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Article

Predicting Alcohol Dependence Symptoms by Young Adulthood: A Co-Twin Comparisons Study

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Abstract

Co-twin comparisons address familial confounding by controlling for genetic and environmental influences that twin siblings share. We applied the co-twin comparison design to investigate associations of adolescent factors with alcohol dependence (AD) symptoms. Participants were 1286 individuals (581 complete twin pairs; 42% monozygotic; and 54% female) from the FinnTwin12 study. Predictors included adolescent academic achievement, substance use, externalizing problems, internalizing problems, executive functioning, peer environment, physical health, relationship with parents, alcohol expectancies, life events, and pubertal development. The outcome was lifetime AD clinical criterion count, as measured in young adulthood. We examined associations of each adolescent domain with AD symptoms in individual-level and co-twin comparison analyses. In individual-level analyses, adolescents with higher levels of substance use, teacher-reported externalizing problems at age 12, externalizing problems at age 14, self- and co-twin-reported internalizing problems, peer deviance, and perceived difficulty of life events reported more symptoms of AD in young adulthood ($ps < .044$). Conversely, individuals with higher academic achievement, social adjustment, self-rated health, and parent–child relationship quality met fewer AD clinical criteria ($ps < .024$). Associations between adolescent substance use, teacher-reported externalizing problems, co-twin-reported internalizing problems, peer deviance, self-rated health, and AD symptoms were of a similar magnitude in co-twin comparisons. We replicated many well-known adolescent correlates of later alcohol problems, including academic achievement, substance use, externalizing and internalizing problems, self-rated health, and features of the peer environment and parent–child relationship. Furthermore, we demonstrate the utility of co-twin comparisons for understanding pathways to AD. Effect sizes corresponding to the associations between adolescent substance use, teacher-reported externalizing problems, co-twin-reported internalizing problems, peer deviance, and self-rated health were not significantly attenuated (p value threshold = .05) after controlling for genetic and environmental influences that twin siblings share, highlighting these factors as candidates for further research.

Keywords: Adolescence; alcohol; co-twin comparisons; longitudinal; young adults

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Alcohol dependence (AD) is a component of alcohol use disorder (AUD) involving tolerance, withdrawal, and continued use despite problems (National Institute on Alcohol Abuse and Alcoholism, 2016). Young adults are at greater risk for AUD than any other age group (Grant et al., 2015), and being diagnosed with AD by young adulthood has lasting effects on physical and mental health in late life (Haber et al., 2016). Therefore, characterizing adolescent predictors of later AD is critical to identify relevant targets for preventive intervention efforts and to mitigate long-term consequences of AD symptoms.

Prior work has identified a series of adolescent factors related to young adult alcohol problems, including conduct disorder (CD) symptoms, aggression, higher levels of alcohol consumption, and depressive symptoms (Edwards et al., 2016; Huurre et al., 2010; Merline et al., 2008). However, the vast majority of studies examining adolescent predictors of AD are conducted on samples of unrelated individuals, and between-family differences remain an unaddressed potential confound. As a result, associations may reflect a causal effect of the adolescent factor on later AD, shared genetic liability, overlapping environmental influences, or a combination of these possibilities. Evaluating confounding by familial factors is, therefore, important for understanding pathways to AD and for developing effective intervention efforts. For example, there is evidence that overlapping genetic influences contribute to the correlation between CD symptoms and substance use (Verweij et al., 2016), and socioeconomic status (SES) is related

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to both adolescent conduct problems (Piotrowska et al., 2015) and rates of substance use disorders (Galea et al., 2004). If the prospective association between CD and AD is substantially reduced when controlling for shared familial influences, this suggests that intervention efforts aiming to reduce conduct problems in adolescence are not likely to reduce risk for later alcohol problems. On the other hand, if the magnitude of the association between CD symptoms and AD after accounting for between-family differences is largely the same as in the population, this would highlight conduct problems as a relevant target for preventive intervention.

Co-twin comparisons offer a complementary tool to other standard methods, such as statistical covariates, to address potential confounding by between-family factors. By evaluating whether differences between co-twins in risk or protective factors predict differences in AD symptoms, this type of design controls for all measured and unmeasured genetic and environmental influences that twin siblings share. In prior analyses of self-report alcohol measures from a population-based sample of Finnish twins (n = 3,402), we applied the co-twin comparison design to evaluate adolescent predictors of young adult alcohol use and intoxication frequency (Stephenson et al., 2020). Though many risk and protective factors were related to a composite of these alcohol use behaviors in individual-level analyses, only adolescent academic achievement, substance use, and alcohol expectancies remained substantially and significantly associated with alcohol misuse in co-twin comparisons, suggesting that these predictors were robust to family-level confounds.

