16.1).[37] Sensitivity analysis results can be found in the Supplementary Appendix 1.

Table 1. Sociodemographic Characteristics

Characteristic	Total Sample (N = 485)	No Mood Disorder (n = 129)	Any Mood Disorder (n = 356)	*P* Value
Age, mean ± SD, y	11.2 ± 3.2	11.0 ± 3.0	11.3 ± 3.3	.41
SES, mean ± SD	1.9 ± 0.9	1.7 ± 0.8	1.9 ± 1.0	.03
Male, n (%)	281 (58)	65 (50)	216 (61)	.04
White, n (%)[a]	339 (93)	86 (91)	253 (94)	.24

[a]Smaller sample size: total sample: total n = 364; no mood disorder: total n = 95; any mood disorder: total n = 269.
Abbreviation: SES = socioeconomic status.

RESULTS

Sociodemographic Characteristics

In our sample of 485 youths, 356 (73%) developed a subthreshold or full mood disorder and 129 (27%) did not. As shown in Table 1, there were significant differences between those who did and did not develop a mood disorder in socioeconomic status (SES) and sex. Those who developed a mood disorder were of lower SES and had a greater percentage of males compared to those who did not. There were no significant differences between the groups in age or race.

Identification of Any Mood Disorder by Polygenic Risk Scores

As shown in Table 2, the fit statistics were the best for the base model + all 5 PRSs, with the lowest Akaike Information Criterion (AIC) (AIC = 1.110) and second lowest Bayesian Information Criterion (BIC) (BIC = −2,427.326). The BIC, which penalizes more heavily for complex models, was slightly lower in the base model + ADHD PRS (BIC = −2,440.554) compared to the base model + all 5 PRSs. The base model + all 5 PRSs had the highest Nagelkerke R^2 ($R^2 = 0.114$), with the 5 PRSs explaining 9.8% of the variance when comparing this model to the base model ($R^2 = 0.016$). The base model + ADHD PRS had the next highest Nagelkerke R^2 ($R^2 = 0.081$), with the ADHD PRS explaining 6.5% of the variance when comparing this model to the base model. The base model + BPD PRS, base model + MDD PRS, base model + ADHD with DBD PRS, and base model + Aggression PRS performed no better than the base model itself, explaining only 0.05%–1.5% of the variance. All comparisons marked significant at $P < .01$ were statistically significant after correction for multiple comparisons.

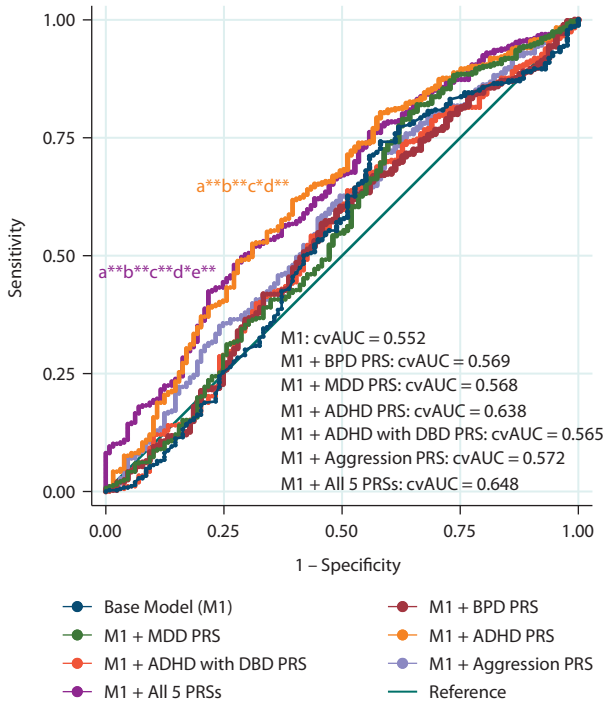
The cross-validated mean AUC statistics for the 7 models ranged from 0.552 for the base model to 0.648 for

Table 2. Comparison of Fit Statistics and Predictive Utility for 7 Different Models Predicting Any Mood Disorder vs No Mood Disorder From Demographic Characteristics and Polygenic Risk Scores in Youth (N = 485)

