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Genetic and non-genetic predictors of risk for opioid dependence

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Abstract

Background. Elucidation of the interaction of biological and psychosocial/environmental factors on opioid dependence (OD) risk can inform our understanding of the etiology of OD. We examined the role of psychosocial/environmental factors in moderating polygenic risk for opioid use disorder (OUD).

Methods. Data from 1958 European ancestry adults who participated in the Yale-Penn 3 study were analyzed. Polygenic risk scores (PRS) were based on a large-scale multi-trait analysis of genome-wide association studies (MTAG) of OUD.

Results. A total of 420 (21.1%) individuals had a lifetime diagnosis of OD. OUD PRS were positively associated with OD (odds ratio [OR] 1.42, 95% confidence interval [CI] 1.21–1.66). Household income and education were the strongest correlates of OD. Among individuals with higher OUD PRS, those with higher education level had lower odds of OD (OR 0.92, 95% CI 0.85–0.98); and those with posttraumatic stress disorder (PTSD) were more likely to have OD relative to those without PTSD (OR 1.56, 95% CI 1.04–2.35).

Conclusions. Results suggest an interplay between genetics and psychosocial environment in contributing to OD risk. While PRS alone do not yet have useful clinical predictive utility, psychosocial factors may help enhance prediction. These findings could inform more targeted clinical and policy interventions to help address this public health crisis.

Original Article

*PJN and JDD are co-first authors.

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Introduction

The opioid epidemic has been a growing national public health crisis over the past two decades. In 2020, it was estimated that approximately 2.7 million US individuals had an opioid use disorder (OUD) (Substance Abuse and Mental Health Services Administration, 2022). In 2021, 107622 individuals died of drug overdose, with opioids accounting for more than 75 percent (84 741) of all overdose deaths (National Center for Health Statistics, 2022).

Studies on the epidemiology of OUD have focused on the role of psychosocial and environmental risk factors for the development and maintenance of OUD (Strain, 2022). For example, childhood maltreatment (e.g. sexual, physical, or emotional abuse/neglect) has been identified as a risk factor for OUD (Santo et al., 2021; Somer, 2019), as have social or family environments that allow for substance misuse (Webster, 2017). Psychiatric disorders such as major depressive disorder (MDD) (Na, Scodes, Fishman, Rotrosen, & Nunes, 2022b) and posttraumatic stress disorder (PTSD) (Somer, 2019), which often co-occur among individuals with OUD, are additional risk factors for OUD (Strain, 2022). Furthermore, socioeconomic factors such as low educational attainment (e.g. not graduating from high school), and low income have been identified as key risk factors for both OUD and opioid overdose deaths (Altekruse, Cosgrove, Altekruse, Jenkins, & Blanco, 2020).

In addition to psychosocial and environmental factors, genetic factors are a significant contributor to OUD risk. The impact of family history of OUD and other substance use on OUD risk is well documented (Grant et al., 2016). Genome-wide association studies (GWAS) have identified genetic variants linked to OUD risk (Deak & Johnson, 2021; Gelernter & Polimanti, 2021; Zhou et al., 2020a), including the mu-opioid receptor gene locus (*OPRM1*). Since 2022, large-scale GWAS efforts have greatly increased the discovery of OUD-related risk loci including 14 loci identified in a study of OUD (Kember et al., 2022) and 19 loci in a study of OUD that leveraged information from other substance use disorders (SUDs) using the multi-trait analysis of GWAS (MTAG) approach (Deak et al., 2022). Polygenic risk scores (PRS) derived from large GWAS are increasingly being used to quantify the association between genetic

variation and OUD risk. For example, the MTAG analysis (Deak et al., 2022) yielded a PRS that accounted for 3.8% of the variance in OUD diagnosis (Deak et al., 2022).

Understanding the interplay between genetic liability and psychosocial and environmental factors in psychiatry (Mullins et al., 2016) could account for more variance than either set of factors individually. This could enhance the identification of individuals at risk for various disorders. Emerging research has investigated PRS-by-environment correlates in psychiatric phenotypes including MDD (Mullins et al., 2016), bipolar disorder (Polimanti et al., 2018), and suicidal thoughts (Na et al., 2022a). However, to our knowledge, no study has examined the genetic susceptibility for OUD in the context of environmental and psychosocial factors. Approaches using PRS derived from large-scale GWAS to investigate gene-environment interactions could advance our understanding of the biopsychosocial etiology of OUD and identify modifiable psychosocial and environmental targets for clinical and policy interventions.