In the current study, we build on these prior analyses (Stephenson et al., 2020) to examine the adolescent predictors of clinically significant alcohol problems, which were assessed in an intensively studied subsample of our Finnish twins in young adulthood (N = 1286 individuals from 581 complete pairs; Rose et al., 2019). Delineating the adolescent predictors of clinically significant alcohol problems is important in light of findings that alcohol use and AD clinical criteria are related but distinct phenotypes: only 1 in 10 USA adults who engage in binge drinking meet diagnostic criteria for AD (Esser et al., 2014). Twin data indicate only partially overlapping genetic influences (Dick et al., 2011), a finding supported by genome-wide association studies on alcohol consumption and AUD (Liu et al., 2019; Walters et al., 2018). Moreover, different patterns of adolescent predictors have emerged for heavy drinking and AD in studies conducted with samples of unrelated individuals (Merline et al., 2008), highlighting the need to elucidate pathways to AD using the co-twin comparison design. The expanded assessment protocol for the intensively studied group of FinnTwin12 participants also permitted us to examine a set of key neuropsychological and clinical psychiatric correlates of AD, which were uniquely assessed in this subsample.

To this end, we investigated a series of adolescent domains previously shown to predict young adult alcohol problems or AD, including academic achievement (Kendler et al., 2017), substance use (Huurre et al., 2010; Merline et al., 2008), externalizing problems (Edwards et al., 2016; Merline et al., 2008), internalizing problems (Marmorstein, 2009), executive functioning (Latvala et al., 2009; Mahmood et al., 2013), peer environment (Guo et al., 2001; Huurre et al., 2010), physical health (Wong et al., 2015), and parent–child relationship characteristics (Donaldson et al., 2016). First, we estimated the association of each adolescent domain with AD symptoms using an individual-level Poisson mixed-effects model. We then conducted co-twin comparisons to evaluate whether the magnitude of each association was attenuated after accounting for genetic and environmental influences shared by co-twins. Our preregistered hypotheses (https://osf.io/3vrn5/register/565fb3678c5e4a66b5582f67) were informed by prior work characterizing the genetic and environmental architecture of each adolescent factor and, when available, associations of each adolescent factor with alcohol misuse or problems. We expected that associations of academic achievement (Benner et al., 2014), externalizing problems (Edwards & Kendler, 2012), physical health (Korhonen et al., 2009; Silventoinen et al., 2007), and parent–child relationship characteristics (Latendresse et al., 2010; Savage et al., 2018) with AD symptoms would be significantly attenuated within the co-twin comparison design, whereas relations of alcohol expectancies (Samek et al., 2013) and stressful life events (Boardman et al., 2011) with later AD would be similar across individual-level and co-twin comparison analyses. We did not forward specific hypotheses for early adolescent substance use (Do et al., 2015; Irons et al., 2015), internalizing problems (Ehringer et al., 2006; Savage et al., 2016), executive functioning (Friedman et al., 2016; Latvala et al., 2011), and features of the peer environment (Edwards et al., 2015; Savage et al., 2018) due to mixed evidence from prior research.

Materials and Methods

Sample

Participants included 1035 families from FinnTwin12 (Rose et al., 2019), a longitudinal, population-based study of Finnish twins who were selected for intensive study partially on the basis of parental alcohol use (28% chosen based on parental scores on the Malmo-Modified Michigan Alcoholism Screening Test; Kristenson & Trell, 1982). Adolescent predictors were from interview and questionnaire assessments at ages 12 (n = 2,070 respondents) and 14 (n = 1,852 interviews). In young adulthood (average age = 22 years, range = 20−26 years), participants completed a semistructured psychiatric assessment interview. We limited analyses to 1286 individuals (581 complete twin pairs; 42% monozygotic; and 54% female) who completed the young adult follow-up assessment. Among those interviewed at age 14, sex significantly predicted young adult participation (OR = 5.48, 95% CI [2.64, 11.36]), such that females (78% retention rate) were more likely to participate in follow-up than males (62% retention rate). Zygosity and AD symptoms at age 14 did not significantly predict study retention.

