**Associations Between Stress-Sensitivity Polygenic Risk Scores and Psychopathology in the Adolescent Brain Cognitive Development (ABCD) Study**

Kate Scheuer and Jennifer Forsyth

Department of Psychology, University of Washington

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**Introduction**

Adolescence is a time of significant growth and opportunity marked by changes with potentially lifelong consequences (Dahl et al., 2018). Mental health is an important aspect of adolescent development, and mental health concerns in adolescence have serious, long-lasting implications for psychological and physical health (Centers for Disease Control and Prevention, 2023). Adolescent psychiatric disorders are common, with a global prevalence of 25% (Silva et al., 2020), and many indicators of youth mental health have worsened over the past decade (Centers for Disease Control and Prevention, 2023).

Genetic risk and stressful environments are two key contributing factors to adolescent mental health. Psychiatric disorders are highly heritable, and large genome-wide association studies (GWAS) have played a key role in identifying genetic risk variants for disorders such as attention deficit hyperactivity disorder (ADHD), anxiety disorders, bipolar disorder, eating disorders, major depressive disorder (MDD), posttraumatic stress disorder (PTSD), and schizophrenia (ADHD Working Group of the Psychiatric Genomics Consortium (PGC) et al., 2019; Bourque et al., 2024; Howard et al., 2019; Lee et al., 2019; Levey et al., 2020; Nievergelt et al., 2024). Genetic risk for a given psychiatric disorder depends on variants across many different genomic regions, each of which individually have very small effect sizes. Polygenic risk scores (PRS) typically capture overall genetic risk by creating a weighted sum of risk variants identified by GWAS for a given trait. PRS can be used to better understand complex relationships between genetic variants and other biological and contextual risk factors for psychiatric disorders. When combined with other variables, PRS could potentially also be a useful component in clinical decision-making tools (Murray et al., 2021).

In addition to genetic influences on stress-related psychiatric disorders, there is strong evidence for the role of social and environmental stress exposure in the development of psychopathology. Likelihood of developing a psychiatric disorder increases as exposure to adversity increases, and children exposed to adverse experiences are approximately twice as likely to develop a mental disorder compared to unexposed peers (McLaughlin et al., 2019). Stress exposure is often assessed using self-report or interview-based measures such as the Adverse Childhood Experiences Questionnaire (ACE-Q), the Life Events Scale (LES), or the PTSD module of the Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS) (Felitti et al., 1998; Kobak et al., 2013; Tiet et al., 1998). Frequently, the number of stressful experiences to which an individual has been exposed is summed to generate a measure of cumulative stress exposure. While the specific types of adverse events identified in each measure vary, cumulative adverse event scores are generally associated with increased psychopathology. Higher scores on the ACE-Q were linked to increased levels of depression, drug abuse and alcoholism, and suicide attempts (Felitti et al., 1998). Increased negative lifetime event exposure quantified by the LES was associated with increased emotion-driven impulsivity, psychotic-like experiences, and externalizing and internalizing symptoms in adolescents (Barnhart et al., 2022; Karcher et al., 2022; Weiss et al., 2023). Finally, exposure to larger numbers of potentially traumatic events as measured with the KSADS PTSD module tended to increase adolescent risk for depression, anxiety, PTSD, oppositional defiant disorder, conduct disorder, ADHD, and suicidality (Thompson et al., 2022).

Broader family- and community-level factors can present additional stress exposures which further increase risk for psychopathology. School environmental factors such as engagement were significantly related to symptoms of internalizing, externalizing, anxiety, and depression in adolescents (Qiu & Liu, 2023; Thapaliya et al., 2021). Lower levels of household income and parental education and higher neighborhood poverty were also associated with increased externalizing symptoms (Maxwell et al., 2021; Teeuw et al., 2023). The exposome is designed to capture individual-level stressors such as cumulative adverse events as well as family- and community-level stressors, and higher exposome scores have been associated with increased psychopathology. For example, a study with over 11000 adolescents demonstrated that individuals with higher exposome scores based on 348 environmental variables tended to have higher levels of self- and parent-reported psychopathology. When combined with basic demographic information, a model including these exposome scores was able to capture 38.2% of the variance in the psychopathology p-factor (Hoffman et al., 2024; Moore et al., 2022).

One way that these environmental factors can impact psychopathology is through changes to the hypothalamic-pituitary-adrenal (HPA) axis. Transient changes in cortisol levels following an acute stressor can be adaptive. Typically, a stressful event activates the HPA axis and causes the hypothalamus to release corticotropin-releasing hormone (CRH) which stimulates release of adrenocorticotropic hormone and the subsequent release of cortisol from adrenal cortex (Palamarchuk et al., 2023). Cortisol binds to glucocorticoid receptors (GRs) and produces systemic changes in metabolism, cognition, and cardiovascular and immune function designed to prepare the body to address the source of stress (Dickerson & Kemeny, 2004). GR activation also creates negative feedback, decreasing HPA axis activity and returning the system to homeostasis (Jimeno & Rubalcaba, 2023). However, chronic or sustained stress can provoke longer-term, maladaptive changes in cortisol responses with negative physical and psychological consequences (Hoffman et al., 2024; Palamarchuk et al., 2023; Zorn et al., 2017). Repetitive stress exposure is a risk factor for psychological disorders such as anxiety, MDD, and schizophrenia (Zorn et al., 2017), and HPA axis hyperactivity has been linked to anxiety and depression (Palamarchuk et al., 2023). Abnormal HPA axis responsiveness was also associated with PTSD-like behavior in offspring of rats with unusually exaggerated or blunted responses to cortisol (Monari et al., 2024). Specific changes in HPA axis activity can differ based on sex, psychiatric disorder, and whether the disorder is active or in remission (Zorn et al., 2017).

Disrupted HPA axis function in individuals with psychiatric disorders has also been linked to changes in gene expression. Although there were no differences in baseline gene expression in glutamatergic neurons from combat veterans, exposure to a GR agonist provoked differential expression of 402 genes between cells derived from patients with and without PTSD, and these genes were enriched in postmortem brain tissue from individuals with PTSD (Seah et al., 2022). Additionally, PRS created based on gene changes following chronic glucocorticoid administration moderated the relationship between exposure to early life adversity and diagnoses of adult psychotic disorders (Arcego et al., 2024).