We analyzed data from the Yale-Penn 3 cohort (Deak et al., 2022) to evaluate the following aims: (1) to examine the main effect of an OUD PRS derived from an MTAG analysis (Deak et al., 2022) after adjusting for psychosocial and environmental risk factors for OUD; (2) to measure the effects of the interaction of OUD PRS with the psychosocial environment (i.e. education level [Altekruse et al., 2020], early exposure to traumas [Santo et al., 2021] and substances [Webster, 2017]) and psychiatric disorders (i.e. MDD, PTSD [Strain, 2022]) in relation to opioid dependence (OD), and (3) to evaluate the gain in predictive power when genetic and clinical data are combined. The psychosocial and environmental factors that were examined as potential moderators were selected based on previous literature on risk factors for OUD and OD (Altekruse et al., 2020; Na et al., 2022b; Santo et al., 2021; Somer, 2019; Strain, 2022; Webster, 2017).

Methods

Participants

Data were analyzed from 1958 European-ancestry (EUR) adults who participated in the Yale-Penn Study 3 cohort, a study focused on the genetics of SUDs and related conditions. Data for Yale-Penn 1 and Yale-Penn 2 (Zhou et al., 2020a, 2020b) were included in the OUD meta-GWAS used to create the PRS and thus the target sample was restricted to the Yale-Penn 3 sample to prevent overlap. Participants were recruited from five US sites (Gelernter et al., 2014). All participants were interviewed by trained interviewers using the Semi-Structured Assessment for Drug Dependence and Alcoholism (SSADDA), which offers a comprehensive diagnostic assessment of psychiatric and SUDs and information on respondents' psychosocial and environmental characteristics (Pierucci-Lagha et al., 2007). The study protocol was approved by the Institutional Review Board at each site and all participants provided written informed consent.

Genotyping

Genotyping of the Yale-Penn cohorts has been described previously (Sherva et al., 2016). Briefly, genotyping of Yale-Penn 3 was completed in the Gelernter laboratory at Yale School of Medicine using the Illumina multi-ethnic global array containing 1 779 819 single nucleotide polymorphisms. Following genotyping and quality control, imputation was performed using Minimac3 (Das et al., 2016) as incorporated in the Michigan Imputation Server (https://imputationserver.sph.umich.edu) (Michigan imputation server: Free next-generation genotype imputation service) and the Haplotype Reference Consortium reference panel (McCarthy et al., 2016). Standard quality control procedures were used, which included restricting variants to those with a minor allele frequency > 0.01, a Hardy–Weinberg Equilibrium p value > 1.0×10^{-6}, and an imputation quality (INFO score) > 0.8.

Polygenic Risk Score

The OUD PRS calculated in the current study was based on summary statistics from a GWAS of OUD and related SUDs using MTAG (Deak et al., 2022). Given evidence of high positive genetic correlation ($r_g = 0.77–0.82$) between GWAS meta-analyses of OUD, alcohol use disorder (Zhou et al., 2020b), and cannabis use disorder (Johnson et al., 2020), a joint-analysis of these three SUDs using MTAG was performed (Turley et al., 2018). MTAG (Turley et al., 2018) is an approach that can increase GWAS statistical power for a trait of interest, in this case OUD, by including closely related traits to enhance genetic discovery. Using a leave-one-out approach (excluding Yale-Penn 3 from the OUD GWAS meta-analysis), the MTAG-based OUD PRS was a stronger predictor of OD in Yale-Penn 3 subjects than the OUD-only PRS (Deak et al., 2022) and thus was selected as the PRS predictor for the current analysis (Deak et al., 2022).

The OUD PRS was calculated for Yale-Penn 3 participants using PRS-CS (Ge, Chen, Ni, Feng, & Smoller, 2019) and summed across chromosomes and standardized using PLINK (Purcell et al., 2007). Related individuals (second-degree relatives or closer) in Yale-Penn 3 were identified and one individual from each relationship pair was excluded from the analysis, which yielded $N = 1958$. Variants included in the PRS were limited to those in HapMap 3 (International HapMap, 3 Consortium, 2010). The 1000 genomes EUR reference panel was used (1000 Genome Project Consortium et al., 2015) across analytic steps.

The OUD PRS was then included in the respective models described below, which covaried age, sex, and the first 10 within-ancestry genetic principal components.