Measures

Adolescent risk and protective factors. At ages 12 and 14, twins reported on their depressive symptoms; activities; sleeping difficulties; parental autonomy granting, discipline, monitoring, tension, and warmth; time spent with parents; alcohol expectancies; and pubertal development. At age 14, participants also reported their cigarette use; daily smoking; frequency of alcohol use and intoxication; aggression; impulsivity; truancy; depression; self-esteem; social anxiety; adjustment; peer deviance, drinking, drug use, and smoking; physical health; physical activity; stressful life events; and perceived difficulty of those events. Executive functions (inhibition, set-shifting, and visuospatial ability) and DSM-III-R clinical criterion counts for AD, attention deficit hyperactivity disorder (ADHD), CD, marijuana abuse, oppositional defiant disorder (ODD), anorexia nervosa, bulimia, and overanxious disorder were also measured at age 14. Aggression, impulsivity, depression, social anxiety, and adjustment were reported by parents, teachers, classmates, and co-twins. Grade point average was reported by parents and teachers. Table 1 provides additional measurement information for each adolescent factor.

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Table 1. Adolescent predictors of alcohol dependence

ACA	Grades	'Which twin had the higher grade point average last spring?'; PR age 12
		Grade point average using the Finnish GPA system (1 = *below 6* to 5 = *above 9*); TR ages 12 and 14
SUB	Alcohol dependence	DSM-III-R clinical criterion count from the adolescent version of the SSAGA (Bucholz et al., 1994); age 14
	Cigarette smoking	Two items: 'Have you ever smoked?', 'How many cigarettes have you smoked?' Recoded, such that 0 = *never smoked* to 4 = *smoked more than 50 cigarettes* (Dick et al., 2007); age 14
	Daily smoking	Present smoking habits (0 = *smokes, but not daily* to 1 = *smokes at least once per day*); age 14
	Frequency of alcohol use	'How often do you drink alcohol?' Recoded as days of drinking per month; age 14
	Frequency of intoxication	'How often do you drink alcohol so that you get at least slightly intoxicated?' Recoded as days intoxicated per month; age 14
EXT	ADHD symptoms	DSM-III-R clinical criterion count from the adolescent version of the SSAGA (Bucholz et al., 1994); age 14
	Conduct disorder symptoms	DSM-III-R clinical criterion count from the adolescent version of the SSAGA (Bucholz et al., 1994); age 14
	Aggression	Aggression subscale of MPNI (Pulkkinen et al., 1999); PR age 12; CR and SR age 14; TR ages 12 and 14
		Classmate nominations on aggression sub-scale of the MPNI (Pulkkinen et al., 1999); FR age 12
	Conduct disorder symptoms	DSM-III-R clinical criterion count from the adolescent version of the SSAGA (Bucholz et al., 1994); age 14
	Impulsivity	Hyperactivity–impulsivity subscale of MPNI (Pulkkinen et al., 1999); PR age 12; CR and SR age 14; TR ages 12 and 14
		Classmate nominations on hyperactivity–impulsivity subscale of the MPNI (Pulkkinen et al., 1999); FR age 12
	Marijuana abuse symptoms	DSM-III-R clinical criterion count from the adolescent version of the SSAGA (Bucholz et al., 1994); age 14
	Oppositional defiant disorder	DSM-III-R clinical criterion count from the adolescent version of the SSAGA (Bucholz et al., 1994); age 14
	Truancy	'Have you ever skipped school?' From the adolescent version of the SSAGA (Bucholz et al., 1994); age 14
INT	Anorexia nervosa	DSM-III-R clinical criterion count from the adolescent version of the SSAGA (Bucholz et al., 1994); age 14
	Bulimia	DSM-III-R clinical criterion count from the adolescent version of the SSAGA (Bucholz et al., 1994); age 14
	Depression	Depression sub-scale of MPNI (Pulkkinen et al., 1999); PR age 12; CR and SR age 14
		Classmate nominations on depression subscale of the MPNI (Pulkkinen et al., 1999); age 12
	Depressive symptoms	27-item Children's Depression Inventory (Kovacs, 1992); age 14
	Overanxious disorder	DSM-III-R clinical criterion count from the adolescent version of the SSAGA (Bucholz et al., 1994); age 14
	Self-esteem	10-item Rosenberg Self-Esteem Scale (Rosenberg, 1965); age 14
	Social anxiety	Social anxiety sub-scale of MPNI (Pulkkinen et al., 1999); PR age 12; CR and SR age 14
		Classmate nominations on social anxiety subscale of the MPNI (Pulkkinen et al., 1999); age 12
EXEC	Inhibition	Contrast score for inhibition versus color-naming trials (Lippa & Davis, 2010) on the California Stroop Test (Homack & Riccio, 2004); age 14
	Set-shifting	Time to complete the Trail Making Test Parts A and B (Tombaugh, 2004). Recoded as a percentile score; age 14
	Visuospatial ability	Total points on the Wechsler Intelligence Scales for Children-Revised (WISC-R) mazes (Kezer & Arik, 2012); age 14
PEER ENV	Adjustment	Adjustment sub-scale of MPNI (Pulkkinen et al., 1999); PR age 12; CR and SR age 14; TR ages 12 and 14
		Classmate nominations on adjustment sub-scale of the MPNI (Pulkkinen et al., 1999); age 12
	Leisure time activities	Three items: frequency of spending 'time with friends in your home', 'time with friends in their home', 'time with friends in places where youth meet up' (1 = *daily* to 5 = *never*). Recoded as number of activities with friends per month; ages 12 and 14
	Organized activities	Frequency of participation in 'clubs, boy/girl scouts, or other organized activities' (1 = *daily* to 5 = *never*). Recoded as number of organized activities per month; ages 12 and 14
	Peer deviance	Number of friends who drink, smoke, use drugs, or get into trouble at school (Salvatore et al., 2014); age 14
	Peer drinking	Number of friends who drink alcohol (1 = *none* to 4 = *more than 5*); age 14
	Peer drug use	Number of acquaintances who have tried drugs (1 = *none* to 4 = *more than 5*); age 14
	Peer smoking	Number of friends who smoke cigarettes (1 = *none* to 4 = *more than 5*); age 14
	Sports participation	Frequency of participation in team sports (1 = *daily* to 5 = *never*). Recoded as number of sports-related activities per month; ages 12 and 14