Variable	Base Model (M1)[†]	M1 + BPD PRS	M1 + MDD PRS	M1 + ADHD PRS	M1 + ADHD With DBD PRS	M1 + Aggression PRS	M1 + All 5 PRSs
AIC	1.160	1.161	1.156	1.118	1.159	1.153	1.110
BIC	−2,424.286	−2,419.718	−2,422.096	−2,440.554	−2,420.416	−2,423.332	−2,427.326
Nagelkerke R^2	0.016	0.021	0.028	0.081	0.023	0.031	0.114
Mean cvAUC statistic	0.552	0.569	0.568	0.638[a**b***c*d**]	0.565	0.572	0.648[a**b***c**d***e*]
95% CI of Mean cvAUC statistic	0.461–0.581	0.495–0.612	0.492–0.613	0.571–0.685	0.479–0.597	0.502–0.616	0.586–0.697

All *P* values are based on comparisons to the base model or a single disorder model.
[a]Versus base model (M1).
[b]Versus M1 + BPD PRS.
[c]Versus M1 + MDD PRS.
[d]Versus M1 + ADHD with DBD PRS.
[e]Versus M1 + Aggression PRS.
*$P < .05$.
**$P < .01$.
[†]Base model (M1) predicts any mood disorder vs no mood disorder from age and sex. The PRS predictors added in subsequent models are standardized. All *P* values are based on comparisons to the base model or a single disorder model.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, AIC = Akaike Information Criterion, BIC = Bayesian Information Criterion, BPD = bipolar disorder, cvAUC = cross-validated mean area under the curve, DBD = disruptive behavior disorder, MDD = major depressive disorder, PRS = polygenic risk score.

Figure 1. Receiver Operating Characteristic (ROC) Curves for the 7 Models Tested to Predict Any Mood Disorder Versus No Mood Disorder in Youth



[a]Versus base model (M1).
[b]Versus M1 + BPD PRS.
[c]Versus M1 + MDD PRS.
[d]Versus M1 + ADHD with DBD PRS.
[e]Versus M1 + Aggression PRS.
*$P < .05$.
**$P < .01$.
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, BPD = bipolar disorder, cvAUC = cross-validated mean area under the curve, DBD = disruptive behavior disorder, MDD = major depressive disorder, PRS = polygenic risk score.

the base model + all 5 PRSs (Table 2, Figure 1). Pairwise comparisons revealed that the base model + ADHD PRS performed significantly better at identifying youths with any mood disorder than all the other models except for the base model + Aggression PRS and the base model + all 5 PRSs. The base model + all 5 PRSs performed significantly better at identifying youths with any mood disorder than all the other models except for the base model + ADHD PRS. A detailed report of the sensitivities and specificities at different thresholds in the base model + 5 PRSs ROC curve can be found in the Supplementary Table 1.

When included in the base model individually, the BPD PRS (OR = 1.14; $P = .20$; 95% CI, 0.93–1.40) and ADHD with DBD PRS (OR = 1.17; $P = .13$; 95% CI, 0.95–1.45) were not significantly associated with any mood disorder, but the MDD PRS (OR = 1.23; $P = .047$; 95% CI, 1.00–1.52), ADHD PRS (OR = 1.65; $P < .001$; 95% CI, 1.33–2.05), and Aggression PRS (OR = 1.27; $P = .02$; 95% CI, 1.03–1.56) were significant before correction for multiple testing. Higher MDD, ADHD, and Aggression PRSs were associated with increased odds of having a mood disorder. When all 5 PRSs were included in the base model at the same time, only the ADHD PRS (OR = 1.68; $P < .001$; 95% CI, 1.34–2.10) and Aggression PRS (OR = 1.33; $P = .01$; 95% CI, 1.07–1.66) remained significant.

DISCUSSION

Although genetic associations among psychiatric disorders have been well documented,[10] this study is the first to use PRSs for several psychiatric disorders to identify the presence of mood disorders in youth. Using PRSs for ADHD, MDD, BPD, DBDs, and aggression, we could modestly identify mood disorders (operationalized as subthreshold or full presentation) in a set of independent family studies. These models extend evidence for transdiagnostic components of psychiatric illness using

genetic data and demonstrate that PRSs computed using traditional diagnostic boundaries can be leveraged within a transdiagnostic approach to child psychopathology.

