Gene-Environment Interplay Beyond Interactions: Psychosocial Environments Mediate Genetic Effects Underlying Externalizing Behavior Trajectories

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Abstract

Studies using polygenic scores (PGS) often focus on one form of gene-environment interplay–interaction–while neglecting the possibility of mediation, where genetic effects operate indirectly through psychosocial environments. In this study, we used data from the National Longitudinal Study of Adolescent to Adult Health (N = 20,745) to characterize latent trajectories of substance use (SUB) and antisocial behavior (ASB) from ages 13 to 41 and computed PGS (N = 5,025) for externalizing behaviors to investigate both interaction and mediation effects for SUB and ASB trajectories. Environmental factors examined were supportive parenting, delinquent peer affiliation, school connectedness, and neighborhood connectedness. Results showed no evidence of interaction effects. The association of PGS with SUB and ASB trajectories operated *indirectly* through psychosocial environments, most prominently via deviant peer affiliation, which mediated 16.5 - 37.3% of total genetic effects. Findings highlight how the interplay between nature and nurture goes beyond interactions alone.

Keywords: gene-environment interplay, externalizing behavior, polygenic scores, indirect effects, development.

Externalizing (EXT) behaviors are characterized by impulsivity and undercontrol, typically manifested in observable actions towards the external environment (Krueger et al., 2002). EXT behaviors in adolescence are associated with negative outcomes in adulthood, including lower educational achievement and more legal difficulties (Gornik et al., 2022), lower income (Vergunst et al., 2023), and emotional problems such as depression and anxiety (Hamdi & Iacono, 2014). Several environmental risk factors for EXT behaviors (e.g., poor parental monitoring, deviant peer affiliation) have been identified (Fortuin et al., 2015; Pinquart, 2017), and many intervention programs target these risk factors (Tully & Hunt, 2016). However, not all individuals who experience these risk factors exhibit EXT problems during adolescence or even later in life. Interplay between the environment and individual factors, such as genetics, may impact the development of EXT behaviors (Neiderhiser & Chen, 2023). Investigation of mechanisms of gene-environment interplay will not only add to our etiological understanding of EXT behaviors, but also help to identify at-risk individuals who may be most influenced by adverse environmental contagions (J. Li et al., 2019). However, much remains unknown regarding how gene-environment interplay unfolds over time for the development of EXT behaviors, especially now that this field has moved beyond candidate gene approaches into the post-genome-wide association era (Barr & Dick, 2019).

Genetics of EXT

Twin studies suggest that between 50-80% of the variation in EXT behaviors is attributable to genetic factors within a given population (Krueger et al., 2002). More recently, genome wide association studies (GWASs) have identified an emerging number of single nucleotide polymorphisms (SNPs) associated with EXT behaviors. Karlsson-Linnér and colleagues (2021) conducted a GWAS of EXT behaviors in a pooled sample of 1.5 million individuals, for which a

genetic factor for EXT was estimated using GWAS summary statistics for problematic alcohol use, lifetime smoking initiation, lifetime cannabis use, general risk tolerance, attention-deficit/hyperactivity disorder (ADHD), age at first sex, and number of sexual partners. Their GWAS identified 579 SNPs associated with the EXT factor, including variants in cell adhesion molecule 2 gene, paired basic amino acid cleaving enzyme gene, and other genes related to self-regulation and risk-tolerance, highlighting a robust genetic basis for the development of EXT.

This GWAS, along with several others conducted on specific EXT-related constructs such as attention-deficit/hyperactivity disorder (Demontis et al., 2019), antisocial behaviors (ASB; Tielbeek et al., 2017), and alcohol dependence (Walters et al., 2018), have shown that EXT behaviors are *polygenic* (Plomin & Simpson, 2013), such that they are not influenced by any single gene alone, but by many SNPs across the genome, each exerting a small effect. Researchers can quantify polygenic risk for EXT behaviors using polygenic scores (PGS), which are calculated as the sum of the number of risk alleles an individual carries across the genome, weighted by the risk alleles' associations with EXT behaviors (Purcell et al., 2007). However, genes alone do not explain all variance underlying EXT outcomes. The development of EXT behaviors is also influenced by the *interplay* between genetic and environment influences (Plomin & Viding, 2022). For one, genetic effects may be moderated by exposures to psychosocial environments (i.e., gene-environment interaction; GxE). In fact, genomic research has historically centered their investigations around GxE underlying EXT outcomes. In contrast, few polygenic-environment studies have formally explored the possibility that psychosocial environments may mediate associations between polygenic risks and outcomes.

Gene-Environment Interactions Underlying EXT behaviors

The prominence of GxE effects for EXT behaviors have been well-characterized in twin studies (Hicks et al., 2009), which have generally shown that additive genetic effects underlying EXT are magnified in adverse environments (Samek et al., 2017). These studies on GxE have significant theoretical importance, as they describe the boundaries of genetic influences on EXT behaviors across varying socioenvironmental contexts and support downstream investigation of developmental mechanisms (i.e., differential susceptibility vs. diathesis-stress) and neurocognitive factors (i.e., temperament) for EXT behaviors (Roisman et al., 2012). A limitation of twin studies is that genetic, environmental, and GxE effects can only be estimated through variance decomposition rather than directly measured. Thus, it remains unclear how SNPs across the genome transact with environmental influences in the development of EXT.

PGS can be used to characterize SNP effects in the context of GxE. Of note, PGS generated from the GWAS performed on EXT (Karlsson Linnér et al., 2021) explained 10% of the variance in EXT outcomes across two separate samples. Yet, while GxE studies for EXT that leverage PGS are still in their infancy, the emerging pattern of results from these studies have been inconclusive at best. We summarize several of these findings here. First, He and Li (2021) used data from The National Longitudinal Study of Adolescent to Adult Health (Add Health; N = 4,722) and reported no significant ADHD PGS x maltreatment exposure interaction in predicting ADHD symptoms. Ksinan and colleagues (2022) also did not detect a significant interaction between PGS for risky behaviors and maternal closeness in predicting alcohol use, cannabis use, and ASB in adulthood in Add Health. Leveraging the Adolescent Brain Cognitive Development Study (ABCD; N = 5,991), a study by Su and colleagues studies (2022) found no robust interaction of PGS for alcohol use disorder with parenting style and family conflict in predicting childhood impulsivity. A study by Trevino et al. (2024) used the same ABCD dataset, PGS, and

environmental variables and found no evidence of GxE underlying adolescent rule-breaking behaviors and aggressive behaviors. Lastly, a study of 76,465 individuals by Hannigan and colleagues (2024) in the Norwegian Mother, Father, and Child Cohort Study found no evidence for GxE between PGS for ADHD and maternal alcohol use in predicting childhood behavioral problems.

In prior studies that did provide evidence for GxE, findings either showed small effect sizes or had noteworthy limitations. For example, based on a sample of children (N = 6,687) participating in the Twins Early Development Study, Plomin and Colleagues (2022) reported that the interaction of PGS for ADHD with a general environmental risk principal component (i.e., family socioeconomic status, medical risk, household chaos, maternal postnatal depression, life events) explained only up to 0.4% of the variance in EXT psychopathology (i.e., conduct disorder symptoms). Another study from the Quebec Longitudinal Study of Child Development (N = 721) found a significant GxE between PGS for ASB and harsh parenting in predicting ASB at age 17, but that effect was not replicated at age 13 or 15 (Acland et al., 2024). Lastly, Salvatore and colleagues (2015) analyzed data from the Collaborative Study on the Genetics of Alcoholism (N = 246 adolescents and 190 young adults) and reported significant interactions of PGS for EXT with parental monitoring and peer deviance in predicting criterion counts for alcohol and illicit drug dependence and abuse, antisocial personality disorder, and conduct disorder in the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*), 4th Edition. However, the authors computed PGS using GWAS summary statistics generated from a sample of relatives with known alcohol use problems who were enrolled in the same study, possibly leading to an overfitted measure of genetic risk.

Overall, despite the predictive power afforded by employing PGS, GxE effects for EXT outcomes remain elusive. Contradictory results from the above studies may be due to variability in social environments, EXT phenotypes (i.e., ADHD, AUD, rule-breaking and aggressive behaviors) and age groups that were investigated, whereas future research may benefit from modeling and comparing GxE effects for multiple behaviors and multiple environments across development (Harden et al., 2015). Further investigation of GxE using PGS is warranted by its clinical significance, as a better understanding of PGS-environment interaction potentially enables the identification of individuals most susceptible to genetic and environmental risks or most receptive of preventive and therapeutic interventions (Manuck & McCaffery, 2014).

The Case for Mediation in Underlying Gene-Environment Interplay

One of the challenges in examining GxE is the prominence of gene-environment correlations, or rGE (Boivin et al., 2013; Scarr & McCartney, 1983). Traditionally, tests of GxE assume independence between genetic and environmental factors (Duncan & Kefford, 2021). A correlation between genetic and environmental factors (i.e., rGE) is thought to inflate the false-positive rate for testing GxE and confound causal inferences (Jaffee & Price, 2012). To account for rGE, researchers have residualized the genetic and the environment measure on one another or controlled for their quadratic effects (Dick et al., 2015; Salvatore et al., 2014). Others assume gene-environment independence without explicitly modeling rGE (Plomin et al., 2022).

