**Comparing Association between Psychopathology-Related Outcomes and Stress-Sensitivity and Psychiatric Polygenic Risk Scores in the Adolescent Brain Cognitive Development (ABCD) Study**

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* Stress activates HPA axis
* Hypothalamus releases corticotropin-releasing hormone which is part of corticotropin-releasing factor family with urocortin from brainstem, CRH stimulates release of adrenocorticotropic hormone which stimulates release of cortisol from adrenal cortex (Palamarchuk et al., 2023)
* HPA axis activity related to psych disorders
  + Decrease BDNF in hippocampus associated with GR desensitization and risk for psychiatric disorders when exposed to stress (Palamarchuk et al., 2023)
  + Fkbp5 gene close to glucocorticoid-responsive element, polymorphism linked to GR activation and PTSD risk, cortisol responses to stress, risk for depression, GR resistance evidenced by decreased ACTH and plasma cortisol after exposure to dexamethasone in depressed individuals (Palamarchuk et al., 2023)
  + Increased methylation NR3C1 in hippocampus and subsequent decreased gene expression and decreased hippocampal glucocorticoid receptor density, increased anxious and depressed responses following stress linked to childhood maltreatment (Cao et al., 2024)
  + Higher levels of IL-5, IL13, IL-17, TNFα, IFNγ, CRP in subjects with schizophrenia compared to controls but not interaction between effect of history of ACEs and shiczohprenia vs controls on these levels
  + At baseline no diff in gene exp between human induced pluripotent stem cell-derived glutamatergic neurons from combat veterans with PTSD and without PTSD but when exposed to hydrocortisone 402 genes responded differentially in PTSD vs non-PTSD cells, these genes were enriched in dlPFC and OFC postmortem tissue (Seah et al., 2022)
  + Offspring of rats with low corticosterone responses themselves had low corticosterone responses to stress, decreased size in multiple hippocampal regions, increased mineralocorticoid/glucocorticoid receptor ratios in hippocampal areas, fewer but longer bouts of REM sleep, and in males but not females fear extinction deficits and increased susceptibility to fear relapse compared to controls; high corticosterone responders also had smaller hippocampal regions but no change in fear extinction compared to controls (Monari et al., 2024)
  + If MDD and female then lower baseline cortisol and decreased cortisol response to stress compared to controls; if remitted MDD and female then no difference in cortisol response to stress but still lower baseline cortisol compared to controls; if MDD and male then increased baseline cortisol compared to controls but no difference in cortisol response to stress and no differences in cortisol if remitted MDD and male (Zorn et al., 2017)
  + If anxiety and female then no difference in baseline cortisol but decreased cortisol response to stress, no diff in cortisol if anxiety and male; if specifically social anxiety disorder and male but not female then no change in cortisol response to stress but increased baseline cortisol level (Zorn et al., 2017)
  + Decreased baseline cortisol if schizophrenia and male or female but decreased cortisol response to stress if schizophrenia and male but not female (Zorn et al., 2017)
  + Repetitive stress exposure risk factor for psychological disorders such as anxiety, MDD, schizophrenia (Zorn et al., 2017)
  + Change in cortisol in response to stress are adaptive if transient but if chronic or sustained can lead to allostatic overload and be harmful if chronic or sustained (Zorn et al., 2017) and if chronic or sustained then can lead to allostatic overload and eventually allostatic failure which is harmful/maladaptive (Palamarchuk et al., 2023)
  + Increased glucocorticoid responses ie hypercortisolemia linked with anxiety and depression (Palamarchuk et al., 2023)
* Experimentally-derived stress-sensitivity PRS linked with responses to stress and expression of genes related to psych disorders
  + Identify SNPs in genes related to stress response ie that ‘changes their activity upon dex treatment and were termed dex-responsive regulatory elements (DREs)’ as proxy for genes that might be related to responses to adverse events (Penner-Goeke et al., 2022)
  + “DRE and dex SNP-DRE associated etranscripts are enriched in genes differentially expressed in post-mortem cerebral cortex of affected subjects across five neuropsychiatric disorders (SCZ, autism spectrum disorder (ASD), MDD, bipolar disorder (BPD), and alcohol abuse disorder (AAD)) as cpmared to control subjects” (Penner-Goeke et al., 2022)
  + “dex SNP-DREs are more specific to psychiatric traits than the veh SNP-DREs, which are enriched for various non-psychiatric disorders” (Penner-Goeke et al., 2022)
  + Functional gene scores for DRE genes associated with ‘differences in physiological stress measures’, sig pos corr cortisol change following psychological stress task, impaired eyeblink startle habituation and increased eyeblink startle magnitude (Penner-Goeke et al., 2022)
  + Out of range of SNPs chose one related to transcriptional regulation of NUAK2 and another to regulation of FOXC1 (Penner-Goeke et al., 2022)
* Previous relationships already shown between PRS for psych disorders and emotional and behavioral problems
  + PRS calculated via basic/standard method for panic disorder, schizophrenia correlated with child psychosis (Qiu & Liu, 2023)
  + MDD PRS from (Howard et al., 2019) for white non-Hispanic participants only sig pos associated with CBCL scores for anxious/depressed, somatic, social, thought, attention, rule-breaking but not aggressive or withdrawn/depressed after correction for multiple tests, no change if only used participants of European ancestry (Wainberg et al., 2022)
  + ADHD PRS from (ADHD Working Group of the Psychiatric Genomics Consortium (PGC) et al., 2019) for white non-Hispanic participants only sig pos associated with attention subscale in CBCL but no other subscales, no change if only used participants on European ancestry (Wainberg et al., 2022)
  + Externalizing disorder PRS calculated with PRS-CS for participants of European ancestry only prospectively (baseline to wave 1 or wave 2) positively predicted ADHD and conduct problems and negatively predicted internalizing symptoms measured based on selected CBCL items; externalizing disorder PRS did not predict rate of change in any of these problems from baseline to wave 1 or wave 2 (Lahey et al., 2024)
