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Article

Educational Attainment Polygenic Scores: Examining Evidence for Gene–Environment Interplay with Adolescent Alcohol, Tobacco and Cannabis Use

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Abstract

Genes associated with educational attainment may be related to or interact with adolescent alcohol, tobacco and cannabis use. Potential gene–environment interplay between educational attainment polygenic scores (EA-PGS) and adolescent alcohol, tobacco, and cannabis use was evaluated with a series of regression models fitted to data from a sample of 1871 adult Australian twins. All models controlled for age, age^2, cohort, sex and genetic ancestry as fixed effects, and a genetic relatedness matrix was included as a random effect. Although there was no evidence that adolescent alcohol, tobacco or cannabis use interacted with EA-PGS to influence educational attainment, there was a significant, positive gene–environment correlation with adolescent alcohol use at all PGS thresholds (ps <.02). Higher EA-PGS were associated with an increased likelihood of using alcohol as an adolescent (ΔR^2 ranged from 0.5% to 1.1%). The positive gene–environment correlation suggests a complex relationship between educational attainment and alcohol use that is due to common genetic factors.

Keywords: polygenic scores; educational attainment; alcohol; cannabis; tobacco

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Introduction

Educational attainment has significant beneficial impacts on quality of life, including better self-reported health and longevity and less physical disability, dementia, and mood and anxiety disorders (Davies et al., 2018; Erickson et al., 2016; Kaplan et al., 2017; Lager & Torssander, 2012; Nguyen et al., 2016; Wang, 2021). Although the effects of educational attainment on physical and mental health are partially attenuated after taking into account socioeconomic factors, like income and access to health care, the association with positive physical and mental health benefits remains significant (Kaplan et al., 2017). Educated individuals, therefore, seem to have overall better health outcomes than those who are less educated.

Educational outcomes are influenced by many factors, both genetic and environmental. Across 28 twin studies in 16 countries, genetic factors accounted for approximately 43% of the variance in educational attainment (Silventoinen et al., 2020). Single-nucleotide polymorphism, or SNP,-based heritability estimates are much lower at 14.7% (Lee et al., 2018), suggesting a substantial proportion of remaining missing heritability (Manolio et al., 2009). Polygenic scores (PGSs) based on these common genetic signals account for as much as 11% of the variance in educational outcomes in independent samples (Lee et al., 2018). When compared to other PGSs, which reflect the aggregate influence of common genetic variants, the educational attainment PGS (EA-PGS) stands out as the most predictive within the behavioral sciences.

Although genetic factors play a considerable role in educational attainment, environmental contributions to educational attainment are also substantial. Twin studies suggest that approximately 31% of the variance in educational attainment is due to shared environmental factors (influences that make twins more similar, including the rearing environment) and 26% to unique environmental influences (influences that make twins more dissimilar, including experiences specific to each twin (Silventoinen et al., 2020). Additionally, genetic influences may still be mediated or moderated by the environment, suggesting a substantial role for environmental factors in influencing educational attainment (Bates et al., 2018; Cheesman et al., 2020; Kong et al., 2018).

Adolescent substance use is one environmental factor that is known to be associated with educational attainment. Numerous studies show that adolescent substance use is related to increased rates of dropping out of high school and of not completing college (Davis et al., 2022; Grant et al., 2012; Rose et al., 2014; Verweij et al., 2013; Waldron et al., 2018). However, no studies have yet examined whether adolescent substance use may interact with genetic factors associated with educational attainment to influence the actual level of education an individual attains.