However, most psychosocial environmental variables are known to be quite heritable themselves (Kendler & Baker, 2007). As such, the presence of rGE may reflect more than just a statistical confound, but rather, a related phenomenon where certain environments might *mediate* genetic effects on EXT. This is supported by many twin/adoption studies. For example, heritable factors related to temperamental traits have been shown to evoke a harsher parenting style, which

partially mediates the genetic effects on early EXT behavior (Klahr et al., 2013). Another study by Schulz-Heik and colleagues (2010) leveraged the twin sample in Add Health and found that maltreatment was associated with conduct problems indirectly through shared genetic influences, which accounted for 62-74% of their total covariance.

Compelling evidence has also emerged with respect to psychosocial environments as mediators of PGS effects on EXT outcomes. Using data from the Add Health (N = 7,674), a study by Li (2019) revealed that PGS for ADHD was not only directly but also indirectly associated with trajectories of EXT behaviors (i.e., substance use and ASB) through the effects of the school environment. Likewise, based on a Dutch longitudinal sample of adolescents (N = 2,734; TRacking Adolescents' Individual Lives Survey), a study by Kretschmer and colleagues (2022) showed that the association between PGS for EXT and EXT behaviors in early adulthood (i.e., aggressive behavior, ADHD symptoms, risk tolerance, substance use behavior, and sexual risk-taking) was partially explained by the effects PGS on family dysfunction in childhood and adolescence, although the mediation effect was only significant when childhood EXT behaviors were not accounted for. These studies and others (Baldwin et al., 2023; Elam et al., 2022) suggest that certain environments, such as adverse childhood experiences, parental relationships and peer influences, may serve as indirect pathways linking genetic risks and EXT phenotypes. The finding of psychosocial environments as mediators of genetic effects may indicate a form of a developmental cascade, where genetic effects for EXT may gradually accumulate "outside of the skin" in the form of environmental protective and risk factors (Elam et al., 2023; Reiss & Leve, 2007). On the other hand, this finding may also mean that even highly heritable traits and conditions like EXT problems can still be mitigated via psychosocial interventions, suggesting malleability in heritability (Jaffee & Price, 2007).

While there is rather consistent support for environmental mediation of PGS effects, the environmental mediator and the magnitude of the mediation effect may vary based on the operationalization of EXT and by age. Research on multiple EXT phenotypes across development may offer novel insights into how mediation effects operate across development (DiLalla & DiLalla, 2018). Moreover, moderated and mediated forms of gene-environment interplay may operate simultaneously (Lemery-Chalfant et al., 2013). To illustrate, children with high genetic liability for EXT may evoke less supportive parenting from their parents that in turn, prospectively predict worse EXT outcomes (de la Paz et al., 2023). At the same time, low levels of supportive parenting may simultaneously moderate the genetic effects, such that the association of the child's genetic risks with EXT behaviors becomes stronger. It is also possible that one form of gene-environment interplay may be particularly prominent during certain developmental periods but not others (Kendler, 2010). For instance, a prior study by Samek and colleagues (2015) leveraged 1,382 twin pairs from the Minnesota Twin Family Study and examined GxE and rGE effects of parent-child relationship problems on ASB and substance use behaviors (SUB). They found that while GxE was prominent in earlier developmental periods (i.e., late adolescence), rGE may be responsible for developmental changes in ASB and SUB in adulthood (Kendler, 2010). It is only possible through modeling moderation and mediation in parallel within the same model to illustrate a more saturated picture of how genetic and environmental effects operate on EXT behaviors.

Adolescent Psychosocial Environments for Gene-Environment Interplay

Adolescence is a crucial developmental period characterized by heightened neural and social plasticity: adolescents develop rapidly in terms of their representation of the social world and have high sensitivity to emotions and to social contexts and relationships (Baker et al., 2025;

Sebastian et al., 2010). The navigation of social environments in adolescence therefore has important implications for downstream development and adjustment, including for EXT behaviors, often above and beyond experiences earlier in life (Andersen et al., 2021; Kendler, Jaffee, et al., 2011). For the current study, we focus on a subset of prominent adolescent psychosocial environments that have well-established associations with EXT behaviors (Brumley & Jaffee, 2016): parent (Pinquart, 2017), peer (Reijntjes et al., 2011), school (Wang et al., 2020), and neighborhood environments (Jennings et al., 2018). As the very first social relationships one establishes, relationships with parents have long lasting effect on EXT behaviors (Gard et al., 2017). Specifically, a meta-analysis by Pinquart (2017) showed that a lack of *supportive parenting* (e.g., warmth) was one of the most powerful predictors of future EXT behaviors. Regarding peer environment, *delinquent peer affiliation*, a crucial factor to consider as adolescents gain autonomy in selecting their social environments (Kendler et al., 2007), was found to socialize adolescents towards developing more EXT problems (Monahan et al., 2014). Finally, school and neighborhood are broader social institutions where parental and peer contexts are situated (Bronfenbrenner & Ceci, 1994). In particular, poor *school connectedness* (e.g., feelings of belonginess and support from others in school) and *neighborhood connectedness* (e.g., socialization and cohesion with neighbors) predict higher levels of EXT behaviors in the future (Morrison et al., 2019; Visser et al., 2021). Collectively, these four variables represent an array of psychosocial environments across multiple levels of analysis that may shape the development of EXT behaviors through gene-environment interplay (Reiss & Leve, 2007).

While these environmental variables have indeed been found to moderate and/or mediate genetic effects (Boardman et al., 2014; Hicks et al., 2009; Kendler, Gardner, et al., 2011; J. J. Li, 2019; Meyers et al., 2013; Samek et al., 2017), many studies examined one variable at a time,

ignoring the possibility that different environments may respond to and interact with heritable influences in parallel. Importantly, spurious gene-environment interplay may arise due to confounding by other correlated environmental factors (VanderWeele et al., 2013). For example, a twin study by Hicks and colleagues (2009) found significant GxE effects on *DSM* disorders with each of four correlated (r = .18 - .57) environments: academic engagement, peer affiliation, parent-child relationship, and stressful life events. However, because GxE was tested in separate models for each environment without covarying out other environmental variables, it is unclear which particular environment was the most relevant factor driving the observed GxE effects. Therefore, it is important to investigate the conditional effects of multiple environmental factors by modeling them in parallel models of gene-environment interplay.

Heterogeneity in EXT Behaviors

Another caveat in the study of EXT is its operationalization. EXT encompasses multiple dimensions of behaviors that not only frequently co-occur but are also highly heterogenous in their presentation and etiology (Burt & Klump, 2012; Mullins-Sweatt et al., 2022; Wright et al., 2017). Substance use behaviors (SUB) and antisocial behaviors (ASB) are two prominent dimensions of EXT behaviors (Krueger et al., 2007) that have clear connections to disorders and clinical syndromes in the *DSM* (American Psychiatric Association, 2013). Importantly, SUB and ASB have been associated with both shared and unique genetic signatures (Krueger et al., 2002; McAdams et al., 2012), cognitive and personality markers (Brislin & Patrick, 2019; Hall et al., 2021; Ruiz et al., 2008), and psychosocial factors (Buil et al., 2017; Obando et al., 2014).

Much of the previous research on gene-environment interplay overlooks the heterogeneity in EXT behaviors by combining several traits into EXT composite scores (Hatoum et al., 2018; Roskam, 2019; Salvatore et al., 2015; Samek et al., 2015). For example, a GxE study by

Kretschmer and colleagues (2022) measured EXT in adulthood using a composite score of self-report aggressive behavior, ADHD symptoms, risk tolerance, substance use, and sexual risk taking. The degree to which their results are generalizable, therefore, depends on how similarly EXT is operationalized across samples. In contrast, studies that explicitly address such phenotypic heterogeneity may have the opportunity to unveil on the generality vs. specificity in the etiology of EXT behaviors (Wendt et al., 2020). For example, a study by Elam and colleagues (2021) controlled for the covariance between aggression and substance use and discovered an specific genetic pathway to adult substance use disorders through substance-related offending. The study of gene-environment interplay may similarly benefit from separating heterogeneous EXT behaviors, such as SUB and ASB.

Developmental Considerations in Gene-Environment Interplay

Finally, development is a critical consideration when studying gene-environment interplay (Kendler, Jaffee, et al., 2011). The initiation, stability, and change in EXT behaviors differ at the individual level and may be related to genetics, environment factors, and their interplay. In their seminal work, Moffitt and colleagues (2002) described a taxonomy for the development of ASB using data from the Dunedin Longitudinal Study and classified individuals into trajectory groups, including a life-course-persistent (i.e., high levels of ASB across childhood and adulthood), an adolescence-limited (i.e., ASB peaks in adolescence but decrease afterwards), and a low-chronic trajectory (moderate levels of ASB from childhood to adulthood). Since then, latent-class trajectories have been consistently identified for both SUB and ASB in several prominent longitudinal datasets, including the Fast Track project (Miller et al., 2010) the Dunedin Multidisciplinary Health and Development Study (Odgers et al., 2008), among others.

