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A phenome-wide association study of externalizing polygenic risk in the Adolescent Brain Cognitive Development (ABCD) study

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Abstract

Background. Externalizing disorders encompass a range of disinhibited behaviors that typically manifest in youth and are linked with adverse psychological and social outcomes. Polygenic liability to externalizing behaviors has been associated with psychiatric and disease phenotypes in adults. Identifying correlates of genetic risk in youth—prior to the emergence of more impairing manifestations of externalizing behaviors (e.g. substance use disorders)—could improve our etiological understanding and inform targeted prevention efforts.

Methods. We conducted a phenome-wide association study (PheWAS) to test whether externalizing (EXT) polygenic scores (PGS) were associated with up to 1,697 psychosocial, behavioral, environmental, and health-related phenotypes among youth of European-like genetic ancestry. PheWAS data came from the baseline (n = 4,931, mean age = 9.93 ± 0.63 years, 46.9% female) and two-year follow-up (n = 4,507, 12.02 ± 0.66 years, 47.0% female) data collection waves of the Adolescent Brain Cognitive Development Study[SM] (ABCD Study®). Secondary analyses examined within-family effects and moderation by biological sex.

Results. EXT PGS was associated with 268 and 352 phenotypes at baseline and follow-up, respectively, following Bonferroni correction at each wave. The strongest associations were observed with externalizing behaviors, screen time/media use, caffeine consumption, sleep disturbances, and poor school performance. Effects were attenuated by 59%–64% within family, on average, with five predominantly externalizing phenotypes remaining significantly associated with within-family PGS. There was limited evidence of moderation by biological sex.

Conclusions. These results broadly characterize the early phenotypic correlates of an externalizing polygenic score and can be used to generate hypotheses about phenotypes that might represent mechanisms or future prevention targets.

Introduction

Externalizing behaviors, which encompass various forms of behavioral disinhibition (Krueger et al., 2021), are common, often arise in childhood (externalizing disorder prevalence by age 17 ≥ 10.1%; Danielson et al., 2021), and can persist into adulthood in forms such as antisocial behavior and substance use disorders (SUDs; Hicks, Iacono, & McGue, 2012; Iacono, Malone, & McGue, 2008; King, Iacono, & McGue, 2004; Krueger et al., 2021; Young et al., 2006). Higher levels of externalizing behaviors across the life span are also associated with lower academic achievement (Hinshaw, 1992; Kulkarni, Sullivan, & Kim, 2021), employment and occupational impairments (Alaie, Svedberg, Ropponen, & Narusyte, 2023), lower responsiveness to stressors (Konzok et al., 2021), involvement in the criminal justice system, and increased risk for early mortality (Jokela, Ferrie, & Kivimäki, 2009). Thus, understanding the etiology of childhood externalizing behaviors is a critical public health priority.

Externalizing symptoms are moderately heritable, with twin-based studies showing that 20%–74% of the variability in their expression is attributable to genetic factors (Burt, 2009; Faraone &

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Larsson, 2019; Maes et al., 2004; van den Bree, Johnson, Neale, & Pickens, 1998; Verweij et al., 2010). Twin studies have further demonstrated that a common externalizing factor underlies a significant portion of heritability across externalizing disorders, with this predisposition expressed as attention deficit hyperactivity (ADHD) and oppositional defiant disorder (ODD) earlier in development before progressing, among some individuals, to conduct disorder, problematic substance use, and antisocial behavior (Cicchetti & Rogosch, 2002; Kagan, 1969; Petersen, Choe, & LeBeau, 2020). Genome-wide association studies (GWAS) have yielded SNP-based heritability estimates of 0.05–0.22 (Deak & Johnson, 2021; Demontis et al., 2019; Karlsson Linnér et al., 2021; Tielbeek et al., 2017) and have revealed the genetic architecture of externalizing behaviors to be highly polygenic. Indeed, the largest GWAS on externalizing behaviors identified hundreds of SNPs associated with a common latent genetic factor that captured shared genetic liability for ADHD, problematic alcohol use, lifetime cannabis use, smoking initiation, age at first sexual intercourse, number of sexual partners, and general risk tolerance among adults (Barr & Dick, 2020; Baselmans et al., 2022; Dick et al., 2008; Karlsson Linnér et al., 2021). Polygenic scores (PGS) based on discovery results of this externalizing factor have shown good predictive utility, accounting for up to 10.5% of the variance in externalizing behaviors in adults (Karlsson Linnér et al., 2021). In childhood and adolescent populations, there is also evidence to support the predictive performance of externalizing (EXT) PGS in relation to an array of behavioral and mental health outcomes. For example, several empirical studies have linked higher externalizing PGS to increased risk for ADHD, ODD, conduct disorder, and substance use and problematic use, with up to 5% of variance accounted for (Brislin et al., 2024; Choi et al., 2025; Kuo et al., 2021; Reddy et al., 2025; Tanksley et al., 2025). These findings dovetail with longstanding theories of externalizing psychopathology, which posit that different phenotypic manifestations of externalizing share common mechanisms that may emerge early in life and unfold across development. Given the range of adverse outcomes associated with externalizing behaviors, an important next step is to clarify whether correlates of externalizing may reflect shared underlying or unique genetic liability. Phenome-wide Association Studies (PheWAS) adopt an agnostic approach to test the association between genetic variation and a broad array of phenotypes (Bastarache, Denny, & Roden, 2022). This methodology broadens the scope of analysis beyond discrete hypothesis testing, enabling potential replication of previously identified effects, as well as the identification of novel associations that may provide a strong basis for hypothesis generation in future work. A prior PheWAS of EXT PGS examined associations with 1,335 case–control disease phenotypes in adults and identified associations with mental (e.g. ADHD symptoms), behavioral (e.g. suicidal ideation and attempt behaviors), and physical health outcomes (e.g. obesity, HIV infection) (Karlsson Linnér et al., 2021).

