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Genetic influences for distinct impulsivity domains are differentially associated with early substance use initiation: Results from the ABCD Study

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Abstract

Background. Impulsivity is among the strongest correlates of substance involvement (i.e. a broad continuum of substance-related behaviors), and distinct domains (e.g. sensation seeking [SS] and urgency) are differentially correlated, phenotypically and genetically, with unique substance involvement stages. Examining whether polygenic influences for distinct impulsivity domains are differentially predictive of early substance use initiation – a major risk factor for later problematic use – may improve our understanding of the role of impulsivity in addiction etiology.

Methods. Data collected from participants of genetically inferred European ancestry enrolled in the Adolescent Brain Cognitive Development Study^{SM} (n = 4,808) were used to estimate associations between polygenic scores (PGSs) for UPPS-P impulsivity domains (i.e. SS, lack of premeditation [LPREMED]/perseverance [LPERSEV], and negative/positive urgency [NU/PU]) and substance (i.e. any, alcohol, nicotine, and cannabis) use initiation by age 15 years. Mediation models examined whether child impulsivity (ages 9–11 years) mediated links between PGSs and substance use initiation.

Results. SS-PGS was significantly associated with any substance and alcohol use initiation (odds ratio [ORs] > 1.10, $ps_{FDR} < 0.05$). LPERSEV and NU/PU PGSs were nominally associated with alcohol and nicotine use initiation, respectively (ORs > 1.06, $ps < 0.05$, $ps_{FDR} > 0.05$). No significant associations were observed for LPREMED-PGS or cannabis use initiation. Measured impulsivity domains accounted for 5–9% of associations between UPPS-P PGSs and substance use initiation.

Conclusions. Genetic influences for distinct impulsivity domains have differential associations with early substance use initiation, with SS showing the most robust associations, highlighting valuable etiological insight into the earliest stages of substance involvement that may be leveraged to improve prevention and intervention strategies.

Introduction

Impulsivity reflects a broad tendency to act quickly without consideration of potential consequences in response to salient external stimuli or internal drives (Whiteside & Lynam, 2001). It is among the strongest correlates of substance involvement (i.e. a broad continuum of substance-related behaviors including early experimentation or initiation, escalating use, and problematic use) and is considered a predispositional risk factor for substance use disorders (SUDs; de Wit, 2009; Verdejo-García, Lawrence, & Clark, 2008). Consistent with this notion, impulsivity is moderately heritable and genetically correlated with substance involvement (Bezdjian, Baker, & Tuvblad, 2011; Sanchez-Roige et al., 2023), and elevated impulsivity during childhood and adolescence predicts substance use initiation and escalating use (Quinn & Harden, 2013; Watts, Doss, Bernard, & Sher, 2024).

Contemporary models conceptualize "impulsivity" as an amalgamation of partially overlapping, but distinct domains, including sensation seeking (SS; i.e. tendency to seek novel experiences), lack of perseverance (LPERSEV; i.e. tendency to not finish what is started), lack of premeditation (LPREMED; i.e. tendency to act without forethought), and negative urgency (NU) and positive urgency (PU; i.e. tendency to act rashly during negative and positive mood states, respectively), rather than as a unitary construct (Cyders & Smith, 2008; Whiteside & Lynam, 2001). As studies have consistently shown that distinct impulsivity domains are differentially associated with substance use outcomes, particularly alcohol, examining them separately is critical for understanding their roles in substance involvement and SUD risk (Strickland & Johnson, 2021).

SS is more strongly linked to substance initiation and use (i.e. consumption and frequency), whereas NU and PU and LPREMED are more closely tied to substance-related problems and SUDs (Coskunpinar, Dir, & Cyders, 2013; McCarty, Morris, Hatz, & McCarthy, 2017; Peeters et al., 2014; Stamates & Lau-Barraco, 2017; Stautz & Cooper, 2013). Thus, SS may be more relevant in earlier stages of substance use, while urgency and LPREMED may be more relevant in the transition to SUDs. Developmental frameworks (e.g. dual-systems models; Shulman et al., 2016) emphasizes the importance of developmental mismatches between reward sensitivity and cognitive control, suggesting that heightened reward sensitivity (e.g. SS) during early adolescence may promote experimentation, which can progress into heavier use in the context of still-developing self-regulatory capacity (e.g. LPREMED). Clarifying which aspects of impulsivity are most genetically implicated in early initiation – a key SUD risk factor (Behrendt, Wittchen, Höfler, Lieb, & Beesdo, 2009) – may advance etiological models of addiction by identifying putative risk pathways that could inform the design of developmentally appropriate, domain-specific prevention and intervention strategies (Conrod et al., 2025; Finn et al., 2025; Kozak et al., 2019; Tomko, Bountress, & Gray, 2016).

