APPENDIX A: SUPPLEMENTARY METHODS, TABLES AND FIGURES

SUPPLEMENTARY METHODS:

**Population Stratification:**

 We described population stratification as follows: First, we filtered single nucleotide polymorphisms (SNPs) with minor allele frequency < 5% and then pruned our genetic data to remove SNPs with r2 > 0.2 within a window size of 50 kilobases at each step size of 5 SNPs. Next, we used SMARTPCA to derive genetic principal component (PC) scores from our pruned genetic data (Patterson, Price, & Reich, 2006; Price et al., 2006). We used the genetic variant normalization formula recommended by Price et al. (2006). Participants with PC scores greater than six standard deviations from the mean were removed with this process repeated five times (Price et al., 2006). Finally, we regressed the top three genetic PC scores on the polygenic risk scores for attention-deficit/hyperactivity (PRSADHD) and used the resulting residual PRS for all analyses (Figure S2).

SUPPLEMENTARY RESULTS:

**Child Gender and CBCL Scores:**

Large cohort studies provide some evidence for gender differences in child mental health symptoms (e.g., de Bruijn, van Bakel, & van Baar, 2009; Gerardin et al., 2011; Hicks et al., 2007; O'Donnell, Glover, Barker, & O'Connor, 2014). Thus, we explored whether or not child gender should be included as a covariate in our analyses. We used the anova() function in R to see if gender would improve the model fit. We compared a model that consider the Best-Fit PRSADHD, maternal depression during pregnancy (CES-Dpre scores), and maternal depression at 60 months (CES-D60mths scores) (see Model 1 below) versus a model like Model 1 that also consider child gender (Model 2 below). The inclusion of child gender did not significantly improve model fit for child i) total, ii) internalizing, or iii) externalizing symptoms (all p > 0.05) and thus was not considered in subsequent analyses.

Model 1: CBCL ~ PRSADHD + CES-Dpre + PRSADHD×CES-Dpre + CES-D60mths

Model 2: CBCL ~ PRSADHD + CES-Dpre + PRSADHD×CES-Dpre + CES-D60mths + Gender

SUPPLEMENTAL TABLES

|  |  |  |
| --- | --- | --- |
| Parameter | Model 1a | Model 1b |
|  | Estimated Beta (Std. Error) | Estimated Beta (Std. Error) |
| PRSADHD | -0.92 (0.28)\*\*\* | -1.15 (0.32)\*\*\* |
| CES-Dpre |  0.10 (0.06) |  0.23 (0.14) |
| CES-D60mths |  0.20 (0.06)\*\* |  0.34 (0.14)\* |
| PRSADHD×CES-Dpre |  0.28 (0.08)\*\*\* |  0.26 (0.08)\*\* |
| PRSADHD×CES-D60mths |  - |  0.12 (0.09) |
| CES-Dpre×CES-D60mths |  - | -0.04 (0.04) |
|  | Model 1a Fit | Model 1b Fit |
| R2 |  0.180 |  0.193 |
| F (df) |  9.974 (4, 182)\*\*\* |  7.166 (6, 180)\*\*\* |
| BIC |  555.5 |  563.0 |

Table S1. Regression analyses of child internalizing problems. Model 1a includes the PRSADHD, maternal CES-D scores during pregnancy (CES-Dpre), maternal CES-D scores at 60 months after birth (CES-D60mths) main effects and the interaction between PRSADHD and CES-Dpre (PRSADHD×CES-Dpre). Model 1b is similar to Model 1a, with additional interactions between PRSADHD and CES-D60mths (PRSADHD×CES-D60mths), and CES-Dpre and CES-D60mths (CES-Dpre×CES-D60mths), as this model properly controls for potential confounders (Keller, 2014). Model 1a fit is not significantly different from Model 1b fit (n.s.). BIC = Bayesian information criterion. \*p < 0.05, \*\*p < 0.01, \*\*\*p < 0.001

|  |  |
| --- | --- |
| Parameter | Extended Model |
|  | Estimated Beta (Std. Error) |
| PRSADHD | -1.96 (1.31) |
| CES-Dpre | -0.87 (0.68) |
| CES-D12mths | -0.11 (0.19) |
| CES-D60mths |  0.28 (0.16) |
| Ethnicity: Mixed Caucasian | -0.69 (0.61) |
| Ethnicity: Non-Caucasian |  1.57 (0.86) |
| Gender: Female/Male |  0.03 (0.41) |
| Birth Weight |  0.00 (0.00) |
| Maternal Age at Birth | -0.08 (0.04) |
| PRSADHD×CES-Dpre |  0.27 (0.10)\*\* |
| PRSADHD×CES-D12mths |  0.11 (0.10) |
| CES-Dpre×CES-D12mths |  0.04 (0.05) |
| PRSADHD×CES-D60mths |  0.04 (0.10) |
| CES-Dpre×CES-D60mths | -0.02 (0.05) |
| PRSADHD×Ethnicity: Mixed Caucasian |  0.37 (0.39) |
| PRSADHD×Ethnicity: Non-Caucasian | -0.42 (0.42) |
| CES-Dpre×Ethnicity: Mixed Caucasian |  0.27 (0.18) |
| CES-Dpre×Ethnicity: Non-Caucasian | -0.33 (0.23) |
| PRSADHD×Gender: Female/Male |  0.23 (0.22) |
| CES-Dpre×Gender: Female/Male | -0.01 (0.12) |
| PRSADHD×Birth Weight |  0.00 (0.00) |
| CES-Dpre×Birth Weight |  0.00 (0.00) |
| PRSADHD×Maternal Age at Birth |  0.06 (0.02)\* |
| CES-Dpre×Maternal Age at Birth |  0.02 (0.01) |
|  | Model Fit |
| R2 |  0.310 |
| F (df) |  2.899 (24, 155)\*\*\* |
| BIC |  596.2 |