Importantly, these trajectories groups may differ etiologically. For example, earlier-onset and persisting forms of EXT were theorized to be more neurogenetic in nature than EXT behaviors that begins and peaks in adolescence but decreases afterwards (Dilalla & Gottesman, 1989; Moffitt, 1993). A twin study by Isen and colleagues (Isen et al., 2022) showed higher levels of heritability for a persistent trajectory of delinquency but minimal heritability for other lower-risk trajectories. J. J. Li (2019) found that a PGS for ADHD was more strongly associated with an early onset trajectory of EXT than one characterized by low levels of EXT behaviors. Other studies have also found psychosocial, temperamental, and neurocognitive factors that were differentially associated with specific latent class trajectories of EXT behaviors (Barker & Maughan, 2009; Carlisi et al., 2020; Isen et al., 2022; J. J. Li, 2017; Sasia et al., 2025). Therefore, it is plausible that gene-environment interplay contributes to trajectory groups of EXT behaviors in distinctive ways. However, studies that directly test for gene-environment interplay on latent trajectories of EXT behaviors across the lifespan are rare.

The Current Study

In this study, we simultaneously tested two forms of gene-environment interplay on EXT behaviors where adolescent psychosocial environments (i.e., supportive parenting, delinquent peer affiliation, school connectedness, and neighborhood connectedness) were modeled to *moderate* and *mediate* effects of EXT PGS on developmental trajectories of SUB and ASB measured from ages 13 to 41. First, we hypothesize that adolescent psychosocial environments moderate the effect of EXT PGS in predicting trajectories of SUB and ASB, such that PGS effect is magnified in less supportive and higher risk environments. Second, we hypothesize that EXT PGS predicts less supportive and higher risk psychosocial environments, which in turn mediate the PGS effects on SUB and ASB trajectories. We note that the second hypothesis was not

preregistered. Finally, we explored whether there are differences in the moderation and mediation effects across our four correlated yet distinct environmental variables and across phenotypically and developmentally heterogenous forms of EXT behaviors.

Transparency and Openness

Preregistration

While our analyses regarding GxE were pre-registered (https://osf.io/859ma), our analyses regarding the mediation effects were not, and there were important deviations and additions to the preregistration, which we transparently report in this manuscript and Supplemental Table 1.

Data, materials, code, and online resources

This study used restricted-access data from the Add Health study (https://addhealth.cpc.unc.edu/data/#restricted-use). Analysis code and output are available online (https://github.com/lichendong/2024_ge_interplay_ext_trajectory).

Reporting

We report how we determined all data exclusions, all manipulations, and all measures in the current study.

Ethical approval

This study abides by the 1964 Helsinki Declaration, its amendments, and comparable ethical standards and was approved by the University of Wisconsin-Madison Institutional Review Board (UW-Madison IRB# 2015-1189). Consent to participate was obtained by the Add Health study.

Methods

Participants

Add Health is a prospective study of a nationally representative sample of adolescents in the United States who were in grades 7-12 during the 1994-95 school year. Over 90,000 adolescents

were initially sampled from the population through a stratified set of qualifying high schools. 20,745 adolescents were then randomly selected from the previous school sample and administered the in-home interview at Wave I, including oversamples from underrepresented populations. Including Wave I, participants were followed from adolescence to adulthood for five waves of data collection to date: Wave I (1994–1995, grades 7–12, $N = 20,745$), Wave II (1995–1996, grades 8–12, $N = 14,738$), Wave III (2001–2002, ages 18–26, $N = 15,197$), Wave IV (2007–2008, ages 24–32, $N = 15,701$), and Wave V (Aged 33-43, $N = 12,300$). Information on attrition across waves was documented by Harris and colleagues (2019). The full Add Health sample at Wave I included 50.5% female and 61.45% who self-identified racially-ethnically as "White" 23.17% "Black or African American", 7.64% "Asian or Pacific Islander", 3.57% "Native American", 16.99% "Hispanic", and 9.64% as "Other"[1].

At Wave IV, saliva samples were collected from consenting participants, who were then genotyped using the Illumina Human Omni-1Quad BeadChip for the majority of samples or the Illumina Human Omni-2.5 Quad BeadChip. Quality control procedures were conducted at the participant level (i.e., removing participants with call rates < 90%, poor duplicate concordance, unclear sex chromosomes, identifier abnormalities) and the marker level (i.e., removing variants with call rate < 90%, alignment uncertainty, tri-allelic status, duplicate discordance, ancestry specific Hardy-Weinberg Equilibrium $p < 5 \times 10^{-5}$, and minor allele frequency < 0.5%). Genotype data from Omni-1 and Omni-2.5 arrays were merged and imputed to the 1000 Genomes Phase 3 imputation panel using the GLGC/GIANT protocol. Imputed genotype data containing 9,664,514 markers were available for a total of 9,974 Add Health participants. The

[1] Proportions of self-identified racial-ethnic identities sum larger than 100% because participants are asked to indicate all appropriate identities that apply.

Add Health genotyped sample also included 2,014 individuals from 975 families with varying genetic resemblances (i.e., twin/sibling). To account for this nonindependence, we included one random individual from each genetically related cluster in our analyses.

Genetic ancestry refers to genomic similarities that result from inheriting DNA from common ancestors. Population stratification can arise due to differences in genetic variation between genetic ancestries and may confound genotype-phenotype associations. We operationalized the genetic ancestry of Add Health participants using genetic principal components (PCs) that were extracted from the full genotyped sample (Braudt & Harris, 2020). To form the European, African, East Asian, and Hispanic genetic ancestries, means and standard deviations of the first two PCs were calculated for groups of participants who self-identified as non-Hispanic white, non-Hispanic Black, Asian, and Hispanic, respectively. Participants were considered genetically similar to one ancestry group if they fell within two standard deviations above or below the means of the first two PCs for that respective group.

Race-ethnicity, on the other hand, are "a socio-politically constructed system for classifying and ranking human beings according to subjective beliefs about shared ancestry based on perceived innate biological similarities" (National Academies of Sciences, Engineering, and Medicine et al., 2023). Importantly, race-ethnicity are social constructs and afford no biological/genetic interpretation. While race and ethnicity are not assumed to causally influence EXT behaviors, self-identified race-ethnicity are important covariates above and beyond genetic ancestry, because the social experiences associated with racial-ethnic identities, such as differences in culture and experiences of disadvantage and marginalization (Reck et al., 2024; Yasui & Dishion, 2007), may confound genetic and environmental effects on EXT behaviors, thereby confounding gene-environment interplay. While items in Add Health did not

comprehensively assess social experiences tied to race-ethnicity (e.g., cultural socialization), self-identified race-ethnicity at Wave I can be used to account for potential confounding.

To simultaneously control for population stratification and social experiences associated with racial-ethnic identities, we first stratified the Add Health participants into four subsamples of individuals with genetic similarity to the European, African, East Asian, and Hispanic ancestries. Further, we pruned down each subsample to participants who are concordant on their genetic ancestry designation and self-reported racial-ethnic identity (Price et al., 2006). For example, the European ancestry subsample only included individuals who are genetically similar to European ancestry and also self-identified as non-Hispanic White.

Our main analysis was conducted on 5,025 individuals with genetic similarity to European ancestry who also self-identified as non-Hispanic White, because of the large sample size and better portability of our PGS. This subsample is 53.1% female and has an average age of 16.01 (SD = 1.72) and household income of 51,429 dollars (SD = 48,053) at Wave 1. Supplemental Table 2 shows detailed descriptives statistics for other subsamples of individuals with genetic similarity to African (n = 1,728), East Asian (n = 382), and Hispanic (n = 773) ancestries.

Measures

Polygenic Scores for EXT (PGS_{EXT})

PGS_{EXT} was calculated based on a well-powered GWAS on EXT behaviors (Karlsson Linnér et al., 2021) in PRS-CS (Ge et al., 2019). Summary statistics from this GWAS were selected for computation because of its superior predictive performance relative to other GWASs (Demontis et al., 2019; Tielbeek et al., 2017; Walters et al., 2018), its use of Genomic Structural Equation Modeling to minimize measurement error, and its identification of genetic variants related to a broad spectrum of EXT behaviors, including both SUB and risk taking phenotypes.

Briefly, PRS-CS uses Bayesian continuous shrinkage priors to weight coefficients of individual SNPs in GWAS summary statistics based on external linkage disequilibrium reference panels to account for linkage disequilibrium and optimize posterior effect sizes of SNPs. Studies have found PGS generated from PRS-CS to have better predictive performance and generalizability across genetic ancestries (Ahern et al., 2023). The first 20 genetic PCs were estimated using GCTA (Yang et al., 2011), and PGS_{EXT} was residualized on the PCs to further control for population stratification and standardized within each ancestry group (Khan et al., 2022).

SUB

SUB was assessed from Waves I to V. Three highly similar items were assessed at each wave, measuring participants' alcohol, marijuana, and cigarette use (e.g., "During the past 30 days, on how many days did you use marijuana?"). These items were measured on different scales across waves and were therefore recoded to reflect a consistent scale ranging from 0 to 6, with zero indicating no substance use and six indicating daily/almost daily substance use. The items were then summed to create a composite score at each wave (range = 0-18). Composite scores were calculated only for participants with no missing data on individual items at each wave. Polychoric correlations were used to generate ordinal alphas as measures of reliability of the SUB scale across waves (ordinal αs = .82, .80, .68, .56, .50 for Wave I, II, III, IV and V). We note that the decrease in alphas over Waves was expected, and explained by the following: 1) Add Health participants attained legal access to substances as adults at Wave III; thus, there is more response variability (and lower alphas) after Wave III; 2) legality of marijuana in different states shifted across Waves; 3) later Waves of measurement were less zero-inflated due to initiation and higher levels of substance use; 4) older adults "specialize" in the use of certain

substances while adolescents are more likely to experiment multiple substances (Palmer et al., 2009), and/or 5) a change in response scale of the items at Wave IV and V.