All impulsivity domains are moderately heritable (h^2 = 0.27–0.50) and exhibit both shared and unique genetic components (Bezdjian et al., 2011; Friedman et al., 2020). Genome-wide association studies (GWASs) have revealed that while some impulsivity domains are highly genetically correlated (e.g. NU and PU [rG = 0.78]), others are moderately (e.g. LPERSEV and LPREMED [rG = 0.50]), or even weakly correlated (e.g. SS and LPERSEV [rG = 0.01]; Sanchez-Roige et al., 2023), with genetic correlations potentially varying across developmental stages (Deng, Belisario, Munafò, & MacKillop, 2025). Differential patterns are also observed for genetic overlap with substance use and SUDs: NU, PU, and LPREMED display similar moderate genetic correlations with both substance use and SUDs (rG = 0.38–0.46), whereas SS is more strongly genetically correlated with substance use (rG = 0.27) versus SUDs (rG = 0.10; Miller & Gizer, 2024; Vilar-Ribó et al., 2025). Like domains of impulsivity, SUDs exhibit shared genetic architecture, reflecting a common genetic risk factor alongside substance-specific influences (Hatoum et al., 2023; Kendler, Jacobson, Prescott, & Neale, 2003; Miller, Bogdan, Agrawal, & Hatoum, 2024), and early initiation across substances likewise demonstrates a common source of genetic risk (Richmond-Rakerd et al., 2016).

Consistent with phenotypic literature and genetic correlations demonstrating stronger associations with use phenotypes, SS polygenic scores (PGSs), which reflect cumulative GWAS-based genetic propensity (Wray et al., 2021), are associated with early binge drinking frequency over and above alcohol-related and other impulsivity PGSs (Miller, Spychala, Slutske, Fromme, & Gizer, 2025). SS may serve as a plausible mechanism through which genetic influences on substance involvement emerge, as it partially mediates associations between PGSs for risky behaviors and alcohol use/problems and alcohol use behaviors in young adult samples (Ksinan, Su, Aliev, Workgroup, & Dick, 2019; Lannoy, Heron, Hickman, & Edwards, 2023). These mediational studies suggest that a portion of genetic influences on drinking patterns in development is attributable to the direct expression of distinct impulsivity domains, providing a foundation for examining similar indirect associations in more scarcely explored phenotypes, such as early substance use initiation.

The present study examined whether genetic influences for distinct impulsivity domains (i.e. SS, LPERSEV, LPREMED, NU, and PU PGSs) are associated with substance use initiation (i.e. any, alcohol, nicotine, and cannabis) at an early age (i.e. <15 years) in 4,808 children from the Adolescent Brain Cognitive Development Study[SM] (ABCD Study®) who most closely resemble European ancestry reference populations. Both phenotypic and genetic evidence suggest SS is particularly relevant for initiation and substance use (vs. SUDs), whereas other impulsivity domains are more consistently related to problematic use and SUDs (Stautz & Cooper, 2013; Vilar-Ribó et al., 2025). As such, we hypothesized that SS PGS would be the strongest impulsivity PGS predictor of early substance use initiation, with other impulsivity domain PGSs also showing positive associations. Research examining differential associations between impulsivity domains and initiation of substances other than alcohol is relatively sparse (e.g. Vergés, Littlefield, Arriaza, & Alvarado, 2019). Thus, we conducted exploratory substance-specific analyses to examine whether impulsivity domain PGSs may be differentially associated with less frequent forms of early substance initiation (i.e. nicotine and cannabis). Finally, we leveraged parallel mediation models (e.g. Ksinan et al., 2019) to examine whether indirect PGS effects operate through domain-specific impulsivity expression in childhood or through expression of other targetable domains (Conrod et al., 2025). Potential cross-domain associations may reflect shared genetic etiology across facets of impulsivity that developmentally contribute to substance use initiation, and parallel mediation allows for direct comparison of these pathways within a unified model, offering insight into the specificity, or lack thereof, of genetic influences on behavior. We hypothesized that domain-specific expression would account for an appreciable portion of associations between PGSs and substance use initiation, such that effects on early substance use initiation would partially be accounted for by corresponding phenotypic expression, with smaller contributions arising from the expression of other impulsivity domains.

Methods

Participants

The ABCD Study® is a longitudinal study of brain and behavioral development in children and adolescents, which recruited 11,875 children aged 9–11 years (born between 2005 and 2009) at baseline (2016–2018) from 21 US research sites (Volkow et al., 2018). It includes a family-based component, in which some participants were twins, triplets, and non-twin siblings. Parents/caregivers provided written informed consent, and children assent, to a research protocol approved by the institutional review board at each site (https://abcdstudy.org/sites/abcd-sites.html). Phenotypic data from data release 5.1 were obtained from the National Institute of Mental Health Data Archive (https://nda.nih.gov/abcd). Analyses were limited to individuals with non-missing impulsivity and substance use data whose genetic ancestry was similar to European ancestry reference populations (n_{analytic} = 4,808) due to the lack of relevant discovery GWAS in other ancestries and evidence that genomic influences meaningfully differ across ancestries (Kachuri et al., 2024); applying PGSs to samples that are not genetically similar to the ancestry of the original GWAS may contribute to health disparities by producing false positive and negative results (Martin et al., 2017, 2019).

