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Polygenic risk and childhood adversity as moderators of drug and alcohol withdrawal symptoms

Angela Han [a,1], Christal N. Davis [a,b,1], Zeal Jinwala [a,b], Jackson SooHoo [a], Joel Gelernter [c,d], Richard Feinn [e], Henry R. Kranzler [a,b,*]

[a] Center for Studies of Addiction, Department of Psychiatry, University of Pennsylvania School of Medicine, Philadelphia, PA 19104, USA
[b] Mental Illness Research, Education, and Clinical Center, Crescenz VAMC, Philadelphia, PA 19104, USA
[c] Department of Psychiatry, Yale University School of Medicine, New Haven, CT 06520, USA
[d] VA Connecticut Healthcare System, West Haven, CT 06516, USA
[e] Department of Medical Sciences, Frank H. Netter School of Medicine at Quinnipiac University, North Haven, CT 06473, USA

A B S T R A C T

Introduction: Reducing or stopping substance use can result in withdrawal symptoms in physically dependent individuals. Appropriate management of withdrawal symptoms may be critical to the safety of individuals with substance use disorders (SUDs) and could help prevent a return to substance use. Although childhood adversity and genetic factors contribute to the development of SUDs, their individual and joint effects on withdrawal symptoms and severity are less clear. This study is a secondary analysis of existing data in which we examined the main and interactive effects of genetic variation and adverse childhood events (ACEs) on the severity of withdrawal from tobacco, alcohol, and opioids.

Methods: Participants were 10,275 individuals (4851 of African-like (AFR) ancestry and 5424 of European-like (EUR) ancestry) from the Yale-Penn sample. Tobacco, alcohol, and opioid withdrawal symptoms and 10 ACEs were measured using a semi-structured diagnostic instrument. Multivariate regression models examined the association of SUD polygenic scores (PGS), ACEs, and their interaction with withdrawal severity and individual withdrawal symptoms.

Results: ACEs were positively associated with withdrawal severity, except for opioid withdrawal among AFR individuals. Among EUR individuals, PGS were positively associated with tobacco and alcohol withdrawal severity. There was a negative interaction between ACEs and PGS on tobacco withdrawal severity and specific tobacco withdrawal symptoms.

Conclusions: Individuals who experience ACEs and, to a lesser extent, those with higher PGS for SUDs, are susceptible to more severe withdrawal symptoms. In EUR individuals, there was evidence for a complex interplay of genetic and environmental factors on substance withdrawal. These exploratory findings require independent validation.

1. Introduction

Substance use disorders (SUDs), characterized by impaired control over substance use, continued use despite negative consequences, tolerance, and withdrawal (American Psychiatric Association, 2013), are a major public health problem. In 2022, 48.7 million people in the United States were affected by one or more SUDs (SAMHSA, 2022). A critical feature of many substances that are misused is their ability to activate the brain's reward system, often leading to neuroadaptations that contribute to substance-induced syndromes, including withdrawal (Saunders and Latt, 2021). Withdrawal symptoms, which occur following a reduction in or cessation of substance use (American Psychiatric Association, 2013), can threaten the safety of affected individuals and present a barrier to effective treatment by increasing the risk of a return to substance use, as substance use temporarily relieves withdrawal symptoms (Budney et al., 2008; Buffalari et al., 2012).

Withdrawal is a complex syndrome with both physiological and cognitive components. For any given substance, the specific withdrawal symptoms that individuals experience, and their severity, can vary greatly. Although years of use and the number of SUD criteria endorsed are each positively associated with withdrawal severity, these factors explain less than a quarter of the variance in withdrawal severity (McGregor et al., 2005). Thus, other factors, not yet identified, also play a role in determining whether withdrawal occurs and how severe it is. Particularly understudied are distal factors, such as genetic risk and the early childhood environment, which may moderate withdrawal symptoms.

Although genome-wide association studies (GWAS) of withdrawal

* Correspondence to: Center for Studies of Addiction, University of Pennsylvania, 3535 Market Street, Suite 500, Philadelphia, PA 19104, USA.
E-mail address: kranzler@pennmedicine.upenn.edu (H.R. Kranzler).
[1] These authors contributed equally

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severity are limited (Jensen et al., 2017; Leventhal et al., 2022; Smith et al., 2018; Wang et al., 2012), GWAS of SUDs have identified hundreds of associated single nucleotide polymorphisms (SNPs) across SUDs (e.g., (Kember et al., 2022; Toikumo et al., 2024; Zhou et al., 2023). Summary statistics from GWAS make it possible to estimate an individual's genetic liability using polygenic scores (PGS). Previous studies have shown that PGS moderate the age of onset and progression of SUDs (Kranzler et al., 2023; Yeung et al., 2022). Similarly, PGS for alcohol use disorder (AUD), opioid use disorder (OUD), smoking initiation, and lifetime cannabis use were associated with withdrawal from each of the substances, except cannabis (Kember et al., 2023). Whereas the strength of these associations differed across withdrawal symptoms, some symptoms may be more reliable and robust indicators of genetic liability for SUDs and potentially serve as behavioral markers of risk.