(*Continued*)

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Table 1. (*Continued*)

HEA	Self-rated health	'How do you rate your health?' (1 = *very poor* to 5 = *very good*); age 14
	Physical activity	'How often do you exercise or do sports during your free time?' (1 = *never* to 7 = *just about every day*). Recoded as number of times engaged in physical activity per month; age 14.
	Sleeping Difficulties	'How often have you experienced difficulties falling asleep since last summer?' (0 = rarely or never to 4 = *about once a month*). Recoded as number of nights affected by sleeping problems per month; ages 12 and 14
PARENTS	Autonomy granting	Four items: 'My parents listen to my opinions', 'My parents give me credit', 'My parents encourage me to be independent', 'My parents try to clear things by talking when I've behaved badly' (1 = *rarely* to 4 = *never*) (Latendresse et al., 2010); ages 12 and 14
	Discipline	Two items: 'My parents punish me if I do something I'm not supposed to' (1 = *rarely* to 4 = *never*); 'strict' home atmosphere (1 = *does not hold true* to 5 = *holds completely true*) (Latendresse et al., 2010); ages 12 and 14
	Monitoring	Three items: 'My parents know my plan for the day', 'My parents know my interests, activities, and whereabouts', 'My parents know where I am and who I'm with when I'm not at home' (1 = *rarely* to 4 = *never*) (Latendresse et al., 2010); ages 12 and 14
	Tension	Three items: home atmosphere is 'unfair', 'quarrelsome', 'indifferent' (1 = *does not hold true* to 5 = *holds completely true*) (Latendresse et al., 2010); ages 12 and 14
	Time with parents	Six items: frequency of engaging in 'discussions', 'movies', 'sports', 'hobbies', 'camping/traveling/visiting', and 'outdoor recreation' with parents (1 = *every day* to 5 = *never*). Recoded as number of activities with parents per month; ages 12 and 14
	Warmth	Four items: home atmosphere is 'warm/caring', 'encouraging/supportive', 'trusting/understanding', 'open' (1 = *does not hold true* to 5 = *holds completely true*) (Latendresse et al., 2010); ages 12 and 14
UNCAT	Alcohol expectancies	Degree to which alcohol makes people 'sleepy', 'talkative', 'sad', 'angry', 'ill', 'friendly', 'confused', 'mean', 'content', 'fun', 'depressed' (1 = *never* to 3 = *often)*; ages 12 and 14
	Difficulty of life events	'How difficult were these changes for you overall?' (1 = *changes have been positive* to 5 = *changes have been difficult*); age 14
	Life events	Checklist of 15 stressful life events experienced in the past two years; age 14
	Pubertal development	Pubertal Development Scale (Petersen et al., 1988). Recoded as within-sex z-scores; ages 12 and 14