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We hypothesize that those with a high genetic potential for educational attainment who uses substances as an adolescent will attain a lower level of education than would be predicted from their EA-PGS alone. In Moffitt's proposed developmental taxonomy of antisocial behavior (Moffitt, 1993), she described a subset of individuals who continue to engage in antisocial behavior across the lifespan rather than desisting following adolescence due to experiencing developmental 'snares' whose effects cascade over time. One proposed developmental snare that can increase the likelihood of poorer outcomes in adulthood is adolescent substance use and addiction (Moffitt, 1993). Substance-using adolescents are at increased risk of making decisions or experiencing consequences early on in life that close them off from future opportunities (Hussong et al., 2004; Malone et al., 2004; McGee et al., 2015). For example, even individuals with a high genetic propensity for educational attainment may struggle to reach their potential when early substance use produces neurological impairments in areas of the brain responsible for goal direction or logical thinking (Kaag et al., 2017; Lubman et al., 2007; Squeglia et al., 2009; Squeglia et al., 2015), results in strained relationships with teachers, parents or peers who perceive and label substance-using adolescents as 'bad eggs' (Catalano et al., 1996; Silva et al., 2018; Walden, McGue et al., 2004; Wentzel, 1999), or takes considerable time away from educational pursuits due to spending substantial time obtaining, using or recovering from the effects of substances (Bryant & Zimmerman, 2002; Chou et al., 2006; Henry & Thornberry, 2010).

In the current study, we evaluated this hypothesis by testing whether adolescent alcohol, tobacco and cannabis use would significantly moderate the impact of an EA-PGS on the highest level of education attained. We hypothesized that a negative interaction would exist between adolescent substance use and EA-PGS, such that the effect of PGSs on educational attainment would be reduced among adolescents who used substances. Evidence for gene–environment correlations was also evaluated (i.e., EA-PGS predicting adolescent substance use), but we did not have any specific hypotheses regarding these analyses.

Materials and Methods

Genotype and phenotype data were available for 1871 adult twins (432 monozygotic (MZ) females, 264 MZ males, 451 dizygotic (DZ) females, 260 DZ males and 464 twins from opposite sex pairs) in the Australian Twin Registry. Both twins from MZ pairs were included despite having identical genotypes, as each may differ in their substance use or educational attainment and provides unique phenotypic information. Participants were primarily of European ancestry (Lynskey et al., 2002). Just over half of the sample was female (60.0%) and the remainder (40.0%) were male. On average, participants were 30 years old ($M = 29.97$, $SD = 2.41$, range 24–36).

Measures

Adolescent alcohol, tobacco and cannabis use. As part of a larger assessment based on the Australian version of the Semi-Structured Assessment for the Genetics of Alcoholism (Bucholz et al., 1994), participants were asked about lifetime use of alcohol, tobacco and cannabis. Individuals who endorsed having used a substance were then asked when they first initiated use. Adolescent use was defined as using a substance prior to the age of 18 years. Among a subset of 217 participants, the four year test–retest reliability of the adolescent use variables ranged from good to excellent (alcohol: intraclass correlations [ICC] = 0.77 [0.70–0.83], tobacco: ICC = 0.62 [0.50–0.71] and cannabis: ICC = 0.82 [0.76–0.87]).

Educational attainment. Educational attainment was assessed by asking, 'What is the highest educational level you have completed?'. Response options were harmonized across Australian Twin Registry cohorts (Slutske et al., 2022), resulting in a five-level ordinal variable that ranged from not completing primary school to obtaining a postgraduate degree. In the current sample, 20.9% of participants did not complete high school, 42.5% completed a high school degree, 8.7% completed technical/teachers' college, 17.7% completed an undergraduate degree and 10.2% completed a postgraduate degree.

PGSs for educational attainment (EA-PGS). The EA-PGS were calculated from genotype dosages imputed to the 1000 genomes (phase 3 release 5) reference panel. Genomewide association studies (GWAS) summary statistics from Lee et al. (2018) were obtained with the exclusion of the contribution of 23andMe (final sample $n = 758{,}338$). These summary statistics were then used for PGS calculation, which was performed according to the traditional clumping and thresholding method (Choi et al., 2020). The clumping and thresholding approach, which is the most basic and historically most common approach to calculating PGSs, uses the effect size estimates obtained from the GWAS results to weight each SNP according to its association with a phenotype of interest, such as educational attainment (Choi et al., 2020). Independent SNPs are selected based on a chosen linkage disequilibrium (LD) standard, which helps account for the nonrandom association of alleles that are located close by one another on a chromosome. The independent SNPs that are associated with educational attainment below a certain p-value threshold are then summed to obtain a polygenic measure of an individual's genetic propensity for educational attainment. SNPs with low imputation quality ($r^2 < .6$) and minor allele frequency below 1% were excluded. The most significant independent SNPs were selected using PLINK 1.9 (Chang et al., 2015; Purcell & Chang, 2015) in order to correct for signal inflation due to LD (criteria LD $r^2 < .1$ within windows of 10 MBp). A total of eight different PGSs were calculated using different p-value thresholding of the GWAS summary statistics: $p < 5e\text{-}8$, $p < 1e\text{-}5$, $p < .001$, $p < .01$, $p < .05$, $p < .1$, $p < .5$ and $p < 1$. Resulting PGSs were z-standardized (mean = 0, standard deviation = 1).