Table S2. Results for an extended regression models for internalizing problems. The extended model includes the PRSADHD, maternal CES-D scores during pregnancy (CES-Dpre), maternal CES-D scores at 12 months postpartum (CES-D12mths), maternal CES-D scores at 60 months postpartum (CES-D60mths), ethnicity, gender, birth weight, and maternal age at birth. It also includes interactions between PRSADHD or CES-Dpre and each term to control for potential confounding interactions with our variables of interest, following the recommendation by Keller (2014). BIC = Bayesian information criterion. \*p < 0.05, \*\*p < 0.01, \*\*\*p < 0.001

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| GO Domain | Term | Ratio | p-value | FDR |
| Cellular Component | neuron part | 536 / 1052 | 1.80E-11 | 2.02E-08 |
| cell periphery | 1383 / 2992 | 3.02E-11 | 2.02E-08 |
| plasma membrane bounded cell projection | 640 / 1290 | 7.33E-11 | 2.75E-08 |
| plasma membrane | 1352 / 2927 | 8.25E-11 | 2.75E-08 |
| cell projection | 656 / 1329 | 1.29E-10 | 3.43E-08 |
| neuron projection | 442 / 861 | 3.93E-10 | 8.74E-08 |
| postsynapse | 194 / 336 | 5.84E-10 | 1.11E-07 |
| dendrite | 239 / 430 | 8.97E-10 | 1.50E-07 |
| somatodendritic compartment | 321 / 605 | 1.43E-09 | 2.12E-07 |
| synapse | 329 / 623 | 1.76E-09 | 2.34E-07 |
| Biological Process | nervous system development | 873 / 1741 | 1.79E-13 | 2.07E-09 |
| generation of neurons | 603 / 1171 | 9.74E-12 | 5.61E-08 |
| neurogenesis | 635 / 1243 | 1.60E-11 | 6.14E-08 |
| system process | 609 / 1194 | 6.78E-11 | 1.95E-07 |
| signaling | 1432 / 3058 | 3.71E-10 | 8.54E-07 |
| regulation of cell projection organization | 290 / 527 | 1.21E-09 | 2.32E-06 |
| cognition | 180 / 304 | 1.47E-09 | 2.37E-06 |
| regulation of plasma membrane bounded cell projection organization | 288 / 524 | 1.64E-09 | 2.37E-06 |
| plasma membrane bounded cell projection morphogenesis | 238 / 422 | 2.14E-09 | 2.74E-06 |
| regulation of nervous system development | 365 / 687 | 2.39E-09 | 2.76E-06 |

Table S3. Gene Ontology enrichment analysis using the SNPs from the Best-Fit xPRS. Ratio is the number of network objects in the xPRS to the number of network objects in the Best-Fit PRSADHD. GO = Gene Ontology. FDR = False discovery rate corrected p-value.

SUPPLEMENTARY FIGURES



Figure S1. Association between child polygenic risk scores (PRS) for attention-deficit/hyperactivity disorder (ADHD) and ADHD symptoms in MAVAN. Child ADHD symptoms were assessed using the self-report Dominic Interactive Assessment at 72 months. The panels show the line of best fit between ADHD symptoms and PRS for ADHD at p-value thresholds of 0.001, 0.01, 0.1, 0.2, 0.27, 0.5, 0.7, and 1.0. The PRS in (A) were derived using the ADHD GWAS results from Neale et al. (2010). These scores were used for all analyses in the current study. The PRS in (B) were derived using the ADHD GWAS results of the cohort described by Demontis et al. (2019) which included European and Chinese participants. The PRS in (C) were derived using the ADHD GWAS results of the European subset from Demontis et al. (2019). The dashed line is the Best-Fit PRS at p-value threshold of 0.27 identified in the main interaction analyses of the current study. Overall, these plots illustrate that the PRS for ADHD using Neale et al. (2010) GWAS is a better predictor of ADHD symptoms in the MAVAN cohort. \*p < 0.05



Figure S2. Child polygenic risk score (PRSADHD) distribution across the population at p-value thresholds = 0.01, 0.1, 1.0 before (A) or after (B) adjustment for population structure. PT = P-value threshold.



Figure S3. P-value (A) and R2 (B) curve plots of child polygenic risk score for attention-deficit/hyperactivity disorder (PRSADHD) × maternal antenatal depression interaction model in the prediction of child total, internalizing, and externalizing problems. (A) Child PRSADHD (at p-value thresholds > 0.01) interacted with maternal antenatal depression to predict child total and internalizing problems but not externalizing problems. (B) Blue labels indicate the PRS p-value threshold with the greatest proportion of variance explained (highest R2 value i.e., the “Best-Fit” PRS). Solid red line: p = 0.05. Dashed red line: p = 0.01. Dotted red line: p = 0.001.



Figure S4. Gene Ontology enrichment of the interaction-based polygenic risk score (xPRS). The top ten terms from the results of the enrichment analysis of SNPs/genes within the xPRS and Cellular Components or Biological Processes are shown. P-values were calculated based on the proportion of network objects that coincide with the background network object list of the Best-Fit polygenic risk score for attention-deficit/hyperactivity disorder (PRSADHD).

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