Note: ACA, Academic Achievement; SUB, Early Adolescent Substance Use; EXT, Externalizing Problems; INT, Internalizing Problems; EXEC, Executive Functioning; PEER ENV, Peer Environment; HEA, Physical Health; PARENTS, Relationship with Parents; UNCAT, Uncategorized Predictors; CR, co-twin-reported; FR, peer-reported; PR, parent-reported; SR, self-reported; TR, teacher-reported; DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised; MPNI, Multidimensional Peer Nomination Inventory; SSAGA, Semistructured Assessment for the Genetics of Alcoholism; WISC-R, Wechsler Intelligence Scale for Children, Revised.

Alcohol dependence symptoms. Lifetime DSM-IV AD clinical criterion counts were measured in young adulthood using the Semistructured Assessment for the Genetics of Alcoholism (SSAGA; Bucholz et al., 1994).

Statistical Methods

Construction of factor scores for adolescent risk and protective factors. We grouped adolescent predictors into the following domains: academic achievement, early adolescent substance use, externalizing problems, internalizing problems, executive functioning, peer environment, physical health, and relationship with parents. We performed item reduction using a split-half exploratory factor analysis (EFA) and confirmatory factor analysis (CFA) approach, randomly selecting one twin from each pair for inclusion in each split-half. We determined the number of retained factors within each domain using parallel analysis (Horn, 1965). We then conducted factor analysis in the first split-half using the 'umxEFA' function in the R {umx} package (Bates et al., 2019), using a factor-loading cutoff of 0.30.

Next, we conducted CFAs in the first split-half using the 'cfa' function in the R {lavaan} package, with a comparative fit index (CFI) > 0.90 and a standardized root mean squared residual (SRMR) < 0.08 as criteria for acceptable model fit (Hu & Bentler, 1999). We conducted CFAs in the second split-half to confirm acceptable model fit and then used the 'lavPredict' function in the R {lavaan} package (Rosseel, 2012) to derive factor scores for the full sample within each domain. Several variables (alcohol expectancies, life events, perceived difficulty of life events, and pubertal development) did not logically fit into the domains identified above and were examined separately (i.e., not included in item reduction).

Individual-level and co-twin analyses. First, we examined associations of each factor score with AD clinical criterion count in individual-level analyses, using a Poisson generalized linear mixed model to account for nonindependence of the data. Individual-level analyses were conducted using the R {glmmTMB} package (Brooks et al., 2017) and included sex as a covariate. We specified a separate model for each factor score to avoid potential issues with colinearity or suppression effects.

Each factor score was then examined using a twin fixed-effects model. This model examines whether differences between twins in purported risk or protective factors predict differences in AD symptoms, effectively controlling for genetic and environmental influences shared by co-twins. In the equation, $Y_{ij} = \beta X_{ij} + \gamma W_j + \alpha_j + \epsilon_{ij}$, the effect of the vector of within-family risk factors X on Y for twin i in family j is conditional upon a vector of covariates that vary between families (e.g., SES), W, and another vector of unmeasured fixed effects that vary between families, α, plus a random error term, ϵ_{ij}. In a comparison of two twins, the equation could be expressed as $Y_{2j} - Y_{1j} = (\beta X_{2j} + \gamma W_j + \alpha_j + \epsilon_{2j}) - (\beta X_{1j} + \gamma W_j + \alpha_j + \epsilon_{1j}) = \beta(X_{2j} - X_{1j}) + (\epsilon_{2j} - \epsilon_{1j})$. The effects of all covariates that do not vary within families are, therefore,

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cancelled out of the model (Fitzmaurice et al., 2011). Fixed-effects Poisson models were estimated using the R {pglm} package (Croissant & Millo, 2018) and included sex as a covariate in opposite-sex twin pairs. We adopted $p < .05$ as the criterion for statistical significance in all analyses, given that our directional hypotheses and analytic plan were preregistered (Nosek et al., 2018; Rubin, 2017).