Data Analysis

First, correlations between EA-PGS and study variables (adolescent substance use and educational attainment) were examined. Following this, mixed effect regressions were conducted using the pedigreemm package (Vazquez et al., 2010) in RStudio (RStudio Team, 2018). All models included age, age^2, sex, cohort, the first five genetic principal components (accounting for genetic ancestry) and imputation batch as fixed effects covariates. Potential issues with confounding (Keller, 2014) were explored by testing for interactions between EA-PGS and sex, age, and cohort and between adolescent substance use and sex, age, and cohort. These interactions were nonsignificant across all models ($ps > 0.08$). Genetic relatedness among individuals in the sample was accounted for as a random effect using a genetic relatedness matrix created using the kinship2 package (Sinnwell et al., 2014).

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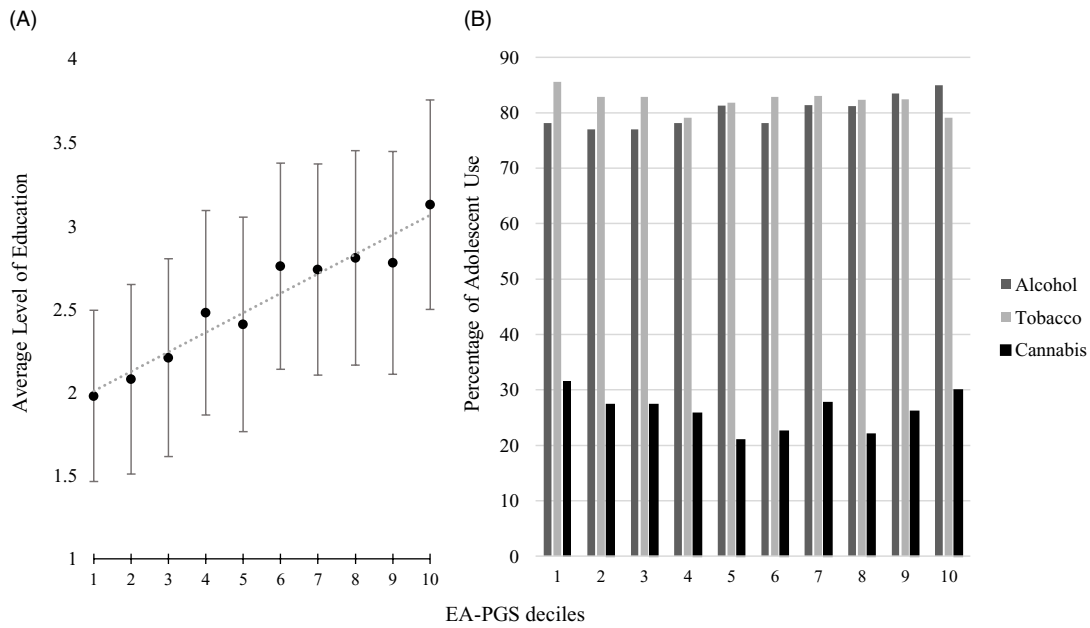

Fig. 1. Levels of average education (Panel A) and adolescent substance use (Panel B) across deciles of educational attainment polygenic scores (EA-PGS).
Note: Error bars in Panel A indicate standard deviations. An education level of 1 indicates not completing high school, 2 indicates completing high school, 3 indicates completing technical/teachers' college and 4 indicates completing an undergraduate degree. Higher EA-PGS deciles indicate greater genetic propensity for educational attainment.