Phenotypic traits studied

Opioid dependence

Lifetime DSM-IV OD (American Psychiatric Association, 1994) was assessed using the SSADDA (Pierucci-Lagha et al., 2007). Interviewing methods and the diagnostic reliability of the SSADDA have been described previously (Pierucci-Lagha et al., 2007). The OD diagnosis demonstrated excellent test-retest ($\kappa = 0.94$) and interrater ($\kappa = 0.91$) reliability (Pierucci-Lagha et al., 2007). Studies have also shown a high kappa value between OD and DSM-5 OUD (Boscarino et al., 2011).

Sociodemographic variables

Age, sex (male *v.* female), partnered status (partnered *v.* not partnered), annual household income ($ 0–9999, $ 10 000–19 999, $ 20 000–29 999, $ 30 000–39 999, $ 40 000–49 999, $ 50 000–74 999, $ 75 000–99 999, $ 100 000–149 999, $ 150 000 or more/year) data were collected.

Potential moderating variables

Potential moderators of the OUD PRS association with OD were selected based on identified risk factors for OUD and genetic

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studies of OD and OUD (Altekruse et al., 2020; Na et al., 2022b; Santo et al., 2021; Somer, 2019; Strain, 2022; Webster, 2017). We evaluated interactions between OUD PRS and the following variables in relation to OD based on previous findings: education level (Altekruse et al., 2020), quality of relationship with primary caregiver (Caspers, Cadoret, Langbehn, Yucuis, & Troutman, 2005), early exposure to traumas (Santo et al., 2021), early substance use in the household (Webster, 2017), and MDD and PTSD diagnoses (Strain, 2022). Variables that may be prone to reverse causation (i.e. a result of OUD), such as income, employment status, relationship status and quality were excluded from the interaction analyses.

Education was assessed with the question: '*What is the highest grade in school you completed?*' Responses were categorized as (1) less than high school (1–11 year(s)); (2) high school graduate (12 years); (3) some college (13–15 years); and (4) bachelor's degree or higher (⩾16 years).

Quality of early relationship with primary caregiver was assessed with the following question: '*How would you describe the quality of your relationship with your main caregiver up to age 13?*' Response options were *Excellent, Very good, Good, Fair,* or *Poor*.

Witnessed violence before 13 was assessed with the question: '*Did you ever witness or experience a violent crime, like a shooting or a rape, by age 13?*' Response options were *No* or *Yes*.

Sexual abuse before 13 was assessed with the question: '*By the time you were age 13, were you ever sexually abused?*' Response options were *No* or *Yes*.

Physical abuse before 13 was assessed with the question: '*By the time you were age 13, were you ever beaten by an adult so badly that you needed medical care, or had marks on your body that lasted for more than 30 days?*' Response options were *No* or *Yes*.

Substance use in household before 13 was assessed with the question: '*Were you ever aware of adults in your household, or your older siblings, drinking enough to get drunk, or using drugs or alcohol, by the time you were 13?*' Response options were *No* or *Yes*.

Lifetime MDD diagnosis was assessed with the SSADDA, which uses the DSM-IV lifetime diagnosis algorithm for the disorder (American Psychiatric Association, 1994).

Lifetime PTSD diagnosis was assessed with the SSADDA, which uses the DSM-IV lifetime diagnosis algorithm for the disorder (American Psychiatric Association, 1994).

Other substance dependence

Lifetime DSM-IV alcohol, cannabis, cocaine, and other dependence (American Psychiatric Association, 1994) were assessed using the SSADDA (Pierucci-Lagha et al., 2007). Interviewing methods and the diagnostic reliability of the SSADDA have been described previously (Pierucci-Lagha et al., 2007).

Data analysis

Data analyses proceeded in three steps. First, we conducted chi-square and univariate analyses of variance to compare sociodemographic, psychosocial, environmental and psychiatric characteristics by OD status. Second, we correlated the OUD PRS with potential moderating variables. Third, we conducted a multivariable logistic regression analysis to examine associations between OUD PRS, environmental and psychosocial factors, and their interaction in relation to the presence or absence of OD. These analyses were adjusted for age, sex, top 10 within-ancestry principal components, interactions of OUD PRS by age and sex, and significant environmental and psychosocial factors by age and sex. A backward elimination estimation approach was employed to identify significant (likelihood ratio p value < 0.05) OUD PRS × environment and psychosocial interaction terms for the 8 potential moderating variables (i.e. education level, quality of relationship with primary caregiver, witnessed trauma, sexual abuse, physical abuse, and substance use in household before age 13, lifetime MDD diagnosis, and lifetime PTSD diagnosis). Predicted probabilities of OD were then computed and plotted to illustrate significant interaction effects. Lastly, a relative importance analysis (Tonidandel & LeBreton, 2010) was conducted to quantify the relative variance in OD that was explained by each of the statistically significant variables identified in the regression analysis.