Penner-Goeke et al. (2022) leveraged HPA axis responses to the GR agonist dexamethasone to create an experimentally-derived stress-sensitivity genetic score. This score was associated with physiological stress responses and differentially-expressed genes in postmortem brain tissue of individuals with psychiatric disorders. Beginning with a set of 3,662 SNPs linked to dexamethasone responsiveness in a prior genome-wide expression quantitative trait locus (eQTL) analysis (Arloth et al., 2015), they identified 547 of these dexamethasone-responsive SNPs which were in regulatory elements (SNP-DREs). Transcripts associated with these SNP-DREs were enriched in postmortem cortical brain tissue from individuals with schizophrenia, autism spectrum disorder, MDD, bipolar disorder, and alcohol and substance use disorders. Penner-Goeke et al. (2022) then used Mendelian randomization based on a meta-GWAS of psychiatric disorders to select 79 of these SNP-DREs causally linked to psychiatric illness and created a weighted genetic score based on the SNP-DREs. Baseline cortisol levels did not differ based on genetic score, but subjects with higher scores had higher cortisol levels 30 minutes after completing a social stress task compared to subjects with lower scores. Higher genetic scores were also associated with increased eyeblink startle response magnitude and decreased startle habituation in a fear conditioning task. SNP-DREs have therefore been linked to psychiatric disorders via differential gene expression in postmortem tissue and physiological stress-sensitivity markers. A logical extension of this work is to examine whether PRS derived from the SNP-DREs used to create the genetic scores can be linked directly to psychiatric diagnoses and psychopathology. *RQ1:*  What relationship, if any, is there between an experimentally-derived stress-sensitivity PRS and psychiatric diagnoses and symptoms of psychopathology?

The proposed stress-sensitivity PRS is unique in that it captures experimentally-derived, genetic-based sensitivity to cortisol based on responses to the GR agonist dexamethasone, whereas PRS are typically created based on summary statistics from large GWAS. This standard approach is well-established, and prior work using data from adolescents has identified significant relationships between psychopathology and panic disorder, schizophrenia, MDD, ADHD, and externalizing disorder PRS (Lahey et al., 2024; Qiu & Liu, 2023; Teeuw et al., 2023; Wainberg et al., 2022). However, PRS created based on GWAS summary statistics rely on associations between genetic variants and the target trait which can make it difficult to identify causal variants and their associated underlying mechanisms. The stress-sensitivity PRS capitalizes on results of an experimental manipulation, thus illuminating a mechanistic pathway between the identified variants (SNP-DREs) and outcomes significantly associated with the PRS. The second research question in this study compares the experimentally-derived stress-sensitivity PRS and standard, GWAS-derived PRS. *RQ2:* How does the variance in psychiatric diagnoses or symptoms of psychopathology explained by an experimentally-derived stress-sensitivity PRS compare to that explained by PRS for psychiatric disorders calculated based on GWAS summary statistics?

In addition to additive genetic and environmental effects on psychopathology, prior work has demonstrated a role of gene by environment interactions in psychiatric symptoms and diagnoses. For example, internalizing and externalizing scores for adolescents were best explained by models including genome-exposome interactions (Choi et al., 2022). MDD PRS and anxiety PRS also interacted with measures of stress such that there was a stronger relationship between PRS and depression or anxiety symptoms, respectively, for individuals exposed to higher levels of stress (Wang et al., 2023). Interactions between a genetic score based on four HPA axis genes (which encode GRs, a CRH receptor, and a co-chaperone which inhibits GR activity (Palamarchuk et al., 2023)) and environmental factors were also associated with adolescent symptoms of depression and anxiety. Higher levels of childhood maltreatment were linked with increased comorbid depression and anxiety symptoms in individuals with high levels, but not those with low levels, of this HPA axis-related genetic score (Cao et al., 2024). Given the impact of gene by environment interactions on psychopathology, the final research question of this study explores potential interactions between the stress-sensitivity PRS and environmental factors. *RQ3:* How do environmental factors as defined by the exposome or by a cumulative adverse event score affect the relationships between stress-sensitivity or psychiatric disorder PRS and psychopathology?

Overall, the proposed study uniquely approaches the relationship between genetics and psychopathology by using an experimentally-derived stress-sensitivity PRS. By directly investigating the relationship between the stress-sensitivity PRS and psychopathology (RQ1), it extends prior work which indirectly linked these variables based on changes in postmortem brain tissue of individuals with psychiatric disorders and physiological markers of stress reactivity which differed based on subject PRS. This study also takes a novel approach to examining links between genetics and psychiatric outcomes by comparing the experimentally-derived stress-sensitivity PRS with more traditional PRS created based on GWAS summary statistics (RQ2). Finally, the present study furthers our understanding of the role of gene by environment interactions on psychopathology by analyzing the combined effects of the stress-sensitivity PRS and two different types of environmental measures (RQ3).