Regression models predicting the highest level of education attained were fitted including interactions between adolescent substance use and PGSs at each threshold. Change in model R^2 was used to estimate the amount of variance explained by the interaction. A test of potential gene–environment correlation was conducted by examining EA-PGS as a predictor of adolescent alcohol, tobacco and cannabis use[1]. The Benjamini–Hochberg false discovery rate (FDR) correction was used to account for multiple tests.

Results

The rates of adolescent substance use were 80.1% for alcohol, 82.2% for tobacco and 26.1% for cannabis. The mean ages of first trying substances were 15.66 for alcohol ($SD = 2.73$), 13.69 ($SD = 3.24$) for tobacco and 18.69 ($SD = 3.42$) for cannabis. As expected, the EA-PGS was significantly correlated with the highest level of education attained ($p < .0001$; see Figure 1, Panel A). There were modest positive correlations between the EA-PGS and adolescent alcohol use ($r = .05$ to $.07$; see Figure 1, Panel B), but PGSs were not significantly correlated with tobacco or cannabis use (see Table 1 for all correlations).

Main Effects

Adolescent substance use (with the exception of adolescent alcohol use) and the EA-PGS were each independently and significantly associated with the highest level of education attained. Adolescent alcohol use did not significantly predict educational attainment ($\beta = 0.07$, $SE = 0.07$, $\Delta R^2 = .00$, $p = .30$) and explained between just 0.02 and 0.1% of the variance after accounting for EA-PGS. Adolescent tobacco use was a significant predictor of educational attainment ($\beta = -0.27$, $SE = 0.10$, $\Delta R^2 = .01$, $p = .006$) and explained 0.2 to 0.7% of the variance in educational attainment after inclusion of the EA-PGS. Adolescent cannabis use significantly predicted lower educational attainment ($\beta = 0.37$, $SE = .07$, $p = 4.5 \times 10^{-7}$) and accounted for between 2.5 and 3.9% of the variance in educational attainment after EA-PGS inclusion in the model. As expected, the EA-PGS accounted for between 2.4 and 6.5% of the variance in educational attainment after accounting for adolescent alcohol, tobacco or cannabis use (see Tables S1, S2 and S3 in Supplemental Materials).

Adolescent Substance Use and EA-PGS Interactions

There were no significant interactions observed between adolescent substance use and EA-PGS. Tables 2–4 present the results for alcohol, tobacco and cannabis use, respectively. The inclusion of the substance use * PGS interaction terms accounted for a negligible amount of variance in educational attainment level (<1%).

Gene–Environment Correlation Models

There was evidence for a positive gene–environment correlation with adolescent alcohol use at all eight PGS thresholds after FDR adjustment. Higher genetic propensity for educational attainment was associated with a greater likelihood of using alcohol as an adolescent. The EA-PGS accounted for between 0.5 and 1.1% of the variance in adolescent alcohol use (see Table 5 and Figure 2). On the other hand, the EA-PGS did not significantly predict adolescent tobacco (see Table 6) or cannabis use (see Table 7) and accounted for a negligible proportion of variance in their use (see Figure 2).

Discussion

Consistent with previous research supporting the strong predictive ability of the EA-PGS (Belsky et al., 2019; Jansen et al., 2018; Lee et al., 2018), genetic propensity for educational attainment was significantly associated with the highest level of education completed

[1]We recognize that adolescent substance use may not strictly fit the lay definition of an environment; however, this is the language that is typically used in psychiatric genetic research (Pereira et al., 2022; Spinath, 2010). Here, we refer to environment broadly to include exposure to substances.