Several factors might explain the failure of the BPD and MDD PRSs to identify these disorders. We studied youth who were 6 to 17 years of age, but the samples that generated the PRSs were mostly ascertained as adults. One interpretation of our findings is that the genomic etiology of the early-onset mood disorders associated with ADHD differs from the genomic etiology of adult-onset mood disorders. If so, there may be a neurodevelopmental mood disorder associated with ADHD and aggression. The ADHD PRS may have been significantly predictive in this sample due to its ability to identify an ADHD-specific depression, which could also explain the overrepresentation of males in the group with any mood disorder. Consistent with this idea, Levitan et al[38] proposed a neurodevelopmental theory of depression and inflammation associated with obesity and metabolic dysfunction, which are also seen in ADHD.[39–41]

It would be reasonable to suspect that our inclusion of subthreshold cases of BPD and MDD may have limited the success of those PRSs in identifying any mood disorder since both GWASs include only cases meeting full criteria. If the genetic risk architecture of subthreshold disorders differs from that of the corresponding full-threshold disorders, the former would be less accurately identified by PRSs generated by the latter type of sample. However, results were similar when we identified only full mood disorders, which is consistent with the continuum theory of psychiatric disorders.[10]

We followed up the single PRS models by testing a model that included age, sex, and all 5 PRSs. This model had an AUC of 0.65, the highest among the models we tested. This was a significant improvement from all models except the base + ADHD PRS model. Compared with the ADHD PRS model, the 5 PRSs model also had a lower variance among cross-validation folds. In the base + 5 PRSs model, only the ADHD and Aggression PRSs were significantly associated with any mood disorder after controlling for age, sex, and the other PRSs. This finding suggests that, while the inclusion of multiple PRSs was not enough to significantly improve identification in our sample, it is noteworthy that the Aggression PRS was associated with the development any mood disorder even after controlling for the ADHD PRS.

This study has several limitations. The study sample used here differs from the population that would be screened as part of a transdiagnostic clinical staging paradigm. We are also limited by using PRSs as the only genetic sources of information, as that may have limited the flexibility of the models to represent the genetic architecture of the complex disorders we are attempting to identify. Because allele frequencies differ across races and ethnicities, more work is needed to collect data from underrepresented groups. The data sets we used in these analyses were also included as part of larger GWAS studies that were used to estimate PRSs. This could lead to overestimation of the classification performance of overlapping PRSs, but given the large size of the GWAS relative to the overlapping data sets used here, the impact is likely minimal. In our analysis, 8 of 485 children were related, which could also lead to overestimating classification performance. Given the lack of significance of any principal components and the minimal use of related individuals, the impact of this limitation is likely small. Because of insufficient sample size, we were not able to do separate predictions of concurrent and future mood disorders. Future work should address this issue.

While our models identifying any mood disorder using genetic data show the potential of using genetic information alone, further improvements might be made by using genetic risk profiles alongside clinical interviews and other biomarkers in screening for these disorders. While the complementarity of genetic data with other sources of data in mood disorders still needs to be investigated, studies in other disorders have found that combining genetic data with other data sources leads to improved classification.[42,43] The low classification performance of the models presented here makes it unlikely that they would be clinically useful individually and therefore do not warrant reporting conditional probability or other more clinically relevant metrics, nor are they relevant to any specific clinical setting. Instead, our study shows that, in this opportunistic sample gathered from data available to us, the genetics a child is born with are modestly predictive of that child's developing a mood disorder with simple models. If further genetic risk modeling improvements are made and used alongside the clinical interviews currently implemented in screening, we may eventually improve detection of patients at risk for mood disorders.

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Straight Talk about Your Child's Mental Health; Oxford University Press: *Schizophrenia: The Facts*; and Elsevier: *ADHD: Non-Pharmacologic Interventions*. He is also Program Director of www.adhdinadults.com. **Drs Doyle** and **Hess** have received grant support from the National Institute of Mental Health (NIMH). **Ms DiSalvo** and **Mr Barnett** have no disclosures.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Childhood and Adolescent Mental Health section. Please contact Karen D. Wagner, MD, PhD, at kwagner@psychiatrist.com.

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Supplementary Material

Article Title: Identifying Pediatric Mood Disorders From Transdiagnostic Polygenic Risk Scores: A Study of Children and Adolescents

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List of Supplementary Material for the article

1. Appendix 1 Supplementary Methods and Results

2. Table 1 Detailed report of sensitivity and specificity

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Appendix 1

Supplementary Methods

Diagnostic Assessments

In all six studies, psychiatric assessments of subjects younger than 18 were made with the Kiddie Schedule for Affective Disorders – Epidemiologic Version (K-SADS-E) [Orvaschel, 1987 #3938]. For subjects 12 and younger, diagnoses were based on independent interviews with parents. For subjects 13 to 17, diagnoses were based on independent interviews with parents and direct interviews with children and adolescents. Data were combined such that endorsement of a diagnosis by either reporter resulted in a positive diagnosis.