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Table 1. Sample descriptives by substance use initiation group

	Substance naïve n = 2,910)	Substance use initiation (n = 1,898)
Demographics		
Baseline age (years; mean ± SD)	9.89 ± 0.63	9.99 ± 0.63
Female sex (n, %)	1,421 (48.8%)	835 (44.0%)
Baseline impulsivity traits (mean ± SD)		
Sensation seeking	9.67 ± 2.59	10.40 ± 2.60
Lack of perseverance	6.94 ± 2.17	7.26 ± 2.24
Lack of premeditation	7.68 ± 2.24	8.23 ± 2.36
Negative urgency	8.23 ± 2.54	8.74 ± 2.53
Positive urgency	7.54 ± 2.75	7.90 ± 2.82
Impulsivity PGS (% in top decile [95% CI])		
SS-PGS	9.00 [8.02, 10.10]	11.50 [10.2, 13.10]
LPERSEV-PGS	9.93 [8.90, 11.10]	10.10 [8.84, 11.60]
LPREMED-PGS	9.73 [8.70, 10.90]	10.40 [9.13, 11.90]
NU-PGS	9.62 [8.60, 10.70]	10.60 [9.28, 12.10]
PU-PGS	9.18 [8.18, 10.30]	11.30 [9.93, 12.80]

Note: The substance naïve group reflects participants endorsing no substance use from baseline to 3-year follow-up, while the substance use initiation group reflects participants having endorsed initiation of any substance during this timeframe. To compare groups descriptively, UPPS-P polygenic score deciles were calculated across the full sample and the proportion of each group falling into the top score decile was estimated along with 95% confidence intervals. Continuous polygenic scores were used in association models. Abbreviations: PGS, polygenic score; SS, sensation seeking; LPERSEV, lack of perseverance; LPREMED, lack of premeditation; NU, negative urgency; PU, positive urgency.

Impulsivity domains

Impulsivity domains were measured at baseline using the 20-item abbreviated UPPS-P Impulsive Behavior Scale-Youth Version, which provides a valid and reliable assessment of these traits in youth (Cronbach's α = 0.50–0.78; Cyders et al., 2007; Watts, Smith, Barch, & Sher, 2020). The UPPS-P captures the following five impulsivity domains, each with four items: (1) SS, (2) LPERSEV, (3) LPREMED, (4) NU, and (5) PU (Table 1 and Supplementary Table S1). Items are rated on a Likert scale of 1 (*agree strongly*) to 4 (*disagree strongly*); scores are reverse-coded, as needed, and summed, so that higher scale scores indicate more impulsivity.

Substance use initiation

Annual in-person (i.e. baseline and 1-, 2-, and 3-year follow-ups [FU3]) and mid-year phone (i.e. 6, 18, and 30 months) interviews assessed substance use by age 15 years (Lisdahl et al., 2018). Youth endorsing use at any assessment from baseline to FU3 (i.e. lifetime use by age 15 years) were included in substance use initiation groups (Miller et al., 2024). Youth endorsing use only in the context of religious ceremonies were coded as having missing data to restrict comparisons to use outside these settings (n_{alcohol} = 432; n_{nicotine} = 18). See Supplementary Table S2 for a list of study release variables used to code substance use initiation.

Alcohol use initiation (n = 1,778; 37.0%) was defined as 'sipping' (n = 1,658 without full drink) or 'full drinks' (n = 120) of alcohol. This definition of any use, inclusive of sipping, was used (1) to provide more consistent definitions of use across substances, (2) due to prior evidence that sipping is similarly associated with externalizing as full drinks in youth (Watts et al., 2021; Watts et al., 2024), and (3) to maintain consistency with other ABCD Study definitions (Miller, Baranger, et al., 2024; Watts et al., 2021; Watts et al., 2024). ***Nicotine use initiation*** (n = 201; 4.2%) was defined as use of nicotine products in any form. ***Cannabis use initiation*** (n = 75; 1.6%) was defined as use of cannabis in any form, except synthetic cannabis or cannabis-infused alcoholic drinks, which were included under any substance use. ***Any substance use initiation*** (n = 1,898; 39.5%) was defined as alcohol, nicotine, or cannabis use initiation, or undirected/recreational use of any other substances (n = 87: $n_{\text{inhalants}}$ = 27, $n_{\text{prescription sedatives}}$ = 17, $n_{\text{stimulants}}$ = 16, $n_{\text{synthetic cannabis}}$ = 13, $n_{\text{OTC cough/cold medicine}}$ = 7, n_{opioids} = 7, $n_{\text{hallucinogens}}$ = 4, and n_{other} = 6). ***Substance naïve youth*** (n = 2,910; 60.5%) endorsed no substance use from baseline to FU3 and had non-missing FU3 data to protect against misclassification of participants with an unknown FU3 status (n = 327). Notably, there was considerable overlap among initiation of alcohol, nicotine, and cannabis with alcohol use initiation representing the vast majority of substance use initiation (94%; Supplementary Figure S1). Observed rates of substance use initiation, including sips, in the current analytic sample are similar to those in the full ABCD sample up to age 13 years (Sullivan et al., 2022) but higher than other national studies (e.g. Monitoring the Future and National Survey on Drug Use and Health) that do not consider alcohol sipping in their conceptualizations of initiation (Patrick, Miech, Johnston, & O'Malley, 2024; Substance Abuse and Mental Health Services Administration, 2025).