Results

The average age of participants (n = 1958) was 41.5 years (S.D. = 15.1: range 16–84), 52.0% were female, and 21.5% (n = 420) had OD. Table 1 presents descriptive statistics of the sample by OD status. After Bonferroni correction, group differences were observed for all of the study variables ($p < 0.05/16 = 0.0031$). Individuals with OD were younger and more likely to be male, had fewer years of education and lower household income, and were less likely to be partnered. They were also more likely to have witnessed violence, been sexually or physically abused, report substance use in the household before age 13, and a lower quality of relationship with their primary caregiver and lifetime diagnoses of MDD and PTSD.

Results of multivariable logistic regression analysis

As shown in Table 2, OUD PRS, male sex, substance use in household before age 13, and PTSD were positively associated with OD, whereas age, education level, household income, and being partnered were negatively associated. The Nagelkerke R^2 of the initial multivariable model without interaction terms was 0.468.

Figure 1 shows results of a relative importance analysis. Annual household income and education level explained 25.9 and 22.7% of the total explained variance of the multivariable model (R^2 = 0.468), respectively. Age explained 18.7%, and partnered status explained 15.3% of this variance. OUD MTAG PRS explained 8.0% of this variance, and sex and substance use in the household before age 13 explained 5.7% and 3.6%, respectively.

Interactions of OUD PRS × psychosocial and environmental factors

Two psychosocial and environmental factors – education level (p = 0.003) and lifetime PTSD diagnosis (p = 0.045) – showed significant interaction effects with OUD PRS in relation to OD after adjusting for all other variables in the multivariable model. Other potential moderating variables were not retained in the final model (all $p > 0.05$).

Figure 2 shows the probability of OD by education level and OUD PRS separately, and the interaction between OUD PRS and education level. The highest probability of OD was observed among individuals with higher OUD PRS and less than a high school education. Specifically, among individuals with higher OUD PRS, those with higher education were less likely to have an OD diagnosis (odds ratio [OR] 0.92, 95% confidence interval [CI] 0.85–0.98). For example, among individuals in the highest

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Table 1. Sociodemographic, trauma, and psychiatric characteristics by opioid dependence status

	No OD *N* = 1538 78.5%	OD *N* = 420 21.5%		
	Mean (s.d.) or *N* (%)	Mean (s.d.) or *N* (%)	Test of difference	*p*
Age	43.3 (15.7)	35.5 (10.8)	11.86	<0.001
Sex			64.73	<0.001
Male	673 (43.8)	267 (63.6)		
Female	865 (56.2)	153 (36.4)		
Partnered	558 (36.3)	42 (10.0)	130.20	<0.001
Education level			377.97	<0.001
Less than high school	92 (6.0)	107 (25.5)		
High school graduate	217 (14.1)	138 (32.9)		
Some college	392 (25.5)	142 (33.8)		
Bachelor's degree or higher	836 (54.4)	32 (7.6)		
Annual household income			164.82	<0.001
< $ 50 000	911 (59.2)	386 (91.9)		
$ 50 000 +	627 (40.8)	34 (8.1)		
Witnessed violence before 13	67 (4.4)	51 (12.7)	38.49	<0.001
Sexually abused before 13	125 (8.2)	64 (15.9)	25.24	<0.001
Physically abused before 13	39 (2.6)	39 (9.7)	49.60	<0.001
Substance use in household before 13	497 (32.7)	161 (60.0)	108.22	<0.001
Quality of early relationship with primary caregiver			53.51	<0.001
Excellent	723 (47.3)	148 (35.9)		
Very good	371 (24.2)	80 (19.4)		
Good	247 (16.1)	95 (23.1)		
Fair	116 (7.6)	54 (13.1)		
Poor	60 (3.9)	26 (6.3)		
Psychiatric disorder				
MDD	102 (6.6)	195 (46.4)	537.37	<0.001
PTSD	108 (7.0)	82 (19.5)	62.41	<0.001
Other substance dependence				
Alcohol dependence	278 (20.2)	266 (85.0)	488.77	<0.001
Cannabis dependence	102 (7.1)	195 (60.6)	537.37	<0.001
Cocaine dependence	131 (8.6)	295 (76.6)	817.18	<0.001
Other dependence	20 (1.3)	102 (24.3)	381.25	<0.001

Note. MDD, major depressive disorder; OD, opioid dependence; PTSD, posttraumatic stress disorder; SUD, substance use disorder.