In addition to genetic risk, environmental factors, such as adverse childhood events (ACEs), contribute to the development of SUDs (al'Absi et al., 2017; Kranzler et al., 2024; Na et al., 2024; Ossola et al., 2021) and may also affect withdrawal symptoms. For example, after 24 hours of abstinence, individuals who smoke and had a history of early life adversity experienced greater distress and withdrawal symptoms than those with low levels of adversity (al'Absi et al., 2018). Similarly, among individuals with a cocaine use disorder, the magnitude of the reduction in withdrawal symptoms during detoxification was less among individuals with a history of childhood maltreatment than those without such a history (Francke et al., 2013). Childhood adversity may moderate withdrawal symptoms through stress-related mechanisms, such as alterations in the hypothalamic-pituitary-adrenal (HPA) axis and cortisol regulation (al'Absi et al., 2018; Singleton et al., 2023). Whereas these biological pathways are also influenced by genetic factors (Sawyers et al., 2021; Schatzberg et al., 2013), genetic risk could interact with environmental exposures like ACEs to moderate withdrawal severity.

In the current study, we examined how genetic liability for SUDs (indicated by PGS) and childhood adversity are associated with withdrawal severity and the endorsement of specific withdrawal symptoms from alcohol, tobacco, and opioids. Using data from a sample recruited to examine genetic risk for SUDs, we conducted a secondary analysis to evaluate the main and interactive effects of genetic variation and ACEs on withdrawal severity. We hypothesized that, whereas withdrawal occurs more commonly in OUD and TUD than AUD (Alvand et al., 2023; Cui et al., 2022; Gopaldas et al., 2023), suggesting that it is a more intrinsic feature of the two disorders, PGS would be more strongly associated with withdrawal from opioids and tobacco than alcohol. Conversely, we hypothesized that an environmental variable—childhood adversity—would show greater associations with alcohol withdrawal than either opioid or tobacco withdrawal. We had no hypotheses regarding associations at the individual symptom level.

2. Methods

Fig. 1 provides an overview of the study design. The report follows the STROBE guidelines (https://www.equator-network.org/reporting-guidelines/strobe/). Because the study was not pre-registered, the findings reported here should be considered exploratory.

2.1. Participants

Participants comprised 10,275 individuals (M_{age} = 40.59, SD = 11.72; 56.20 % male; Table 1) from the Yale-Penn sample, which was recruited at five academic sites: Yale University, UConn Health, the University of Pennsylvania, the Medical University of South Carolina, and McLean Hospital. Participants were recruited over a 20-year period at these sites using various recruitment methods. Information is not available for individuals who were excluded during screening. The interviewed sample included nearly equal numbers of individuals of African-like (AFR; n = 4851, 47.21 %) and European-like genetic