In order to understand the etiology of externalizing behaviors, it is important to examine these associations in developmental samples, given the early onset of many externalizing behaviors and varying genetic influences across development. For example, there is evidence that the heritability of externalizing behaviors increases from childhood to adolescence (Elam & DiLalla, 2021; Kendler, Schmitt, Aggen, & Prescott, 2008; Meyers et al., 2014; Thomas et al., 2023), underscoring the importance of studying these associations in specific age groups (see Choi et al., 2025 for evidence that associations do not differ across age groups). Identifying correlates of EXT PGS in childhood and early adolescence may also facilitate discovery of shared and unique expressions of genetic risk across developmental periods and early markers of risk prior to the development of more severe externalizing behaviors (e.g. SUDs).

In the current study, we examined associations between EXT PGS and up to 1,697 phenotypes across two waves of data reflecting late childhood and early adolescence in the Adolescent Brain Cognitive Development (ABCD) study. Leveraging data from late childhood and early adolescence, we aimed to determine the phenotypic correlates of EXT PGS largely prior to substance use engagement to reduce the likelihood that the observed associations reflect downstream consequences of alcohol or drug use. This approach allows for a clearer interpretation of phenotypes that may precede or be correlated with the emergence of externalizing behaviors.

Using this deeply phenotyped, developmental sample, we were able to test associations not only with psychiatric disorders, but also subthreshold symptoms that may appear prior to the onset of discrete disorders, as well as broader phenotypes within the domains of mental health and behavior, identity, cognition, screen time and media use, attitudes toward and use and accessibility of substances, peer behavior, prenatal exposures, physical health, and family, school, and neighborhood environments.

Because externalizing PGS associations reflect a combination of direct genetic effects and effects related to population stratification, assortative mating, and/or passive gene–environment correlation (Hugh-Jones, Verweij, Pourcain, & Abdellaoui, 2016; Martin et al., 2019), we also conducted within-family analyses to obtain estimates that more closely approximate direct genetic effects. Further, given sex differences in the prevalence and expression of externalizing behaviors (Eme, 2018; Fernandez Castelao & Kröner-Herwig, 2014), we examined whether biological sex significantly moderated associations between EXT PGS and the phenotypes under study. This work may provide insights into the expression of genetic risk for externalizing behaviors earlier in life and may generate hypotheses for future work to explore mechanisms through which EXT PGS influences behavioral expression.

Methods

Participants

Participants were children from the Adolescent Brain Cognitive Development[SM] (ABCD) Study, the largest longitudinal study of brain development and child health and behavior in the United States. Children (n = 11,875, mean ± SD age = 9.91 ± 0.62 years at baseline, 47.85% female, 52.1% white) were recruited from 21 research sites across the United States (Garavan et al., 2018). Parents/caregivers provided written informed consent, and children provided verbal assent to a research protocol approved by the institutional review board at each site (https://abcdstudy.org/sites/abcd-sites.html). The analytic sample consisted of individuals most genetically similar to European reference populations (EUR) who were assessed at the baseline (n = 4,931, mean age = 9.93 ± 0.63 years, 46.9% female) and the two-year follow-up (n = 4,507, 12.02 ± 0.66 years, 47.0% female; see Table 1 for a description of the sample). Data for the present study came from data release 4.0, previously extensively curated for PheWAS (Gorelik et al., 2023; Paul et al., 2024). All included phenotypes with documented errors addressed in data release 7.0 were updated to this most recent release (Supplement).

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Table 1. Sample descriptive statistics

Variable	Mean (SD)/*n* (%)
Sex (female)	2,315 (46.9)
Sexual orientation[a]	
Gay or lesbian	181 (4.2; 162 female)
"Maybe" gay or lesbian	167 (3.9; 127 female)
Age (years)	9.93 (0.63)
Household income	
<$35,000	310 (6.6)
$35,000–$49,999	264 (5.6)
$50,000–$74,999	639 (13.6)
$75,000–$99,999	822 (17.4)
$100,000–$199,999	1,955 (41.5)
≥$200,000	722 (15.3)
Highest caregiver education	
Less than high school	25 (0.51)
High school degree/equivalent	157 (3.2)
Some college/associate degree	946 (19.2)
College degree	1,559 (31.6)
Master's degree	1,533 (31.1)
Doctorate/professional degree	708 (14.4)

Note: Sample descriptive information from the baseline wave of the Adolescent Brain Cognitive Development (ABCD) Study.
[a]Measured at the two-year follow-up wave.

Polygenic scores

Polygenic scores were computed based on summary statistics from the large multivariate GWAS of externalizing behavior (ADHD, problematic alcohol use, lifetime cannabis use, lifetime smoking initiation, age at first sexual intercourse, number of sexual partners, and general risk tolerance; N = 1,492,085; Karlsson Linnér et al., 2021) conducted primarily in adults. Polygenic Risk Score–Continuous Shrinkage (PRS-CS), a Bayesian polygenic prediction method that uses a continuous shrinkage prior on SNP effects to infer posterior SNP weights (Ge et al., 2019), was used to generate PGS for externalizing behavior in ABCD. The samples used in the externalizing GWAS were exclusively from EUR populations. Because polygenic prediction is less informative when applied to target samples that are not genetically similar to the population included in the original discovery GWAS (in our case, EUR), PGS were computed in 4,931 participants most genetically similar to European genomic ancestry. See Supplemental Methods for additional detail on genotyping, quality control, and imputation. Summary statistics for the 23andMe cohort were obtained under an agreement with 23andMe that protects the privacy of the 23andMe participants (http://research.23andme.com/collaborate/#dataset-access for more information).

