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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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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