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Table 1. Correlations between EA-PGS, adolescent substance use and educational attainment

EA-PGS	Threshold	Adolescent alcohol use	Adolescent tobacco use	Adolescent cannabis use	Educational attainment
PGS1	$p < 5e\text{-}8$	*.05*	.00	−.04	**.18**
PGS2	$p < 1e\text{-}5$	*.05*	−.04	−.03	**.20**
PGS3	$p < .001$	*.05*	−.02	−.05	**.23**
PGS4	$p < .01$	*.06*	−.02	−.03	**.27**
PGS5	$p < .05$	*.07*	−.01	−.03	**.27**
PGS6	$p < .1$	*.07*	.00	−.02	**.27**
PGS7	$p < .5$	*.07*	−.02	−.01	**.28**
PGS8	$p < 1$	*.07*	−.02	−.01	**.28**

Note: Italics indicates significance at $p < .05$. Bold indicates significance at $p < .0001$. EA-PGS = educational attainment polygenic score.

Table 2. Incremental effects of adolescent alcohol use * EA-PGS interaction

EA-PGS threshold	Estimate	Standard error	*p* value	ΔR^2
$p < 5 * 10^{-8}$	−.047	.069	.497	.0002
$p < 1 * 10^{-5}$	−.086	.070	.220	.0006
$p < .001$	−.100	.072	.167	.0004
$p < .01$	−.125	.072	.084	.0011
$p < .05$	−.095	.071	.179	.0006
$p < .1$	−.077	.071	.279	.0003
$p < .5$	−.076	.072	.296	.0002
$p < 1$	−.080	.072	.269	.0003

Note: EA-PGS = educational attainment polygenic scores.

Table 3. Incremental effects of adolescent tobacco use * EA-PGS interactions

EA-PGS threshold	Estimate	Standard error	*p* value	ΔR^2
$p < 5 * 10^{-8}$	.012	.094	.899	$9.0 * 10^{-7}$
$p < 1 * 10^{-5}$	.032	.094	.731	$4.21 * 10^{-5}$
$p < .001$	.019	.093	.837	$2.91 * 10^{-5}$
$p < .01$	.031	.091	.730	$3.9 * 10^{-5}$
$p < .05$	−.021	.092	.822	$2.78 * 10^{-5}$
$p < .1$	.002	.092	.983	$-3.1 * 10^{-7}$
$p < .5$	−.044	.094	.644	$8.81 * 10^{-5}$
$p < 1$	−.047	.095	.621	.0001

Note: EA-PGS = educational attainment polygenic scores.

in this Australian sample. EA-PGS accounted for as much as 6.5% of the variation in the highest level of education completed. In addition, adolescent tobacco and cannabis use (but not alcohol use) were negatively and independently associated with the highest level of education completed after accounting for the EA-PGS. This is consistent with recent work also identifying independent effects for EA-PGS and smoking PGS on academic success and educational attainment (Hicks et al., 2021).

In the case of alcohol use, there was evidence for a gene–environment correlation, such that higher genetic propensity for educational attainment was associated with an increased likelihood of having used alcohol as an adolescent. Though these effects were relatively small, explaining between just 0.5 and 1.1% of the variance in adolescent alcohol use, they were consistent with previous research that found a small positive gene–environment correlation between socioeconomic status and alcohol consumption (Pasman et al., 2020). Similarly, past research has shown positive correlations between parental education (which is in part influenced by genetic factors that are passed on to offspring) and adolescent alcohol use (Bachman et al., 1981; Zucker & Harford, 1983). A possible interpretation is that the same genetic factors that give rise to a positive educational environment could contribute to greater access to alcohol in the home as a result of more highly educated parents having more disposable income, a factor that has been found to predict greater adolescent alcohol use (Bellis et al., 2007; Lintonen & Nevalainen, 2017; Østergaard et al., 2018).

The passive gene–environment correlation effects could also be due to broader neighborhood factors at work. Individuals who inherit genetic variants associated with higher educational attainment from their parents may be more likely to live in advantaged neighborhoods that are conducive to adolescent alcohol use. For example, one study found that young boys within families that moved from low-income to higher-income neighborhoods showed increases in their alcohol use (Kling et al., 2007). Other research has also established a link between residing in a more advantaged and educated neighborhood and greater alcohol use (Slutske et al., 2016). Parents in more affluent neighborhoods may engage in less monitoring of children, as the environment is deemed to be safer (Patrick et al., 2012).