PheWAS phenotypes

Briefly, 1,271 and 1,697 phenotypes were selected at baseline and follow-up, respectively, following rigorous quality control procedures implemented to ascertain relevance and sufficient endorsement (i.e. at least 100 non-missing values for continuous phenotypes, and at least 100 non-missing values per category for dichotomous phenotypes)for each phenotype. Phenotypes spanned the following broad domains: *identity, cognition, physical development, physical health, prenatal/postnatal and early development (baseline only), life events, family environment, neighborhood/external environment, peer environment, school-related, screentime/media use, substance use and perceptions, substance-related environment, family behavior and mental health, and child behavior and mental health.* See Supplemental Methods and previously published PheWAS in ABCD for a more detailed description of phenotype selection and curation (Gorelik et al., 2023; Paul et al., 2024).

PheWAS analyses

Consistent with prior work (e.g. Paul et al., 2024), continuous phenotypes with skew ≥|1.96| were winsorized to 3 standard deviations. Phenotypes that remained skewed following winsorization were inverse normal transformed. All other continuous variables were standardized. The lme4 package (Bates, Mächler, Bolker, & Walker, 2015) in R was used to run linear (for continuous outcomes) and generalized linear (for dichotomous outcomes) mixed effects models, with random intercepts included for family and study site. Covariates included age at assessment, biological sex and the first 10 ancestral principal components; follow-up analyses additionally included a variable indicating whether the assessment had been in-person, remote, or hybrid given the COVID-19 pandemic.

We applied Bonferroni correction to correct for multiple testing, which we applied to all p-values (i.e., 1,271 and 1,697) separately within each PGS. Because the Bonferroni approach may be overly conservative given correlations among phenotypes, false discovery rate (FDR)-corrected p-values are also presented.

Within-family analyses

Among non-singleton participants (baseline n = 1,631 [n = 805 families], follow-up n = 1,485 [n = 734 families], EXT PGS was decomposed into between- and within-family variance, using the family mean PGS and each individual's deviation from that family mean PGS, respectively (Supplemental Methods; Paul et al., 2024; Selzam et al., 2019). Both between- and within-family PGS were entered into the regression simultaneously. Only phenotypes significantly associated with EXT PGS in the primary PheWAS were included in the within-family analyses, and Bonferroni correction was applied across the number of tests.

Given the reduced sample size in the within-family analyses, the resulting within-family betas were compared with those from the primary PheWAS to aid in interpretation of the findings. Further, for each phenotype, assuming that true within-family effects would be equal to population estimates, observed power was calculated as the probability of detecting the effect given the observed within-family standard error, under Bonferroni-corrected alpha levels.

Sex moderation analyses

We included an interaction term between participant sex and the EXT PGS in predicting each of the 992 and 1,355 phenotypes at baseline and follow-up, respectively, that had sufficient sample sizes for both males and females (e.g. sex-specific phenotypes related to pubertal development were excluded, as were phenotypes with fewer than 100 data points for males or females; Supplemental Methods). To properly account for confounding, all moderator-by-covariate interactions were additionally included (Keller, 2014).

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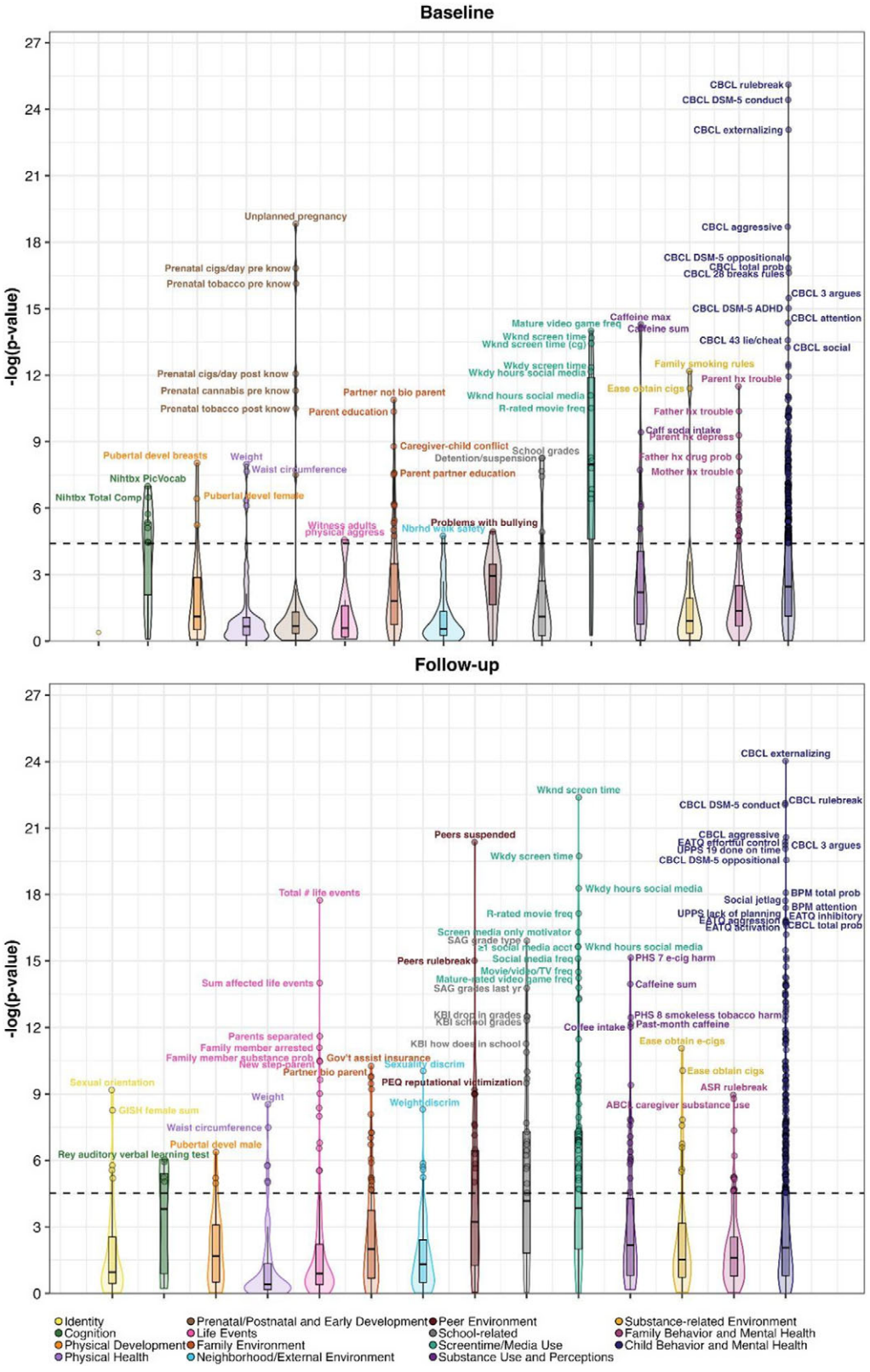


