Psychology of Addictive Behaviors

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Online First Publication, March 13, 2023. https://dx.doi.org/10.1037/adb0000915

AMERICAN PSYCHOLOGICAL ASSOCIATION

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ISSN: 0893-164X

https://doi.org/10.1037/adb0000915

Genetic and Shared Environmental Factors Explain the Association Between Adolescent Polysubstance Use and High School Noncompletion

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Objective: Examine the nature of the relationship between adolescent polysubstance use and high school noncompletion. ***Method:*** Among a sample of 9,579 adult Australian twins (58.63% female, $M_{age} = 30.59$), we examined the association between the number of substances used in adolescence and high school noncompletion within a discordant twin design and bivariate twin analysis. ***Results:*** In individual-level models controlling for parental education, conduct disorder symptoms, childhood major depression, sex, zygosity, and cohort, each additional substance used in adolescence was associated with a 30% increase in the odds of high school noncompletion ($OR = 1.30$ [1.18, 1.42]). Discordant twin models found that the potentially causal effect of adolescent use on high school noncompletion was nonsignificant ($OR = 1.19$ [0.96, 1.47]). Follow-up bivariate twin models suggested genetic (35.4%, 95% CI [24.5%, 48.7%]) and shared environmental influences (27.8%, 95% CI [12.7%, 35.1%]) each contributed to the covariation in adolescent polysubstance use and early school dropout. ***Conclusions:*** The association between polysubstance use and early school dropout was largely accounted for by genetic and shared environmental factors, with nonsignificant evidence for a potentially causal association. Future research should examine whether underlying shared risk factors reflect a general propensity for addiction, a broader externalizing liability, or a combination of the two. More evidence using finer measurement of substance use is needed to rule out a causal association between adolescent polysubstance use and high school noncompletion.

Public Health Significance Statement
Genetic and shared environmental factors largely accounted for the association between using multiple substances in adolescence and not completing high school.

Keywords: adolescent, polysubstance use, substance use, educational attainment, discordant twin analysis

Supplemental materials: https://doi.org/10.1037/adb0000915.supp

Polysubstance use refers to use of more than one substance within a given time frame and is common among adolescents. For example, a cohort study of Canadian adolescents found that 53% of those who used substances had used more than one (Zuckermann et al., 2020), and a United States study found that as many as 33% of adolescents reported polysubstance use before age 16 (Moss et al., 2014). Other studies obtained similar rates of adolescent polysubstance use (Tomczyk et al., 2016). Critically, when compared to use of a

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This work was supported by National Institute on Drug Abuse Grant K02DA032573 (Arpana Agrawal). Funding sources had no involvement in study design; in the collection, data analysis, or interpretation of the data; in the writing of the report; and in the decision to submit the article for publication.

The original data collection was approved by the institutional review boards at Washington University and QIMR Berghofer, and the secondary analysis of this data was determined to be exempt by the University of Missouri's institutional review board (Project No. 1209709; Secondary Data Analyses of Australian Twin Registry Cohorts II and III).

Christal N. Davis played a lead role in conceptualization, formal analysis, and writing of original draft. Ian R. Gizer played a supporting role in writing of review and editing and an equal role in supervision. Arpana Agrawal played a lead role in funding acquisition and a supporting role in writing of review and editing. Dixie J. Statham played a lead role in project administration and a supporting role in writing of review and editing. Andrew C. Heath played a supporting role in funding acquisition and writing of review and editing. Nicholas G. Martin played a supporting role in funding acquisition and writing of review and editing and an equal role in project administration. Wendy S. Slutske played a lead role in supervision and writing of review and editing.

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single substance, polysubstance use is associated with increased negative outcomes, including greater rates of comorbid psychopathology (Smith et al., 2011), physical health problems (White et al., 2013), and high school noncompletion (Kelly et al., 2015).

The number of different substances used appears to matter among those who engage in polysubstance use. For example, the *number* of substances used was more important than the *types* of substances used when predicting suicide attempts among a sample of over 8,000 individuals (Borges et al., 2000), and the number of substances used has been shown to be linearly related to rates of depression; anxiety; aggression; and deaths by accident, suicide, overdose, or homicide (Brådvik et al., 2009; Hakansson et al., 2011). Although studies have demonstrated an overall relation between polysubstance use and educational attainment (Chan et al., 2020; Kelly et al., 2015; Tan et al., 2020; Vergunst et al., 2022), these studies have not tested whether risk for educational noncompletion increases among those who use a greater number of substances.

Understanding the association between polysubstance use and high school completion is of particular interest given that individuals who do not complete high school are at substantially increased risk for experiencing a multitude of problems in adulthood, including being arrested, being fired from jobs, having poor health, and experiencing early mortality (Krueger et al., 2015; Lansford et al., 2016; Vaughn et al., 2014). Given the link between high school completion and future health outcomes (Krueger et al., 2015; Lansford et al., 2016; Vaughn et al., 2014), reducing high school dropout rates has been identified as a public health concern by the Centers for Disease Control and Prevention (Freudenberg & Ruglis, 2007) and the American Public Health Association (2018). Finally, differences in high school graduation rates contribute to racial and ethnic disparities in income and health (Hahn & Truman, 2015; Orfield et al., 2004). Therefore, improving the identification of potential risk factors and adolescents who may be in danger of early dropout could lead to substantial benefits for public health and more equitable access to resources.