Extensively trained and supervised psychometricians with undergraduate degrees (or graduate degrees for the ADHD linkage study) in psychology or a related field conducted all interviews. For the pediatric ADHD studies, ADHD linkage study, and the controlled BPD study, raters were blind to the ascertainment status of the families. For the BPD family study, raters were blind to the study assignment and whether the subject was a proband or sibling. For the adult ADHD study, raters were blind to the subject's ascertainment status, ascertainment site, and all prior assessments. To assess the reliability of our overall diagnostic procedures, we computed kappa coefficients of agreement by having experienced, blinded, board-certified child and adult psychiatrists and licensed experienced clinical psychologists diagnose subjects from audiotaped interviews made by the assessment staff. Based on 500 assessments from interviews of children and adults, the median kappa coefficient was 0.98 for the pediatric ADHD studies, adult ADHD study, and the controlled BPD study, and 0.99 for the BPD family study. Based on 173 assessments from interviews of children and adults, the median kappa coefficient was 0.99 for the ADHD linkage study.

Socioeconomic status (SES) was measured using the 5-point Hollingshead scale [Hollingshead, 1975 #1715]. A higher score indicates being of a lower socioeconomic status.

Polygenic Risk Scores

All participants provided blood for DNA extraction and genomewide genotyping of 585,979 SNPs on the Illumina PsychArray. A minimum call rate of 98% was set to exclude variants and individuals with missing data. In addition, we removed variants that showed significant departure from Hardy-Weinberg equilibrium ($p < 1\times10\text{-}6$) and variants with a minor allele frequency (MAF) less than 1%. Following these steps, data 504,432 variants were retained. The Michigan Imputation Server was used to perform automated haplotype phasing with Eagle v.2.4 and imputation of missing genotypes with Minimac4 based on the Haplotype Reference Consortium (version r1.1 2016), a reference panel of 64,940 haplotypes from individuals of predominantly European ancestry. After genotype imputation, quality control steps were performed to exclude variants with a MAF less than 1%, variants with a call rate under 98%, and variants that were not robustly imputed ($R2 < 90\%$). In order to detect variation between patients due to ancestry, we performed a principal component analysis (PCA) on directly genotyped variants that exhibited a minimum MAF of 10% and approximate linkage equilibrium (Plink command: --indep-pairwise 100 10 0.2). Variants found in the extended major histocompatibility (MHC)

locus of chromosome 6 (24mb – 35mb) were excluded to avoid biasing our PCA due to extensive linkage disequilibrium (LD). Top principal components (PCs) were included in initial analyses to check and adjust for potential confounding due to ancestry.

At the time of writing, we used published genome-wide summary statistics from the largest available genome-wide association meta-analyses of ADHD, ADHD with DBD, MDD, BPD, and aggression to compute PRSs [Demontis, 2019 #27482][Stahl, 2019 #27883][Wray, 2018 #27873][Demontis, 2021 #28727]. We used imputed genome-wide SNP genotypes (n SNPs = 8,063,863) to calculate PRSs for three neuropsychiatric disorders (ADHD, BPD, and MDD). All PRSs were computed using the conventional LD-pruning and p-value thresholding (P+T) method [Purcell, 2009 #20218]. Pre-processing steps were followed to exclude uncommon SNPs (MAF < 10%), insertions and deletions, variants in the extended MHC locus, variants with a imputation quality score less than 90%, strand-ambiguous variants (i.e., CG, AT), and variants not included in our target dataset from the GWAS summary statistics. We then used Plink v.1.9 to perform a greedy pruning of SNP associations (or "clumping") such that the resultant SNP set was largely LD-independent. The parameters used for the clumping algorithm were as follows: --clump-p1 1.0 –clump-p2 1.0 –clump-kb 250 –clump-r2 0.1. When computing PRSs in our dataset, we chose the p-value threshold that was reported to have maximized the phenotype variance explained (R2) in a sample that was independent from the initial training sample that was used to derive the PRS formula (ADHD: $p \leq 0.2$; BPD: $p \leq 0.01$; MDD: $p \leq 0.05$; aggression: $p < 0.1$ [Elam, 2018 #28784]. ADHD with DBD was an exception to this criteria; in absence of a reported best p-value threshold, we computed PRS for ADHD with DBD using a threshold of $p < 0.5$. PRSs were standardized to a mean of zero and unit variance for downstream statistical analyses.

Statistical Analysis

The PCs and PRSs were standardized based on the means and standard deviations of the current sample. For each model, we assessed goodness of fit using Akaike's Information Criterion (AIC), Bayesian Information Criterion (BIC), and Nagelkerke's pseudo-R2. When comparing AIC and BIC values across models, lower values indicate a better fit model. When comparing Nagelkerke's pseudo-R2 values across models, higher values indicate a greater percentage of variance explained by the model. The amount of variance explained by the PRS variables is calculated as the difference of Nagelkerke's pseudo-R2 in the model including the PRS compared with the base model.