Figure 1. Violin Manhattan plot of PheWAS results (**top**: Baseline; **bottom**: follow-up), grouped and colored by phenotype domain. The horizontal line indicates the threshold of Bonferroni significance. Note: CBCL, "Child Behavior Checklist"; ASR, "Adult self-report"; SDS, "Sleep Disturbance Scale for Children"; cg, "caregiver"; SAG, "School Attendance and Grades"; PHS, "Perceived Harm of Substance Use"; SRPF, "School Risk and Protective Factors"; GISH, "Gender Identity and Sexual Health"; Nihtbx, "NIH Toolbox"; RAVLT, "Rey Auditory Verbal Learning Test"; PDS, "Pubertal Development Scale"; FES, "Family Environment Scale"; PMQ, "Parental Monitoring Survey"; ABCL, "Adult Behavior Checklist".

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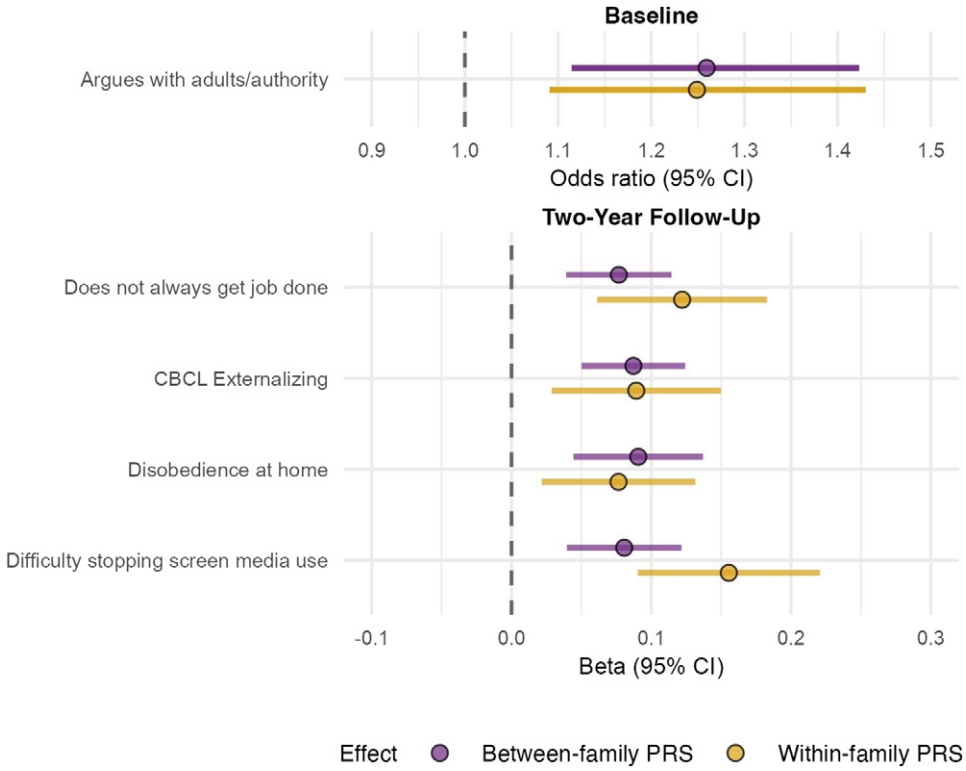


Figure 2. Within-family PheWAS results. PGS were decomposed into between- and within-family variance and entered into mixed-effects models simultaneously as predictors of phenotypes that were significantly associated with the PGS following Bonferroni correction. Depicted here are the Bonferroni-corrected significant within-family PGS associations (in yellow), alongside the respective between-family PGS effect (purple). Point estimates reflect odds ratios (top, baseline) and standardized betas (bottom, two-year follow-up), and error bars represent 95% confidence intervals.

Covarying for baseline externalizing

To test whether EXT PGS associations persist beyond phenotypic externalizing, we included baseline CBCL externalizing problems as a covariate in analyses with follow-up phenotypes.

Results

Out of 1,271 and 1,697 phenotypes selected at baseline and follow-up, respectively, 267 (21.0%) and 346 (20.4%) were significantly associated with EXT PGS after Bonferroni correction (685 (53.9%) and 907 (53.4%) following FDR correction; Figures 1 and 2, Supplementary Tables S1 and S2, Supplementary Figures S1 and S2). At both waves, most EXT PGS associations occurred within the child mental health domain (n = 182 [68.1% of all significant baseline associations] and n = 171 [49.4% of all significant follow-up associations]). These were predominantly positive associations with phenotypes related to externalizing behavior and symptoms.