ASB

ASB was assessed from Waves I to V. Five highly similar items were assessed at each wave, measuring participants' aggressive and non-aggressive rule-breaking behaviors (e.g., damaging property, stealing something greater than $50, selling drugs, pulling a knife or gun on someone, shooting or stabbing someone). While there were more items related to ASB in Add Health, only these items were measured across all five waves. Responses were dichotomized to reflect the presence/absence of each behavior and summed to create a composite score (range = 0-5) at each wave. Composite scores were calculated only for participants with no missing data on individual items at each wave. Ordinal alphas were calculated using polychoric correlations (ordinal αs = 87, .87, .81, .83, .83 for Wave I, II, III, IV and V).

Supportive Parenting

At Wave I, participants self-reported on how they were parented as adolescents: seven items and five items measured aspects of supportive parenting of the resident mother and father, respectively, including perceived parental care (e.g., "how much do you think your [parent] cares about you?"), closeness (e.g., "how close do you feel to your [parent]?"), warmth (e.g., "your [parent] is warm and loving toward you"), communication (e.g., "you are satisfied with the way your [parent] and you communicate with each other"), and overall satisfaction of the relationship (e.g., "overall, you are satisfied with your relationship with your [parent]"). The maternal and paternal scales both showed high reliability with Cronbach's αs = .85 and .88, respectively. A standardized composite score was therefore generated for each parent of individuals that has at least 60% of non-missing data across the items. The prorated average of supportive parenting

scores between the two parents (r = .45) was then used to measure overall supportive parenting in the family. Because single parentship may impact the level and interpretation of supportive parenting, single- vs. two-parent status was elicited as a covariate.

Delinquent Peer Affiliation

At Wave I, participants were asked how many of their three closest friends smoked at least one cigarette each day, smoked marijuana at least once a month, and drank alcohol at least once a month. Participants were also asked about how often they took part in a fight where their group of friends fought against another group of people in the past 12 months. These four items (smoking, marijuana, alcohol, group fighting) showed moderate reliability (α = .69) and were standardized to create a composite score of delinquent peer affiliation for individuals who have at least 60% of non-missing data across the items.

School Connectedness

At Wave I, six items assessed the participants' feelings of belongingness (e.g., "you feel like you are part of your school,"), interpersonal connectedness (e.g., "you feel close to people at your school,"), teacher support (e.g., "your teachers care a lot about you," "teachers treat students fairly"), and safety (e.g., "you feel safe in your school") in the school context. These items were rated on the same five-point scale and showed high reliability (α = .77). A standardized composite score was calculated from the scale to measure participant school connectedness for individuals who have at least 60% of non-missing data across the items.

Neighborhood Connectedness

At Wave I, six items measured neighborhood collective socialization (e.g., "you know most of the people in your neighborhood," "in the past month, you have stopped on the street to talk with someone who lives in your neighborhood"), satisfaction (e.g., "on the whole, how happy are

you with living in your neighborhood?"), and safety (e.g., "do you feel safe in your neighborhood?"). These items demonstrated moderate reliability (α = .64) and were standardized to create a composite score for neighborhood connectedness for individuals who have at least 60% of non-missing data across the items.

Analyses

Step 1: Growth Mixture Models (GMMs)

First, composite scores of SUB and ASB were modeled using GMMs across all five Waves of data in the full Add Health sample, spanning ages 13 to 41 (Sasia et al., 2025). GMM is a group-based analytic method to identify latent classes of growth trajectories that allows for within-class variation of the growth parameters (Jung & Wickrama, 2008). GMM was employed because alternative methods, such as latent growth curve analysis, assume that growth parameters fall into a single normal distribution, which may create biases and reduce our ability to capture qualitative differences across potential subtypes. Because of age heterogeneity within each Add Health Wave, data were grouped by participant age rather than by Wave of data collection, resulting in "missing data by design" (i.e., across 29 timepoints from age 13 to 41, each participant would have at most five valid observations at ages when Add Health collected their data). These missing data and missing composite scores of SUB and ASB at specific waves were accounted for using Full Information Maximum Likelihood Estimation. Zero-inflated Poisson models were estimated to account for non-normal distributions of SUB and ASB scores. Trajectories were modeled with intercept-only, linear, quadratic, and cubic trends, and the number of latent classes extracted varied from two to six. The optimal SUB and ASB models were then selected based on fit indices (i.e., Akaike Information Criterion [AIC], Bayesian Information Criterion [BIC], sample-adjusted BIC, and adjusted Lo-Mendell-Rubin [LMR] test),

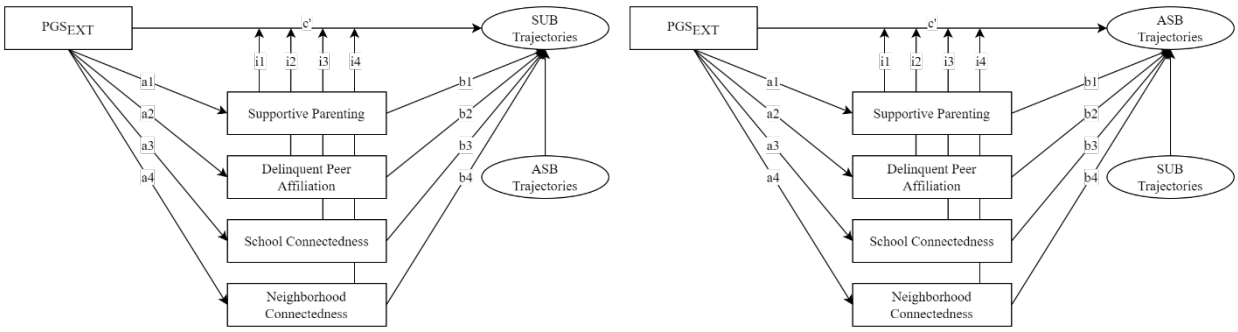
interpretability, parsimony, and consistency with prior literature. Entropy is also reported as a metric for classification quality (Celeux & Soromenho, 1996). GMMs were fit to the entire Add Health sample regardless of race/ethnicity or biological sex because prior studies have reported small to no differences in the form factors of SUB and ASB trajectories in Add Health (Morrison et al., 2019; Odgers et al., 2008). After selecting the best fitting models for SUB and ASB, most likely trajectory group membership is estimated for each participant, and this membership variable is used in downstream path analysis.

Step 2: Path Analysis

A path model (Figure 1) was estimated for each genetic ancestry subsample in Mplus (Muthén & Muthén, 1998). First, we regressed each environmental variable (see section below) on PGS_{EXT} and the covariates using linear regression (a paths). Next, we modeled membership into SUB trajectories and into ASB trajectories separately as functions of PGS_{EXT} (c' path), the psychosocial environments (b paths), their respective bivariate interactions (i paths), and the covariates using multinomial logistic regression. The environmental variables were therefore modeled in parallel as moderators and mediators of the effects of PGS_{EXT}. Missing data were handled using model using Full Information Maximum Likelihood estimation with Monte Carlo numerical integration. Nonparametric confidence intervals were obtained by percentile bootstrapping procedures using 1,500 bootstrap resamples (Preacher & Hayes, 2008).

Figure 1.

Path Model to Assess Environmental Moderation and Mediation of PGS_{EXT} Effects on SUB (left) and ASB (right) Trajectories



Note. SUB, substance use behavior. ASB, antisocial behavior. Other covariates and residual variances and covariances were modeled but omitted from this figure for clarity. Paths from PGS_{EXT} to the psychosocial environments were modeled as multiple regressions. Paths from PGS_{EXT}, the psychosocial environments, and their interactions to SUB and ASB trajectories were modeled as multinomial logistic regressions.

Covariates. Covariates for path analysis include participant biological sex, participant age, number of parents in the household (i.e., single- vs. two-parent family), parental education, and household income, all measured at Wave I. Biological sex, age, and number of parents were assessed via participant self-report. Two items assessed the highest level of education attained by residential parents of the participants and were recoded to represent six levels of education. These items were then averaged across the parents of each participant to estimate overall parental education. Parents of the participants also reported their annual family income before tax. Due to skewness, raw family income was log-transformed. These covariates and appropriate PGS-covariate interactions are controlled for in all regression paths in the path model. Finally, since SUB and ASB trajectories are interrelated due to a shared EXT factor (Cramer's $V = .20$), group membership of ASB was dummy coded and entered as a covariate when predicting SUB trajectories, and vice versa, to examine genetic and environmental interplay effects that are specific to either SUB or ASB. No covariates were used in the estimation of the GMMs.

Multiple Testing Correction. Given the multi-categorical nature of our trajectory variables, multiple significance tests were carried out for each interaction or mediation effect of interest. Thus, we used a more stringent, Bonferroni-corrected threshold (i.e., 99% Bootstrapped Confidence Interval) to determine statistical significance.