OUD PRS quartile (highest genetic risk), those with a Bachelor's degree or higher education had a 5-fold lower probability of OD relative to those with less than high school education (12.3% *v.* 62.4%).

Figure 3 shows the interaction between OUD PRS and PTSD, which showed the highest probability of OUD among individuals with high OUD PRS and PTSD. Specifically, among individuals with higher OUD PRS, those with PTSD were more likely to have OD than those without PTSD (OR 1.56, 95% CI 1.04–2.35). For example, among individuals in the highest OUD PRS quartile (highest genetic risk), those with PTSD had 48% higher probability of OD relative to those without PTSD (46.4% *v.* 31.4%).

Discussion

We found that OUD PRS derived from a large scale MTAG analysis (Deak et al., 2022) was positively associated with risk for OD, even after adjusting for known psychosocial risk factors for OD and OUD. In addition, we identified two independent psychosocial/environmental correlates that moderated the effect of OUD PRS on risk for OD – education level and lifetime PTSD diagnosis.

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Table 2. Results of multivariable logistic regression analyses in relation to opioid dependence

	B	S.E.	Wald	*p*	OR (95% CI)
Age	−0.054	0.007	65.71	<0.001	0.95 (0.94–0.96)
Male sex	0.760	0.157	23.54	<0.001	2.14 (1.57–2.91)
Partnered	−1.118	0.160	48.71	<0.001	0.33 (0.24–0.45)
Education level	−0.738	0.082	80.68	<0.001	0.48 (0.41–0.56)
Annual household income	−0.273	0.039	49.78	<0.001	0.76 (0.71–0.82)
Witnessed violence before 13	0.073	0.285	0.06	0.780	1.09 (0.62–1.89)
Sexually abused before 13	0.026	0.246	0.01	0.916	1.05 (0.65–1.89)
Physically abused before 13	0.358	0.338	1.12	0.290	1.49 (0.76–2.91)
Substance use in household before 13	0.775	0.156	24.76	<0.001	1.93 (1.40–2.67)
Quality of relationship with primary caregiver	0.036	0.063	0.32	0.571	1.04 (0.92–1.17)
OUD PRS	0.349	0.080	18.80	<0.001	1.42 (1.21–1.66)
PTSD	0.527	0.242	4.72	0.030	1.69 (1.05–2.72)
MDD	−0.031	0.202	0.02	0.879	0.97 (0.65–1.44)
OUD PRS × education level	−0.087	0.036	5.81	0.003	0.92 (0.85–0.98)
OUD PRS × PTSD	0.446	0.207	4.64	0.045	1.56 (1.04–2.35)

Note. Adjusted for the top 10 within-ancestry principal components.
CI, confidence interval; OR, odds ratio; OUD, opioid use disorder; MDD, major depressive disorder; PTSD, posttraumatic stress disorder; S.E., standard error.

The significant main effect of the OUD PRS on OD risk aligns with previous literature demonstrating cumulative effects of common genetic variants on risk for OD (Crist, Reiner, & Berrettini, 2019). This association remained significant after accounting for major sociodemographic (i.e. age, sex, education level, household income, partnered status) and psychiatric risk factors (i.e. childhood adversities, co-occurring psychiatric disorders such as MDD and PTSD). To our knowledge, this is the first study that observed a persistent association between OUD PRS and risk for OD after controlling for major psychosocial and environmental variables. This finding demonstrates the potential utility of OUD PRS in identifying individuals at increased genetic risk for OUD in both clinical and community-based settings, though larger, more informative GWAS of OUD are needed to maximize the variance in OUD risk accounted for by PRS.

Education moderated the deleterious effect of OUD PRS in relation to OD risk. Previously, lower education level, in particular a failure to graduate from high school, was identified as a key risk factor for OUD, fatal drug use, and opioid overdose deaths (Altekruse et al., 2020; Martins, Sampson, Cerda, & Galea, 2015; Schepis, Teter, & McCabe, 2018). For example, in a study of 14 553 young adult respondents, OUD was most prevalent among those who dropped out of high school (Schepis et al., 2018). A study of 4 million survey responses from the 2008–2015 National Death Index found that relative to adults with graduate degrees, those with only a high school diploma had more than double the risk of death by opioid overdose (hazard ratio = 2.48, 95% CI 2.00–3.06). In addition, the lack of a Bachelor's degree has been highlighted as a key determinant of what they call 'deaths of despair (i.e. deaths by drug overdose, alcohol-related diseases, and suicide)' (Case & Deaton, 2020). An implication of our finding that education moderated the effect of OUD PRS on OD risk is that interventions and/or policy measures that increase retention in school could help to mitigate the risk for OD, especially among individuals with higher polygenic liability for OUD.