Polygenic scores

Details regarding genomic data processing and quality control are provided in Supplementary Methods. Five UPPS-P GWAS were used to generate PGSs for each of the five UPPS-P domains (h^2_{SNP} = 0.06–0.10; N = 132,132–133,517): SS (SS-PGS), LPERSEV (LPERSEV-PGS), LPREMED (LPREMED-PGS), NU (NU-PGS), and PU (PU-PGS; Supplementary Table S3; Sanchez-Roige et al., 2023). GWAS participants were research-consented European ancestry adults (median age = 54 years) from the research participant base of the consumer genetics and research company 23andMe, Inc., who responded to a research survey including the 20-item short-form version of the UPPS-P (Cyders, Littlefield, Coffey, & Karyadi, 2014; Sanchez-Roige et al., 2023). Single-nucleotide polymorphism (SNP) weights for PGSs were generated using PRS-CS (v1.0.0), a Bayesian polygenic prediction method that infers posterior SNP effect sizes under continuous shrinkage priors using GWAS summary statistics and an external linkage disequilibrium reference panel (1,000 Genomes Project phase 3; Ge, Chen, Ni, Feng, & Smoller, 2019). *First*, the 'auto' feature of PRS-CS was used to learn the global shrinkage parameter from the data using a fully Bayesian approach with 10,000 Markov chain Monte Carlo iterations, a burn-in sample of 5,000, and a thinning interval of 5. *Second*, the --score function in PLINK (v2.0; Chang et al., 2015) was used to compute PGSs in the ABCD sample using PRS-CS-derived weights for 866,844 overlapping HapMap3 SNPs with the 1,000 Genomes European ancestry sample used as the reference panel for linkage disequilibrium.

Statistical analysis

All continuous variables were z-scored before analyses. Substance use initiation groups (i.e. any [n = 1,898], alcohol [n = 1,778], nicotine [n = 201], cannabis [n = 75] vs. substance naïve [n =

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2,910]) were logistically regressed on the five UPPS-P PGSs (i.e. SS-PGS, LPERSEV-PGS, LPREMED-PGS, NU-PGS, and PU-PGS) using separate models (i.e. for each UPPS-P PGS and substance use initiation group). Dichotomous substance use initiation contrasts (i.e. lifetime use vs. naïve) were used as outcome variables, rather than specific timing of onset, to focus on early initiation (i.e. by age 15 years) and due to power concerns with modeling age of initiation, which may be characterized by heavy positive skew given the prevalence of baseline endorsement of sipping and less frequent endorsements of new onset within the narrow age range from baseline to FU3. Given the small sample sizes for nicotine and cannabis use initiation and the shortage of prior literature establishing domain-specific links with impulsivity, these analyses were viewed as exploratory. All analyses were conducted using maximum likelihood with robust standard errors estimation in Mplus 8.11 (Muthén & Muthén, 1998–2024) via the MplusAutomation R package (v1.1.1; Hallquist & Wiley, 2018). Fixed-effect covariates included baseline age, age-squared, sex, familial relationship (i.e. sibling, twin, and triplet), and 10 genomic principal components. Participants were nested within recruitment site (i.e. stratum) and families (i.e. cluster) to account for the nonindependence of data and adjust standard errors. Pubertal status as an additional fixed-effect covariate was examined *post hoc* and did not meaningfully impact observed associations (Supplementary Table S4). Multiple testing was adjusted using a 5% false discovery rate (FDR) correction separately within each substance use initiation contrast for the five UPPS-P PGSs tested.

For any nominally significant association between UPPS-P PGSs and substance use initiation variables (i.e. uncorrected p < 0.05), two additional analyses were conducted. *First*, multiple regression with all UPPS-P PGSs included simultaneously was conducted to evaluate whether associations were independent of other UPPS-P PGSs. *Second*, parallel mediation models were used to examine the degree to which UPPS-P baseline measures accounted for associations between UPPS-P PGSs and substance use initiation. Here, in each model, baseline UPPS-P scale scores for each domain were entered as parallel mediators of associations between UPPS-P PGSs and substance use initiation. Monte Carlo integration was used to account for missing baseline UPPS-P measures (n = 4). Significance of indirect associations (i.e. mediation) were assessed using 95% confidence intervals (CIs) computed via Monte Carlo simulation of estimated model parameters and their associated asymptotic sampling covariance matrices (20,000 simulations) using the *monteCarloCI* function in the semTools R package (v0.5–6; Jorgensen et al., 2022; MacKinnon, Lockwood, & Williams, 2004; Preacher & Selig, 2012). Estimates of the proportion of total effects (i.e. sum of direct and indirect effects of PGSs) on substance use initiation significantly mediated by baseline UPPS-P measures were obtained by calculating the ratio of indirect effect estimates for each significant path to the total effect estimate.