Results

Adolescent Risk and Protective Factors

First, we categorized adolescent predictors into a series of domains, including academic achievement, early adolescent substance use, externalizing problems, internalizing problems, executive functioning, peer environment, physical health, and relationship with parents. We then performed item reduction using a split-half EFA and CFA approach, which involved: (1) parallel analysis to identify the number of latent factors that should be retained; (2) EFA in the first split-half sample to investigate which observed variables contributed to latent factors within each domain; (3) CFA in the first split-half sample to evaluate model fit and adjust the model specification, if needed; (4) CFA in the second split-half sample to confirm acceptable model fit; and (5) CFA in the full sample to derive factor scores. We summarize the results of these analyses by domain below. The results of parallel analysis are described in Table 2, and factor loadings for EFA in the first split-half sample can be found in the Supporting Information (Table S1). For adolescent predictors that were included in the computation of factor scores, descriptive statistics and factor loadings are shown in Table 3.

Academic achievement domain. Within the academic achievement domain, parent- and teacher-reported grades were included as indicators. Parallel analysis indicated that one factor should be retained (Table 2). In EFA, only teacher-reported grades at ages 12 and 14 exhibited factor loadings above 0.30. Therefore, we computed a mean score to be used in individual-level and co-twin comparison analyses.

Early adolescent substance use domain. Frequency of alcohol consumption, frequency of intoxication, AD clinical criterion count, frequency of cigarette use, and a binary measure of daily cigarette use were included as indicators. Parallel analysis indicated that one factor should be retained (Table 2); only daily smoking exhibited a factor loading below 0.30 in EFA (Table S1) and was not carried forward for subsequent analyses. CFA in the first split-half sample demonstrated acceptable model fit (CFI = 0.940, SRMR = 0.041). Therefore, we did not modify the model before conducting CFAs in the second split-half (CFI = 0.908, SRMR = 0.051) and full samples (CFI = 0.970, SRMR = 0.032). Factor loadings are reported in Table 3.

Externalizing problem's domain. Eighteen potential predictors were categorized in the externalizing problems domain. Parallel analysis indicated that four factors should be retained (Table 2). The following indicators exhibited factor loadings above 0.30 (Table S1) and were carried forward for CFA in the first split-half sample: for *Factor 1,* ADHD, CD, and ODD clinical criterion counts; teacher-, self-, and co-twin-reported impulsivity at age 14; and teacher-, self-, and co-twin-reported aggression at age 14; for *Factor 2,* peer-reported impulsivity and aggression

Table 2. Criteria for factor retention

	Eigenvalue	Minimum significant eigenvalue	Proportion of variance	Cumulative proportion of variance
ACA	**1.708**	**1.169**	**0.569**	**0.569**
	0.891	1.04	0.297	0.866
	0.401	0.974	0.134	1.000
SUB	**2.398**	**1.266**	**0.480**	**0.480**
	1.095	1.123	0.219	0.699
	0.653	1.037	0.131	0.829
	0.447	0.983	0.089	0.919
	0.407	0.919	0.081	1.000
EXT	**4.963**	**1.458**	**0.292**	**0.292**
	1.861	**1.330**	**0.109**	**0.401**
	1.319	**1.272**	**0.078**	**0.479**
	1.219	**1.212**	**0.072**	**0.551**
	1.128	1.171	0.066	0.617
	0.984	1.134	0.058	0.675
	0.888	1.094	0.052	0.727
	0.813	1.057	0.048	0.775
	0.723	1.022	0.043	0.817
	0.662	0.989	0.039	0.856
	0.552	0.960	0.032	0.889
	0.470	0.927	0.028	0.916
	0.441	0.894	0.026	0.942
	0.326	0.858	0.019	0.962
	0.292	0.830	0.017	0.979
	0.224	0.793	0.013	0.992
	0.136	0.747	0.008	1.000
INT	**4.078**	**1.489**	**0.227**	**0.227**
	2.250	**1.348**	**0.125**	**0.352**
	1.428	**1.285**	**0.079**	**0.431**
	1.400	**1.235**	**0.078**	**0.509**
	1.112	1.187	0.062	0.570
	1.095	1.149	0.061	0.631
	0.975	1.107	0.054	0.685
	0.901	1.075	0.050	0.735
	0.848	1.041	0.047	0.783
	0.704	1.003	0.039	0.822
	0.604	0.973	0.034	0.855
	0.529	0.942	0.029	0.885
	0.481	0.909	0.027	0.911
	0.435	0.883	0.024	0.935
	0.376	0.844	0.021	0.956
	0.298	0.814	0.017	0.973
	0.265	0.774	0.015	0.988
	0.222	0.737	0.012	1.000
	3.175	**1.391**	**0.198**	**0.198**