Among individuals with higher OUD PRS, those with PTSD had a higher risk of OD. The high co-occurrence of OUD and PTSD has been shown in numerous studies (Dahlby & Kerr, 2020; Jones & McCance-Katz, 2019; Mills, Teesson, Ross, & Peters, 2006). Many explanations for the link between the two disorders have been posited, including the 'self-medication hypothesis (Dahlby & Kerr, 2020),' in which an individual with PTSD attempts to alleviate his or her PTSD symptoms by using opioids. In a study that matched 4025 individuals exposed to opioid analgesics from the National Epidemiologic Survey on Alcohol and Related Conditions III, PTSD was linked to increased risk of OUD after exposure to opioid analgesics (Hassan, Le Foll, Imtiaz, & Rehm, 2017). Based on these findings, it has been suggested that clinicians should monitor closely when prescribing opioids to individuals with a history of PTSD (Wilcox, 2017). Thus, in the future, OUD PRS may have utility in personalizing prescribing patterns for those with PTSD. However, given the cross-sectional nature of our data, this finding should be interpreted with caution, as it is also possible that OD could have contributed to the development of PTSD (Danovitch, 2016).

Each of the environmental covariates retained in the final model explained more variance in OD than did OUD PRS. The relative importance analysis revealed that the selected environmental factors, such as annual household income and education level, explained on average 3-fold greater variance than the OUD PRS. Putting together all available information allows for accurate risk predictions based mostly on environmental covariates, with an additional contribution by the genetic data. Thus, current claims of clinically meaningful genetic risk prediction in OUD should be viewed skeptically. We showed previously that a commercially-available kit purporting to predict OUD risk clinically on the basis of a small number of 'candidate gene' variants, does not predict OUD at all, but does predict ancestry (Hatoum et al., 2021). This result is not surprising as our genome-wide genetic data do not yet account for a clinically meaningful proportion

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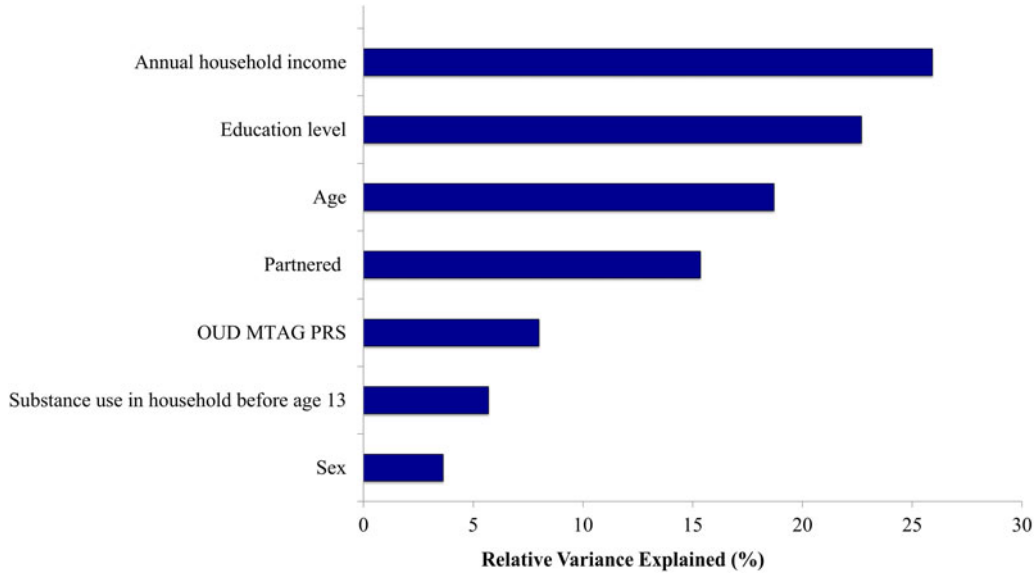

Figure 1. Results of relative importance analysis in relation to opioid dependence.
Note. OUD, opioid use disorder; MTAG, multi-trait analysis of genome-wide association studies; PRS, polygenic risk scores.
Relative variance explained reflects the proportion of the total variance explained in the multivariable model without interaction terms ($R^2 = 0.468$).