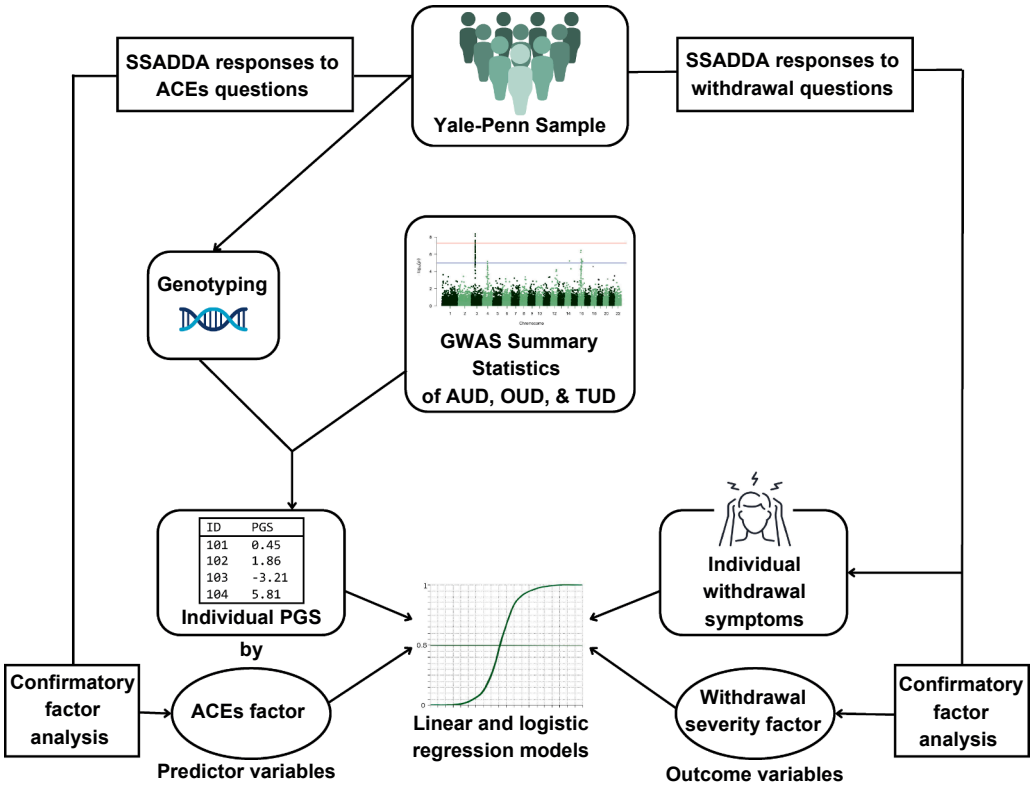

Fig. 1. Overview of the study design. SSADDA = Semi-Structured Assessment for Drug Dependence and Alcoholism, GWAS = genome-wide association study, ACEs=adverse childhood events, AUD=alcohol use disorder, OUD=opioid use disorder, TUD=tobacco use disorder, PGS=polygenic scores.

Table 1
Sample characteristics (N = 10,275).

Characteristic	Prevalence (N) or Mean ± SD
Sex	
Male	56.20 % (n = 5775)
Female	43.80 % (n = 4500)
Age	40.59 ± 11.72
Genetic Ancestry	
European-like	52.79 % (n = 5424)
African-like	47.21 % (n = 4851)
Self-Reported Race	
White	48.96 % (n = 5030)
Black/African American	44.64 % (n = 4587)
Other	6.40 % (n = 658)
Married	56.89 % (n = 5846)
Education (in years)	12.78 ± 3.04
Employed	57.50 % (n = 5908)
Substance Dependence	
Tobacco	52.90 %
Alcohol	50.95 %
Opioids	30.49 %

ancestry (EUR; n = 5424, 52.79 %). We excluded other genetic ancestry groups from the analysis because their small size provided inadequate statistical power. Because the Yale-Penn sample was recruited to study the genetics of alcohol, opioid, and cocaine dependence, individuals with these disorders were oversampled. Healthy control participants were recruited as a comparison group.

All procedures were approved by the institutional review board at each recruitment site, and participants gave written informed consent at enrollment. Genome-wide microarray genotyping was conducted using the Illumina HumanOmni1-Quad microarray. Genotypes were phased using SHAPEIT4 and imputed with Minimac4, leveraging the African Genome Resources and 1000 Genomes Project reference panels (Genomes Project ConsortiumAuton, 2015; Das et al., 2016; Delaneau et al., 2019). Genetic ancestry was determined using SNPs shared between Yale-Penn and the 1000 Genomes phase 3 reference panels. Using PLINK 1.9, we calculated ten ancestry principal components (PCs), and genetic ancestry was assigned based on distance of the PCs from 1000 Genomes phase 3 reference samples (Chang et al., 2015). Quality control procedures excluded variants based on minor allele frequency (<1 %) and imputation quality (INFO < 0.7) (Kember et al., 2023).

2.2. Measures

Withdrawal Symptoms. Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV; (American Psychiatric Association, 2000) withdrawal symptoms for tobacco, alcohol, and opioids were assessed using the Semi-Structured Assessment for Drug Dependence and Alcoholism (SSADDA) (Pierucci-Lagha et al., 2007; Pierucci-Lagha et al., 2005). Prior to assessing SUD criteria, the SSADDA assesses whether respondents used a substance enough to expose them to risk of an SUD. For tobacco, the instrument assesses whether respondents smoked at least 100 cigarettes in their lifetime. For alcohol, it assesses whether respondents ever consumed a full drink of alcohol, and for opioids, it assesses whether respondents used an opioid at least 11 times in their lifetime. All individuals who endorsed these levels of use were queried regarding the presence of SUD criteria, including withdrawal symptoms. When assessed by the SSADDA, the inter-rater reliability of withdrawal is good-to-excellent ($\kappa = 0.65$ for tobacco to 0.90 opioids) (Pierucci-Lagha et al., 2005). Table 2 shows the prevalence of withdrawal symptoms.