  + ADHD with comorbid disruptive behavior disorder PRS, antisocial behavior PRS, irritability PRS, and self-regulation/addiction PRS calculated with basic/standard PRS for subjects of European ancestry only all significantly associated with externalizing, aggressive, and rulebreaking CBCL subscales (Teeuw et al., 2023)
* Unique measure because experimentally derived vs from GWAS summary stats
* RQ1: What relationship, if any, is there between an experimentally-derived stress-sensitivity PRS and emotional and behavioral problems? How does the variance explained by an experimentally-derived stress-sensitivity PRS compare to that explained by PRS for psychiatric disorders calculated based on GWAS summary statistics?
* H1:
* In addition to genetics strong evidence that psych issues influenced by exposure to environmental exposure to adversity
  + As measured with exposome: Overall psychopathology associated with exposome [as defined based on 348 environmental variables including LES but not any genetic data], psychopathology most strongly linked with day-to-day experiences subfactor, including general exposome rather than just parental education and demographics greatly increased variance explained in overall psychopathology, no diff based on sex, some diff based on race/ethnicity, (Moore et al., 2022)
  + As measured with cumulative adverse event measure: ???
  + As adversity inc likelihood of developing psychopathology also inc (McLaughlin et al., 2019)
  + If experience childhood adversity then chance of developing mental disorder approximately double (McLaughlin et al., 2019)
  + Increased exposure to traumatic events as measured with the KSADS associated with increased anxiety as measured with the CBCL (Marusak et al., 2022)
  + Greater levels of neighborhood poverty as measured with the ADI linked to higher externalizing symptoms as measured with the CBCL (Maxwell et al., 2021)
  + Suicidality, suicidal ideation, self-harm (Nelson et al., 2020) (Metzler et al., 2017) (Felitti et al., 1998)
  + Depression (Nelson et al., 2020) (Metzler et al., 2017) (Lacey & Minnis, 2020) (Felitti et al., 1998)
  + Alcoholism, drug abuse (Felitti et al., 1998)
  + Positive emotion-driven impulsivity only ie not negative emotion-driven impulsivity at baseline predicted what study refers to as ‘childhood trauma’ based on LES at year 2 follow-up, no sex diff (Goncharenko, 2022) (Weiss et al., 2023)
  + increased lifetime negative life event exposure as measured with LES at year 1 associated with increased negative and positive emotion-driven impulsivity at year 2 (Weiss et al., 2023)
  + both lifetime as assessed at year 1 with LES and past year as assessed at year 2 with LES negative event exposure associated with negative and positive emotion-driven impulsivity, no sex diff (Goncharenko, 2022) (Weiss et al., 2023)
  + increased number of life events reported as being negative associated with increased number of psychotic-like experiences (Karcher et al., 2022)
  + Increased exposure to ACEs as 11-12 predicted increased externalizing and internalizing ‘in later adolescence among a sample of African American youth’ (Barnhart et al., 2022)
  + Higher number of life events reported as negative by parent and by youth based on LES associated with increased internalizing and externalizing symptoms but “for youth-reported models that included either (a) only ACEs that were related to the non-familial environment (e.g., excluding family-specific ACEs; Supplemental Fig. 6) or (b) a PCA-derived family environment score that included other indices of family environment (e.g., parental monitoring, parental acceptance; Supplemental Fig. 7), while the major of results replicated, family economic status no longer strongly interacted with family conflict to predict ACEs.” [but study did nto control for psychopathology or baseline negative event exposure] (Barnhart et al., 2022)
  + increased number life events reported as engative associated with increased internalizing and externalizing symptoms
  + Higher adjusted odds ratio ie more likely to have depression, suicidality, PTSD, ODD, CD, ADHD, anxiety measured based on KSADS if more potentially traumatic events measured with KSADS-5 PTSD module even if account for polyvictimization (Thompson et al., 2022)
  + Exposure to potentially traumatic events as measured with KSADS-5 PTSD module tended to increase risk for both internalizing and externalizing disorders (not just one or the other) suggesting transdiagnostic effects, more likely to have comorbid psych disorders as number of potentially traumatic events increases (Thompson et al., 2022)
  + Developmental adversity associated with increased risk of psychosis (Qiu & Liu, 2023)
  + Increased family conflict, maternal substance use, parental psychopathology, structural connectivity in attentional network and decreased school engagement, SES, structural connectivity in posterior cerebellar network linked with increased externalizing problems (Qiu & Liu, 2023)
  + Increased maternal substance use, parental psychopathology, structural connectivity in salience network and decreased school engagement linked with increased internalizing problems (Qiu & Liu, 2023)
  + Increased developmental adversity and family conflict and decreased structural connectivity in anterior default mode network and SES linked with increased psychosis (Qiu & Liu, 2023)
  + Household income and parental education (collinear, together 2.3% variance), marital status, race, sex (1.5% variance) sig related to externalizing measured with CBCL, higher externalizing scores if white vs black or Hispanic or Asian, effect of externalizing based mostly on aggressive subscale (Teeuw et al., 2023)
  + Increased comorbid anxiety and depression symptoms if childhood maltreatment, more likely for girls compared to boys
  + History of ACEs more common in individuals with schizophrenia vs controls
  + School risk, neighborhood safety, household income, early life stress and area crime (but not air pollution, population density and not family conflict because correlated with early life stress) significantly affected anxiety and depression symptoms as measured based on selected items from the CBCL (Thapaliya et al., 2021)