To date, however, studies examining the relation between polysubstance use and educational attainment milestones have not been able to assess whether effects are causal in nature. The discordant twin design is useful for testing whether a potentially causal relationship exists between an environmental exposure and an outcome because it can control for genetic and shared environmental confounding of the association. Several discordant twin studies examined the nature of the relationship between adolescent use of individual substances and reduced educational attainment (Davis et al., 2023; Grant et al., 2012; Rose et al., 2014; Verweij et al., 2013; Waldron et al., 2018); however, none focused on polysubstance use. One previous discordant twin study (Davis et al., 2023) included polysubstance use as a covariate when examining the relation between use of individual substances and high school noncompletion. Polysubstance use significantly attenuated the effect of any given substance on educational noncompletion, highlighting the importance of considering co-occurring substance use when evaluating the effects of individual substances. However, this previous study did not examine the nature of the relationship between adolescent polysubstance use and educational attainment, as the focus was instead on identifying individual substances that increased the odds of not completing schooling (Davis et al., 2023).

The Present Study

The present study utilizes two complementary behavioral genetic methods to examine the relation between adolescent polysubstance use and high school noncompletion within a large sample of Australian twins. The first method is the discordant twin design, which can tease apart potential causal drug exposure effects from confounding factors like genetics and shared rearing environments; it provides a strong test of quasi-causality when restricted to monozygotic (MZ) twins who share all of their genetic information (McGue et al., 2010). We anticipated the association would be partially explained by familial factors common to adolescent polysubstance use and high school noncompletion and partially explained by a potentially causal effect of adolescent polysubstance use on high school noncompletion. To better isolate the potentially causal effect of adolescent polysubstance use on high school noncompletion, we controlled for shared risk factors, including parental education, sex, cohort (to account for changes over time in high school completion rates), and measures of childhood externalizing (i.e., conduct disorder [CD] symptoms) and internalizing (i.e., childhood-onset major depression) symptomatology. While CD symptoms and major depression do not capture the full spectrum of externalizing and internalizing features, their inclusion as covariates does allow us to better parse the effects of polysubstance use from those of a general psychopathology liability on education. Following up on the results of the discordant twin analyses, the second method consisted of bivariate twin analyses evaluating the extent to which familial influences common to adolescent polysubstance use and high school noncompletion were genetic or environmental. We expected both would contribute to their shared etiology. This study's design and its analyses were not preregistered.

Method

Participants

Participants were from two adult cohorts of the Australian Twin Registry (ATR-II and ATR-III; detailed information on the sample and measures are reported in Davis et al., 2023). The sample size was 9,579 individual twins (2,422 monozygotic female twins, 1,566 monozygotic male twins, 1,892 dizygotic (DZ) female twins, 1,330 DZ male twins, 2,263 opposite-sex twins, and 106 twins missing zygosity information). 58.63% self-identified as female and 41.37% as male, and the mean age was 30.59 years (SD = 2.63, range = 23–40). Informed consent was obtained for all participants, and secondary analysis of these data was approved by the institutional review board. Researchers can request access to the use of Australian Twin Registry data sets.

Measures

Participants completed telephone interviews based on the Australian version of the Semi-Structured Assessment for the Genetics of Alcoholism (Bucholz et al., 1994). Interviews were completed between 1996 and 2000 for ATR-II and between 2005 and 2009 for ATR-III. Used in the present study were assessments of participants' own educational attainment, their parents' educational attainment, demographic characteristics, childhood-onset major depression, CD symptomatology, and adolescent substance use.

Adolescent Substance Use

The substance use assessment included lifetime use or misuse of alcohol, tobacco, cannabis, stimulants, hallucinogens, cocaine, inhalants, opiates, sedatives, solvents, and phencyclidine (PCP). Those who endorsed ever using a substance were asked the first age at which they used the substance. An adolescent substance use variable was created by summing the number of substances used at any time prior to age 18. This variable demonstrated excellent test–retest reliability (intraclass correlation coefficient = 0.91 [0.88, 0.93]; Davis et al., 2023). See Supplemental Table S1 for the prevalence of couse across substance classes. While definitions vary (Hindocha & McClure, 2021; Sokolovsky et al., 2020; Yurasek et al., 2017), for our purposes, we define couse as use of both substances in adolescence, though not necessarily at the same time.

Personal Educational Attainment

The highest level of completed education was assessed. Given differences in the available response options across cohorts, responses were harmonized (see Slutske et al., 2022), resulting in a five-level ordinal variable ranging from not completing high school to obtaining a postgraduate degree (see Table 1). A binary variable indicating completion/noncompletion of high school was created for the present study; this outcome was chosen given that the effect of polysubstance use was significantly different across levels of education, violating the proportional odds assumption of ordinal regression (see Supplemental Materials, for additional details).