Results

Any substance use initiation

Higher SS-PGS was associated with a greater likelihood of any substance use initiation (n_{any} = 1,898; odds ratio [OR] = 1.108, 95% CI = [1.042, 1.179], p = 0.001, p_{FDR} = 0.005; Figure 1 and Supplementary Table S5), which remained significant when including all UPPS-P PGS simultaneously in the model (OR = 1.106, 95% CI = [1.035, 1.182], p = 0.003, p_{FDR} = 0.015; Supplementary Table S6). The parallel mediation model revealed that elevated baseline SS (β_{indirect} = 0.009, 95% CI = [0.002, 0.017]) and LPREMED (β_{indirect} = 0.006, 95% CI = [0.001, 0.011]) indirectly linked heightened SS-PGS to any substance use initiation, accounting for 8.9 and 5.3% of this association, respectively (Figure 2a and Supplementary Table S7). No other PGS were significantly associated with any substance use initiation (Figure 1 and Supplementary Table S5).

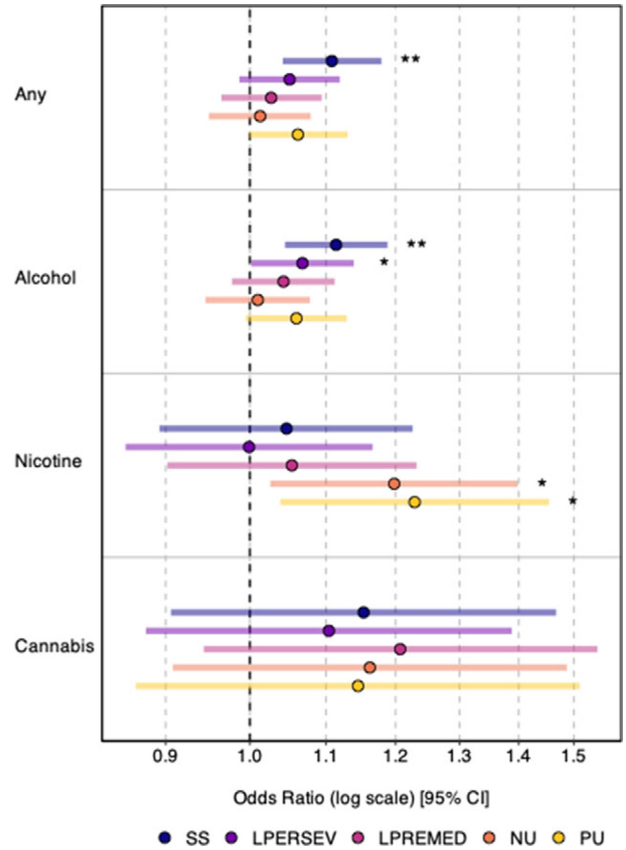

Figure 1. Associations between UPPS-P PGSs and substance use initiation. Odds ratios and 95% confidence intervals, presented on a log scale, for associations between each UPPS-P PGS and substance use variable from separate regression models. SS, sensation seeking; LPERSEV, lack of perseverance; LPREMED, lack of premeditation; NU, negative urgency; PU, positive urgency. *p < 0.05, **p_{FDR} < 0.05.

Alcohol use initiation

Higher SS-PGS was significantly associated with a greater likelihood of alcohol use initiation (n_{alcohol} = 1,778, SS-PGS: OR = 1.114, 95% CI = [1.045, 1.188], p = 0.003, p_{FDR} = 0.005; Figure 1 and Supplementary Table S5), which remained significant when including all UPPS-P PGSs simultaneously in the model (OR = 1.111, 95% CI = [1.039, 1.189], p = 0.002, p_{FDR} = 0.010; Supplementary Table S6). Baseline SS (β_{indirect} = 0.010, 95% CI = [0.002, 0.019]) and LPREMED (β_{indirect} = 0.005, 95% CI = [0.001, 0.010]) indirectly linked heightened SS-PGS to alcohol use initiation, accounting for 9.1 and 4.4% of this association, respectively (Figure 2b and Supplementary Table S8).