Another possible explanation is that highly educated parents pass on genetic variants associated with educational attainment and also place significant pressures on their children to achieve in school, which could contribute to drinking to cope (Luthar, 2003). Adolescents who reported that their parents overemphasized their academic achievements had higher rates of substance use than adolescents who reported that their parents prioritized their personal character instead (Luthar & Becker, 2002). Although adolescents from affluent families are privileged in many ways, there is also evidence that they are more likely than less affluent youth to engage in substance use as a way of coping with depression and anxiety (Luthar & Becker, 2002; Luthar & D'Avanzo, 1999; Luthar & Latendresse, 2005). These possibilities suggest that adolescents with high genetic propensity for educational attainment may be at greater risk for adolescent alcohol use. Whether this translates into the experience of alcohol-related problems is a question for future research.

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Table 4. Incremental effects of adolescent cannabis use * EA-PGS interactions

EA-PGS threshold	Estimate	Standard error	*p* value	ΔR^2
$p < 5 * 10^{-8}$	−.077	.070	.274	.0008
$p < 1 * 10^{-5}$	−.113	.070	.106	.0017
$p < .001$	−.053	.069	.450	.0040
$p < .01$	−.015	.068	.830	$2.31 * 10^{-5}$
$p < .05$	.050	.068	.465	.0048
$p < .1$	.043	.068	.525	.0004
$p < .5$	.019	.068	.780	$8.14 * 10^{-5}$
$p < 1$	.009	.068	.894	$2.56 * 10^{-5}$

Note: EA-PGS = educational attainment polygenic scores.

Table 5. Results of models predicting adolescent alcohol use from EA-PGS

EA-PGS threshold	Estimate	Standard error	*p* value	ΔR^2
$p < 5 * 10^{-8}$	**.147**	**.065**	**.023**	**.005**
$p < 1 * 10^{-5}$	**.150**	**.065**	**.021**	**.006**
$p < .001$	**.151**	**.065**	**.020**	**.006**
$p < .01$	**.169**	**.065**	**.009**	**.008**
$p < .05$	**.191**	**.065**	**.003**	**.010**
$p < .1$	**.189**	**.065**	**.004**	**.009**
$p < .5$	**.211**	**.065**	**.001**	**.011**
$p < 1$	**.204**	**.065**	**.002**	**.011**

Note: Bold indicates false discovery rate-corrected *p* value <.05. EA-PGS, educational attainment polygenic scores.

Table 6. Results of models predicting adolescent tobacco use from EA-PGS

EA-PGS threshold	Estimate	Standard error	*p* value	ΔR^2
$p < 5 * 10^{-8}$	−.003	.086	.973	$-1.56 * 10^{-6}$
$p < 1 * 10^{-5}$	−.135	.086	.119	.004
$p < .001$	−.080	.086	.352	.002
$p < .01$	−.058	.085	.499	$8.92 * 10^{-4}$
$p < .05$	−.022	.085	.799	.0001
$p < .1$	−.017	.085	.846	$9.04 * 10^{-5}$
$p < .5$	−.056	.085	.508	$8.43 * 10^{-4}$
$p < 1$	−.058	.085	.498	$8.78 * 10^{-4}$

Note: EA-PGS = educational attainment polygenic scores.

Table 7. Results of models predicting adolescent cannabis use from EA-PGS

EA-PGS threshold	Estimate	Standard error	*p* value	ΔR^2
$p < 5 * 10^{-8}$	−.083	.063	.193	.002
$p < 1 * 10^{-5}$	−.057	.063	.361	.001
$p < .001$	−.095	.062	.124	.003
$p < .01$	−.048	.062	.436	$6.39 * 10^{-4}$
$p < .05$	−.045	.062	.471	$5.37 * 10^{-4}$
$p < .1$	−.035	.062	.574	.0003
$p < .5$	−.013	.063	.841	$3.72 * 10^{-5}$
$p < 1$	−.016	.063	.795	$6.42 * 10^{-5}$

Note: EA-PGS, educational attainment polygenic scores.