  + Allostatic load defined as composite measure of salivary DHEA, blood cholesterol, glycemia, blood pressure, waist circumference ie theoretically physical markers of stress linked with increase symptoms of psychopathology even after adjusting for parental education, household income, race, ethnicity, sex, and age; allostatic load partially mediated relationship between exposomic burden and symptoms of parent but not self-reported psychopathology [(Hoffman et al., 2023) as preprint, full text not available but actually published as (Hoffman et al., 2024)]
* Genetics and adversity → psych outcomes
  + SES but not family environment, maternal substance use, school environment, developmental adversity, or parental psychopathology correlated with PRS calculated via basic/standard method for autism, anxiety, social anxiety, panic disorder, bipolar disorder, MDD, schizophrenia (Qiu & Liu, 2023)
  + Youth externalizing as measured with CBCL at age 12-13 controlling for externalizing at age 12-13 62% explained by nonshared environmental (E) and 38% additive genetic (A) effects based on twin study, E moderated by family cultural values as reported by parents but not youth(Rea-Sandin et al., 2024)
  + Relationship between psych-related PRS and ACE exposure could be due to child’s behavior (genetic) leading to ‘harsh parenting or stress responses in their parents’ ie gene by environment correlation or due to common genetics between parent with psychopathology and child with psychopathology (Baldwin et al., 2022)
  + Odds ratio 1.09 for experiencing ACEs based on PRS for overall mental health problems, strongest for PRS for schizophrenia, depression, and ADHD compared to other mental health PRS, did not differ based on specific kind of ACE (Baldwin et al., 2022)
  + Relationship between ACE and internalizing or externalizing explained by genetic in some things but not others: genetic confounding explains large part of relationship for parent separation, criminality and substance abuse but nor for parental mental illness or child maltreatment (Baldwin et al., 2022)
  + Models with genetic, environmental (life events, proximal contextual, broad contextual), and gene x environment interactions (with life events and proximal context but not broad context) best fit internalizing and externalizing scores on CBCL using novel genetics-based REML approach with matrices and environmental exposure measures at baseline (or life events scale at year 1) for subjects of european ancestry, in American admixed group gene x environment effects sig for ext but not int, in african ancestry group larger gene x environment effects compared to european (Choi et al., 2022)
  + Adding environmental exposome effects to model of internalizing which already included genetic effects had little/no impact suggesting independence but adding environmental exposure sig decreased genetic effects on externalizing so environment could mediate genetic effects or genetic effects could affect both environment and externalizing (Choi et al., 2022)
  + PRS for MDD calculated with PRS-CS with summary stats from (Howard et al., 2019) and (Levey et al., 2020) sig pos related to allostatic load defined as composite measure of salivary DHEA, blood cholesterol, glycemia, blood pressure, waist circumference for European but not african ancestry adolescents; sig pos related to psychopathology for European but not African ancestry youth partially mediated by allostatic load for European ancestry youth; no sig increase in variance explaining allostatic load when added MDD-PRS to model already including exposome; interaction between MDD-PRS and exposomic burden such that stronger relationship between exposomic burden and allostatic load if higher MDD-PRS [(Hoffman et al., 2023) as preprint, full text not available but actually published as (Hoffman et al., 2024)]
  + PRS for PTSD calculated with PRS-CS and exposomic burden both individually but not interaction sig pos related to allostatic load in European ancestry participants and allostatic load sig mediated relationship between PRS for PTSD and total problems CBCL score, results not reported for African ancestry [(Hoffman et al., 2023) as preprint, full text not available but actually published as (Hoffman et al., 2024)]
  + Polygenic score based on four HPA-axis genes (FKBP5, NR3C2, NR3C1, GRHR1) not associated with anxiety or depression symptoms but interaction between polygenic score and maltreatment such that if higher polygenic score then more maltreatment associated with higher risk severe vs mild comorbid depression/anxiety symptoms, mainly due to effects of emotional neglect and abuse rather than other types maltreatment, no difference based on gender
  + Interaction between maltreatment and recent interpersonal stress such that recent interpersonal stress associated with stronger changes in depressive symptoms if childhood maltreatment if high but not low stress-related polygenic score as above (Sun & Cao, 2024)
  + MDD PRS and bipolar disorder PRS created with PRS-CS and validation with PRSice2, participants of European ancestry only, MDD PRS sig related to cumulative number of stressful life events before most severe depressive episode, no sig effect of bipolar PRS (Hosang et al., 2024)
  + Depression PRS from (Howard et al., 2019) anxiety PRS calculated using basic/standard PRS methods for subjects of European ancestry only, depression PRS sig associated with dep symptoms and anxiety PRS sig associated with anxiety symptoms, interaction between dep PRS and stress such that stronger effect of PRS on dep or anx symptoms if more stressfult life events, childhood trauma (only for dep, not anxiety), loneliness, long-term difficulties, or dec social support (Wang et al., 2023)
* HPA axis and adversity → psych outcomes
  + More ACEs associated with increased IL-6 and TNFα, IL-6 but not TNFα partially mediated relationship between increased ACEs and increased depressive symptoms (Zagaria et al., 2024)
  + Polygenic score created based on gene changes in hippocampus of female macaques following chronic betamethasone administration moderated relationship between exposure to early life adversity and adult psychotic disorder diagnosis (Arcego et al., 2024)
* RQ2: 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 emotional and behavioral problems?
* H2:

Brief literature review

rationale

This part should be 5-10 pages total

Increased stress sensitivity has been linked to conditions such as major depressive disorder (MDD) and social anxiety disorder (SAD) (Farmer & Kashdan, 2015; Hasler et al., 2004). This suggests that the stress sensitivity PRS may be related to MDD and SAD diagnoses based on the KSADS-COMP and the following CBCL subscales: internalizing, anxious/depressed, withdrawn/depressed, social problems, somatic problems (physiological symptoms which are often associated with anxiety).

Penner-Goeke et al. (2023) found that the stress sensitivity SNPs were associated with individuals with MDD who had previously experienced trauma. While they did not find a relationship between these SNPs and PTSD, they suggested that may be due to methodological constraints, as they were using data from a potentially underpowered GWAS. The stress sensitivity PRS in the proposed study may therefore be associated with PTSD diagnoses based on the KSADS-COMP.

SNPs in genetic regions linked to the HPA axis were able to predict ADHD symptom severity (van der Meer et al., 2017). This suggests that the stress sensitivity PRS in the proposed study might be associated with ADHD diagnoses based on the KSADS-COMP and increased scores on the CBCL attention subscale.

Because stress sensitivity has also been liked to increased risk of psychosis (Reininghaus et al., 2016), the stress sensitivity PRS may be associated with increased scores on the CBCL thought problems subscale.