Results

Descriptive Statistics. Supplemental Table 2 shows descriptive statistics of all study variables in the full Add Health sample and in each genetic ancestry subsample. Supplemental Tables 3-6 show bivariate correlations between study variables within each subsample. Supplemental Tables 7-8 show information on missing data for GMM, and Supplemental Tables 9-10 show information on missing data for path analysis.

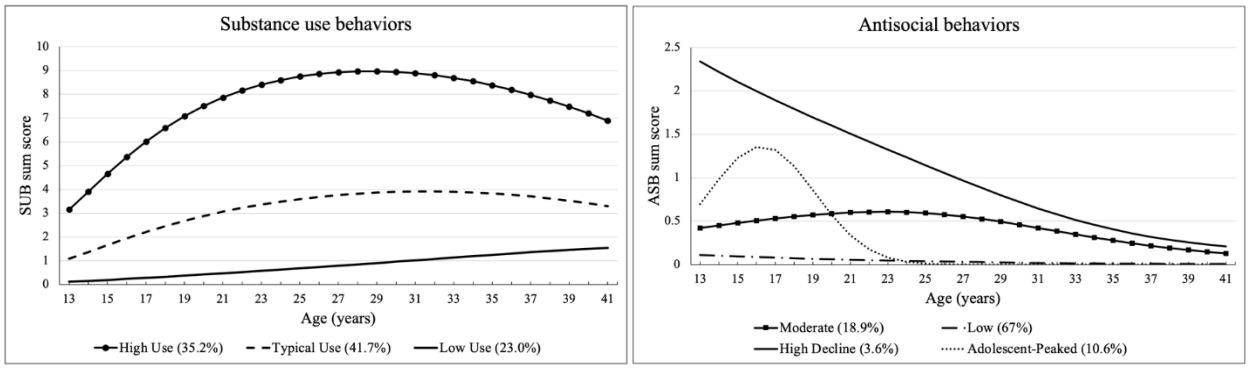
GMM of SUB and ASB. Supplemental Tables 11-12 show GMM fit indices for SUB and ASB, respectively. Fit indices for cubic models were not reported because those models failed to converge, likely because the model became too complicated for five waves of data. For SUB, the selected model was a three-class quadratic model, where individuals were classified into a Low Use trajectory (23.0%[1]), a Typical Use trajectory (41.7%), and a High Use trajectory (35.2%, see Figure 2). The Typical trajectory was labeled as such because it was the most prevalent. Although the six-class quadratic solution resulted in slightly better fit indices, the three-class model was preferred for parsimonious reasons (the six-class solution had almost identical classes) as well as theoretical and empirical alignment with prior studies (P. Chen & Jacobson, 2012; Windle, 2020). For ASB, the selected model was a four-class quadratic solution, including a Low trajectory (67.0%), a Moderate trajectory (18.9%), an Adolescent-Peaked trajectory (10.6%), and a High-Decline trajectory (3.6%, see Figure 2), which was supported by excellent fit indices and consistency with prior findings using samples of a similar age range (F. R. Chen & Jaffee, 2015; Odgers et al., 2008). We note that the selected ASB model has relatively low entropy (.58) and therefore further examined the classification table of the model (Supplemental Table 13). While the classification quality is better for the High-Decline and Low trajectories, Moderate and Adolescent-Peaked trajectories were classified with more error, which is noted as a limitation. The latent-class trajectories of SUB and of ASB that were the most prevalent among the entire Add Health sample (i.e., the Typical trajectory of SUB and the Low trajectory of ASB) were treated as reference trajectories for multinomial logistic paths in downstream path analysis. Within our European-ancestry subsample (N = 5,025), 2,171 individuals belong to the High trajectory, 746 to the Low trajectory, and 2,108 to the Typical trajectory of SUB. As for ASB, 91

[1] Percentage in the parentheses represents the proportion of the full Add Health sample at Wave I (N = 20,745).

individuals belong to the High-Decline trajectory, 643 to the moderate trajectory, 304 to the Adolescent-Peaked trajectory, and the vast majority, 3,987, to the Low trajectory.

Figure 2.

GMM Trajectories of SUB (left) and ASB (right) from Ages 13 to 41.



Note. SUB, substance use behavior. ASB, antisocial behavior. Estimated means of the latent class trajectories of SUB (i.e., frequency of alcohol, marijuana, and cigarette use) and ASB (i.e., property damage, stealing something greater than $50, selling drugs, pulling a knife or gun on someone, and shooting or stabbing someone) from age 13 to 41. The percentages calculated were based on the full Add Health sample (N = 20,745).

Environmental Main Effects. Supplemental Table 14 shows path analysis results for SUB and ASB among individuals with genetic similarity to European ancestry. Being 1 standard deviation (SD) higher in terms of delinquent peer affiliation led to an 88% increase in odds of belonging to the High trajectory (Odds Ratio [OR] = 1.88 [99% CI = 1.67 – 2.10]) and a 49% decrease in odds of belonging to the Low trajectory (OR = 0.51 [99% CI = 0.40 – 0.62]), relative to the Typical trajectory. With a 1 SD increase in school connectedness, the odds of belonging to the High relative to the Typical trajectory was reduced by 17% (OR = 0.83 [99% CI = 0.75 – 0.91]); the odds of belonging to the Low relative to the Typical trajectory was not significantly different (OR = 0.97 [99% CI = 0.85 – 1.12]). Supportive parenting did not significantly impact the odds of belonging to the High (OR = 0.98 [99% CI = 0.89 – 1.07]) or to the Low trajectory (OR = 1.12 [99% CI = 0.97 – 1.32]), relative to the Typical trajectory. Similarly, neighborhood connectedness did not significantly impact the odds of belonging to the High (OR = 0.98 [99% CI = 0.90 – 1.08]) or to the Low trajectory (OR = 0.89 [99% CI = 0.79 – 1.01]), relative to the Typical trajectory.

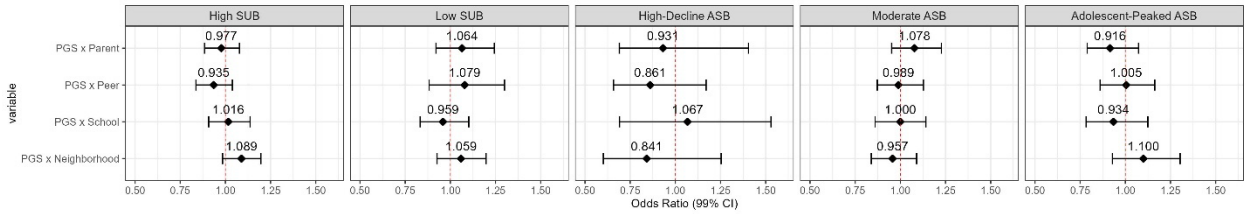
For ASB, being 1 SD higher in terms of supportive parenting led to a 19% decrease in odds of belonging to the Moderate trajectory (OR = 0.81 [99% CI = 0.72 – 0.93]) and a 19% decrease in odds of belonging to the Adolescent-Peaked trajectory (OR = 0.81 [99% CI = 0.70 – 0.93]) relative to the Low trajectory, but its association with odds of belonging to the High trajectory (OR = 0.83 [99% CI = 0.59 – 1.17]) did not reach significance. Being 1 SD higher in terms of delinquent peer affiliation was significantly associated with 250% greater odds of belonging to the High-Decline trajectory (OR = 3.50 [99% CI = 2.61 – 5.09]), 24% greater odds of belonging to the Moderate trajectory (OR = 1.24 [99% CI = 1.09 – 1.42]), and 117% greater odds of belonging to the Adolescent-Peaked trajectory (OR = 2.17 [99% CI = 1.87 – 2.56]), relative to

the Low trajectory. Being 1 SD higher in terms of school connectedness was associated with a 24% decrease in odds of belonging to the Adolescent-Peaked trajectory (OR = 0.76 [99% CI = 0.64– 0.89]) relative to the Low trajectory, while its association with odds of belonging to the High-Decline (OR = 0.69 [99% CI = 0.47 – 1.03]) or with the Moderate trajectory (OR = 0.90 [99% CI = 0.79 – 1.03]) did not reach statistical significance. Lastly, neighborhood connectedness was not significantly associated with the odds of belonging to the High-Decline (OR = 0.95 [99% CI = 0.68 – 1.41]), the Moderate (OR = 1.01 [99% CI = 0.89 – 1.16]), or the Adolescent-Peaked trajectory (OR = 1.00 [99% CI = 0.85 – 1.20]), relative to the Low trajectory.

GxE (Figure 3). For SUB, none of the interaction terms were statistically significant in predicting membership into the High trajectory relative to the Typical trajectory, including PGS_{EXT} interactions with supportive parenting (OR = 0.98 [99% CI = 0.89 – 1.08]), delinquent peer affiliation (OR = 0.94 [99% CI = 0.84 – 1.04]), school connectedness (OR = 1.02 [99% CI = 0.91 – 1.14]), or neighborhood connectedness (OR = 1.09 [99% CI = 0.98 – 1.20]). We also found no significant PGS_{EXT} interactions with supportive parenting (OR = 1.06 [99% CI =0.92 – 1.24]), delinquent peer affiliation (OR = 1.08 [99% CI = 0.88 – 1.30]), school connectedness (OR = 0.96 [99% CI = 0.83 – 1.10]), or neighborhood connectedness (OR = 1.06 [99% CI = 0.93 – 1.20]) in predicting membership into the Low relative to the Typical trajectory.