Parental Educational Attainment

In addition to reporting their own educational attainment, each twin reported their mother and father's highest education level. Parental educational attainment was assessed as a five-level ordinal variable (see Table 1). There was substantial agreement within twin pairs for maternal (k = 0.63 [0.61, 0.65]) and paternal (k = 0.66 [0.64, 0.68]) educational attainment levels.

Childhood-Onset Major Depression

The criteria from the *Diagnostic and Statistical Manual of Mental Disorders, fourth edition-text revision* for major depression were assessed (American Psychiatric Association, 2000). Screening began by asking participants if they ever experienced at least 2 weeks of feeling persistently depressed/sad, much less interested in things, or unable to enjoy things. Individuals who endorsed any of these items were assessed for the remaining symptoms. After all the individual symptoms were assessed, participants were asked if they ever experienced a period of at least 2 weeks in which five or more symptoms occurred together nearly every day and the age at which they experienced their most severe and earliest episodes. Participants who reported any episode of major depression occurring prior to age 18 were coded as having childhood-onset major depression.

CD Symptoms

The diagnostic criteria for *Diagnostic and Statistical Manual of Mental Disorders, fourth edition-text revision* CD were assessed

Table 1
Sample Characteristics

Variable	Full sample		ATR-II cohort		ATR-III cohort		Test of cohort differences	
	%	*N*	%	*N*	%	*N*	$\chi^2(df)$	*p* value
Childhood major depression (%)	4.15	397	3.10	194	6.13	203	50.15(1)	<.0001
Conduct disorder diagnosis (%)	13.24	1,262	15.48	963	9.03	299	82.52(1)	<.0001
Personal educational attainment							1593.87(4)	<.0001
Less than high school	18.26	1,749	22.36	1,401	10.51	348		
Completed high school	33.07	3,167	43.24	2,709	13.83	458		
Completed technical/teachers' college	15.34	1,469	8.59	538	28.11	931		
Completed undergraduate degree	20.47	1960	16.65	1,043	27.69	917		
Completed postgraduate degree	12.86	1,232	9.16	574	19.87	658		
Maternal educational attainment							470.72(4)	<.0001
Less than high school	54.44	5,214	57.29	3,589	49.06	1,625		
Completed high school	22.36	2,141	25.86	1,620	15.73	521		
Completed technical/teachers' college	10.47	1,003	8.57	537	14.07	466		
Completed undergraduate degree	7.87	754	5.24	328	12.86	426		
Completed postgraduate degree	4.86	465	3.05	191	8.27	274		
Paternal educational attainment							527.59(4)	<.0001
Less than high school	55.65	5,330	59.23	3,711	48.88	1,619		
Completed high school	16.79	1,608	19.89	1,246	10.93	362		
Completed technical/teachers' college	10.65	1,020	6.50	407	18.51	613		
Completed undergraduate degree	9.72	931	8.95	561	11.17	370		
Completed postgraduate degree	7.18	688	5.43	340	10.51	348		
	M	*SD*	*M*	*SD*	*M*	*SD*		
Conduct disorder symptoms	1.02	1.46	1.12	1.52	0.84	1.32	114.02(11)	<.0001
No. of substances used in lifetime	3.37	1.74	3.15	1.66	3.80	1.81	518.06(11)	<.0001
No. of substances used in adolescence	2.02	1.15	1.92	1.10	2.21	1.24	525.29(10)	<.0001

Note. ATR = Australian Twin Registry; *df* = degrees of freedom.

(American Psychiatric Association, 2000). Participants were asked to only consider behaviors that occurred before age 18. Although the *Diagnostic and Statistical Manual of Mental Disorders, fourth edition-text revision* requires that two criteria ("often stays out at night" and "often truant from school") occur before age 13, these age requirements were not imposed in the interview. The 15 symptoms were summed for a CD symptom count variable, which demonstrated adequate internal consistency (Cronbach's $\alpha = 0.66$) and test–retest reliability (intraclass correlation coefficient = 0.84 [0.79, 0.88]; Davis et al., 2023).

Analytic Plan

Descriptive and multilevel model analyses were conducted within SAS Version 9.4 (SAS Institute, 2013). Two-level generalized mixed-effects logistic regressions were conducted to examine the effect of adolescent polysubstance use on high school noncompletion. Mixed-effects models were used because of the inherent clustering of twin data, with individual twins nested within twin pairs. Both Level 1 and Level 2 variances were estimated along with a random intercept. Model estimated coefficients were exponentiated to produce odds ratios (*OR*s) representing the change in the odds of not completing high school.

Models were initially run at the individual level taking into account the nonindependence of twin data. These models examine evidence for an overall effect of adolescent polysubstance use on high school noncompletion and are similar to analyses conducted with unrelated individuals. Potential sex and cohort differences in the effects of polysubstance use were evaluated by including interaction terms. If significant, interaction terms were carried forward into adjusted analyses. Adjusted models included zygosity, sex, cohort, CD symptoms, childhood-onset major depression, and parental education as covariates.