**Methods**

**Sample description**

To address the above questions, the present investigation will use data from the Adolescent Brain Cognitive Development (ABCD) Study, an attractive data source due to its large sample size, demographically diverse subject pool, and extensive data collection. The ABCD Study is an ongoing, longitudinal study which sampled adolescents from across the United States. Subject composition is similar to national demographic composition in terms of race, ethnicity, urbanicity, and sex (Compton et al., 2019). Data are available for 11868 adolescents at baseline when participants were 9-10 years old, and sample attrition has been relatively low (participants at year one: 11220, year two: 10973, year three: 10336). While the full data set for the year four follow-up visit has not been released (data currently available for 3718 participants), based on prior attrition, information should be available for about 9826 adolescents and is expected to be released by the end of the year. The proposed study will use outcome measures from year four follow-up visits, as preliminary data suggest that prevalence for psychopathology is much greater in year four compared to earlier timepoints. In year four, youth participants were 52.82% male, 47.15% female, and 0.02% intersex. Youth parent-reported race was: 79.44% White, 16.10% Black/African American, 0.04% Alaska Native, 0.15% Native Hawaiian, 0.02% Guamanian, 0.09% Samoan, 0.26% other Pacific Islander, 0.92% Asian/Indian, 1.96% Chinese, 1.45% Filipino, 0.75% Japanese, 0.94% Korean, and 0.38% Vietnamese. Combined family household incomes pre-tax were as follows: 1.86% less than $5,000; 1.69% $5,000 through $11,999; 1.43% $12.000 through $15,999; 3.25% $16,000 through $24.999; 4.14% $25,000 through $34,999; 6.56% $35,000 through $49,999; 10.84% $50,000 through $74,999; 12.64% $75,000 through $99,999; 32.92% $100,000 through $199,999; and 16.03% $200,000 and greater.

**Genetics**

Genetic material was collected primarily through saliva, though some participants provided blood samples. Genotyping was performed with Affymetrix Axiom Smokescreen Arrays, and coordinates were aligned with Human Genome hg19 build. The ABCD Data Analysis, Informatics, and Resource Center performed quality control which included removal of variants with more than 10% missingness and removal of subjects with more than 20% missing calls or excessive relatedness (Fan et al., 2023).

**Measures**

***Child Behavior Checklist (CBCL)***

The CBCL is part of the Achenbach System of Empirically Based Assessment and measures emotional and behavioral problems in youth (T. M. Achenbach, 2009). Responses to 113 items are grouped into eight subscales (rule-breaking, aggression, withdrawn/depressed, anxious/depressed, somatic, attention problems, thought problems, and social problems) as well as composite scores for internalizing (withdrawn/depressed, anxious/depressed, and somatic subscales), externalizing (rule-breaking and aggression subscales), and total problems (all subscales). Scores are t-scored based on a mean of 50 points and a standard deviation of 10 points. Values between 65 and 69 are considered subclinical, while scores of 70 or more suggest clinically significant problems. Externalizing, internalizing, and total scores have high internal consistency (Cronbach’s α: .94) and high test-retest reliability (r = .92) (T. Achenbach, 2011). CBCL scores in the ABCD Study reflect caregiver assessments as it was not administered to youth.

***Kiddie Schedule for Affective Disorders and Schizophrenia Version for DSM-5 (KSADS-5)***

The KSADS-5 is a standardized interview with items based on DSM-5 criteria for psychiatric disorders including MDD, ADHD, PTSD, and a variety of anxiety disorders (Kobak et al., 2013). It has good internal reliability (Cronbach’s α = .91) and convergent validity with clinician-administered scales such as the CBCL (Townsend et al., 2020). It also has adequate test-retest reliability (κ = .63 to 1.00) (Kaufman et al., 1997). The present study considers both past and present diagnoses and includes information from both youth and caregiver reports when available. ADHD and PTSD items were not administered to youth.

**Ancestry**

Principal component analysis was performed on unpruned ABCD data using PLINK (Purcell et al., 2007). Prior work identified the first eight principal components (PCs) as the optimal number to account for ancestry in this sample (J. Zhu and M. Hyat, personal communication, February 2024). Samples were separated into three ancestry groups (African, American admixed, and European) using a random forest model derived by combining the ABCD dataset with the HapMap3 reference dataset and using population labels from the HapMap3 to assign continental super-population level ancestry labels with a probability threshold of 0.7 (J. Zhu and M. Hyat, personal communication, February 2024). After applying this threshold, genetic data was available for 3307 participants (2299 European ancestry, 517 African ancestry, 491 American admixed ancestry) in the currently released version of year four data.

**Genetic Relatedness**

To account for genetic relatedness between participants, genetic relatedness matrices (GRMs) were calculated for each ancestry using PLINK (Purcell et al., 2007) based on unpruned ABCD data (J. Zhu and M. Hyat, personal communication, February 2024).

**Polygenic Risk Scores (PRS)**

Stress-sensitivity PRS used for the preliminary results included here were generated with PLINK (Purcell et al., 2007) based on summary statistics from Penner-Goeke et al. (2023). Briefly, a data frame containing risk alleles and their associated effect sizes for each SNP was provided to PLINK, and PLINK then calculated the sum of the risk alleles for each participant weighted by effect size.

Final results will compare stress-sensitivity PRS to PRS for MDD, ADHD, PTSD, and anxiety disorders calculated based on summary statistics from Howard et al. (2019), ADHD Working Group of the Psychiatric Genomics Consortium (PGC) et al. (2019), Nievergelt et al. (2024), and Otowa et al. (2016) respectively. To improve PRS accuracy across ancestry groups, final results will use a more sophisticated method to generate PRS for anxiety, MDD, PTSD, and ADHD (i.e., PRS-Csx (Ruan et al., 2022), BridgePRS (Hoggart et al., 2024), or SBayesRC (Zheng et al., 2024), which incorporate summary statistics across GWAS from multiple ancestry populations and/or biological annotations of SNPs to refine effect size estimates per SNP). These techniques are not applicable to the stress-sensitivity PRS because it was generated experimentally based on results from individuals of unknown ancestry.

**Analysis**

Using the *R* package GENESIS (Gogarten et al., 2019), linear regression will be performed with scores from each of the eight CBCL subscales. Logistic regression was also be performed with lifetime diagnosis of MDD, ADHD, PTSD, and any anxiety disorder other than specific phobia as outcomes. Study site and genetic relatedness (quantified with GRMs) will be modeled as random effects. Subject sex, age, and the first eight ancestry PCs will be fixed effect covariates. Analysis code will be available in a Github repository.