Higher LPERSEV-PGS was also associated with a greater likelihood of alcohol use initiation (OR = 1.068, 95% CI = [1.002, 1.139], p = .043, p_{FDR} = .107, Figure 1). However, this association did not survive FDR correction. Baseline LPERSEV (β_{indirect} = 0.005, 95% CI = [0.001, 0.011]) and LPREMED (β_{indirect} =

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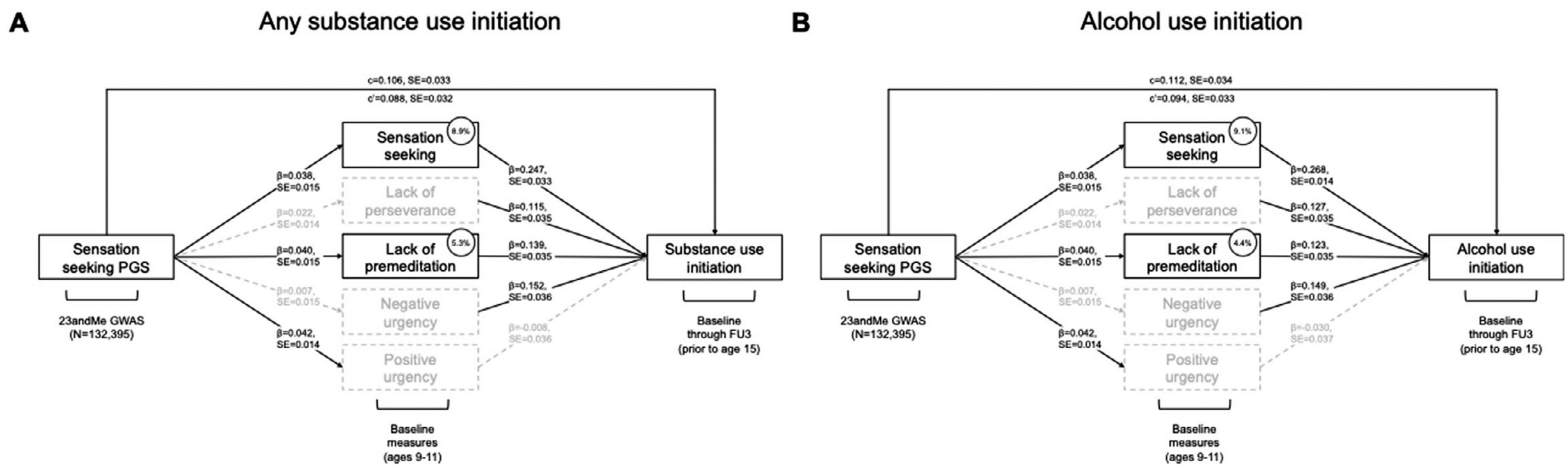

Figure 2. Sensation seeking and lack of premeditation indirectly link sensation seeking PGS to (a) any substance use and (b) alcohol use initiation. Mediational models including all measured UPPS-P domains in parallel. Standardized regression coefficients (β) and standard errors (SEs) are reported along each path. Gray dashed lines indicate individual paths and/or mediation effects with 95% CIs overlapping with 0 (i.e. nonsignificant). Numbers in circles represent the proportion of the association between SS-PGS and the substance use initiation variable that is accounted for by the measured UPPS-P domain (i.e. sensation seeking and lack of premeditation accounted for 8.9 and 5.3% of association between SS-PGS and any substance use initiation, respectively, and 9.1 and 4.4% of the association with alcohol use initiation, respectively).

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0.004, 95% CI = [0.001, 0.009]) indirectly linked heightened LPERSEV-PGS to alcohol use initiation, accounting for 7.7 and 6.4% of these associations, respectively (Supplementary Figure S2 and Supplementary Table S9).

Nicotine use initiation

Higher NU-PGS and PU-PGS were associated with a greater likelihood of nicotine use initiation (n_{nicotine} = 201; NU-PGS: OR = 1.198, 95% CI = [1.026, 1.398], p = 0.022, p_{FDR} = 0.055; PU-PGS: OR = 1.229, 95% CI = [1.039, 1.454], p = 0.016, p_{FDR} = 0.055; Figure 1 and Supplementary Table S5). However, these associations did not survive FDR correction and neither were independent predictors when modeled together (NU-PGS: OR = 1.210, 95% CI = [0.938, 1.339], p = 0.209, p_{FDR} = 0.522; PU-PGS: OR = 1.163, 95% CI = [0.953, 1.420], p = 0.839, p_{FDR} = 0.994; Supplementary Table S6). Baseline NU indirectly linked heightened NU-PGS to nicotine use initiation, accounting for 5.3% of this association (β_{indirect} = 0.009, 95% CI = [0.001, 0.020]; Supplementary Figure S3 and Supplementary Table S10). Both baseline NU and PU similarly indirectly linked heightened PU-PGS to nicotine use initiation (NU-β_{indirect} = 0.010, 95% CI = [0.002, 0.022]; PU-β_{indirect} = 0.010, 95% CI = [0.001, 0.022]), accounting for 5.1 and 5.2% of these associations, respectively (Supplementary Figure S4 and Supplementary Table S11).

Cannabis use initiation

No UPPS-P PGSs were significantly associated with cannabis use initiation (n_{cannabis} = 75; Figure 1 and Supplementary Table S5).