Adverse Childhood Experiences (ACEs). To assess ACEs, we used ten binary items from the SSADDA that reflect abuse, neglect, and household instability prior to age 13. Two items queried the stability of participants' home life: having multiple main caregivers (<3 vs. 3 +) and family relocations (<2 vs. 2 +). Three items reflected traumatic experiences: witnessing or experiencing violent crime (e.g., a shooting or rape), sexual abuse, and physical abuse (i.e., being beaten so badly that medical care was needed, or marks remained on the body for a month or more). Two household-related items were the presence of substance use and regular household smoking. Finally, three protective factors were reverse coded to reflect greater risk: (1) frequency of religious participation (never vs. ever), (2) quality of the participant's relationship with the main caregiver (poor vs. better than poor), and (3) frequency of contact with other relatives (less than monthly vs. monthly or more).

Table 2
Prevalence of withdrawal symptoms among participants assessed for withdrawal.

Symptom	Tobacco (N = 6760)		Alcohol (N = 7528)		Opioid (N = 3744)	
	AFR (N = 3236)	EUR (N = 3524)	AFR (N = 3532)	EUR (N = 3996)	AFR (N = 1168)	EUR (N = 2576)
Irritability	2055 (63.5 %)	2609 (74.0 %)	-	-	-	-
Anxiety	1627 (50.3 %)	2212 (62.8 %)	1081 (30.6 %)	1547 (38.7 %)	-	-
Restlessness	1816 (56.1 %)	2394 (67.9 %)	1177 (33.3 %)	1510 (37.8 %)	-	-
Concentration	1265 (39.1 %)	1741 (49.4 %)	-	-	-	-
Decreased Heart Rate	442 (13.7 %)	351 (10.0 %)	-	-	-	-
Increased Heart Rate	-	-	881 (25.0 %)	1150 (28.8 %)	459 (39.3 %)	1261 (49.0 %)
Depressed Mood	1095 (33.8 %)	1197 (34.0 %)	1316 (37.3 %)	1737 (43.5 %)	620 (53.1 %)	1830 (71.0 %)
Craving	1387 (42.9 %)	1751 (49.7 %)	-	-	783 (67.0 %)	2058 (79.9 %)
Increased Appetite	2098 (64.8 %)	2016 (57.2 %)	-	-	-	-
Insomnia	1039 (32.2 %)	1310 (37.2 %)	933 (26.4 %)	1269 (37.8 %)	759 (65.0 %)	2015 (78.2 %)
Nausea	-	-	625 (17.7 %)	891 (22.3 %)	687 (58.8 %)	1736 (67.4 %)
Weakness	-	-	1158 (32.8 %)	1536 (38.4 %)	-	-
Headaches	-	-	763 (21.6 %)	1082 (27.1 %)	-	-
Hallucinations	-	-	209 (5.9 %)	189 (4.7 %)	-	-
Shaking	-	-	676 (19.1 %)	1017 (25.5 %)	-	-
Pupillary Dilation	-	-	-	-	577 (49.4 %)	1548 (60.1 %)
Chills	-	-	-	-	724 (62.0 %)	1942 (75.4 %)
Sweating	-	-	-	-	735 (62.9 %)	1986 (77.1 %)
Fever	-	-	-	-	464 (39.7 %)	1265 (49.1 %)
Diarrhea	-	-	-	-	709 (60.7 %)	1735 (67.4 %)
Stomachache	-	-	-	-	767 (65.7 %)	1902 (73.8 %)
Eyes Running	-	-	-	-	673 (57.6 %)	1629 (63.2 %)
Nose Running	-	-	-	-	751 (64.3 %)	1888 (73.3 %)
Yawning	-	-	-	-	779 (66.7 %)	1890 (73.4 %)
Muscle Pain	-	-	-	-	743 (63.7 %)	1973 (76.6 %)

Note: AFR = African-like ancestry, EUR = European-like ancestry.

2.3. Polygenic scores

To calculate PGS, we used summary statistics from GWAS for tobacco use disorder (TUD) (Toikumo et al., 2024), AUD (Zhou et al., 2023), and OUD (Kember et al., 2022) conducted in EUR and AFR individuals. GWAS that included Yale-Penn participants were re-run excluding them to ensure independence. Supplementary Table 1 provides detailed information on the cohorts included in the three GWAS. PGS were calculated using polygenic risk scores–continuous shrinkage (PRS-CS) software with the default settings used to estimate shrinkage parameters. PRS-CS generates PGS by inferring the effect sizes of SNPs using GWAS summary statistics. It takes a Bayesian approach to estimate continuous shrinkage priors to adjust effect sizes while accounting for linkage disequilibrium (LD) structure (Ge et al., 2019). To account for population stratification, we used ancestry-matched LD reference panels from the 1000 Genomes Project Phase 3 (Genomes Project ConsortiumAuton, 2015). PGS were calculated and standardized separately within each ancestry group. Whereas PGS are a measure of genetic liability, individuals with higher PGS for an SUD have a higher genetic liability to develop that SUD.