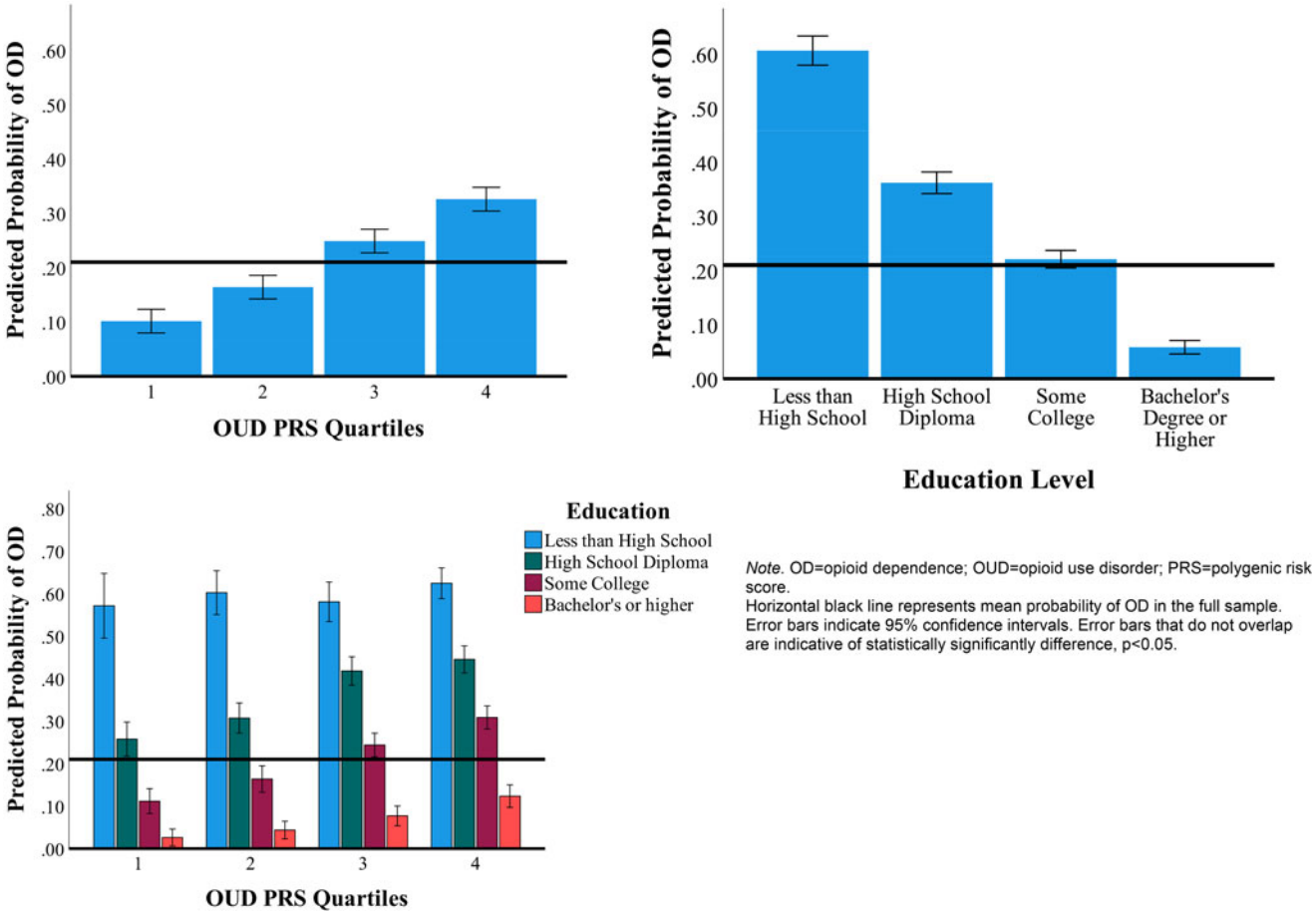

Figure 2. Probability of opioid dependence by OUD PRS, education level, and OUD PRS-by-education.
Note. OD, opioid dependence; OUD, opioid use disorder; PRS, polygenic risk score. Horizontal black line represents mean probability of OD in the full sample. Error bars indicate 95% confidence intervals. Error bars that do not overlap are indicative of statistically significantly difference, $p < 0.05$. Highest PRS quartiles indicate highest genetic risk for OUD, whereas lowest PRS quartiles indicate lowest genetic risk for OUD.