After conducting individual-level analyses, discordant twin models were fit to data from same-sex twin pairs (n = 3,070). These models remove potential sources of familial confounding (e.g., genetic factors and the shared rearing environment) that might contribute to the overall effect of polysubstance use on education (Kendler et al., 1993; McGue et al., 2010). Discordant twin designs model an environmental variable of interest (in this case, the number of substances used in adolescence) in terms of a within-twin-pair coefficient and a between-twin-pair coefficient. The within-twin-pair coefficient reflects variation that is unique to each twin and is calculated as the difference between the number of substances used by an individual twin and the average number of substances used across twins in the twin pair (see Supplemental Table S2, for twin-pair cross-tabulations of substance use). The within-twin-pair component allows us to examine potentially causal effects of using more (or less) substances compared to one's cotwin. The between-twin-pair coefficient reflects variation that is shared among twins in a pair (e.g., genetic factors and the shared environment) and is calculated by averaging the number of substances used by a pair. Therefore, a significant between-twin-pair effect suggests that the genetic or familial environmental factors shared by both twins partially account for the predictor's effect on high school noncompletion. Unadjusted and adjusted models were fit. Potential sources of confounding were explored by including zygosity by within-twin-pair interactions (Turkheimer & Harden, 2014). Genetic confounding is implicated when the within-twin-pair effect is greater among DZ than MZ twins, as evidenced by a significant zygosity by within-twin-pair interaction (Turkheimer & Harden, 2014). We also explored possible sex differences in the effects of the between- and within-twin-pair components by including two interaction terms. Significant interactions were carried forward into adjusted models. Finally, analyses limited to MZ twin pairs (n = 1,709) were conducted as a more stringent test of quasi-causality.

Bivariate twin modeling was conducted with Mplus (Muthén & Muthén, 2017) to follow up on the results of the discordant twin analyses. These analyses are an extension of univariate twin modeling (Martin & Eaves, 1977) and were used to dissect the sources of covariation between adolescent polysubstance use and high school noncompletion and to estimate the genetic and environmental correlations between these two traits. The covariance decomposition and the genetic/environmental correlations both provide distinct information (de Vries et al., 2021). Decomposing the sources of covariation shows the proportion of the phenotypic correlation between two traits that is accounted for by each source (i.e., genetic, shared environmental, or unique environmental). The genetic and environmental correlations, on the other hand, indicate the extent to which genetic/environmental factors underlying high school completion overlap with genetic/environmental factors influencing adolescent polysubstance use.

Two additional sets of analyses were conducted (presented in the Supplemental Materials): (a) a set of discordant and bivariate twin analyses restricted to *illicit* polysubstance use and (b) given that a small subset of individuals dropped out of schooling prior to their substance use onset, discordant twin analyses examining the reverse direction of effects, that is, high school completion status predicting polysubstance use.

Results

There were significant differences between the cohorts in levels of education attained by the twins and their parents (see Table 1). Educational attainment was significantly higher in the more recently born cohort (ATR-III, born 1972–1979 compared to ATR-II, born 1964–1971). There were also cohort differences in the number of substances used, $\chi^2(11) = 518.06$, $p < .0001$, with more substances used among ATR-III than ATR-II twins (Table 1). Alcohol, tobacco, and cannabis were the most prevalently coused substances among the sample (see Supplemental Table S1). Fewer participants (8.62%) reported using other substances during adolescence.

Correlations between study variables for males and females are presented in Table 2. There was a significant negative correlation between the number of substances used in adolescence and high school completion, which was somewhat stronger for males ($r = -0.13$) than females ($r = -0.08$). In the full sample, the number of substances used in adolescence was moderately correlated with CD symptoms (r = 0.41). The number of substances used in the lifetime and in adolescence were both modestly correlated with childhood major depression (rs = 0.09 and 0.10, respectively) within the full sample as well.

Multilevel Models

Individual-Level Models

In unadjusted models, each additional substance used was associated with increased odds of not completing high school (see Table 3). Effects of adolescent polysubstance use on high school

Table 2
Pearson Correlations Among Study Variables

Variable	1	2	3	4	5	6	7
1. No. of substances used in lifetime	—	**0.59**	**0.34**	0.01	**0.09**	**0.09**	**0.09**
2. No. of substances used in adolescence	**0.60**	—	**0.41**	**−0.08**	0.03	0.03	**0.08**
3. Conduct disorder symptoms	**0.37**	**0.42**	—	**−0.18**	−0.05	−0.05	**0.10**
4. High school completion	−0.03	**−0.13**	**−0.17**	—	**0.22**	**0.22**	−0.05
5. Mother's education level	**0.07**	0.02	−0.04	**0.22**	—	**0.48**	0.04
6. Father's education level	0.05	0.01	**−0.09**	**0.26**	**0.51**	—	0.02
7. Childhood major depression	**0.12**	**0.15**	**0.14**	**−0.10**	−0.01	0.00	—

Note. Correlations for females are above the diagonal, correlations for males are below the diagonal. Bold indicates $p < .0001$.

noncompletion did not differ by cohort ($F_{1,3935} = 2.21$, $p = .14$), zygosity ($F_{1,3901} = 0.00$, $p = .98$), or sex ($F_{1,3933} = 2.17$, $p = .14$). After adjusting for covariates, each additional substance used in adolescence was associated with a 30% increase in the odds of not completing high school. Several covariates significantly predicted high school noncompletion (see Table 3).