2.4. Regression models

We first conducted confirmatory factor analyses (CFAs) to generate withdrawal severity factor scores for each of the three sets of withdrawal symptoms. CFAs were performed separately for each substance using the weighted least square mean and variance adjusted estimator in Mplus v8.11 (Muthén LK and Muthén BO). This process yielded tobacco, alcohol, and opioid withdrawal severity latent factors and factor scores for all individuals.

We also derived a latent ACEs factor using the ten childhood environmental variables. The ACEs factor was constructed using a CFA model like those used for the latent withdrawal factors. Individuals with higher ACEs factor scores experienced greater early life adversity. We used a latent variable rather than a summed score of the number of ACEs experienced, as the latter weights each ACE equally. However, ACEs vary in their severity and effects on health (Lacey et al., 2020; Lacey and Minnis, 2020), which is better reflected by a latent factor model, which thereby more clearly demonstrates the the effects that ACEs have on withdrawal. Model fit indices (CFI > 0.9, RMSEA < 0.1, SRMR < 0.08), composite reliability (> 0.7), and significant item loadings were used to evaluate whether the latent factor represented each construct well. Each of the factor models fit the data well. Supplementary Tables 2–5 include further details on the model fit and item loadings for each model. include further details on the model fit and item loadings for each model.

Next, we used multivariate linear regression models to examine the associations of SUD PGS and ACEs factor scores with the corresponding withdrawal severity factors, controlling for age, sex, and the first ten genetic PCs within each ancestry group. We also tested whether ACEs have differential associations with withdrawal severity depending on an individual's genetic liability by including a PGS x ACEs interaction term. Because the scores for ACEs and PGS were standardized, the conditional main effects represent the association when the other variable is at its mean. We present the standardized output so that the model coefficients can be compared and provide an indication of effect size.

Finally, logistic regressions were performed in R to evaluate the main and interactive associations of the PGS and ACEs factor with each individual withdrawal symptom in the two ancestry groups. P-values were adjusted using the Benjamini-Hochberg false discovery rate (FDR) to determine statistical significance (Benjamini and Hochberg, 1995), and results are presented using the FDR-adjusted p-values (or q values). Missing data was minimal (below 5 % for ACEs items and below 1 % for withdrawal items) and did not affect the creation of the factor scores. Thus, the multivariate models that used the factor scores were unaffected by missingness. For the logistic regressions of the individual withdrawal items, the sample sizes were minimally reduced by missingness.

3. Results

3.1. Withdrawal severity

Tobacco Withdrawal Severity. Table 3 shows the results from the multivariate regression models. There were positive associations of ACEs with tobacco withdrawal severity in both AFR (b=.216, SE=.018, $p < .001$) and EUR individuals (b=.262, SE=.016, $p < .001$). In EUR individuals, there was also a positive association with the TUD PGS (b=.062, SE=.020, $p = .002$) and a PGS x ACEs interaction (b= −.065, SE=.017 $p < .001$). The interaction showed that the association between ACEs and tobacco withdrawal severity diminished among individuals with higher TUD PGS. Among AFR individuals, neither the PGS nor the interaction between PGS and ACEs were associated with tobacco withdrawal severity.

Alcohol Withdrawal Severity. Among EUR individuals, both the ACEs factor (b=.240, SE=.016, $p < .001$) and the AUD PGS (b=.040, SE=.016, $p = .014$) were positively associated with alcohol withdrawal severity. Among AFR individuals, only the ACEs factor was positively associated with alcohol withdrawal severity (b=.211, SE=.017, $p < .001$). There were no interactions between ACEs and PGS on this outcome.

Opioid Withdrawal Severity. Among EUR individuals only, the ACEs factor was positively associated with opioid withdrawal severity (b=.098, SE=.020, $p < .001$). Neither PGS nor the PGS x ACEs interaction was associated with opioid withdrawal severity in either ancestry group.

There were modest positive covariances among all three withdrawal factors, indicating that individuals who experienced more severe withdrawal from one substance also experienced more severe withdrawal symptoms from the other substances.