Figure 3.

GxE Effects (in ORs) between PGS_{EXT} and Psychosocial Environments in Relation to SUB and ASB Trajectories.



Note. SUB, substance use behavior. ASB, antisocial behavior. Parent, supportive parenting. Peer, delinquent peer affiliation. School, school connectedness. Neighbor, neighborhood connectedness. The SUB and ASB trajectories shown here were compared to Typical SUB trajectory and Low ASB trajectory, respectively. Point estimates of odds ratios are plotted and labeled. Error bars represent 99% confidence intervals obtained from nonparametric bootstrapping. Red dotted lines represent the null hypothesis (i.e., Odds Ratio = 1.00).

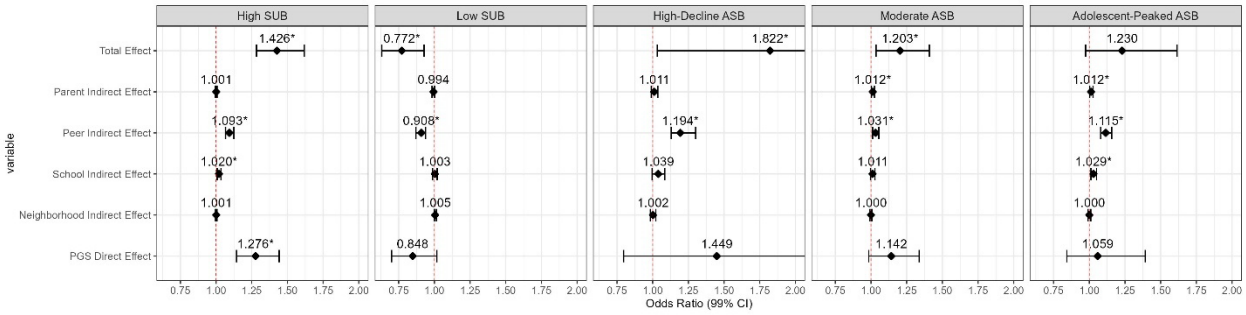
*, 99% confidence interval does not contain the null.

For ASB, GxE effects were not detected in the context of supportive parenting (OR = 0.93 [99% CI = 0.69 – 1.41]), delinquent peer affiliation (OR = 0.86 [99% CI = 0.66 – 1.17]), school connectedness (OR = 1.07 [99% CI = 0.69 – 1.53]), or neighborhood connectedness (OR = 0.84 [99% CI = 0.60 – 1.25]) in predicting membership into the High-Decline trajectory relative to the Low trajectory. Similarly, no GxE effect with supportive parenting (OR = 1.08 [99% CI =0.95 – 1.23]), delinquent peer affiliation (OR = 0.99 [99% CI = 0.87 – 1.13]), school connectedness (OR = 1.00 [99% CI = 0.86 – 1.14]), or neighborhood connectedness (OR = 0.96 [99% CI = 0.84 – 1.09]) was significant in predicting membership into the Moderate relative to the Low trajectory. Finally, no GxE effects were detected in the context of supportive parenting (OR = 0.92 [99% CI = 0.79 – 1.07]), delinquent peer affiliation (OR = 1.01 [99% CI = 0.86 – 1.16]), school connectedness (OR = 0.93 [99% CI =0.78 – 1.13]), or neighborhood connectedness (OR = 1.10 [99% CI = 0.93 – 1.30]) in predicting membership into the Adolescent-Peaked relative to the Low trajectory.

Mediation (Figure 4). Data were considered consistent with our theoretical mediation model if both the PGS_{EXT} total effect and the indirect effect via a psychosocial environment of interest were significant. PGS_{EXT} was found associated with all four psychosocial environments: a 1 SD increase in PGS_{EXT} was associated with .06 SD decrease in supportive parenting (β = .06 [99% CI = -.09 ~ -.02]), .12 SD increase in delinquent peer affiliation (β = .14 [99% CI = .11 ~ .18]), .11 SD decrease in school connectedness (β = -.11 [99% CI = -.14 ~ -.07]), and .05 SD decrease in neighborhood connectedness (β = -.05 [99% CI = -.08 ~ -.01]).

Figure 4.

Mediation Effect (in ORs) between PGS_{EXT} and Psychosocial Environments in Relation to SUB and ASB Trajectories.



Note. SUB, substance use behavior. ASB, antisocial behavior. Parent, supportive parenting. Peer, delinquent peer affiliation. School, school connectedness. Neighbor, neighborhood connectedness. The SUB and ASB trajectories shown here were compared to Typical SUB trajectory and Low ASB trajectory, respectively. Point estimates of odds ratios are plotted and labeled. Error bars represent 99% confidence intervals obtained from nonparametric bootstrapping. Red dotted lines represent the null hypothesis (i.e., Odds Ratio = 1.00).
*, 99% confidence interval does not contain the null.

For SUB, a significant PGS_{EXT} total effect was found in predicting the odds of belonging to the High trajectory, relative to the Typical trajectory. A 1 SD increase in PGS_{EXT} was associated with a 43% increase in these odds (total effect OR = 1.43 [99% CI = 1.28 – 1.62]). Indirect effects through delinquent peer affiliation and school connectedness were significant. A 1 SD increase in PGS_{EXT} was associated with a 9% increase in odds of belonging to the High trajectory indirectly through delinquent peer affiliation (peer indirect effect OR = 1.09 [99% CI =

1.07 – 1.12]) and a 2% increase in those odds indirectly through school connectedness (school indirect effect OR = 1.02 [99% CI = 1.01 – 1.04]). Delinquent peer affiliation mediated 25.1% of this total effect, while school connectedness mediated an additional 5.6%. The direct effect of PGS_{EXT} on the odds of belonging to the High trajectory remained statistically significant (direct effect OR = 1.28 [99% CI = 1.14 - 1.44]) after accounting for indirect effects through the environment. In addition, a significant PGS_{EXT} total effect was also found in predicting the odds of belonging to the Low trajectory, relative to the Typical trajectory. A 1 SD increase in PGS_{EXT} was associated with a 23% decrease in these odds (total effect OR = 0.77 [99% CI = 0.63 – 0.93]). The indirect effect through delinquent peer affiliation was found significant. A 1 SD increase in PGS_{EXT} was associated with an 9% decrease in odds of belonging to the Low trajectory indirectly through delinquent peer affiliation (peer indirect effect OR = 0.91 [99% CI = 0.87 – 0.94]). Delinquent peer affiliation mediated 37.3% of this total effect. The direct effect of PGS_{EXT} on odds of belonging to the Low trajectory became nonsignificant (direct effect OR = 0.85 [99% CI = 0.70 – 1.02]) after accounting for indirect effects through the environment.

For ASB, a significant PGS_{EXT} total effect was found in predicting the odds of belonging to the High-Decline trajectory, relative to the Low trajectory. A 1 SD increase in PGS_{EXT} was associated with an 82% increase in these odds (total effect OR = 1.82 [99% CI = 1.03 – 3.25]). The indirect effect through delinquent peer affiliation was found significant. A 1 SD increase in PGS_{EXT} was associated with a 19% increase in odds of belonging to the High-Decline trajectory indirectly through delinquent peer affiliation (peer indirect effect OR = 1.19 [99% CI = 1.13 – 1.30]). Delinquent peer affiliation mediated 29.6% of this total effect. The direct effect of PGS_{EXT} on odds of belonging to the High-Decline trajectory became nonsignificant (direct effect OR = 1.45 [99% CI = 0.80 – 2.61]) after accounting for indirect effects through the environment.

In addition, a significant PGS_{EXT} total effect was found in predicting the odds of belonging to the Moderate trajectory, relative to the Low trajectory. A 1 SD increase in PGS_{EXT} was associated with a 20% increase in these odds (total effect OR = 1.20 [99% CI = 1.04 – 1.41]). The indirect effects through supportive parenting and delinquent peer affiliation were significant. A 1 SD increase in PGS_{EXT} was associated with a 1% increase in odds of belonging to the Moderate trajectory indirectly through delinquent peer affiliation (parent indirect effect OR = 1.01 [99% CI = 1.00 – 1.03]) and a 3% increase in odds of belonging to the Moderate trajectory indirectly through delinquent peer affiliation (peer indirect effect OR = 1.03 [99% CI = 1.01 – 1.05]). Supportive parenting mediated 6.5% of this total effect, while delinquent peer affiliation mediated an additional 16.5%. The direct effect of PGS_{EXT} on odds of belonging to the Moderate trajectory became nonsignificant (direct effect OR = 1.14 [99% CI = 0.98 – 1.34]) after accounting for indirect effects through the environment. Finally, neither the total effect of PGS_{EXT} (total effect OR = 1.23 [99% CI = 0.97 – 1.61]) nor its direct effect (direct effect OR = 1.06 [99% CI = 0.84 – 1.39]) was significant in predicting the odds of belonging to the Adolescent-Peaked trajectory, relative to the Low trajectory.

Ancestry-Stratified Analyses. Path analysis results for individuals with genetic similarity to African ancestry, East Asian ancestry, and Hispanic ancestry are shown in Supplemental Table 15-17, respectively. In general, no robust GxE or mediation effect was found in these subsamples. The only exception is among individuals that are genetically similar to the African ancestry, where PGS_{EXT} has a significant total effect on the odds of belonging to the Adolescent-Peaked trajectory relative to the Low trajectory, and this effect was mediated by delinquent peer affiliation. This finding, which is different than our main findings among individuals with

genetic similarity to the European ancestry, may reflect heterogeneity in the manifestation of genetic risks for ASB across genetic ancestries and warrants future investigations.