(*Continued*)

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Table 2. (*Continued*)

	Eigenvalue	Minimum significant eigenvalue	Proportion of variance	Cumulative proportion of variance
PEER ENV	**2.444**	**1.296**	**0.153**	**0.351**
	1.659	**1.243**	**0.104**	**0.455**
	1.337	**1.200**	**0.084**	**0.538**
	1.117	1.151	0.070	0.608
	0.995	1.111	0.062	0.670
	0.867	1.075	0.054	0.725
	0.758	1.043	0.047	0.772
	0.741	1.008	0.046	0.818
	0.668	0.976	0.042	0.860
	0.561	0.943	0.035	0.895
	0.528	0.912	0.033	0.928
	0.447	0.880	0.028	0.956
	0.407	0.844	0.025	0.982
	0.253	0.806	0.016	0.997
	0.040	0.765	0.003	1.000
PARENTS	**3.837**	**1.338**	**0.320**	**0.320**
	1.411	**1.246**	**0.118**	**0.437**
	1.289	**1.185**	**0.107**	**0.545**
	1.075	1.140	0.090	0.634
	0.860	1.092	0.072	0.706
	0.735	1.049	0.061	0.767
	0.684	1.007	0.057	0.824
	0.602	0.972	0.050	0.874
	0.493	0.938	0.041	0.915
	0.425	0.901	0.035	0.951
	0.358	0.861	0.030	0.981
	0.231	0.812	0.019	1.000

Note: Retained factors are shown in bold font. ACA, Academic Performance; SUB, Early Adolescent Substance Use; EXT, Externalizing Problems; INT, Internalizing Problems; PEER ENV, Peer Environment; PARENTS, Relationship with Parents.

at age 12; for *Factor 3*, parent-reported impulsivity and aggression at age 12; and for *Factor 4,* teacher-reported impulsivity and aggression at age 12. CFA in the first-split-half sample demonstrated insufficient model fit (CFI = 0.852, SRMR = 0.070). Because the 95% confidence intervals (CIs) for ODD clinical criterion count, self-reported aggression, and twin-reported aggression factor loadings overlapped 0.30, these indicators were removed from the model. CFA was repeated in the first split-half sample and demonstrated acceptable model fit (CFI = 0.918, SRMR = 0.056). Therefore, we did not further modify the model before conducting CFAs in the second split-half (CFI = 0.908, SRMR = 0.053) and full samples (CFI = 0.909, SRMR = 0.048). Indicators included in the computation of factor scores are shown in Table 3.

Internalizing problem's domain. Eighteen potential predictors were categorized in the internalizing problems domain. Parallel analysis indicated that four factors should be retained (Table 2). The following indicators exhibited factor loadings above 0.30 (Table S1) and were carried forward for CFA in the first split-half sample: for *Factor 1,* overanxious disorder clinical criterion count; depressive symptoms at ages 12 and 14; self-esteem; and social anxiety; *for Factor 2,* co-twin-reported depression and social anxiety; for *Factor 3,* peer- and teacher-reported depression and social anxiety; and for *Factor 4,* parent-reported depression and social anxiety. CFA in the first split-half sample yielded unacceptable model fit (CFI = 0.760, SRMR = 0.070). In a series of model modifications, overanxious disorder clinical criterion count, teacher-reported depression and social anxiety, and self-reported depressive symptoms at age 12 demonstrated the lowest factor loadings and were removed from the model. After these modifications, CFA in the first split-half (CFI = 0.919, SRMR = 0.050), second split-half (CFI = 0.928, SRMR = 0.038), and full samples (CFI = 0.926, SRMR = 0.039) demonstrated satisfactory model fit. Indicators included in the computation of factor scores are shown in Table 3.

Executive functioning domain. Inhibition, set-shifting, and visuospatial ability at age 14 were included as indicators within the executive functioning domain. However, in light of low inter-item correlations, each variable was examined separately in individual-level and co-twin comparison analyses.