3.2. Individual withdrawal symptoms

Tobacco Withdrawal Symptoms. Among EUR individuals, ACEs and PGS were associated with experiencing irritability, restlessness, and craving upon tobacco cessation (Supplementary Table 6). ACEs (but not PGS) were associated with anxiety (OR = 1.22 [1.13 – 1.32], q = 1.08E-06), difficulty concentrating (OR = 1.30 [1.21–1.40], q = 1.50E-11), slowed heart rate (OR = 1.15 [1.03 – 1.28], q = 0.028), insomnia (OR

Table 3
Results of regression models for overall withdrawal severity.

	African-like Ancestry			European-like Ancestry		
Withdrawal Factor	**β**	**SE**	**P-Value**	**β**	**SE**	**P-Value**
Tobacco						
ACEs	.216	.018	< .001	.262	.016	< .001
PGS	.019	.019	.302	.062	.020	.002
ACEs*PGS	−.031	.017	.069	−.065	.017	< .001
Alcohol						
ACEs	.211	.017	< .001	.240	.016	< .001
PGS	−.003	.018	.850	.040	.016	.014
ACEs*PGS	.013	.016	.436	−.018	.015	.244
Opioids						
ACEs	.042	.031	.176	.098	.020	< .001
PGS	.013	.034	.693	.047	.081	.564
ACEs*PGS	.014	.028	.605	−.001	.020	.975
Factor Correlations						
Tobacco & Alcohol	.368	.017	< .001	.257	.017	< .001
Tobacco & Opioids	.116	.031	< .001	.242	.021	< .001
Alcohol & Opioids	.129	.030	< .001	.114	.020	< .001

Note: Models are adjusted for sex, age, and first 10 ancestry principal components. ACEs = adverse childhood experiences, PGS = polygenic scores, β = standardized coefficient, SE = standard error. P-values are FDR adjusted.

= 1.23 [1.14 – 1.32], q = 9.64E-08), increased appetite (OR = 1.22 [1.14 – 1.32], q = 3.28E-07), and depressed mood (OR = 1.28 [1.19 – 1.37], q = 3.54E-10). There were gene-by-environment interactions on two symptoms—depressed mood and increased appetite (mood: OR = 0.92 [0.86 – 0.99], q= 0.041; appetite: OR = 0.92 [0.86 – 0.99], q = 0.049). As in the multivariate regression models, among individuals with higher PGS, there was a weaker association of ACEs with the two withdrawal symptoms.

Among AFR individuals, there were no associations between PGS and any of the tobacco withdrawal symptoms, nor were there any interactions between PGS and ACEs (Supplementary Table 6). However, there were associations between ACEs and insomnia (OR = 1.26 [1.17 – 1.36], q = 1.33E-08), craving (OR = 1.22 [1.14 – 1.32], q = 3.08E-07), depressed mood (OR = 1.27 [1.18 – 1.37], q = 4.47E-09), difficulty concentrating (OR = 1.27 [1.18 – 1.37], q = 4.47E-09), restlessness (OR = 1.25 [1.16 – 1.35], q = 6.94E-08), anxiety (OR = 1.26 [1.17 – 1.36], q = 1.28E-08), and irritability (OR = 1.25 [1.16 – 1.36], q = 1.81E-07).

Alcohol Withdrawal Symptoms. Among EUR individuals, ACEs were associated with all alcohol withdrawal symptoms, and PGS was associated with all but three: weakness, headache, and hallucinations (Supplementary Table 7). There were no gene-by-environment interactions on alcohol withdrawal symptoms. Similar results were seen in AFR individuals, except that only ACEs showed associations with the individual alcohol withdrawal symptoms (Supplementary Table 7), with neither PGS nor the gene-by-environment interactions being significant.

Opioid Withdrawal Symptoms. For opioid withdrawal symptoms, the only association was between ACEs and nausea in EUR individuals (OR = 1.35 [1.25 – 1.45], q = 0.013; Supplementary Table 8).

4. Discussion

Our findings provide insight into the associations among childhood adversity, genetic risk, and withdrawal from tobacco, alcohol, and opioids. Consistent with research demonstrating that ACEs contribute to the development and severity of withdrawal (Francke et al., 2013; Palmisano et al., 2024; Sawyers et al., 2021), in EUR individuals, we found associations of the ACEs factor with tobacco, alcohol, and opioid withdrawal severity. In AFR individuals, ACEs were associated with the severity of tobacco and alcohol withdrawal, but not opioid withdrawal. Similarly, at the individual symptom-level, ACEs were associated with nearly all tobacco and alcohol withdrawal symptoms, but ACEs were associated only with nausea after reducing/stopping opioid use. Thus, the extent to which ACEs are associated with withdrawal varies not only by substance but also by individual symptoms, highlighting the complexity of environmental links with withdrawal experiences.