Discussion

Despite the emergence of powerful PGS to capture genetic risks across the genome, gene-environment interplay continues to be a challenge to identify in the context of EXT behaviors. This is in part because most researchers tend to focus on testing for GxE without explicitly considering the possibility of environmental mediation of genetic effects. Studies of gene-environment interplay are further complicated by the excessive heterogeneity of EXT itself (in terms of typology and development). The current study addressed these issues by 1) accounting for the heterogeneity within EXT by examining latent class developmental trajectories of SUB or ASB over a 30-year period in Add Health, and 2) testing for interaction and mediation effects in parallel as they pertained to genetic and psychosocial factors related to EXT. Contrary to our first hypothesis, the results showed limited evidence for GxE effects in predicting SUB and ASB trajectories. However, we found that psychosocial environments, in particular delinquent peer affiliation, partially mediated PGS_{EXT} main effects on both SUB and ASB trajectories.

The developmental trajectories of SUB and ASB identified in the current study were generally consistent with trajectories groups reported in previous analyses (F. R. Chen & Jaffee, 2015; P. Chen & Jacobson, 2012; Odgers et al., 2008; Windle, 2020), each of which also demonstrating heterogeneous forms of development in EXT behaviors across adolescence and adulthood. For SUB trajectories, we found three distinct classes: High, Typical, and Low SUB trajectories. More individuals were in the Typical than the Low trajectory, suggesting that moderate levels of SUB across adolescence and adulthood may be normative (P. Chen & Jacobson, 2012), while individuals who demonstrated highest levels of SUB across adolescence

and adulthood (i.e., in the High trajectory) may experience unique challenges and vulnerabilities. For ASB trajectories, we found four distinct classes: High-Decline, Moderate, Adolescent-Peaked, and Low trajectories. Notably, a decline in the levels of ASB was observed even among individuals who had the highest levels of ASB across adolescence and adulthood (i.e., in the High-Decline trajectory), which may be attributable to attrition bias, a non-clinical sample, and/or a natural desistence from ASB by middle/late adulthood (Sweeten et al., 2013).

In terms of total effects of PGS_{EXT} in predicting the developmental trajectories, individuals with genetic risks were more likely to belong to trajectories characterized by higher levels SUB and ASB. PGS_{EXT} total effects were also the strongest in predicting the odds of belonging to trajectories characterized by the most severe trajectories (i.e., High SUB and High-Decline ASB), but were not significant in predicting the odds of belonging to the Adolescent-Peaked trajectories (J. J. Li, 2019), relative to the reference trajectories (i.e., Typical SUB and Low ASB). These findings were consistent with the developmental taxonomy: individuals who engage in the highest (albeit declining) levels of EXT behaviors across adolescence and adulthood may be subject to increased neurogenetic difficulties when compared to individuals with low levels of EXT behaviors and individuals who engage in relatively high levels of ASB in adolescence but age out during early adulthood (Moffitt, 1993; Sasia et al., 2025).

In terms of GxE, we did not find evidence that PGS_{EXT} effects were moderated by any of the environmental variables we examined in predicting the odds of belonging to the non-reference trajectories of SUB and of ASB. Our results add to a growing body of null findings with respect to GxE effects underlying EXT behaviors when using PGS (Hannigan et al., 2024; He & Li, 2022; Trevino et al., 2024). We offer several explanations for this increasingly common finding in the literature. First, PGS is traditionally computed as the additive sum of risk

alleles that an individual carries across the genome, weighted by the association of each allele with the target phenotype. As such, the estimation of GxE using a cross-product term with PGS is based on two assumptions: 1) all risk alleles interact with the environment; and 2) alleles that are more strongly associated with the target phenotype contribute more to the interaction effect (Duncan & Kefford, 2021). However, these assumptions can be violated, which contribute to biased, imprecise, or in our case, null GxE effects. Since allelic effects are expressed through different molecular pathways, groups of genetic loci that are functionally different may interact with the environment in different directions, magnitudes, or shapes, which are not captured by an additive interaction term. Second, certain forms of GxE (e.g., a "cross-over" interaction) may require genetic variants that have no main effect on the phenotype, but these types of variants are not likely identified by GWASs and computations for downstream PGS (Zhang & Belsky, 2022). Newer methods are being developed to optimize the estimation of GxE by reducing the measurement error in PGS (Miao et al., 2024) or incorporating functional annotation to prioritize genetic variants for GxE analysis (Watanabe et al., 2019). Future research on GxE may consider moving beyond traditional PGS computations and fully capitalize on these methods. Finally, although we and others (Ksinan et al., 2022; Samek et al., 2015) did not find evidence for GxE from the effects of psychosocial environments measured in adolescence, it is possible that GxE may be more prominent during other developmental epochs. For example, several twin studies have shown that supportive early childhood social environments (e.g., high parental emotional support, access to formal childcare, pre-school attendance, etc.) may attenuate the effect of genetic factors for problem behaviors (Cheung et al., 2014; Clark et al., 2018; Middeldorp et al., 2014; Tucker-Drob & Harden, 2013). Notably however, PGSxE studies that focus on childhood environments have been scarce (Plomin et al., 2022).

On the other hand, robust rGE have often been observed with respect to social environments in adolescence across numerous studies (de la Paz et al., 2023; Kretschmer et al., 2022; Ksinan et al., 2022; Kuo et al., 2021, 2022), alluding to the possibility that adolescent social environments may mediate the genetic effects for the development of EXT behaviors. Indeed, in the current study, rGE was observed with all four environmental measures, such that individuals with higher PGS_{EXT} were more likely to experience less supportive and riskier psychosocial environments, including less supportive parenting, higher affiliation with delinquent peers, and less school and neighborhood connectedness. It is possible that these associations were partly driven by the phenomenon of active rGE. For example, individuals with high genetic risks for EXT may be more likely to seek out the company of others who similarly engage in EXT behaviors (Mann et al., 2016). Engagement in EXT behaviors may change the adolescents' values and goals, making it harder for them to relate to their parents and others at school or in the neighborhood (Beerthuizen & and Brugman, 2016). Alternatively, there may be evocative rGE effects as well; for example, adolescents with higher genetic risks for EXT may be more likely sought by their delinquent peers and perceived negatively by their parents, typically developing peers, and others at school or in the community (Akcinar & Baydar, 2016; Vitaro et al., 2005). Last but not least, due to passive rGE, offspring genetic risks for EXT may be indirectly associated with their environments through the effects of their parents - who each contribute to 50% of their DNA to their offspring (Eilertsen et al., 2022; Kong et al., 2018). For example, parental EXT traits may lead to poor parental relationship, permissive parenting, and other environmental risks (M. Chen & Johnston, 2007; Hinnant et al., 2016). Passive rGE may also emerge indirectly via other demographic factors via parents (e.g., socioeconomic status, academic and occupational attainment, living in urban environments) that have downstream correlations with environmental

adversities (Brook et al., 2011). Future research could potentially utilize quasi-experimental (i.e., twin, adoption) designs to test these explanations and identify temperamental, neurocognitive, behavioral, contextual, and sociodemographic factors that explain rGE.

Our findings also showed that PGS_{EXT} effects in predicting SUB and ASB trajectory memberships were partially mediated by adolescent psychosocial environments, adding to existing evidence that at least part of the risk conferring mechanisms measured by PGS_{EXT} may manifest indirectly and non-genetically via the effects of social experiences in adolescence (Baldwin et al., 2023; Elam et al., 2022; Kretschmer et al., 2022; J. J. Li, 2019). Notably, indirect effects of PGS_{EXT} via delinquent peer affiliation were significant across our models for different trajectories of SUB and ASB, suggesting that mediation by delinquent peer affiliation may be a general etiological mechanism that is broadly relevant to phenotypically and developmentally heterogenous forms of EXT. Indirect effects via delinquent peer affiliation had the largest effect sizes, explaining between 16.5% and 37.3% of the PGS_{EXT} total effects above and beyond other psychosocial environments. These results suggest that delinquent peer affiliation may be one major reason why individuals with higher genetic risks were more likely to develop along the more maladaptive trajectories of SUB and ASB (Kuo et al., 2021). Relative to other (i.e., parent, school) social contexts, norms of EXT behaviors in peer groups may be particularly impactful during adolescence, a developmental period characterized by increased social conformity, socio-affective sensitivity, and autonomy seeking (Busching & Krahé, 2018; Fortuin et al., 2015). Affiliation with delinquent peer groups may therefore serve as an intermediate pathway for the effect of PGS_{EXT}, where genetically at-risk adolescents may become exposed to more delinquent peers, which in turn contributes to the development of EXT behaviors (Thompson et al., 2020). Indeed, iatrogenic effects have been observed for peer-based treatment programs, where

individuals high levels of EXT behavior are grouped together and therefore exposed to "deviancy training", potentially because EXT behaviors are normative and rewarded in those groups (Dishion et al., 1999; Moos, 2005). Programs that aim to promote prosocial behaviors in groups of adolescents, however, have yielded promising effects (Caprara et al., 2014).