Supplementary Results

Sensitivity Analysis

Results remained largely the same when we performed a sensitivity analysis restricting the sample to Caucasian patients (N=339). The base model + all five PRSs had the highest Nagelkerke R^2 (R^2=0.127), with the five PRSs explaining 10.1% of the variance when comparing this model to the base model (R^2=0.026). Additionally, the base model + all five PRSs performed significantly better at identifying youths with any mood disorders than the base model, base model + BPD PRS, and base model + Aggression PRS (all $p<0.05$). When all five PRSs were included in the base model at the same time, the associations between the MDD PRS (OR=1.45, p=0.008, 95% CI: 1.10 – 1.90) and ADHD PRS (OR=1.52, p=0.002, 95% CI: 1.16 – 1.99) with having any mood disorder remained significant.

Similarly, results remained largely the same when we performed a sensitivity analysis predicting full mood disorders only (N=445). The base model + all five PRSs had the highest Nagelkerke R^2 (R^2=0.132), with the five PRSs explaining 11.3% of the variance when comparing this model to the base

model (R^2=0.019). Additionally, the base model + ADHD PRS and the base model + all five PRSs performed significantly better than the other five models (all p<0.05), but not each other, at identifying youths with any full mood disorder. When all five PRSs were included in the base model at the same time, the associations between the ADHD PRS (OR=1.76, p<0.001, 95% CI: 1.40 – 2.22) and Aggression PRS (OR=1.32, p=0.02, 95% CI: 1.05 – 1.66) with having any mood disorder remained significant.

Supplementary Table 1

Detailed report of sensitivity and specificity

Cutpoint	Sensitivity	Specificity	Classified	LR+	LR-
(>= .2127..)	100.00%	0.00%	73.40%	1	
(>= .4742..)	97.19%	3.88%	72.37%	1.0111	0.7247
(>= .5055..)	95.51%	10.85%	72.99%	1.0713	0.4141
(>= .5468..)	93.54%	17.05%	73.20%	1.1277	0.3788
(>= .5608..)	90.73%	20.93%	72.16%	1.1475	0.4429
(>= .5940..)	87.36%	23.26%	70.31%	1.1383	0.5435
(>= .6041..)	85.67%	30.23%	70.93%	1.228	0.4739
(>= .6337..)	82.87%	34.11%	69.90%	1.2576	0.5024
(>= .6552..)	79.78%	37.21%	68.45%	1.2705	0.5435
(>= .6699..)	77.25%	41.86%	67.84%	1.3287	0.5435
(>= .684384)	73.88%	44.19%	65.98%	1.3236	0.5912
(>= .698988)	70.51%	46.51%	64.12%	1.3181	0.6341
(>= .7091..)	67.42%	49.61%	62.68%	1.3379	0.6568
(>= .7223..)	64.33%	52.71%	61.24%	1.3603	0.6768
(>= .7333..)	61.24%	55.81%	59.79%	1.3859	0.6945
(>= .7424..)	57.87%	58.14%	57.94%	1.3823	0.7247
(>= .7498..)	55.34%	62.79%	57.32%	1.4872	0.7113
(>= .7629..)	52.53%	66.67%	56.29%	1.5758	0.7121
(>= .7701..)	49.72%	70.54%	55.26%	1.6878	0.7128
(>= .7803..)	46.35%	72.87%	53.40%	1.7083	0.7363
(>= .7907..)	43.26%	75.97%	51.96%	1.8001	0.7469
(>= .7955..)	39.89%	78.29%	50.10%	1.8377	0.7678
(>= .8022..)	36.24%	79.84%	47.84%	1.7979	0.7986
(>= .8105..)	32.30%	80.62%	45.15%	1.6669	0.8397
(>= .8209..)	28.93%	82.95%	43.30%	1.6965	0.8568
(>= .8313..)	25.00%	83.72%	40.62%	1.5357	0.8958
(>= .8437..)	22.19%	87.60%	39.59%	1.7892	0.8883
(>= .8565..)	18.82%	89.92%	37.73%	1.8675	0.9028
(>= .8702..)	16.01%	93.80%	36.70%	2.5818	0.8954
(>= .8824..)	12.36%	95.35%	34.43%	2.6573	0.9192
(>= .899477)	9.55%	99.22%	33.40%	12.3202	0.9116
(>= .9142..)	5.62%	100.00%	30.72%		0.9438
(>= .9417..)	1.40%	100.00%	27.63%		0.986