There was no evidence that adolescent substance use moderated the association between genetic propensity for educational attainment and actual educational outcomes. There are a couple of potential reasons for this nonsignificant finding. One is that the measures of adolescent substance use were of *any* use prior to the age of 18 years. Therefore, many adolescents who endorsed using a substance may have used it only once or a few times. Many of the hypothesized mechanisms that could explain an interaction between genetic propensity for educational attainment and adolescent substance use may require a greater level of substance use involvement or the development of substance use problems. For example, spending considerable time on the use or pursuit of substances at the expense of time spent in educational endeavors would likely involve substance use that had progressed beyond mere experimentation. Similarly, strained relationships with peers and authority figures, such as parents and teachers, would be unlikely to result from a single or even a few instances of substance use. In the current study, only the lifetime number of times used were available, which did not allow for the examination of more intensive use during adolescence.

A second possibility is that substance use even earlier than 18 years might be more likely to demonstrate an interaction with genetic propensity for educational attainment. Given interest in high school completion as an educational outcome, we chose a cutoff (i.e., prior to the age of 18 years) that would establish temporal precedence of adolescent use before reaching the educational milestone. However, alcohol and tobacco were commonly used in the sample at much earlier ages ($M = 15.66$ and 13.69 respectively), and use before the age of 18 years was highly prevalent (80.1% for alcohol and 82.2% for tobacco). The near ubiquity of such substance use in the sample may have rendered it difficult to find moderation effects for these specific substances.

Limitations

These analyses were not without limitations. First, analyses may have suffered from low power to detect interaction effects, which is one of the primary concerns in gene–environment interaction research. One rule of thumb asserts that a sample size four times larger than that needed for main effects is required in order to be sufficiently powered to detect interaction effects (Smith & Day, 1984). Ideally, therefore, these analyses would have included at least several thousand individuals. This lack of sufficient power makes it difficult to rule out the possibility that an interaction between adolescent substance use and genetic propensity for educational attainment may exist, even though such effects were not found in the current study. The use of larger genetic data banks or combining several datasets that include genotype data and assessment of adolescent substance use might be required. A second limitation was the use of the traditional clumping and thresholding method to generate PGSs. Other newer approaches to creating PGSs have been shown to improve predictive power (Ni et al., 2021).

Finally, it is too simplistic to interpret a PGS as indexing just the combined direct impact of genetic variants on a certain behavior

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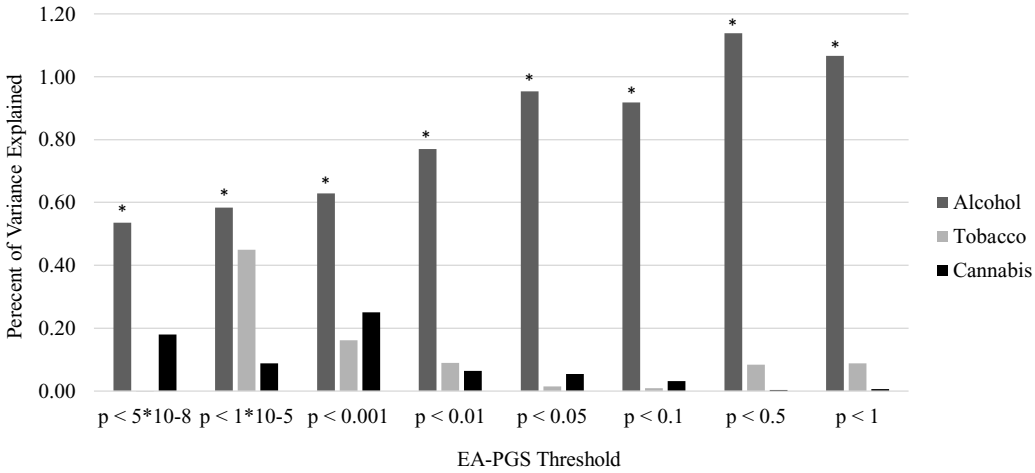

Fig. 2. Percent of variance in adolescent substance use explained by the educational attainment polygenic scores (EA-PGS).
Note: *significance at FDR adjusted *p* value.