Among the strongest associations between the EXT PGS and phenotypes at both waves were Externalizing Problems, DSM-5 Conduct Problems, and Rule-Breaking Behaviors as measured by the Child Behavior Checklist completed by caregivers (CBCL; Bs ≥ 0.12, ps ≤ 8.92e-23), and dozens of associations were observed with phenotypes reflecting impulsive (e.g. UPPS-P scales and items), aggressive (e.g. CBCL Aggressive Problems), and inattentive (e.g. CBCL and Brief Problem Monitor (BPM) teacher-rated Attention Problems) behavior. EXT PGS was also related to a range of phenotypes in other domains, including cognitive ability (e.g. lower cognitive performance and grades), school engagement (e.g. experiencing detention or suspension), higher caffeine consumption, lower parental educational attainment and income, higher weight and waist circumference, sleep disturbances (e.g. total sleep disturbances, disorders of initiating and maintaining sleep), and more screen time (e.g. total screen time, frequency of playing mature-rated video games and watching R-rated movies, time spent on social media).

Of the 803 phenotypes measured and included at both waves, 214 (26.7%) and 188 (23.4%) were significantly associated with EXT PGS at baseline and follow-up, respectively, following Bonferroni correction (467 (58.2%) and 463 (57.7%) following FDR correction); 127 (59.3%–67.6%) showed Bonferroni-significant associations at both waves (359 (76.9%–77.5%) FDR-significant; Supplementary Table S3). Consistent associations included CBCL Externalizing Problems, total screen time, UPPS-P impulsivity scales and items, caffeine consumption, psychotic-like experiences, poorer school performance, family conflict, sleep problems, and lower cognitive performance, among others. A minority of associations showed wave-specific effects: 23 phenotypes were Bonferroni-significant at baseline and not FDR-significant at follow-up, and 17 showed the reverse pattern, of which 4 displayed opposite directions of effect. Seventeen (30.9%) of the significant associations between EXT PGS and items on the K-SADS at baseline did not survive multiple testing correction at follow-up, nor did associations with family variability in smoking rules, caregiver-reported accident proneness, having heard of marijuana, self-reported excitement and craving of new situations, or caregiver self-reported eye problems, and keeping oneself from getting involved with others. Associations specific to follow-up included several related to lower school engagement (e.g. disliking school, not getting along well with teachers, negative self-comparison to peers, boredom at school, lower school performance), screen time/media use (i.e. greater time spent video

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chatting on the weekend), UPPS-P impulsivity items (e.g. not stopping to think before acting, not taking a careful approach), male self-reported pubertal development summary score, and psychotic-like experiences (i.e. feeling confused because something didn't seem real, feeling an invisible energy, creature, or person).

Of the phenotypes only measured at baseline, EXT PGS was significantly associated with 53 phenotypes related to prenatal tobacco and cannabis exposure, family history of drug and alcohol problems, other psychiatric symptoms and purported outcomes (e.g. depression, mania, hospitalization for psychiatric symptoms, and trouble holding jobs/fighting/police problems), and trauma- and stressor-related symptoms. Of phenotypes only assessed at follow-up EXT PGS was significantly associated with 158 phenotypes related to temperament and self-regulation measured via the Early Adolescent Temperament Questionnaire (e.g. lower effortful control, lower inhibitory control, higher negative affect), psychopathology assessed using the youth-reported BPM (e.g. higher total, externalizing, attention, and internalizing problems), as well as phenotypes related to gender identity (i.e. participants assigned female at birth preferring to play with males relative to females and dressing or acting like males during play), sleep disturbances and behaviors (e.g. lengthier and more frequent nighttime awakenings, higher social jetlag), peer behaviors (e.g. spending time with peers who tend to skip school and break rules, experience of reputational victimization and having had rumors and gossip spread about them), lower perceived harm of substance use, and increased stressful life experiences (caregiver- and youth-reported).

Within-family results

The observed power at the Bonferroni-corrected alpha was determined to be at least 0.80 for 21% and 33% of within-family effects at baseline and follow-up, respectively. At baseline, one significant within-family EXT PGS effect was identified for caregiver-reported past "often arguing with adults/authority" in the ODD module of the K-SADS following Bonferroni correction (OR_{within} = 1.26, p_{within} = 2.16e-04, p_{fdr_within} = 0.0427, p_{bonf_within} = 0.0499). EXT PGS exhibited Bonferroni-corrected significant within-family associations with four phenotypes assessed at follow-up, including caregiver-reported difficulty stopping screen media use, caregiver-reported CBCL externalizing problems and disobedience at home, and a self-reported item on the UPPS-P (tendency to not always get the job done; $B_{within} \geq 0.076$, $p_{within} \leq$ 1.36e-04, $p_{fdr_within} \leq 0.0107$, $p_{bonf_within} \leq 0.04568$; Supplementary Tables S4 and S5; Figure 2).

On average, the within-family betas were 36% (range: 0%–97%) and 41% (0%–99.7%) the magnitude of the total effect observed in the full sample at baseline and follow-up, respectively (Supplementary Figure S3). The associations that exhibited the least attenuation within-family were primarily with externalizing-related phenotypes, including K-SADS diagnostic symptoms, Behavioral Activation (BIS/BAS), CBCL, and UPPS-P impulsivity measures at baseline. At follow-up, the within-family effects most closely approximating those from the primary PheWAS included externalizing phenotypes (CBCL, Early Adolescent Temperament Questionnaire, UPPS-P, and BPM), as well as sleep difficulties (e.g. more frequent nighttime awakenings, shorter sleep duration), screen time/media use (e.g. playing video games, difficulty disengaging), and pubertal development (e.g. female self-reported summary score).