In addition to mediation by delinquent peer affiliation, supportive parenting partially mediated the PGS_{EXT} effect in predicting the odds of belonging to the Moderate ASB trajectory relative to the Low ASB trajectory. Less supportive parenting may explain why individuals with higher genetic risks were likely to show moderate levels of ASB across adolescence and adulthood. Adolescents who do not have a supportive relationship with parents may learn maladaptive interpersonal styles, lack social support in face of stress, develop low self-efficacy and -esteem, and fail to develop self-regulation skills, all of which may then contribute to increased levels of ASB (McKee et al., 2008; Rohner, 2004). Despite the significant total effect of PGS_{EXT}, there was no significant indirect effect via supportive parenting in predicting odds of membership into the High-Decline trajectory relative to the Low ASB trajectory. Several studies have found that trajectories like the High-Decline ASB trajectory may be characterized by high heritability and neurogenetic difficulties (Carlisi et al., 2020; Isen et al., 2022). Environmental factors like supportive parenting may have limited impact on the development of High-Decline ASB, thus explaining why it did not mediate the PGS_{EXT} effects on High-Decline ASB. Small cell size of the High-Decline ASB trajectory (i.e., $n = 91$) may also have contributed to the non-significance of this indirect effect.

Moreover, school connectedness partially mediated the PGS_{EXT} effect in predicting the odds of belonging to the High SUB trajectory relative to the Typical SUB trajectory, above and beyond the effects of delinquent peer affiliation. Genetically susceptible adolescents may

subsequently feel less accepted or safe at school, less socially supported, more emotionally distressed, and less inclined to conform to social norms (Gaete et al., 2018). These pressures may in turn increase the risks for engaging in maladaptive substance use (Fletcher et al., 2009). Despite the significant total effect of PGS_{EXT}, there was no significant indirect effect via school connectedness in predicting odds of membership into the Low relative to the Typical SUB trajectory. Our GMM analysis showed that medium levels (i.e., the Typical trajectory), not low levels of SUB, were in fact the most normative of the Add Health sample. It is possible that individuals who belong to the Typical SUB trajectory were not different from those in the Low SUB trajectory in maladaptive ways, and therefore were not differentiated by contextual protective and risk factors like school connectedness. This possibility is consistent with preliminary findings that contextual factors (e.g., peer behaviors, paternal drinking) were nonlinearly associated with levels of SUB (Parra et al., 2017; Zimmerman & Vásquez, 2011).

Mediation effects by supportive parenting and school connectedness were admittedly small in magnitude relative to mediation effects by delinquent peer affiliation, explaining only 5.6% to 6.5% of the total effects. Yet, it suggests that supportive parenting and school connectedness may contribute to the gene-environment interplay for EXT behaviors above and beyond the predominant influence of delinquent peer affiliation. While there were significant indirect effects that predicted the odds of belonging to the Adolescent-Peaked ASB trajectory relative to the Low ASB trajectory, our data were not consistent with the hypothesized mediation model because the total effect of PGS_{EXT} was not significant. One possible explanation for the lack of total effect is that the individuals who engage in high levels of ASB in adolescence but desist from ASB afterwards may be subject to primarily socio-environmental but not genetic risks. Studies have indeed found that trajectories similar to our Adolescent-Peaked trajectory are associated with low

heritability and larger environmental influences (Isen et al., 2022; Rhee & Waldman, 2002). Moreover, the EXT GWAS examined predominantly adult-related phenotypes of EXT (e.g., lifetime cannabis use, number of sexual partners) and/or populations (i.e., UK Biobank, 23andMe, GSCAN) (Karlsson Linnér et al., 2021). Thus, our PGS_{EXT}, which was based on the EXT GWAS, may yield weaker prediction signals for trajectories in which most variation occurs during the adolescent years (i.e., the Adolescent-Peaked ASB trajectory).

The mediation of genetic effects by adolescent psychosocial environments has important theoretical and clinical implications for the development of EXT behaviors. Adolescents take active roles in shaping their social contexts and future development (Sameroff, 2009). In the presence of gene-environment correlations, genetic risks may accumulate "outside of the skin" (Reiss & Leve, 2007), as they shape the social context. Our findings may be consistent with a gene-environment model that is characterized by transactional, rather than purely independent or interactional, processes (Elam et al., 2023). In this framework, individuals with a higher PGS_{EXT} may be particularly at risk for developing EXT behaviors, not only because of their genetic liability, but also because these genetic risks may predispose them to risky adolescent social environments. In other words, the effect of genetic risks cascades through exposure to risky social environments. However, our findings by no means imply that EXT behaviors are any less malleable. Partial mediation of genetic effects by environments may also suggest malleability in heritability, or the possibility for psychosocial interventions to counteract the cascading effect of genetic risks. Crucially, the mediation effects observed pertain to social environments in adolescence, a developmental period characterized by heightened social sensitivity and neuroplasticity (Baker et al., 2025; Sebastian et al., 2010), which may potentiate psychosocial prevention and intervention programs for adolescents to target maladaptive behavioral norms in

the peer groups, problematic dynamics with parents, and low belongingness to schools in order to promote positive developmental outcome, especially for adolescents with heightened genetic risks for EXT behaviors who are more likely exposed to risker environments (Elam et al., 2023).

Finally, we note that the main, GxE, and mediation effects of neighborhood connectedness were all nonsignificant. One explanation may be related to our measurement of neighborhood connectedness, which only focused on cohesion and socialization. There may be other aspects of the neighborhood (e.g., deprivation, substance availability, etc.) that impact the development of EXT behaviors in the presence of genetic liability (Carroll et al., 2023; Dash et al., 2023). Neighborhood connectedness was also correlated with other environmental measures, and the effects of neighborhood connectedness may be better explained by more proximal (i.e., parent, peer) social environments (M. Li et al., 2017; Mrug & Windle, 2009), again highlighting the importance of modeling multiple environments in parallel to examine their conditional effects.

Limitations

First, SUB and ASB were measured with relatively few self-report items, given that only these items were similarly measured across waves. Sampling a broader range of behaviors and potentially informant reports would have provided greater breadth of coverage of the SUB and ASB phenotypes. Add Health also did not collect retrospective reports of SUB and ASB in childhood (i.e., before age 13), thus limiting our ability to take a lifespan approach to the analyses. Second, our selected GMM model for ASB featured a relatively small cell size (i.e., n = 91 in the High-Decline group) and relatively low entropy (i.e., more error in trajectory classification). Thus, replication of these trajectories in other large longitudinal datasets is warranted. Third, we note that there are other GWAS summary statistics we could have utilized in our PGS computation, including those that may even be considered more proximal to SUB

and ASB (Tielbeek et al., 2017; Walters et al., 2018). Yet, these particular GWASs suffer from severe power limitations relative to the GWAS summary statistics we utilized, which featured over 1.5 million individuals across several cohort studies. Fourth, although we reported results in non-European ancestry subsamples, we focused our discussion exclusively on results from the European ancestry subsample. The results reported in Supplemental Materials for other ancestry subsamples are likely underpowered, given that EXT GWAS itself was underpowered for individuals with genetic similarity to non-European ancestries. Future investigations could meta-analyze these results and results from other studies to draw more robust conclusions regarding gene-environment interplay effects as they pertain to non-European individuals. Fifth, we focused our analyses on latent classes of trajectories of EXT, rather than slopes and intercepts, thereby limiting our analyses to between-group differences. While there may be value in modeling within-group variances as a function of gene-environment interplay, this is beyond the scope of the current analysis. Sixth, we measured supportive parenting as a unidimensional construct given our interest in the family-level social environment. More nuanced operationalizations (e.g., maternal vs. paternal parenting) may provide important granularity in the interpretation of parenting effects in our models. Finally, environmental variables were only assessed at Wave I (i.e., in adolescence), limiting our ability to examine how concurrent social environments simultaneously affect EXT behaviors across time. Yet, significant effects observed in this study suggest that social environments measured in adolescence could have lasting impact on development of EXT behavior over almost an impressive 30-year-period.

Conclusions

While studies have shown that phenotypically and developmentally heterogenous forms of EXT behaviors have different etiological processes (Carlisi et al., 2020; Elam et al., 2021; J. J.

Li, 2019), the current study goes beyond prior analyses and provide new insights into gene-environment interplay underlying developmental trajectories of SUB and ASB. In the current study, we found no evidence for GxE underlying the development of EXT behaviors. Instead, we observed indirect effects of PGS_{EXT} through adolescent psychosocial environments, in particular delinquent peer affiliation, highlighting that genetic liability for EXT outcomes may operate through psychosocial mechanisms. Our findings highlight the importance of psychosocial interventions for early EXT behaviors that specifically target or mitigate exposure to high-risk environmental contagions, given that a substantial proportion of the genetic variation underlying risk for EXT outcomes can be explained by peer delinquency and, to a lesser extent, supportive parenting and school connectedness.

Author Contributions

LiChen Dong: conceptualization, methodology, formal analysis, data curation, writing - original draft, visualization, project administration. **A. Brooke Sasia**: resources, formal analysis, data curation, writing - review & editing, visualization. **James J. Li**: conceptualization, methodology, resources, writing - review & editing, supervision, funding acquisition.

Conflicts of Interest

The authors had no conflicts of interest with respect to authorship or publication of this article.

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Supplemental Materials

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