(i.e., X genetic variant causes X trait). Instead, PGSs capture both direct and indirect effects of genetic variants, and this has been most compellingly demonstrated for educational attainment (Kong et al., 2018; Okbay et al., 2022; Selzam et al., 2019). Indirect effects include the contributions of: (1) effects from relatives, such as genetic influences on parents/siblings' socioeconomic status or educational attainment that are not necessarily passed down to offspring but still influence the child's educational attainment, (2) gene–environment correlations, which are correlations between genotypes and certain environmental exposures, and (3) other population level effects, such as assortative mating, which refers to the nonrandom selection of mates who are phenotypically and genetically similar to one another. After controlling for parents' EA-PGS, just 31% of the predictive power of the child's EA-PGS could be attributed to direct effects, which was much less than for other traits examined, including height (83%), body mass index (93%) and cognitive performance (68%; Okbay et al., 2022). Given that many indirect effects are included in the EA-PGS, this may make it difficult to formally detect gene–environment interplay using the typical population-based EA-PGS estimate. An alternative option that may result in a less biased EA-PGS (i.e., one that captures direct effects more exclusively) is the use of within-family GWAS or PGS analyses (Okbay et al., 2022; Selzam et al., 2019).

Future Directions

Heavier adolescent use may be more likely to yield significant genetic moderation effects than *any* adolescent substance use. Future research could make use of more detailed assessments of adolescent substance use to explore this possibility. For example, as the Adolescent Cognitive Brain Development (ABCD) study continues, the in-depth assessment of various substance use behaviors (Lisdahl et al., 2018), in conjunction with collection of genotypic data, may allow for an investigation of this possibility within a contemporary sample.

Future analyses could also make use of more recently developed techniques for generating PGSs (Ni et al., 2021). The new approaches differ from traditional clumping and thresholding in that they more formally model the genetic architecture of a trait. For example, some assume that the effect sizes of genetic variants are drawn from a normal distribution (i.e., LDpred2-Inf and SBLUP), while other approaches (i.e., LDpred2, PRS-CS and SBayesR) estimate the distribution of effect sizes using Bayesian modeling. Although all the novel approaches outperformed the traditional method of clumping and thresholding in a recent comparison, a few approaches stood out as being especially well suited for conducting research on highly polygenic traits such as psychiatric phenotypes (Ni et al., 2021). In particular, SBayesR shows promise for its improvements in polygenic prediction, efficient use of computing power and flexibility (Ni et al., 2021). These features make it one of the most attractive choices for generating PGSs moving forward.

Future studies would also benefit from distinguishing within- and between-family effects of EA-PGS. Given that indirect effects account for a considerable proportion of the variance explained by EA-PGS (Kong et al., 2018; Okbay et al., 2022), the observed relationship with other phenotypes may differ when within-family approaches are utilized rather than traditional population-based estimates. Therefore, potential gene–environment interplay between EA-PGS and adolescent substance use should be evaluated further using PGS estimates derived from within-family GWAS.

Conclusions

Although adolescent substance use did not moderate genetic propensity for educational attainment (i.e., gene–environment interaction), there was evidence for a positive gene–environment correlation between adolescent alcohol use and the EA-PGS, wherein higher EA-PGS scores were associated with an increased likelihood of alcohol use in adolescence. This positive gene–environment correlation suggests a complex relationship between educational attainment and alcohol use that is in part due to common genetic factors. Additional investigations making use of larger datasets, newer methods of generating PGSs and within-family GWAS approaches may provide greater insight into the presence (or lack thereof) of interactions between adolescent substance use and genetic propensity for educational attainment.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/thg.2022.33.

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Data availability. Assurances given to the participants in the relevant studies preclude the release of original data. It may be possible to arrange for interested researchers to access and use the data during a visit to QIMR Berghofer Medical Research Institute.

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Conflict of interest. None to declare.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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