Discordant Twin Models

In the unadjusted model parsing within- and between-twin-pair effects of adolescent polysubstance use, significant associations with high school noncompletion were observed at both levels (within: *OR* = 1.72 [1.39, 2.13]; between: *OR* = 1.48 [1.17, 1.86], see Table 4 and Figure 1, top panel). There was no evidence for genetic confounding in these effects (Zygosity × Within-Twin-Pair interaction: *OR* = 0.70 [0.46, 1.08]). No evidence for sex differences in the within- or between-twin-pair effects emerged (within: *OR* = 0.96 [0.76, 1.21]; between: *OR* = 0.90 [0.76, 1.05]), and effects were similar across cohorts (within: *OR* = 0.96 [0.72, 1.27]; between: *OR* = 0.97 [0.81, 1.17]).

After controlling for covariates, only the between-twin-pair effect of adolescent polysubstance use remained significant (*OR* = 1.30 [1.12, 1.51]), while the within-twin-pair effect was reduced and became statistically nonsignificant (*OR* = 1.19 [0.96, 1.47]; see Figure 1, top panel). Being a member of a twin pair that used more substances in adolescence was associated with a 30% increase in the odds of not completing schooling. Several covariates were significant (see Table 4).

Table 3
Results From Individual-Level Models Predicting High School Noncompletion

Predictor	Unadjusted *OR* [95% CI]	Adjusted *OR* [95% CI]
No. of substances used in adolescence	**1.27 [1.21, 1.33]**	**1.30 [1.18, 1.42]**
Sex (reference = male)	—	0.90 [0.72, 1.13]
Zygosity (reference = DZ)	—	0.87 [0.70, 1.09]
Cohort (reference = ATR-II)	—	**0.59 [0.46, 0.77]**
Conduct disorder symptoms	—	**1.26 [1.17, 1.36]**
Maternal education	—	**0.71 [0.63, 0.80]**
Paternal education	—	**0.59 [0.52, 0.67]**
Childhood major depression	—	0.99 [0.71, 1.39]

Note. Bold indicates significance at $p < .05$. *OR* = odds ratio; CI = confidence interval; DZ = dizygotic; ATR = Australian Twin Registry.

MZ Only Models

When analyses were restricted to MZ twins, both the within- (*OR* = 1.44 [1.04, 2.01]) and between-twin-pair (*OR* = 1.53 [1.10, 2.12]) effects were significant in the unadjusted model (see Table 4 and Figure 1, bottom panel). Effects did not differ for males and females (Within × Sex interaction: *OR* = 1.16 [0.80, 1.67]; Between × Sex interaction: *OR* = 0.83 [0.66, 1.05]). There were also no cohort differences (Within × Cohort interaction: *OR* = 0.72 [0.44, 1.18]; Between × Cohort interaction: *OR* = 0.83 [0.66, 1.05]). After controlling for covariates, the between-twin-pair effect of adolescent polysubstance use remained significant (*OR* = 1.38 [1.11, 1.71]), while the within-twin-pair effect was reduced and became statistically nonsignificant (*OR* = 1.04 [0.75, 1.44]). Several covariates were significantly associated with high school noncompletion (see Table 4).

Illicit Polysubstance Use Models

Any illicit substance use (most typically, cannabis) was associated with greater odds of not completing high school compared to no illicit substance use (adjusted model: *OR* = 1.62 [1.24, 2.12]), and illicit polysubstance use carried additional risk beyond the use of a single illicit substance (adjusted model: *OR* = 1.61 [1.15, 2.28]). See Supplemental Table S3, for the full individual-level model results. Consistent with the analyses of overall polysubstance use, the association between illicit polysubstance use and high school noncompletion was largely attributable to shared familial factors (between-twin-pair: *OR* = 1.38 [1.11, 1.72]) and less so to potentially causal effects (within-twin-pair: *OR* = 1.24 [0.93, 1.64]). See Supplemental Table S4, for full results.

Examining Potential Bidirectional Effects

Given that some individuals in the sample ($n = 825$) dropped out of schooling prior to the age used as a cut-off for classifying adolescent polysubstance use (i.e., prior to age 18), we evaluated evidence for the reverse direction of effects, whereby high school noncompletion predicted adolescent polysubstance use (see Supplemental Tables S5 and S6, for full results). There was no evidence that early school dropout causally increased polysubstance use (within-twin-pair: *OR* = 0.98 [0.85, 1.12]). Instead, familial effects accounted for the association (between-twin-pair: *OR* = 0.81 [0.71, 0.94]).