Discussion

Our study of genetic influences for impulsivity domains and substance use initiation as children enter adolescence revealed three primary findings. *First*, consistent with prior evidence that SS is the impulsivity domain most strongly associated with substance use initiation and continued use in adolescence (Cappelli et al., 2020; Stautz & Cooper, 2013), SS-PGS emerged as the most robust polygenic predictor of early substance use initiation. Notably, consistent with the majority of PGS studies (Bogdan, Baranger, & Agrawal, 2018), effect sizes were small (i.e. ORs < 1.12). *Second*, NU-PGS and PU-PGS showed nominal associations with nicotine use initiation, with largely overlapping effects. *Third*, phenotypically expressed impulsivity accounted for 5–9% of the variance linking PGSs to substance use initiation. These indirect effects were primarily domain-congruent (e.g. SS mediating SS-PGS effects), although domain-incongruent mediation was also observed (e.g. LPREMED mediating SS-PGS effects). Collectively, these findings demonstrate that genetic influences for distinct impulsivity domains differentially predict early substance use initiation, partly through domain-specific phenotypic expression, highlighting the value of GWAS of precise dimensional phenotypes and developmental samples for clarifying the factors influencing the earliest stages of substance involvement. While these findings should be interpreted in light of anticipated small PGS effects and by extension currently limited clinical utility (Bogdan et al., 2018), they offer meaningful insights into the etiological pathways by which genetic influences may contribute to the early emergence of risk for substance involvement, underscoring their potential value for elucidating mechanisms underlying early substance use vulnerability, an essential step in developing more precise prevention and intervention strategies.

Sensation seeking

Individuals with higher SS-PGS were more likely to have initiated any substance and/or alcohol use, with a 1 SD increase predicting ~10% increase in odds of initiation, consistent with phenotypic studies demonstrating that SS predicts early and increasing substance use, particularly alcohol (Cappelli et al., 2020; Jensen, Chassin, & Gonzales, 2017; Stautz & Cooper, 2013). The SS-PGS effect on initiation was partially mediated by childhood phenotypic expression of SS and LPREMED. This extends prior research showing that SS also mediates PGS effects on alcohol consumption in early adulthood (Ksinan et al., 2019; Lannoy et al., 2023) by demonstrating that similar mechanisms may also underlie the early onset of alcohol use. The extent to which SS and related genetic liability are linked to later stages of substance involvement, independent of its effects on early initiation, warrants further study. Notably, associations between SS-PGS and substance use initiation were comparable to, if not larger than, associations with phenotypic expression of SS at baseline. Thus, SS-PGS derived from adult GWAS may capture a broader but related set of genetically influenced propensities that extend beyond the narrow measurement of SS in childhood, highlighting potential differences in genetic influences across developmental stages; in a related line of evidence, developmental trajectories of SS are strongly influenced by genetics (Harden, Quinn, & Tucker-Drob, 2012).

Urgency

NU-PGS and PU-PGS both exhibited nominally significant associations only with nicotine use initiation. While findings from these exploratory analyses did not survive FDR correction, prior work underscores their potential relevance. Urgency has been linked to alcohol and nicotine problems (Coskunpinar et al., 2013; Kale, Stautz, & Cooper, 2018; Stamates & Lau-Barraco, 2017; Stautz & Cooper, 2013), theorized to contribute to withdrawal and craving (Zorrilla & Koob, 2019), and exhibits moderate genetic correlations with SUDs (Sanchez-Roige et al., 2023). Collectively, this evidence suggests that urgency PGSs may capture shared genetic liability with later, more severe stages of substance involvement. Consistent with this notion, fewer parents of ABCD Study participants report easy child access to nicotine relative to alcohol (Martz et al., 2022) and, in the current study, most participants initiating nicotine use (73%) also endorsed alcohol and/or cannabis use initiation, reflecting broader substance involvement. Nicotine initiation itself is also associated with elevated risk of dependence relative to lifetime use of other substances (Lopez-Quintero et al., 2011). Thus, although speculative, especially considering the lack of robustness to multiple testing correction, our observed link between urgency PGSs and nicotine use initiation by age 15 years may index heightened risk of progression that could be evaluated in future ABCD Study waves when substance involvement is expected to increase.

These findings may also inform impulsivity domain conceptualizations. NU-PGS and PU-PGS associations with nicotine use initiation were overlapping, and the phenotypic expression of both urgency domains indirectly linked PU-PGS to nicotine use initiation. This aligns with evidence that PU and NU are highly genetically correlated (rG = .78; Sanchez-Roige et al., 2023) and may reflect a general urgency factor characterized by emotion-based rash action regardless of affective valence (Billieux et al., 2021). At the same time, more nuanced examinations of NU and PU genetic factors suggest differential relations with substance use versus SUDs (Vilar-Ribó et al., 2025). Current PGS methods are not well-suited to leverage this level of nuance, underscoring the need for designs that can parse unique genetic influences across developmental stages of substance involvement.