Phenotypes whose associations with EXT PGS were largely accounted for by between-family effects included teacher-reported externalizing problems, caregiver self-reported behavior problems, prenatal substance exposure, lower cognitive performance, caregiver income and education, family history of psychopathology, the majority of stressful life events items, and peer victimization, as well as some phenotypes spanning the domains of screen time/media use, mostly non-externalizing CBCL items, perceived harm from substance use, peer tolerance of substance use, caffeine consumption, sleep problems, and poor school performance,

Sex moderation results

No significant sex interactions were identified with phenotypes assessed at baseline (Supplementary Table S6). Biological sex significantly moderated two associations with EXT PGS at follow-up (Supplementary Table S7). There was an interaction between sex and the EXT PGS in predicting playing video games (B_{intx} = 0.096, p_{intx} = 9.66e-07, p_{intx_fdr} = 1.31e-03, p_{intx_bonf} = 1.31e-03). Simple slope analyses indicated that the association between the EXT PGS and frequency of playing video games was significant and positive for males (B = 0.094, p = 1.32e-10) but not for female (B = −2.11e-03, p = 0.89) participants. A Johnson–Neyman test indicated that the interaction was significant outside of the EXT PGS range of −3.81 to −1.47. A significant interaction between sex and the EXT PGS was observed in relation to sexual orientation (B_{intx} = 0.070, p_{intx} = 8.90–06, p_{intx_fdr} = 6.03e-03, p_{intx_bonf} = 0.012). Simple slope analyses indicated that among female (B = −0.084, p = 1.81e-11) but not male (B = −0.014, p = 0.22) participants, EXT PGS was negatively associated with identifying as heterosexual. Findings from a Johnson–Neyman test indicated that the interaction was significant outside of the EXT PGS range of −5.51 to −2.01 (Figure 3).

Covarying for baseline CBCL externalizing

On average, the associations between EXT PGS and 346 significant follow-up phenotypes were 71% the magnitude of the original association (range = 15%–101%), and 176 associations remained statistically significant following Bonferroni correction. Associations with externalizing phenotypes, including CBCL and EATQ items and scales, CBCL scales reflecting thought, social, and internalizing problems, sleep problems, and caregiver-child conflict, exhibited the greatest attenuation. By contrast, EXT PGS remained similarly associated with many screentime phenotypes, perceived harm from substance use, caffeine intake, caregivers' and partners' education and income, having heard of various substances, pubertal development, caregiver self-reported substance use, weight and waist circumference, other measures of sleep quantity and quality, stressful life events, and others (Supplementary Table S8).

Discussion

Leveraging the largest GWAS to date on externalizing behaviors, we examined associations between an externalizing (EXT) polygenic score (PGS) and 2,165 unique phenotypes in youth ages 9–13. Three primary findings emerged. First, EXT PGS was broadly associated with phenotypes across multiple domains, with consistent strong and numerous positive associations with externalizing behavior, screen media use, caffeine consumption, sleep problems, and weight and waist circumference, and negatively associated with cognitive and academic functioning. Second, within-family analyses revealed substantial attenuation of these associations. Third, a subset of phenotypes, including impulsivity, conduct-related problems, and screen time, remained statistically significant in within-family analyses, pointing to potentially direct genetic influences or active/evocative gene–environment correlations. Together, these findings characterize the phenotypic correlates of externalizing

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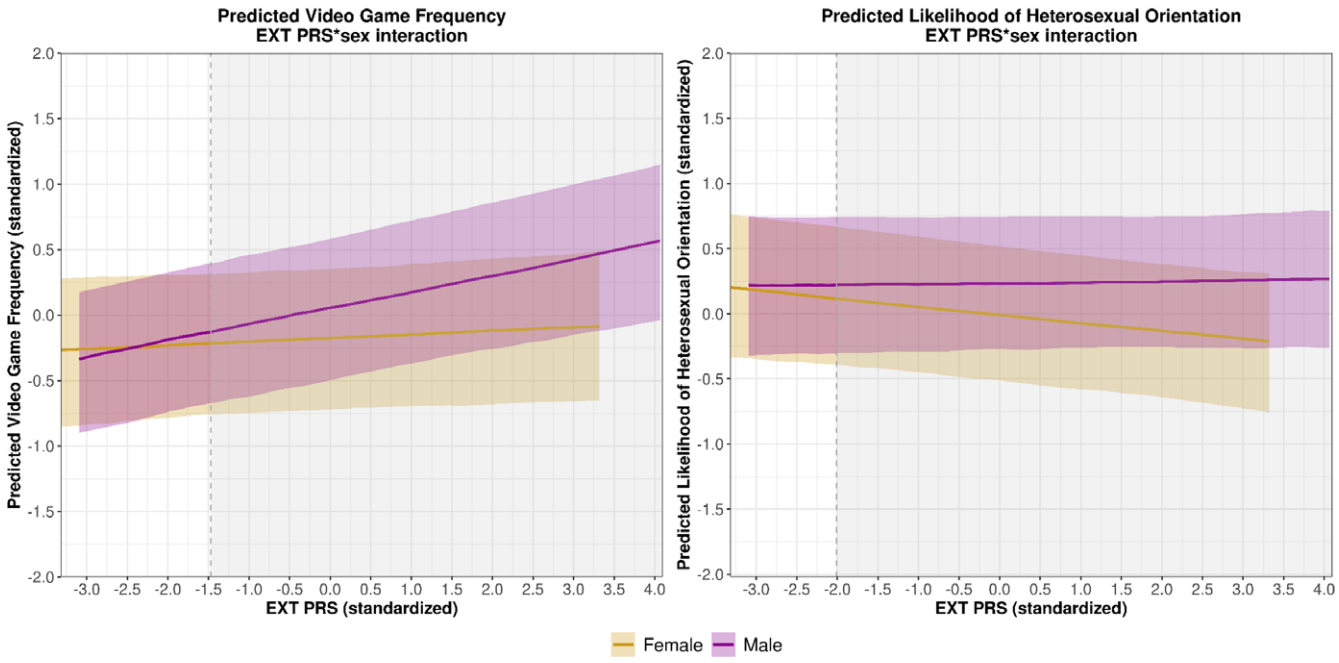


Figure 3. Interactions between EXT PGS and biological sex in the sample of participants genetically similar to EUR. Confidence intervals around the predicted probabilities are shown in yellow (female) and magenta (male). Gray shaded areas indicate Johnson–Neyman intervals for which the interaction is significant.

PGS – a measure of direct genetic effects as well as possible genetic nurture, other forms of gene–environment correlation, non-random mating patterns, population stratification, and confounding – in youth, largely prior to the onset of more severe presentations such as SUD and antisocial personality pathology.