Bivariate Twin Analysis

Within the full sample, genetic sources accounted for 35.4% (95% CI [24.5%, 48.7%]), shared environmental sources accounted

Table 4
Results From Discordant Twin Models Predicting High School Noncompletion

Predictor	Same-sex twin pairs (n = 3,070)		MZ only pairs (n = 1,709)	
	Unadjusted *OR* [95% CI]	Adjusted *OR* [95% CI]	Unadjusted *OR* [95% CI]	Adjusted *OR* [95% CI]
No. of substances used in adolescence				
Within-twin-pair component	**1.72 [1.39, 2.13]**	1.19 [0.96, 1.47]	**1.44 [1.04, 2.01]**	1.04 [0.75, 1.44]
Between-twin-pair component	**1.48 [1.17, 1.86]**	**1.30 [1.12, 1.51]**	**1.53 [1.10, 2.12]**	**1.38 [1.11, 1.71]**
Sex (reference = male)	—	1.09 [0.78, 1.53]	—	0.93 [0.58, 1.49]
Zygosity (reference = DZ)	—	0.94 [0.70, 1.27]	—	—
Cohort (reference = ATR-II)	—	**0.53 [0.38, 0.74]**	—	**0.43 [0.27, 0.68]**
Conduct disorder symptoms	—	**1.25 [1.13, 1.39]**	—	**1.27 [1.09, 1.47]**
Maternal education	—	**0.64 [0.54, 0.77]**	—	**0.69 [0.55, 0.83]**
Paternal education	—	**0.64 [0.55, 0.76]**	—	**0.63 [0.50, 0.79]**
Childhood major depression	—	1.24 [0.81, 1.92]	—	1.59 [0.88, 2.85]

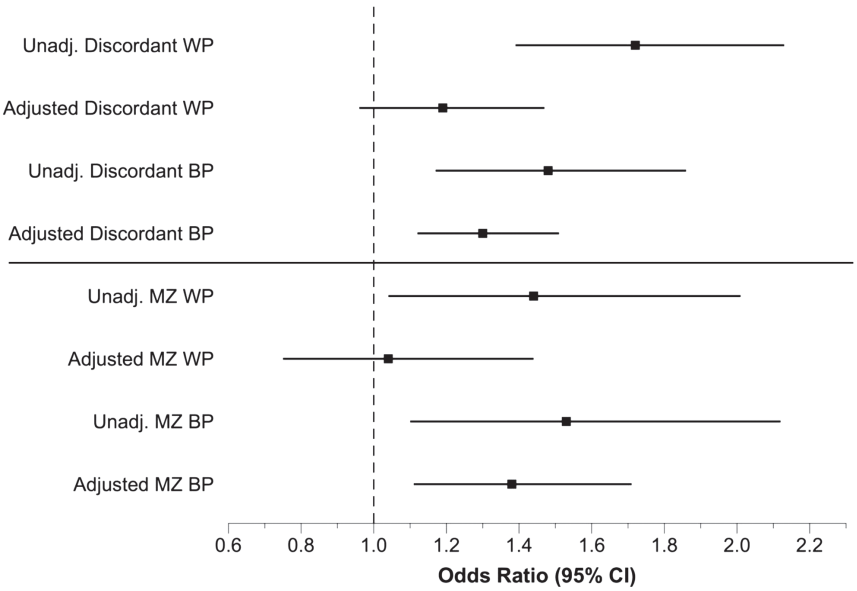
Note. Bold indicates significance. *OR* = odds ratio; CI = confidence interval; MZ = monozygotic; DZ = dizygotic; ATR = Australian Twin Registry. The within-twin-pair component represents a potentially causal effect, while the between-twin-pair component represents the effect of familial environment and genetic factors.

for 27.8% (95% CI [12.7%, 35.1%]), and unique environmental sources accounted for 36.7% (95% CI [33.9%, 38.4%]) of the phenotypic covariation between adolescent polysubstance use and high school noncompletion. The genetic correlation between adolescent polysubstance use and high school noncompletion was estimated at −0.36 (95% CI [−0.99, 0.10]), the shared environmental correlation at −0.05 (95% CI [−0.48, 0.56]), and the unique environmental correlation at −0.09 (95% CI [−0.24, 0.06]), all of which were nonsignificant (see de Vries et al., 2021). More details about univariate and bivariate twin analyses of illicit polysubstance use and high school noncompletion are in the Supplemental Materials.