**Preliminary Results: RQ1**

***Psychopathology-related Symptoms and Behavior***

For individuals of European ancestry, stress-sensitivity PRS was nominally significantly associated with somatic-related symptoms on the CBCL somatic subscale (uncorrected p-value = 0.022, FDR corrected p-value = 0.26), with an increase of 0.281 points for each standard deviation increase in stress-sensitivity PRS. No other CBCL subscale scores were significantly or nominally associated with stress-sensitivity PRS. Compared to average values, girls’ scores were 0.49 points higher on the anxious-depressed (FDR corrected p-value = 0.00058) and 0.40 points higher on the somatic (FDR corrected p-value = 0.0037) subscales, and they were 0.26 points lower on the aggression subscale (FDR corrected p-value = 0.0090). Age did not significantly impact any CBCL scores.

For subjects of African ancestry, CBCL scores did not significantly differ based on stress-sensitivity PRS, sex, or age.

Finally, for individuals of American admixed ancestry, stress-sensitivity PRS was nominally associated with changes in withdrawn-depressed CBCL scores, and a one standard deviation increase in stress-sensitivity PRS was linked to a decrease of 0.67 points on the withdrawn-depressed subscale (uncorrected p-value = 0.026, FDR corrected p-value = 0.32). Stress-sensitivity PRS was not significantly associated with any other CBCL scores. Sex was nominally significantly associated with some CBCL scores. Compared to average values, anxious-depressed and somatic scores for girls were 0.54 points (uncorrected p-value = 0.032, FDR corrected p-value = 0.095), and 0.63 points (uncorrected p-value = 0.018, FDR corrected p-value = 0.073) higher, respectively. Age was not significantly related to any CBCL scores.

***Lifetime Psychiatric Diagnoses***

For individuals of European ancestry, there were no significant relationships between stress-sensitivity PRS or age and any diagnosis. Compared to average values, girls had an increase of 1.48 in odds of receiving a lifetime anxiety diagnosis (FDR corrected p-value = 0.00000000013), an increase of 1.63 in odds of receiving a lifetime MDD diagnosis (FDR corrected p-value = 0.00000000013), and a decrease of 0.72 in odds of receiving a lifetime ADHD diagnosis (FDR corrected p-value = 0.0086). Sex was not significantly associated with lifetime PTSD diagnosis.

For subjects of African ancestry, stress-sensitivity PRS, sex, and age were not significantly associated with likelihood of receiving a lifetime anxiety, ADHD, MDD, or PTSD diagnosis, with the exception that girls had a nominally significant (uncorrected p-value = 0.025, FDR corrected p-value = 0.30) increase of 1.44 in odds of receiving a lifetime MDD diagnosis compared to average values.

Finally, for subjects of American admixed ancestry, stress-sensitivity PRS was not significantly associated with the likelihood of receiving any lifetime diagnosis. For girls, odds of receiving a diagnosis of anxiety or MDD were 1.66 points (FDR corrected p-value = 0.0091) or 1.75 points (FDR corrected p-value = 0.0091) higher on average, respectively. Odds of receiving a lifetime diagnosis of ADHD were also 0.44 points lower on average for girls, but this difference did not survive FDR correction (uncorrected p-value = 0.046, FDR corrected p-value = 0.11). Sex did not significantly affect likelihood of receiving a lifetime PTSD diagnosis. A one standard deviation increase in age was nominally associated (uncorrected p-value = 0.0063, FDR corrected p-value = 0.076) with an increase of 2.69 points in odds of receiving a lifetime MDD diagnosis. Age did not affect likelihood of receiving a lifetime diagnosis of anxiety, ADHD, or PTSD.

**Discussion**

**Anticipated findings**

Based on work in the ABCD Study at baseline, for individuals of European ancestry, MDD PRS is expected to be significantly associated with anxious/depressed, somatic, social, thought, attention, and rule-breaking, but not aggressive or withdrawn/depressed, CBCL subscale scores (Wainberg et al., 2022). Wainberg et al. (2022) also reported that ADHD PRS was significantly associated with only the attention subscale. We expect to replicate these results in data from year four follow-up visits. Hoffman et al. (2024) identified a significant relationship between PTSD PRS and CBCL total problems in individuals of European ancestry using data from year three follow-up visits but did not report results on any CBCL subscale scores. We therefore expect PTSD PRS to be linked with at least one CBCL subscale score.

Across individuals of all ancestries at baseline, Qiu and Liu (2023) did not find significant relationships between PRS for overall anxiety, social anxiety, panic, or phobia and externalizing or internalizing CBCL scores. Based on these findings, we do not expect to find significant associations between anxiety PRS and any CBCL subscale scores.

Published work on the relationship between PRS for psychiatric disorders and psychopathology is much more sparse for individuals of non-European compared to European ancestries. For example, the expected results for MDD and ADHD PRS described above are based on work from Wainberg et al. (2022), who restricted their analysis to individuals of European ancestry only due to “regrettably poor performance of polygenic risk scores calculated from European GWAS to predict psychopathology in non-white individuals.” While a recently-published report on PRS and psychopathology in the ABCD Study included participants of non-European ancestry, the method used to calculate PRS did not specifically account for differences in linkage disequilibrium based on ancestry, and results were not reported separately based on ancestry. Notably, Hoffman et al. (2024) examined the link between MDD PRS and CBCL total problems scores in individuals of African ancestry and failed to find a significant relationship. However, they did not examine CBCL subscale scores, psychiatric diagnoses, or results for individuals of admixed American ancestry.

The generally worse performance of PRS for individuals of non-European compared to European ancestry is believed to mainly reflect methodological limitations, largely due to lower representation of diverse ancestry groups in existing GWAS, rather than genuine genetic differences in causal variants (Hu et al., 2023). Because the stress-sensitivity PRS is experimentally determined rather than reliant on GWAS in which European ancestry individuals are typically over-represented, we expect the stress-sensitivity PRS to explain more of the variation in HPA axis-related psychopathology compared to PRS derived from GWAS summary statistics for individuals of non-European ancestry.