ACEs had a consistently greater association with withdrawal severity than PGS, which were associated with withdrawal severity only for tobacco and alcohol in EUR individuals, while ACEs were associated with withdrawal severity across all substances. Although this suggests that environmental factors such as ACEs may play a more prominent role in withdrawal severity than genetic liability for SUDs, this may inappropriately discount the potential future utility of PGS because of present-day power limitations. As GWAS of more refined withdrawal-specific phenotypes are conducted in larger, more ancestrally diverse samples, the associative power of PGS is expected to increase, and whether PGS may be a clinically-useful predictor at some point cannot yet be known.

We also found differences in the pattern of withdrawal symptoms across substances. Tobacco withdrawal was the most strongly associated with both ACEs and PGS, followed by alcohol. Opioid withdrawal, on the other hand, showed few associations with either ACEs or PGS, despite having the highest endorsement of withdrawal symptoms. This may be due not only to the smaller sample of individuals with OUD, which limited statistical power, but also to the limited variability in opioid withdrawal symptom endorsement, which could obscure associations with ACEs and PGS. These results may also suggest that opioid withdrawal is more strongly influenced by factors not evaluated in this study, such as features in the environment other than ACEs, by epigenetic factors, or, perhaps most likely, by the uniformly strong physiological dependence in individuals who are chronically exposed to opioids (Blaze et al., 2024). These findings also necessarily reflect the differing power for PGS between substances and populations.

Despite the observed differences, withdrawal syndromes across substances may share common biological pathways (O'Sullivan and Schwaber, 2021). For example, studies of individuals who use multiple substances have shown similar withdrawal severity between substances like tobacco and cannabis (Vandrey et al., 2008). The significant covariance observed between withdrawal severity factors provides direct support of this. The consistent association of ACEs with withdrawal across substances further supports this interpretation, as ACEs likely influence mood and behavior through similar stress-related biological pathways (al'Absi et al., 2018; al'Absi et al., 2017).

Childhood adversity may increase vulnerability to more severe withdrawal through heightened stress reactivity and altered neurobiological pathways. Early life adversity has been linked to increased activity in the HPA axis and a greater adrenocorticotropic hormone (ACTH) stress response, both of which are associated with greater distress during withdrawal (al'Absi et al., 2017). Additionally, the overlap between neural circuits involved in stress responses and those implicated in SUDs and craving may amplify withdrawal symptoms in individuals exposed to ACEs (Sahani et al., 2022). Thus, heightened stress reactivity could lead to more intense withdrawal.

In EUR individuals, we also identified gene-by-environment interactions for tobacco withdrawal severity, with interactions at the symptom level for depressed mood and increased appetite. The interactions reflect a weaker association between ACEs and withdrawal severity among individuals with higher PGS. This contrasts with the diathesis-stress model, where genetic risk amplifies the effects of environmental stressors (Samek et al., 2015; Zhao et al., 2022). A more fitting explanation for these findings may be biological embedding, whereby early life adversity becomes biologically ingrained and shapes stress-response systems like the HPA axis (Berens et al., 2017). These changes then increase sensitivity to stress and heighten vulnerability to withdrawal symptoms. Alternatively, in individuals with higher genetic liability, the effects of ACEs on stress reactivity and withdrawal may be overshadowed by genetic influences that confer vulnerability to SUDs—factors which predispose individuals to more substance use, and therefore, greater withdrawal risk. Higher genetic liability may underlie differences in physiological sensitivity to a substance. For example, significant associations have been shown to exist between genetic variants in the mu-opioid receptor and OUD (Gaddis et al., 2022; Kember et al., 2022) and genetic variants in nicotinic acetylcholine receptors and TUD (Liu et al., 2019). These physiological differences in response—unlikely to be affected by exposure to ACEs—could overshadow their effects, resulting in a weakened association with withdrawal symptoms for individuals of higher genetic liability. Although our findings show that, in the context of higher PGS, the associations between ACEs and withdrawal symptoms are less pronounced, this does not diminish the importance of environmental factors. Rather, it highlights the complexity of gene-by-environment interactions and the need for further research to understand how these factors dynamically influence the experience of substance-induced withdrawal. Although our findings show that, in the context of higher PGS, the associations between ACEs and withdrawal symptoms are less pronounced, this does not diminish the importance of environmental factors. Rather, it highlights the complexity of gene-by-environment interactions and the need for further research to understand how these factors dynamically influence the experience of substance-induced withdrawal. and withdrawal symptoms are less pronounced, this does not diminish the importance of environmental factors. Rather, it highlights the complexity of gene-by-environment interactions and the need for further research to understand how these factors dynamically influence the experience of substance-induced withdrawal.