Direct and indirect genetic effects

Our results reinforce recent work suggesting that disambiguating direct (i.e. direct influence of genotype on phenotype) and indirect (i.e. influence of one individual's genotype on the phenotype of another) genetic effects is essential to understanding the genetic etiology of complex phenotypes (Tan et al., 2024; Veller & Coop, 2024). We observed substantial attenuation of population-level PGS estimates after accounting for between-family (i.e. shared familial) effects, with few of the resulting within-family PGS estimates reaching statistical significance following Bonferroni correction. This pattern likely reflects a combination of indirect genetic effects – through population stratification, assortative mating, and/or gene–environment correlation – and reduced precision of within-family estimates. Indeed, observed power to detect the within-family effects obtained was at least 0.80 for fewer than one third of the statistically significant population estimates. Future research is needed with larger sample sizes to increase confidence in the observed associations and improve statistical power to detect within-family effects.

Although most significant within-family PGS associations were with externalizing phenotypes, there was still substantial (>50%) attenuation of effects across both waves for core externalizing phenotypes such as the CBCL externalizing and the CBCL DSM-5 conduct and oppositional defiant disorder scales. This magnitude of attenuation is greater than that reported in prior within-family analyses of EXT PGS conducted in both adult and youth samples (Karlsson Linnér et al., 2021; Tanksley et al., 2025) but more comparable to – though still greater than – that reported among 11–17-year-olds in the Environmental Risk (E-Risk) Longitudinal Twin Study (% attenuation = 46.5%; Tanksley et al., 2025). It is unclear whether certain methodological differences, such as the use of a latent externalizing factor (Karlsson Linnér et al., 2021) or cross-reporter (e.g. parent, teacher) average score (Tanksley et al., 2025) in prior work, may partially account for these differences in attenuation. Notably, however, consistent with patterns documented in Karlsson Linnér et al. (2021), the least attenuated within-family associations included phenotypes related to externalizing behavior and impulsivity, whereas associations with cognitive ability and socioeconomic indicators exhibited substantially greater attenuation within families. Taken together, these findings suggest that associations between EXT PGS and childhood phenotypes in the ABCD study likely reflect a combination of direct and indirect genetic effects, with the relative contribution of each varying by phenotype domain and measurement instrument.

Externalizing phenotypes and heterotypic continuity

Prior studies have shown that EXT PGS is associated with externalizing psychopathology, such as SUD symptoms, conduct disorder, and antisocial behaviors, in adolescence and adulthood (Brislin et al., 2024; Choi et al., 2025; Salvatore et al., 2015; Sasia, Jonas, Waszczuk, & Li, 2025). Our findings extend this work by demonstrating that PGS for externalizing behaviors is also linked to conduct disorder symptoms in children and early adolescents of European-like genetic ancestry, as well as early emerging externalizing phenotypes such as ADHD, ODD symptoms, inattention, and impulsivity. Moreover, associations between EXT PGS and ODD and conduct disorder symptoms at follow-up, for example, were substantially attenuated but still statistically significant when baseline CBCL externalizing problems were added as a covariate, whereas the association with ADHD symptoms did not survive multiple testing correction. Altogether, this pattern of findings aligns with models of externalizing psychopathology development

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and the concept of heterotypic continuity, whereby a general liability to trait impulsivity and behavioral disinhibition manifests differently across development – ADHD symptoms in early childhood may progress to ODD, conduct disorder, problematic substance use, and antisocial personality disorder – alongside changing environmental contexts (Beauchaine & McNulty, 2013; Iacono et al., 2008). As the associations with externalizing behavior were relatively consistent across reporters (i.e. youth, caregiver) and at least nominally significant in within-family analyses, it is possible that these early externalizing phenotypes represent developmentally proximal manifestations of stable externalizing liability in childhood and early adolescence.

Screen time as a correlate of externalizing genetic liability

Screen time and media use phenotypes (e.g. total weekend and weekday hours of use, frequency of playing mature-rated video games), measured at ages 9–13, featured prominently among the associations with EXT PGS and were represented among the few associations remaining significant in within-family analyses. Whether screen media use represents a simple proxy for inattentive symptoms or lies on a putatively causal path between genetic liability and externalizing behaviors remains to be established. Genetic liability for ADHD, measured via ADHD PGS, was previously associated with screen time in the ABCD sample (Yang et al., 2022). Thus, our results here may reflect the contribution of genetic variance in ADHD to the EXT PGS. Alternatively, screen media use may represent a modifiable mediator linking genetic risk to other childhood and early adolescent externalizing behaviors. Previous studies demonstrate modest associations between screen time and externalizing behaviors (Yang et al., 2022). Methods for causal inference are recommended to inform how the associations between externalizing genetic risk, screen time, and externalizing behaviors should be interpreted. Null findings for other phenotypes may be due to inherent limitations of within-family analyses, which are typically restricted to smaller subsamples and thus are less well-powered to detect possible effects.

Other notable correlates of externalizing genetic liability

In addition to externalizing and screen media use, EXT PGS was associated with lower cognitive performance and grades, more sleep disturbances, higher weight and waist circumference, and indicators of environmental disadvantage (e.g. parental education and income). This breadth of associations is consistent with transdiagnostic models of externalizing psychopathology and problem behavior theory, which posit that externalizing symptoms reflect a broad liability for behavioral dysregulation and self-control deficits that underpin myriad outcomes. Many of these associations are small in effect and may be environmentally mediated or reflect gene–environment correlation. Understanding how these associations arise and potentially confer risk for later outcomes will require further work that integrates genetic, family, and environmental data.