Discussion

In this sample of adult Australian twins, we examined the nature of the relationship between adolescent polysubstance use and high school noncompletion. As we hypothesized, the risk for not

Figure 1
Results of Discordant Twin Models Predicting High School Noncompletion From Adolescent Polysubstance Use Levels in MZ and Same-Sex DZ Pairs (Top Panel) and MZ Pairs (Bottom Panel)



Note. Unadj. = unadjusted model; WP = within-twin-pair component; BP = between-twin-pair component; MZ = monozygotic; DZ = dizygotic. Discordant models refer to models conducted in same-sex twin pairs, while MZ models refer to models restricted to only monozygotic twins.

completing high school increased with each additional substance used in adolescence. While the within-twin-pair effect became statistically nonsignificant in adjusted analyses ($OR = 1.19$ [0.96, 1.47]), we cannot conclude that potentially causal effects of adolescent polysubstance use on high school noncompletion do not exist. Given the imprecision of our point estimates, it is possible that causal effects do partially explain the observed association. However, there was more evidence that shared familial factors contributed to the association between adolescent substance use and educational outcomes, consistent with previous twin studies (Bergen et al., 2008; Verweij et al., 2013). Follow-up bivariate twin analyses revealed that genetic and shared environmental sources each contributed (35.4% and 27.8%, respectively) to covariation between the number of substances used in adolescence and high school noncompletion. There was also a moderate genetic correlation ($r_g = -0.36$ [−0.99, 0.10]), consistent with molecular genetic studies that demonstrated genetic correlations between educational attainment and specific substance use phenotypes, such as quantity of alcohol consumed (Jang et al., 2022; Marees et al., 2021), smoking initiation (Jang et al., 2022; Marees et al., 2021), cigarettes smoked per day (Jang et al., 2022; Marees et al., 2021), cannabis use (positively correlated; Jang et al., 2022; Marees et al., 2021; Pasman et al., 2018), and opioid use disorder (Zhou et al., 2020). Therefore, early substance use may act as a useful marker for individuals at higher genetic susceptibility of not completing high school.

Although it could be easy to misinterpret the presence of genetic contributions to the observed association as indicating that certain individuals are unlikely to benefit from prevention or intervention efforts (Harden, 2021), the impacts of genetic effects are routinely moderated and mediated by environmental interventions. For example, eyesight is a highly heritable trait (Hawthorne & Young, 2013) that is routinely treated by environmental means (i.e., by providing individuals with corrective lenses). Similarly, even if genetic, rather than causal, factors contribute to the observed association between polysubstance use and educational outcomes, environmental interventions that adopt a systems-level approach and provide additional support for youth at risk could yield significant benefits. As a marker of genetic liability for not completing high school, adolescent polysubstance use may be useful for identifying individuals who would benefit from increased attention and resources within educational systems.

Recent increased consideration of polysubstance use reflects a growing understanding of the shared etiology of substance use behaviors (Mallard, 2022). While some evidence points to substance-specific causal effects on early school dropout (Grant et al., 2012; Rose et al., 2014; Waldron et al., 2018), our findings on the effects of polysubstance use are consistent with previous studies that suggest much of the risk for adverse outcomes may be driven by factors shared across substances. For example, there is strong evidence that shared genetic factors partially account for the overlap between various substance use behaviors and disorders (Hatoum et al., 2022; Palmer et al., 2012; Schoeler et al., 2021; Sun et al., 2021), and a genetic addiction factor is strongly associated with educational attainment (Schoeler et al., 2021), as well as executive functioning and neurodevelopmental disorders such as attention-deficit/hyperactivity disorder (Hatoum et al., 2022). Furthermore, within a large nationally representative sample, the association between substance use disorders and unemployment, income, and financial problems 3 years later was better explained by a latent addiction factor than by substance-specific effects (Franco et al., 2019).

Polysubstance use likely also shares considerable overlap with a general externalizing factor. A meta-analysis of studies applying multivariate comorbidity models found that associations among alcohol dependence, drug dependence, CD, and antisocial behavior could be explained by a single underlying externalizing factor (Krueger & Markon, 2006). More recently, an analysis of more than 1.5 million individuals revealed substantial genetic correlations among substance use behaviors and other externalizing traits, all of which loaded on a genetic externalizing factor (Karlsson Linnér et al., 2021). This externalizing factor had a moderate negative genetic correlation with educational attainment ($r_g = -0.32$) that was similar in magnitude to the one we observed between polysubstance use and high school completion ($r_g = -0.36$). Regarding polysubstance use specifically, variants in *GABRA2* (implicated in a Genome Wide Association Study of risk-taking behavior, Karlsson Linnér et al., 2019, and externalizing traits, Karlsson Linnér et al., 2021) have been associated with simultaneous polysubstance use (Mallard et al., 2018). While we attempted to control for externalizing features by including CD symptoms as a covariate within our models, a recent meta-analysis suggests that antisocial behaviors may not be good indicators of the proposed antagonism subfactor of the externalizing spectrum (Ringwald et al., 2023). Therefore, it is likely that we were unable to account for important variability related to externalizing traits, making it difficult to isolate polysubstance use effects from those of a general externalizing liability.