Previous work suggests that gene by environment interactions affect psychopathology measures from participants in the ABCD Study. Choi et al. (2022) found that best-fitting models of CBCL externalizing scores included genetic, environment, and gene by environmental effects for individuals of European, African, or American Admixed ancestry. Best-fitting models of CBCL internalizing also included main effects of genes and environment and a gene by environment interaction for subjects of European and African ancestry but not those of American Admixed ancestry. Environmental effects included cumulative exposure to negative life events and proximal contextual factors such as school environment. A recent study from Rea-Sandin et al. (2024) also identified significant effects of gene by environment interactions on psychopathology of youth in the ABCD Study, with family cultural values significantly interacting with additive genetic effects to influence parent-reported youth externalizing, but not internalizing, symptoms. We therefore expect to find significant interactions between stress-sensitivity PRS and environmental measures, though these results may vary based on subject ancestry as in Choi et al. (2022).

**Limitations**

The sample used to perform the eQTL analysis which formed the basis of the stress-sensitivity PRS was small and homogenous (164 Caucasian men from Munich, Germany), which potentially limits its external validity (Arloth et al., 2015). Additionally, ancestry was not reported for the subjects in which the stress-sensitivity PRS was significantly linked to physiological stress responses (Penner-Goeke et al., 2023). However, unlike most PRS which are created based on GWAS summary statistics and are more susceptible to inaccuracies due to linkage disequilibrium differences based on ancestry, the stress-sensitivity PRS was experimentally developed and may therefore be more likely to accurately capture causal variants. As discussed above, causal variants are often consistent across different ancestry groups, though this is not always the case (Hu et al., 2023).

Another potential limitation of the study relies on the release schedule of ABCD Study data. PRS effect sizes tend to be small, necessitating large samples to detect effects. At this time, approximately half of the data from ABCD Study year four follow-up visits has been released, and usable data is currently available for 3718 participants. Acquiring data for the remainder of ABCD Study participants will be an important step in increasing detection power in this study.

**Potential implications**

The proposed study approaches the relationship between genetic variants and psychopathology from the unique angle of an experimentally-derived PRS. It aims to Illuminate the potential utility of this experimentally-derived PRS to identify HPA axis-related genetic variants linked with psychiatric disorders. More broadly, it may demonstrate the utility of developing PRS experimentally to suggest more direct, mechanistic pathways between genes and psychiatric disorders.

**References**

Achenbach, T. (2011). *Encyclopedia of Clinical Neuropsychology*.

Achenbach, T. M. (2009). *The Achenbach system of empirically based assessment (ASEBA): Development, findings, theory, and applications*. University of Vermont, Research Center for Children, Youth, & Families.

ADHD Working Group of the Psychiatric Genomics Consortium (PGC), Early Lifecourse & Genetic Epidemiology (EAGLE) Consortium, 23andMe Research Team, Demontis, D., Walters, R. K., Martin, J., Mattheisen, M., Als, T. D., Agerbo, E., Baldursson, G., Belliveau, R., Bybjerg-Grauholm, J., Bækvad-Hansen, M., Cerrato, F., Chambert, K., Churchhouse, C., Dumont, A., Eriksson, N., Gandal, M., … Neale, B. M. (2019). Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. *Nature Genetics*, *51*(1), 63–75. https://doi.org/10.1038/s41588-018-0269-7

Arcego, D. M., Buschdorf, J.-P., O’Toole, N., Wang, Z., Barth, B., Pokhvisneva, I., Rayan, N. A., Patel, S., De Mendonça Filho, E. J., Lee, P., Tan, J., Koh, M. X., Sim, C. M., Parent, C., De Lima, R. M. S., Clappison, A., O’Donnell, K. J., Dalmaz, C., Arloth, J., … Meaney, M. J. (2024). A Glucocorticoid-Sensitive Hippocampal Gene Network Moderates the Impact of Early-Life Adversity on Mental Health Outcomes. *Biological Psychiatry*, *95*(1), 48–61. https://doi.org/10.1016/j.biopsych.2023.06.028

Arloth, J., Bogdan, R., Weber, P., Frishman, G., Menke, A., Wagner, K. V., Balsevich, G., Schmidt, M. V., Karbalai, N., Czamara, D., Altmann, A., Trümbach, D., Wurst, W., Mehta, D., Uhr, M., Klengel, T., Erhardt, A., Carey, C. E., Conley, E. D., … Sullivan, P. F. (2015). Genetic Differences in the Immediate Transcriptome Response to Stress Predict Risk-Related Brain Function and Psychiatric Disorders. *Neuron*, *86*(5), 1189–1202. https://doi.org/10.1016/j.neuron.2015.05.034

Barnhart, S., Garcia, A. R., & Karcher, N. R. (2022). Adolescent Mental Health and Family Economic Hardships: The Roles of Adverse Childhood Experiences and Family Conflict. *Journal of Youth and Adolescence*, *51*(12), 2294–2311. https://doi.org/10.1007/s10964-022-01671-9

Bourque, V.-R., Poulain, C., Proulx, C., Moreau, C. A., Joober, R., Forgeot d’Arc, B., Huguet, G., & Jacquemont, S. (2024). Genetic and phenotypic similarity across major psychiatric disorders: A systematic review and quantitative assessment. *Translational Psychiatry*, *14*(1), 171. https://doi.org/10.1038/s41398-024-02866-3

Cao, C., Chen, M., Yang, S., Xu, Y., & Gu, J. (2024). Childhood maltreatment, multilocus HPA-axis genetic variation and adolescent comorbidity profiles of depressive and anxiety symptoms. *Child Abuse & Neglect*, *149*, 106683. https://doi.org/10.1016/j.chiabu.2024.106683

Centers for Disease Control and Prevention,. (2023). *Youth Risk Behavior Survey Data Summary & Trends Report: 2011-2021*.