Research on the associations between withdrawal symptoms and ACEs has been limited. However, in one study, childhood trauma was associated with greater oxidative stress during cocaine withdrawal, potentially leading to more severe neurological impairment (Sordi et al., 2020). Such impairments could contribute to specific withdrawal symptoms like difficulty concentrating or hallucinations, offering a possible mechanism for the associations we observed with these symptoms during tobacco and alcohol withdrawal. At the symptom level, there may also be regulation by epigenetic factors that were not accounted for in the present study. For example, methylation at certain loci is strongly associated with severe alcohol withdrawal and withdrawal-associated seizures (Andersen et al., 2024). More research is needed to understand other factors that may play a role in differentiating liability for individual withdrawal symptoms.

This study has several limitations. First, we used PGS derived from GWAS of SUDs rather than withdrawal, which may limit the association with withdrawal symptoms. Additionally, genetic liability for withdrawal may be influenced by factors that PGS do not account for, including epigenetic effects (Biermann et al., 2009; Loftis and Janowsky, 2003; Witt et al., 2020). The GWAS samples for the two ancestry groups differed in size, with the AFR GWAS much smaller than the EUR, yielding less power in AFR individuals. Furthermore, the Yale-Penn sample includes fewer individuals who used opioids than tobacco or alcohol, which likely contributed to the lack of significant results for opioid withdrawal. Our study also focused on childhood adversity, without accounting for other environmental influences, such as peer substance use and parental supervision, which are associated with substance use (Gallegos et al., 2021; Meyer et al., 2024). Another limitation of the ACEs factor is that the items comprising it are from a section of the SSADDA that was created *ad hoc* when the instrument was developed. Thus, it differs from other instruments developed to measure ACEs in that it does not include some items that may also represent ACEs. For example, the SSADDA ACEs assessment does not include physical neglect, the loss of a parent through divorce or abandonment, having a caretaker with a diagnosed mental illness, having a family member in jail, or verbal abuse. Finally, this study does not account for social and environmental effects that vary between groups. Although genetic ancestry is distinct from race or ethnicity, certain individuals may face social categorization that contributes to racial discrimination. Racial discrimination is associated with problematic substance use and severity of substance dependence (Glass et al., 2020; Riley et al., 2021). Discrimination may also act as a chronic environmental stressor, similar to ACEs (Amaro et al., 2021; Boynton et al., 2014), which may augment environmental influences in ways that the present study does not capture.

4.1. Conclusions

This study provides important insights into the roles of childhood adversity and genetic liability in substance withdrawal symptoms and severity. Although much of the existing research on genetic and environmental influences focuses on SUD diagnoses, our study focused on withdrawal from alcohol, tobacco, and opioids, examining both latent severity factors and individual symptoms. The associations of childhood adversity and PGS differed across substances and symptoms, with ACEs consistently having a stronger association with withdrawal severity than PGS. Thus, ACEs should be considered when evaluating risk for severe withdrawal. Incorporating assessments of early life adversity into treatment planning could potentially improve the management of withdrawal symptoms and treatment outcomes. Additionally, the gene-by-environment interactions suggest a need for further research on how genetic and environmental factors jointly shape withdrawal experiences, including the mechanisms by which each influences the manifestation of symptoms. An improved understanding of these associations could inform more effective withdrawal management approaches.

CRediT authorship contribution statement

Angela Han: Writing – original draft, Formal analysis, Conceptualization. **Zeal Jinwala:** Writing – review & editing, Formal analysis. **Christal N. Davis:** Writing – original draft, Supervision, Conceptualization. **Joel Gelernter:** Writing – review & editing, Funding acquisition, Data curation. **Jackson SooHoo:** Writing – review & editing. **Henry R. Kranzler:** Writing – original draft, Supervision, Funding acquisition, Data curation, Conceptualization. **Richard Feinn:** Writing – original draft, Supervision, Formal analysis.

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Declaration of Competing Interest

Dr. Kranzler is a member of advisory boards for Altimmune and Clearmind Medicine; a consultant to Sobrera Pharmaceuticals, Altimmune, and Lilly; the recipient of research funding and medication supplies for an investigator-initiated study from Alkermes; a member of the American Society of Clinical Psychopharmacology's Alcohol Clinical Trials Initiative, which was supported in the last three years by Alkermes, Dicerna, Ethypharm, Imbrium, Indivior, Kinnov, Lilly, Otsuka, and Pear; and an inventor on U.S. provisional patent "Multi-ancestry genome-wide association meta-analysis of buprenorphine treatment response." Dr. Gelernter receives payment for editorial work for *Complex Psychiatry*.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.drugalcdep.2025.112712.

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