When considering which genetically influenced traits might contribute to the observed association between polysubstance use and education, impulsivity and other externalizing traits are likely to be especially important. For example, one recent study using genomic structural equation modeling found that externalizing phenotypes and substance use disorders were all influenced by a single underlying genetic liability (Poore et al., 2022). A second study found that risk-taking helped to explain the association between a genetic addiction factor and other forms of psychopathology (Hatoum et al., 2022). Additionally, neurodevelopmental disorders like attention-deficit/hyperactivity disorder (which loads onto an externalizing factor; Carragher et al., 2014) were strongly genetically associated with an underlying addiction factor (Hatoum et al., 2022). Finally, executive functioning is also a genetically influenced trait that has been shown to contribute to the overlap between various substance use behaviors and other forms of psychopathology (Hatoum et al., 2022; Yang et al., 2022). Impairments in executive functioning may account for some of the shared genetic factors that give rise to both using more substances in adolescence and not completing one's education. Therefore, externalizing liability and executive functioning impairments may be two of the genetically influenced traits underlying the association between polysubstance use and educational attainment.

As our understanding of the etiology of addiction continues to advance with the use of powerful new genetic analysis techniques, efforts are likely to be strengthened by the use of a dimensional approach that transcends traditional diagnostic categories and recognizes substantial comorbidity across substance use, substance use disorders, and broader externalizing behaviors (Hatoum et al., 2022; Karlsson Linnér et al., 2021; Mallard, 2022). Future research should investigate the extent to which polysubstance use may be explained by a general addiction factor, a general externalizing

factor, or some combination of the two. Using latent liability spectrum approaches could allow for the development of a more accurate, nuanced understanding of the etiology of addictive behaviors and to more refined diagnostic models that integrate information across substances.

Finally, while many studies routinely treat educational attainment as an ordinal outcome variable, our findings suggest that researchers should carefully consider whether this is an appropriate choice by first testing for violations of the proportional odds assumption within their data. Within our sample, the association between adolescent polysubstance use and educational attainment was significantly different across levels of education, leading us to focus on a singular educational milestone of importance. Treating educational attainment as an ordinal outcome variable without consideration for possible differential associations could lead to misinterpreting the true relationship between substance use (among other predictors) and education.

Limitations

Despite advantages of a large sample size and use of the discordant twin design, the present study is not without limitations. First, there have been considerable changes in access to higher education in the years since these data were collected (Marks et al., 2000; Vieira et al., 2020). Given this, it will be important to attempt to replicate these findings in a more contemporary sample. Second, although this study fills an important gap in the literature by examining the relationship between adolescent polysubstance use and educational outcomes, it cannot tell us the effects of differing patterns of polysubstance use. It is possible that the use of certain combinations of substances may be more predictive of reduced education than other combinations. Of note, a minority of adolescents in our sample (8.62%) used substances other than alcohol, tobacco, and cannabis in adolescence, so our results may not be applicable to more extensive polysubstance use.

A third limitation is the assessment of *any* adolescent use rather than a measure capturing the extent of use. While participants reported estimates of the number of times they used a substance in their lifetime, we were unable to isolate use specific to adolescence. Therefore, adolescents who merely experimented with multiple substances would be classified similarly as those who engaged in more consistent use of the substances. This obscures potentially important differences between those who experiment with substances and those who develop a persistent pattern of use in adolescence. The effects of persistent adolescent substance use on early school dropout may be more pronounced than those of experimentation, as research on adolescent alcohol and cannabis use has found a dose-dependent relationship with cognitive functioning (Morin et al., 2019; Nguyen-Louie et al., 2015; Winward et al., 2014). However, previous research has also identified the importance of the number of substances used as an indicator of risk for poorer physical health (as measured by limitations in physical activities because of health problems, bodily pain, low vitality, and general health perception; Baggio et al., 2014) and neurological alterations (Kaag et al., 2017, 2018), with at least one study suggesting these effects did not depend on the level of substance use (Kaag et al., 2017).

The present study is also complicated by retrospective recall of adolescent substance use. Individuals are unlikely to be completely accurate in their reporting of substance use behaviors that occurred more than a decade ago. Nonetheless, the high test–retest reliability (intraclass correlation coefficients = 0.91) of the retrospective reports of the number of substances used in adolescence was reassuring. Finally, given that we did not test measurement invariance of our adolescent polysubstance use variable across relevant subgroups (e.g., cohort and sex), it is possible that noninvariance could have biased our results.

Conclusions

Each additional substance used in adolescence was associated with a 30% increase in the odds of not completing high school. When explored further in discordant twin analyses, the effect of adolescent polysubstance use on education appeared to be more attributable to familial-level influences than causal effects, with both genetic and shared environmental factors contributing. The potentially causal association between the number of substances used in adolescence and high school noncompletion became nonsignificant in adjusted models, but we cannot rule out the possibility of causal effects, particularly at more extensive levels of polysubstance use. Although substance-specific pathways to reduced educational attainment may exist (Grant et al., 2012; Rose et al., 2014; Waldron et al., 2018), the association between substance use and negative outcomes such as early school dropout may be best understood by recognizing the shared risk that cuts across the use of various substances.

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Received October 14, 2022
Revision received January 5, 2023
Accepted February 6, 2023 ■