Choi, K. W., Wilson, M., Ge, T., Kandola, A., Patel, C. J., Lee, S. H., & Smoller, J. W. (2022). Integrative analysis of genomic and exposomic influences on youth mental health. *Journal of Child Psychology and Psychiatry*, *63*(10), 1196–1205. https://doi.org/10.1111/jcpp.13664

Compton, W. M., Dowling, G. J., & Garavan, H. (2019). Ensuring the Best Use of Data: The Adolescent Brain Cognitive Development Study. *JAMA Pediatrics*, *173*(9), 809. https://doi.org/10.1001/jamapediatrics.2019.2081

Dahl, R. E., Allen, N. B., Wilbrecht, L., & Suleiman, A. B. (2018). Importance of investing in adolescence from a developmental science perspective. *Nature*, *554*(7693), 441–450. https://doi.org/10.1038/nature25770

Dickerson, S. S., & Kemeny, M. E. (2004). Acute Stressors and Cortisol Responses: A Theoretical Integration and Synthesis of Laboratory Research. *Psychological Bulletin*, *130*(3), 355–391. https://doi.org/10.1037/0033-2909.130.3.355

Fan, C. C., Loughnan, R., Wilson, S., Hewitt, J. K., ABCD Genetic Working Group, Agrawal, A., Dowling, G., Garavan, H., LeBlanc, K., Neale, M., Friedman, N., Madden, P., Little, R., Brown, S. A., Jernigan, T., & Thompson, W. K. (2023). Genotype Data and Derived Genetic Instruments of Adolescent Brain Cognitive Development Study® for Better Understanding of Human Brain Development. *Behavior Genetics*, *53*(3), 159–168. https://doi.org/10.1007/s10519-023-10143-0

Felitti, V. J., Anda, R. F., Nordenberg, D., Williamson, D. F., Spitz, A. M., Edwards, V., Koss, M. P., & Marks, J. S. (1998). Relationship of Childhood Abuse and Household Dysfunction to Many of the Leading Causes of Death in Adults. *American Journal of Preventive Medicine*, *14*(4), 245–258. https://doi.org/10.1016/S0749-3797(98)00017-8

Gogarten, S. M., Sofer, T., Chen, H., Yu, C., Brody, J. A., Thornton, T. A., Rice, K. M., & Conomos, M. P. (2019). Genetic association testing using the GENESIS R/Bioconductor package. *Bioinformatics*, *35*(24), 5346–5348. https://doi.org/10.1093/bioinformatics/btz567

Hoffman, K. W., Tran, K. T., Moore, T. M., Gataviņš, M. M., Visoki, E., Kwon, O., DiDomenico, G. E., Chaiyachati, B. H., Schultz, L. M., Almasy, L., Hayes, M. R., Daskalakis, N. P., & Barzilay, R. (2024). Exposomic and polygenic contributions to allostatic load in early adolescence. *Nature Mental Health*, 1–12. https://doi.org/10.1038/s44220-024-00255-9

Hoggart, C. J., Choi, S. W., García-González, J., Souaiaia, T., Preuss, M., & O’Reilly, P. F. (2024). BridgePRS leverages shared genetic effects across ancestries to increase polygenic risk score portability. *Nature Genetics*, *56*(1), 180–186. https://doi.org/10.1038/s41588-023-01583-9

Howard, D. M., Adams, M. J., Clarke, T.-K., Hafferty, J. D., Gibson, J., Shirali, M., Coleman, J. R. I., Hagenaars, S. P., Ward, J., Wigmore, E. M., Alloza, C., Shen, X., Barbu, M. C., Xu, E. Y., Whalley, H. C., Marioni, R. E., Porteous, D. J., Davies, G., Deary, I. J., … McIntosh, A. M. (2019). Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. *Nature Neuroscience*, *22*(3), 343–352. https://doi.org/10.1038/s41593-018-0326-7

Hu, S., Ferreira, L. A. F., Shi, S., Hellenthal, G., Marchini, J., Lawson, D. J., & Myers, S. R. (2023). *Leveraging fine-scale population structure reveals conservation in genetic effect sizes between human populations across a range of human phenotypes*. https://doi.org/10.1101/2023.08.08.552281

Jimeno, B., & Rubalcaba, J. G. (2023). Modelling the role of glucocorticoid receptor as mediator of endocrine responses to environmental challenge. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *379*(1898), 20220501. https://doi.org/10.1098/rstb.2022.0501

Karcher, N. R., Klaunig, M. J., Elsayed, N. M., Taylor, R. L., Jay, S. Y., & Schiffman, J. (2022). Understanding Associations Between Race/Ethnicity, Experiences of Discrimination, and Psychotic-like Experiences in Middle Childhood. *Journal of the American Academy of Child & Adolescent Psychiatry*, *61*(10), 1262–1272. https://doi.org/10.1016/j.jaac.2022.03.025

Kaufman, J., Birmaher, B., Brent, D., Rao, U., Flynn, C., Moreci, P., Williamson, D., & Ryan, N. (1997). Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): Initial Reliability and Validity Data. *Journal of the American Academy of Child & Adolescent Psychiatry*, *36*(7), 980–988. https://doi.org/10.1097/00004583-199707000-00021

Kobak, K. A., Kratochvil, C. J., Stanger, C., & Kaufman, J. (2013). Computerized screening of comorbidity in adolescents with substance or psychiatric disorders. *Anxiety Disorders and Depression.(La Jolaa, CA)*.

Lahey, B. B., Durham, E. L., Brislin, S. J., Barr, P. B., Dick, D. M., Moore, T. M., Pierce, B. L., Tong, L., Reimann, G. E., Jeong, H. J., Dupont, R. M., & Kaczkurkin, A. N. (2024). Mapping potential pathways from polygenic liability through brain structure to psychological problems across the transition to adolescence. *Journal of Child Psychology and Psychiatry*, jcpp.13944. https://doi.org/10.1111/jcpp.13944

Lee, P. H., Anttila, V., Won, H., Feng, Y.-C. A., Rosenthal, J., Zhu, Z., Tucker-Drob, E. M., Nivard, M. G., Grotzinger, A. D., Posthuma, D., Wang, M. M.-J., Yu, D., Stahl, E. A., Walters, R. K., Anney, R. J. L., Duncan, L. E., Ge, T., Adolfsson, R., Banaschewski, T., … Smoller, J. W. (2019). Genomic Relationships, Novel Loci, and Pleiotropic Mechanisms across Eight Psychiatric Disorders. *Cell*, *179*(7), 1469-1482.e11. https://doi.org/10.1016/j.cell.2019.11.020

Levey, D. F., Gelernter, J., Polimanti, R., Zhou, H., Cheng, Z., Aslan, M., Quaden, R., Concato, J., Radhakrishnan, K., Bryois, J., Sullivan, P. F., the Million Veteran Program, & Stein, M. B. (2020). Reproducible Genetic Risk Loci for Anxiety: Results From ∼200,000 Participants in the Million Veteran Program. *American Journal of Psychiatry*, *177*(3), 223–232. https://doi.org/10.1176/appi.ajp.2019.19030256

Maxwell, M. Y., Taylor, R. L., & Barch, D. M. (2021, May 1). *Evidence That Neighborhood Threat and Brain Volume Mediate the Relationship Between Neighborhood Poverty and Children’s Psychopathology* [Poster].