Finally, increased stress sensitivity was recently linked to more externalizing problems (Borchers et al., 2024), suggesting that the stress sensitivity PRS could be associated with higher scores on the CBCL externalizing, rule-breaking, and aggression subscales.

*H1:* Higher stress-sensitivity PRS will be significantly associated with increased CBCL scores on internalizing, externalizing, total problems, and all eight subscales.

*H2:* Higher stress-sensitivity PRS will be significant associated with meeting criteria for MDD, ADHD, SAD, and PTSD based on the KSADS-COMP.

**Methods**

**Sample description**

The Adolescent Brain Cognitive Development (ABCD) Study is an ongoing, longitudinal study which samples 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. 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. For example, current diagnoses of GAD in year four were 2.8 times larger than those in year two, and current diagnoses of MDD in year four were about four times larger than those in year two. 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 reads 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). Score on 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 Computerized Version for DSM-5 (KSADS-COMP)***

The KSADS-COMP is a standardized interview with items based on DSM-5 criteria for psychiatric disorders such as 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). The KSADS has adequate test-retest reliability (κ = .63 to 1.00) (Kaufman et al., 1997). The present study will consider both past and present diagnoses and will include 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 with the conservative Hardy-Weinberg flag using plink. 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 with a probability threshold of 0.7 (J. Zhu and M. Hyat, personal communication, February 2024). After applying this threshold, genetic data was currently available for 3307 participants (2299 European ancestry, 517 African ancestry, 491 American admixed ancestry) in year four.

**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 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, for each PRS, 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 better account for ancestry-related effects, final results will use a more sophisticated method to generate PRS for anxiety, MDD, and ADHD such as PRS-Csx (Ruan et al., 2022), BridgePRS (Hoggart et al., 2024), or SBayesRC (Zheng et al., 2024). 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 subscales, externalizing, internalizing, and total problems on the CBCL as outcomes. Logistic regression will 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 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**

**Stress-sensitivity PRS**

***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 = 0.92), with an increase of 0.281 points for each standard deviation increase in stress-sensitivity PRS. Neither any other CBCL subscales nor total problems were significantly or nominally associated with stress-sensitivity PRS. Compared to average, girls’ scores were 1.00 point higher on the internalizing (FDR corrected p-value = 0.000045), 0.49 points higher on the anxious-depressed (FDR corrected p-value = 0.00055), and 0.40 points higher on the somatic (FDR corrected p-value = 0.0037) subscales and scores 0.26 points lower on the aggression subscale (FDR corrected p-value = 0.010).

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 and total problem CBCL scores with a a one standard deviation increase in stress-sensitivity PRS linked to a decrease of 0.67 points on the withdrawn-depressed subscale (uncorrected p-value = 0.026, FDR corrected p-value = 0.20) and a decrease of 1.31 points on total problems (uncorrected p-value = 0.023, FDR corrected p-value = 0.20). Stress-sensitivity PRS did not significantly affect any other CBCL scores. Sex nominally significantly affected some CBCL scores. Compared to average, girls’ internalizing, anxious-depressed, and somatic scores were 1.12 points (uncorrected p-value = 0.024, FDR corrected p-value = 0.091), 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 = 0.091) higher, respectively. Age was not significantly related to any CBCL scores.

***Lifetime Psychiatric Diagnoses***

For individuals of European ancestry, compared to average, girls had an increase of 1.48 in odds of receiving a lifetime diagnosis of any anxiety disorder other than panic disorder (FDR corrected p-value = 0.00000000016), an increase of 1.63 in odds of receiving a lifetime MDD diagnosis (FDR corrected p-value = 0.00000000016, and a decrease of 0.72 in odds of receiving a lifetime ADHD diagnosis (FDR corrected p-value = 0.0089) compared to average. Sex did not significantly affect any other CBCL subscale scores and did not significant influence odds of receiving a lifetime PTSD diagnosis. There were no significant relationships between age and any CBCL score or 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 = 0.38) increase of 1.44 in odds of receiving a lifetime MDD diagnosis compared to average.

Finally, for subjects of American admixed ancestry, sex and age, but not stress-sensitivity, affected the likelihood of receiving a lifetime diagnosis of ADHD, anxiety, and MDD. For girls, odds of receiving a diagnosis of anxiety or MDD were 1.66 points (FDR corrected p-value = 0.011) or 1.75 points (FDR corrected p-value = 0.011) 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). 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 = 0.094) 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, MDD, or PTSD.

**Discussion**

Discussion of anticipated findings

Limitations

Potential implications

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