Lack of premeditation

That LPREMED-PGS was not associated with early substance use initiation aligns with evidence that heightened LPREMED may be primarily associated with later stages of substance involvement, including heavy drinking and problematic alcohol use in emerging and young adulthood (Adams, Kaiser, Lynam, Charnigo, & Milich, 2012; Coskunpinar et al., 2013; McCabe et al., 2021). Compared to SS, which exhibits stronger genetic associations with substance use versus SUDs, LPREMED demonstrates similar genetic associations with both (Vilar-Ribó et al., 2025). Nonetheless, ~5% of the associations between SS-PGS and any substance and alcohol use initiation were mediated by baseline LPREMED, suggesting some overlap between genetic influences on SS measured in adulthood and LPREMED in childhood. This is consistent with models highlighting cognitive control effects on both positive and negatively reinforcing aspects of substance involvement (Bogdan, Hatoum, Johnson, & Agrawal, 2023) and evidence that LPREMED potentiates associations between SS and risky substance use (McCabe, Louie, & King, 2015), as well as correlations between SS and structural variability in cortical regions critical to cognitive control (Holmes, Hollinshead, Roffman, Smoller, & Buckner, 2016). Given that SS peaks in mid-adolescence while premeditation development protracts into later adolescence and early adulthood (Harden et al., 2012; Harden & Tucker-Drob, 2011; Steinberg, 2010), their phenotypic and genetic separation may change across development. Low correlations between these traits and their respective PGS in our sample (i.e. *r*s < 0.12; Supplementary Tables S1 and S3) suggest that the observed cross-domain mediation is not solely attributable to phenotypic or PGS overlap, despite higher adult genetic correlations (rG $= 0.271$; Sanchez-Roige et al., 2023). As self-regulatory capacity is still developing in late childhood, it is plausible that early expression of low premeditation may partly reflect genetic propensity for adult SS, highlighting the need for further research on lifespan pathways linking impulsivity domains to substance involvement.

Limitations and future directions

Our study should be interpreted in the context of its limitations. *First*, highlighting calls for genetic research in more diverse populations (Corpas et al., 2025; Martin et al., 2019), multi-ancestral GWAS of these traits are needed to assess generalizability and mitigate disparities. Similarly, as methods for calibrating and transferring PGSs across the continuum of genetic ancestry improve (Kachuri et al., 2024; Lambert et al., 2024), further research is needed to benchmark the performance of these approaches. *Second*, consistent with epidemiological evidence that alcohol is typically the first substance used (Smit et al., 2018), alcohol was the predominant substance initiated in this sample. Thus, it remains unclear whether largely null associations for nicotine and cannabis reflect differences in substance-specific etiology or limited power. Relatedly, using dichotomous initiation variables improved statistical power but limited insight into how these genetic factors may relate to the specific timing of initiation (Choi et al., 2025). As ABCD participants age, modeling links between genetic influences for impulsivity domains and later stages of substance involvement (e.g. escalating use and problematic use) will be important (Miller et al., 2025; Paul et al., 2024). *Third*, consistent with PGSs for other behavioral traits, impulsivity PGSs demonstrated small effect sizes, limiting clinical utility at present despite informing phenotypic and genetic etiology (Bogdan et al., 2018; Ma & Zhou, 2021). *Fourth*, some impulsivity traits, including SS, peak in post-pubertal adolescence before declining in adulthood (Harden & Tucker-Drob, 2011), mirroring substance use patterns (Quinn & Harden, 2013). Impulsivity PGSs derived from adult GWAS (median age = 54 years) may not fully capture developmentally specific influences (Bogdan et al., 2023), consistent with evidence that complex traits may be partially characterized by age-dependent genetic factors (Couto Alves et al., 2019; Pividori, Schoettler, Nicolae, Ober, & Im, 2019; Thomas et al., 2024). *Finally*, environmental factors robustly influence substance involvement (McGue, Elkins, & Iacono, 2000; Rhee et al., 2003), and some genetic effects on substance experimentation may operate through gene–environment correlations (e.g. parental genotype shaping home environment, including socioeconomic status, and access to substances; Sartor et al., 2025). Future research is needed in well-powered samples to carefully attend to methodological challenges associated with gene–environment influences (Bogdan et al., 2018; Duncan & Keller, 2011).

Conclusions

Impulsivity is one of the strongest correlates of substance involvement (de Wit, 2009). Decades of research show that distinct impulsivity domains differentially relate to stages of substance involvement (Coskunpinar et al., 2013; Stamates & Lau-Barraco, 2017; Stautz & Cooper, 2013), and emerging evidence suggests similar patterns for domain-specific genetic influences (Miller & Gizer, 2024; Sanchez-Roige et al., 2023; Vilar-Ribó et al., 2025). Our study demonstrates that genetic influences for distinct impulsivity domains differentially predict early substance use initiation in late childhood and early adolescence, partly mediated by corresponding phenotypic expression. Notably, genetic influences for SS were robustly associated with early substance use initiation. Understanding the genetic underpinnings of developmentally dynamic traits like SS provides crucial insight into the early emergence of SUD risk factors and their progression across the lifespan, informing potential early prevention and intervention strategies.

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