McLaughlin, K. A., Weissman, D., & Bitrán, D. (2019). Childhood Adversity and Neural Development: A Systematic Review. *Annual Review of Developmental Psychology*, *1*(1), 277–312. https://doi.org/10.1146/annurev-devpsych-121318-084950

Monari, S., Guillot De Suduiraut, I., Grosse, J., Zanoletti, O., Walker, S. E., Mesquita, M., Wood, T. C., Cash, D., Astori, S., & Sandi, C. (2024). Blunted Glucocorticoid Responsiveness to Stress Causes Behavioral and Biological Alterations That Lead to Posttraumatic Stress Disorder Vulnerability. *Biological Psychiatry*, *95*(8), 762–773. https://doi.org/10.1016/j.biopsych.2023.09.015

Moore, T. M., Visoki, E., Argabright, S. T., Didomenico, G. E., Sotelo, I., Wortzel, J. D., Naeem, A., Gur, R. C., Gur, R. E., Warrier, V., Guloksuz, S., & Barzilay, R. (2022). Modeling environment through a general exposome factor in two independent adolescent cohorts. *Exposome*, *2*(1), osac010. https://doi.org/10.1093/exposome/osac010

Murray, G. K., Lin, T., Austin, J., McGrath, J. J., Hickie, I. B., & Wray, N. R. (2021). Could Polygenic Risk Scores Be Useful in Psychiatry?: A Review. *JAMA Psychiatry*, *78*(2), 210. https://doi.org/10.1001/jamapsychiatry.2020.3042

Nievergelt, C. M., Maihofer, A. X., Atkinson, E. G., Chen, C.-Y., Choi, K. W., Coleman, J. R. I., Daskalakis, N. P., Duncan, L. E., Polimanti, R., Aaronson, C., Amstadter, A. B., Andersen, S. B., Andreassen, O. A., Arbisi, P. A., Ashley-Koch, A. E., Austin, S. B., Avdibegoviç, E., Babić, D., Bacanu, S.-A., … Koenen, K. C. (2024). Genome-wide association analyses identify 95 risk loci and provide insights into the neurobiology of post-traumatic stress disorder. *Nature Genetics*, *56*(5), 792–808. https://doi.org/10.1038/s41588-024-01707-9

Otowa, T., Hek, K., Lee, M., Byrne, E. M., Mirza, S. S., Nivard, M. G., Bigdeli, T., Aggen, S. H., Adkins, D., Wolen, A., Fanous, A., Keller, M. C., Castelao, E., Kutalik, Z., Der Auwera, S. V., Homuth, G., Nauck, M., Teumer, A., Milaneschi, Y., … Hettema, J. M. (2016). Meta-analysis of genome-wide association studies of anxiety disorders. *Molecular Psychiatry*, *21*(10), 1391–1399. https://doi.org/10.1038/mp.2015.197

Palamarchuk, I. S., Slavich, G. M., Vaillancourt, T., & Rajji, T. K. (2023). Stress-related cellular pathophysiology as a crosstalk risk factor for neurocognitive and psychiatric disorders. *BMC Neuroscience*, *24*(1), 65. https://doi.org/10.1186/s12868-023-00831-2

Penner-Goeke, S., Bothe, M., Kappelmann, N., Kreitmaier, P., Kaya, E., Pöhlchen, D., Kühnel, A., Czamara, D., BeCOME working group, Glaser, L. V., Roeh, S., Ködel, M., Monteserin-Garcia, J., Rummel, C., Arloth-Knauer, J., Diener-Hölzl, L., Woelfel, B., Sauer, S., Riesenberg, S., … Binder, E. B. (2022). *Assessment of glucocorticoid-induced enhancer activity of eSNP regions using STARR-seq reveals novel molecular mechanisms in psychiatric disorders* [Preprint]. Genetic and Genomic Medicine. https://doi.org/10.1101/2022.05.18.22275090

Penner-Goeke, S., Bothe, M., Rek, N., Kreitmaier, P., Pöhlchen, D., Kühnel, A., Glaser, L. V., Kaya, E., Krontira, A. C., Röh, S., Czamara, D., Ködel, M., Monteserin-Garcia, J., Diener, L., Wölfel, B., Sauer, S., Rummel, C., Riesenberg, S., Arloth-Knauer, J., … Binder, E. B. (2023). High-throughput screening of glucocorticoid-induced enhancer activity reveals mechanisms of stress-related psychiatric disorders. *Proceedings of the National Academy of Sciences*, *120*(49), e2305773120. https://doi.org/10.1073/pnas.2305773120

Purcell, S., Neale, B., Todd-Brown, K., Thomas, L., Ferreira, M. A. R., Bender, D., Maller, J., Sklar, P., de Bakker, P. I. W., Daly, M. J., & Sham, P. C. (2007). PLINK: A Tool Set for Whole-Genome Association and Population-Based Linkage Analyses. *American Journal of Human Genetics*, *81*(3), 559–575.