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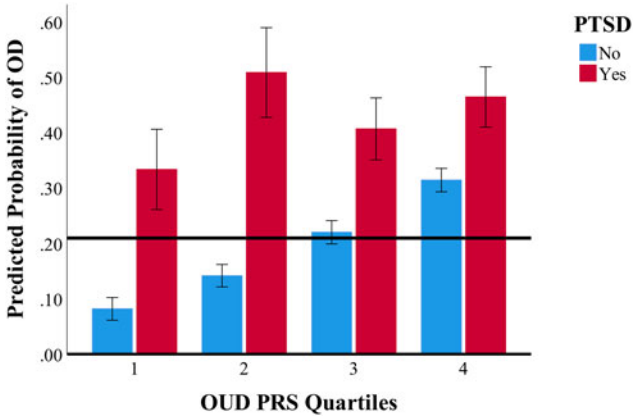

Figure 3. Interaction of PTSD and OUD PRS in relation to the probability of opioid dependence.
Note. OD, opioid dependence; OUD, opioid use disorder; PRS, polygenic risk score; PTSD, posttraumatic stress disorder.
Horizontal black line represents mean probability of OD in the full sample.
Error bars indicate 95% confidence intervals. Error bars that do not overlap are indicative of statistically significantly difference, $p < 0.05$. Highest PRS quartiles indicate highest genetic risk for OUD, whereas lowest PRS quartiles indicate lowest genetic risk for OUD.

of OD risk despite comprising many more variants – and especially, many more variants shown to be significantly associated with the target trait – than commercially-available kits.

This study has several limitations. First, due to the cross-sectional nature of the study, it is not possible to ascertain the causal and temporal relations among the factors examined. However, given that most OD cases develop after high school, it is likely that educational attainment and early life adversities preceded the onset of the disorder, though it is possible that PTSD developed after its onset. Second, the relatively small size of the target sample limited the statistical power to detect other significant main effects or environmental moderators. Relatedly, to preserve statistical power, only interactions between OUD PRS and significant environmental variables with age and sex were force-entered into the multivariable model; further research in larger samples that include all possible PRS-by-covariate and environmental variable-by-covariate interactions(Keller, 2014) is needed to evaluate the robustness of the identified environmental moderators of OUD PRS in predicting OD. Third, the measures of environmental and psychosocial factors utilized in this study were based on self-report, and largely binary and retrospective in nature. Future study using a more structured, multidimensional measure is needed. Fourth, the study sample was comprised entirely of EUR individuals due to lack of sufficient non-EUR GWAS data available for PRS analysis. Additionally, the Yale-Penn study 3 cohort was intentionally designed to recruit individuals with SUDs. Thus, it is unclear whether the results of the study can be generalized either to non-EUR populations or to the general population of EUR individuals. Larger PRS-by-environment interaction studies are needed in more diverse, population-based samples.

Conclusion

Notwithstanding these limitations, results of this study showed that OUD polygenic risk was associated with OD even after considering a number of known major risk factors for OD and OUD. Further, lower education and the presence of a PTSD diagnosis were also associated with OD and moderated the association between OUD PRS and OD. Our results demonstrate the potential utility of examining OUD PRS in combination with psychosocial and environmental factors to understand the biopsychosocial etiology of OD and to develop prediction models for the disorder. Research is needed to replicate and extend these findings to other samples, elucidate the biopsychosocial mechanisms linking OUD PRS to risk for OD, and evaluate the efficacy of clinical and policy measures targeting key moderators of OUD PRS in mitigating risk for OD.

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Competing interests. In the past three years, Dr Na has received royalties from Wolters Kluwer. Dr Kranzler is a member of scientific advisory boards for Dicerna Pharmaceuticals, Sophrosyne Pharmaceuticals, Clearmind Medicine, and Enthion Pharmaceuticals; a consultant to Sophrosyne Pharmaceuticals; and a member of the American Society of Clinical Psychopharmacology's Alcohol Clinical Trials Initiative, which during the past three years was supported by Alkermes, Dicerna, Ethypharm, Lundbeck, Mitsubishi, and Otsuka. Drs. Kranzler and Gelernter are named as inventors on PCT patent application #15/878640 entitled: 'Genotype-guided dosing of opioid agonists,' filed 24 January 2018 and issued on 26 January 2021 as U.S. Patent No. 10900082. Dr Gelernter is paid for his editorial work on the journal *Complex Psychiatry*. Drs. Deak and Pietrzak report no competing interests.

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