A comparison of the present study's findings with a recent PheWAS of SUD genetic liability in the ABCD study (Paul et al., preprint) reveals both convergence and differentiation. More specifically, externalizing, screen time, caffeine consumption, and sleep disturbance phenotypes showed largely convergent associations with SUDs and EXT PGS, whereas cognition and environmental adversity phenotypes exhibited more distinct patterns of association. Further, after covarying for baseline phenotypic externalizing problems, the majority of SUD PheWAS associations remained significant. Together, these findings suggest that there is both substantial overlap and variation across the phenotypic expression of SUD and externalizing genetic liability among children genetically similar to EUR. Alongside evidence of partially distinct genetic architecture underlying facets of impulsivity (Mallard et al., 2025) and associations between genetic liability to these facets and early substance initiation (Kinstler et al., 2025; Vilar-Ribó et al., 2025), these results highlight the utility of measuring and examining associations with both broad (e.g. "externalizing") and precise (e.g. specific SUDs and facets of impulsivity) phenotypes (Poore et al., 2023).

Sex moderation

We observed limited evidence of sex differences in associations between EXT PGS. Sex significantly moderated the association between EXT PGS and frequency of playing video games, such that there was a stronger positive association among males. This finding aligns with evidence that males typically engage more frequently in screen-based gaming activities and are at greater risk for problematic gaming, particularly when impulsivity or disinhibited traits are present (Lemmens, Valkenburg, & Gentile, 2015; Paulus, Ohmann, von Gontard, & Popow, 2018). It is possible that this finding reflects sex-specific behavioral expression of genetic risk and/or gendered socialization processes, such as cultural norms and parental expectations that encourage males more than females to play video games, that amplify observable genetic predispositions through differential environmental exposure (Forte et al., 2023; Marco-Gracia & Beltrán Tapia, 2022). Additionally, females higher in EXT PGS were more likely to endorse identifying as gay or lesbian. Externalizing captures a spectrum of behaviors that may reflect earlier disengagement from expected norms and lead to endorsement of phenotypes that are less common. Given the small number of individuals identifying as gay or lesbian, as well as the spectrum of behavior captured by "externalizing," caution should be taken regarding the interpretation of these results.

Limitations

Several limitations of the current study should be considered. First, analyses were restricted to youth genetically similar to EUR due to the exclusively European ancestry composition of the discovery GWAS and the well-documented reduction in PGS predictive accuracy accompanying increasing genetic distance between the discovery and target samples (Ding et al., 2023; Martin et al., 2019). Our findings may not equitably generalize to other populations, emphasizing the need for both more diverse GWAS samples and methodological advancements that improve gene identification efforts and the portability of polygenic scores across the spectrum of genetic ancestry.

Second, the discovery sample on externalizing behaviors was conducted primarily in adults (Karlsson Linnér et al., 2021), which may have limited the predictive ability of our EXT PGS given differences in developmental periods. However, the fact that we observed positive associations between a polygenic score for externalizing behaviors and early life externalizing symptom indicators suggests that genetic loci underpinning this construct may be stable, aligning with recent work (Choi et al., 2025; Deng et al., 2025) and underscoring the potential benefits of using adult-derived GWAS to examine polygenic associations in youth before some experience more impairing symptoms and consequences. Nevertheless, the

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field would greatly benefit from large GWAS on externalizing phenotypes conducted in children and adolescents and subsequent EXT PGS analyses in this population.

Third, although we examined sex as a potential moderator of EXT PGS–phenotype associations, the number of significant interactions was limited. This may reflect limited power to detect interactions with small effects and/or the relatively narrow developmental window examined (ages 9–13), a period during which sex differences in the behavioral expression of genetic liability may be subtle or still emerging (see also Choi et al., 2025). Biological variation in pubertal timing, as well as gendered socialization and contextual factors, could also mask or moderate these associations, an important area for future research inquiry. The PGS training data combined male and female participants (Karlsson Linnér et al., 2021). Future GWAS of adult EXT could compute the EXT factor separately for males and females, allowing separate scores that may not be perfectly correlated and could reveal more differences.

Finally, the PheWAS approach does not inherently yield insights about mechanisms underlying the associations identified. The within-family analyses – though less well-powered than the primary analyses – suggested that many of the associations arose as a combination of direct (i.e. causal genetic influences) and indirect (e.g. through genetic influences on parental behavior) genetic effects, likely in addition to various sources of confounding. Although the associations that persisted within-family are not fully attributable to population stratification, assortative mating, or passive gene-environmental correlation (e.g. family socioeconomic status, neighborhood-level exposures that are correlated with EXT PGS), they may still be vulnerable to confounding from active or evocative gene-environment correlation, such as prenatal exposures and peer behavior that are associated with EXT PGS and differ between siblings. Examining such factors, particularly in larger samples of siblings, as well as triangulating evidence across complementary approaches such as longitudinal mediation analyses, Mendelian Randomization, and dynastic effect ("genetic nurture") models will be important for improving mechanistic understanding.

Conclusion

In the current study, we present a phenome-wide atlas of associations between an externalizing polygenic score and phenotypic measures in childhood and early adolescence. Many of these associations were attenuated in within-family analyses, suggesting that they may arise from confounding by a combination of population stratification, assortative mating, and gene–environment correlation. Future work that considers possible mechanisms of these associations, such as indirect genetic effects, will be a valuable addition to the literature. Several associations with conduct problems, impulsivity, and screen time were robust to these forms of confounding. It is unclear whether screen time/media use is best understood as an expression of predisposition toward reward-seeking behavior and/or an etiological factor in externalizing, and studies that apply causal methods to test these competing hypotheses are recommended. Overall, our findings highlight the utility of using an adult GWAS-derived externalizing PGS to examine potentially correlated phenotypes in youth who have not yet exhibited more severe externalizing behaviors. Researchers could explore whether targeting externalizing risk earlier in the developmental course may offset the expression of genetic vulnerability and correlated risk factors that could emerge as more impairing externalizing behaviors in adulthood.

Supplementary material. The supplementary material for this article can be found at http://doi.org/10.1017/S003329172610631X.

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