Qiu, A., & Liu, C. (2023). Pathways link environmental and genetic factors with structural brain networks and psychopathology in youth. *Neuropsychopharmacology*, *48*(7), 1042–1051. https://doi.org/10.1038/s41386-023-01559-7

Rea-Sandin, G., Del Toro, J., & Wilson, S. (2024). The Heritability of Psychopathology Symptoms in Early Adolescence: Moderation by Family Cultural Values in the ABCD Study. *Behavior Genetics*, *54*(1), 119–136. https://doi.org/10.1007/s10519-023-10154-x

Ruan, Y., Lin, Y.-F., Feng, Y.-C. A., Chen, C.-Y., Lam, M., Guo, Z., Stanley Global Asia Initiatives, Ahn, Y. M., Akiyama, K., Arai, M., Baek, J. H., Chen, W. J., Chung, Y.-C., Feng, G., Fujii, K., Glatt, S. J., Ha, K., Hattori, K., Higuchi, T., … Ge, T. (2022). Improving polygenic prediction in ancestrally diverse populations. *Nature Genetics*, *54*(5), 573–580. https://doi.org/10.1038/s41588-022-01054-7

Seah, C., Breen, M. S., Rusielewicz, T., Bader, H. N., Xu, C., Hunter, C. J., McCarthy, B., Deans, P. J. M., Chattopadhyay, M., Goldberg, J., Desarnaud, F., Makotkine, I., Flory, J. D., Bierer, L. M., Staniskyte, M., NYSCF Global Stem Cell Array® Team, Bauer, L., Brenner, K., Buckley-Herd, G., … Yehuda, R. (2022). Modeling gene × environment interactions in PTSD using human neurons reveals diagnosis-specific glucocorticoid-induced gene expression. *Nature Neuroscience*, *25*(11), 1434–1445. https://doi.org/10.1038/s41593-022-01161-y

Silva, S. A., Silva, S. U., Ronca, D. B., Gonçalves, V. S. S., Dutra, E. S., & Carvalho, K. M. B. (2020). Common mental disorders prevalence in adolescents: A systematic review and meta-analyses. *PLOS ONE*, *15*(4), e0232007. https://doi.org/10.1371/journal.pone.0232007

Teeuw, J., Mota, N. R., Klein, M., Blankenstein, N. E., Tielbeek, J. J., Jansen, L. M. C., Franke, B., & Hulshoff Pol, H. E. (2023). Polygenic risk scores and brain structures both contribute to externalizing behavior in childhood—A study in the Adolescent Brain and Cognitive Development (ABCD) cohort. *Neuroscience Applied*, *2*, 101128. https://doi.org/10.1016/j.nsa.2023.101128

Thapaliya, B., Calhoun, V. D., & Liu, J. (2021). Environmental and genome-wide association study on children anxiety and depression. *2021 IEEE International Conference on Bioinformatics and Biomedicine (BIBM)*, 2330–2337. https://doi.org/10.1109/BIBM52615.2021.9669291

Thompson, E. L., Lever, N. A., Connors, K. M., Cloak, C. C., Reeves, G., & Chang, L. (2022). Associations between potentially traumatic events and psychopathology among preadolescents in the Adolescent Brain and Cognitive Development Study ®. *Journal of Traumatic Stress*, *35*(3), 852–867. https://doi.org/10.1002/jts.22793

Tiet, Q. Q., Bird, H. R., Davies, M., Hoven, C., Cohen, P., Jensen, P. S., & Goodman, S. (1998). Adverse Life Events and Resilience. *Journal of the American Academy of Child & Adolescent Psychiatry*, *37*(11), 1191–1200. https://doi.org/10.1097/00004583-199811000-00020

Townsend, L., Kobak, K., Kearney, C., Milham, M., Andreotti, C., Escalera, J., Alexander, L., Gill, M. K., Birmaher, B., Sylvester, R., Rice, D., Deep, A., & Kaufman, J. (2020). Development of Three Web-Based Computerized Versions of the Kiddie Schedule for Affective Disorders and Schizophrenia Child Psychiatric Diagnostic Interview: Preliminary Validity Data. *Journal of the American Academy of Child & Adolescent Psychiatry*, *59*(2), 309–325. https://doi.org/10.1016/j.jaac.2019.05.009

Wainberg, M., Jacobs, G. R., Voineskos, A. N., & Tripathy, S. J. (2022). Neurobiological, familial and genetic risk factors for dimensional psychopathology in the Adolescent Brain Cognitive Development study. *Molecular Psychiatry*, *27*(6), 2731–2741. https://doi.org/10.1038/s41380-022-01522-w

Wang, R., Lifelines Cohort Study, Hartman, C. A., & Snieder, H. (2023). Stress-related exposures amplify the effects of genetic susceptibility on depression and anxiety. *Translational Psychiatry*, *13*(1), 27. https://doi.org/10.1038/s41398-023-02327-3

Weiss, N. H., Goncharenko, S., Forkus, S. R., Ferguson, J. J., & Yang, M. (2023). Longitudinal Investigation of Bidirectional Relations Between Childhood Trauma and Emotion-Driven Impulsivity in the Adolescent Brain Cognitive Development Study. *Journal of Adolescent Health*, *73*(4), 731–738. https://doi.org/10.1016/j.jadohealth.2023.05.027

Zheng, Z., Liu, S., Sidorenko, J., Wang, Y., Lin, T., Yengo, L., Turley, P., Ani, A., Wang, R., Nolte, I. M., Snieder, H., LifeLines Cohort Study, Aguirre-Gamboa, R., Deelen, P., Franke, L., Kuivenhoven, J. A., Lopera Maya, E. A., Sanna, S., Swertz, M. A., … Zeng, J. (2024). Leveraging functional genomic annotations and genome coverage to improve polygenic prediction of complex traits within and between ancestries. *Nature Genetics*, *56*(5), 767–777. https://doi.org/10.1038/s41588-024-01704-y

Zorn, J. V., Schür, R. R., Boks, M. P., Kahn, R. S., Joëls, M., & Vinkers, C. H. (2017). Cortisol stress reactivity across psychiatric disorders: A systematic review and meta-analysis. *Psychoneuroendocrinology*, *77*, 25–36. https://doi.org/10.1016/j.psyneuen.2016.11.036