Peer environment domain. Sixteen potential predictors were categorized in the peer environment domain. Parallel analysis indicated that four factors should be retained (Table 2). The following indicators exhibited factor loadings above 0.30 (Table S1) and were carried forward for CFA in the first split-half sample: for *Factor 1*, leisure time activities at ages 12 and 14; for *Factor 2,* peer deviance, drinking, drug use, and smoking; for *Factor 3*, parent-, peer-, self-, teacher-, and co-twin-reported social adjustment; and for *Factor 4,* sports involvement at ages 12 and 14. However, when CFA was conducted in the first split-half sample, factor loadings for Factor 4 were not statistically significant. Therefore, CFA was repeated in the first split-half sample with the first three latent factors and demonstrated acceptable model fit (CFI = 0.922, SRMR = 0.058). We did not further modify the model before conducting CFAs in the second split-half (CFI = 0.927, SRMR = 0.059) and full samples (CFI = 0.920, SRMR = 0.054). Indicators included in the computation of factor scores are shown in Table 3.

Physical health domain. Physical activity, self-rated health, and sleeping difficulties were included as indicators in the physical health domain. However, in light of low inter-item correlations, each variable was examined separately in individual-level and co-twin comparison analyses.

Relationship with parent's domain. Twelve potential predictors were categorized in the relationship with parent's domain. Parallel analysis indicated that three factors should be retained (Table 2). The following indicators exhibited factor loadings above 0.30 (Table S1) and were carried forward for CFA in the first split-half sample: for *Factor 1,* parental autonomy granting, monitoring, warmth, and tension at age 12; for *Factor 2,* parental autonomy granting, monitoring, warmth, and tension at age 14; and for *Factor 3*, parental discipline at ages 12 and 14. Though CFA in the first split-half sample demonstrated acceptable model fit (CFI = 0.906, SRMR = 0.051), factor loadings for Factor 3 were not statistically significant when CFA was conducted in the second split-half sample. Therefore, CFA was repeated in the

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Table 3. Descriptive statistics and factor loadings for adolescent predictors and alcohol dependence outcome

		Mean (*SD*)	Range	ICC [95% CI]	λ [95% CI]
ACA	Mean Score (*Academic Achievement*)				
	Grades (TR; age 12)	3.56 (0.68)	1–5	0.60 [0.54, 0.66]	–
	Grades (TR; age 14)	3.57 (0.83)	1–5	0.59 [0.52, 0.65]	–
SUB	Factor 1 (*Adolescent Substance Use*)				
	Alcohol dependence symptoms	1.04 (2.14)	0–8	0.60 [0.54, 0.65]	0.72 [0.67, 0.77]
	Cigarette smoking	0.93 (1.27)	0–4	0.71 [0.66, 0.74]	0.61[0.55, 0.66]
	Frequency of alcohol use	0.49 (1.08)	0–6	0.60 [0.55, 0.65]	0.82 [0.77, 0.87]
	Frequency of intoxication	0.23 (0.63)	0–6	0.63 [0.58, 0.68]	0.89 [0.84, 0.94]
EXT	Factor 1 (*Age 14 Externalizing*)				
	ADHD symptoms	0.76 (1.69)	0–13	0.28 [0.20, 0.35]	0.44 [0.38, 0.50]
	Conduct disorder symptoms	0.81 (1.30)	0–8	0.36 [0.29, 0.43]	0.42 [0.36, 0.48]
	Aggression (TR; age 14)	0.33 (0.48)	0.00–2.60	0.49 [0.41, 0.56]	0.67 [0.61, 0.74]
	Impulsivity (CR; age 14)	0.82 (0.56)	0.00–2.83	0.14 [0.05, 0.22]	0.63 [0.57, 0.70]
	Impulsivity (SR; age 14)	0.82 (0.47)	0.00–2.67	0.33 [0.24, 0.40]	0.58 [0.51, 0.64]
	Impulsivity (TR; age 14)	0.51 (0.67)	0.00–3.00	0.43 [0.35, 0.51]	0.81 [0.75, 0.87]
	Factor 2 (*FR Externalizing*)				
	Aggression (FR; age 12)	14.63 (15.73)	0.00–83.17	0.57 [0.51, 0.62]	0.83 [0.77, 0.88]
	Impulsivity (FR; age 12)	17.27 (20.74)	0.00–100.00	0.54 [0.48, 0.60]	0.96 [0.91, 1.01]
	Factor 3 (*PR Externalizing*)				
	Aggression (PR; age 12)	0.59 (0.40)	0.00–2.33	0.62 [0.56, 0.66]	0.56 [0.49, 0.62]
	Impulsivity (PR; age 12)	0.72 (0.52)	0.00–2.86	0.42 [0.35, 0.49]	0.95 [0.86, 1.04]
	Factor 4 (*TR Externalizing*)				
	Aggression (TR; age 12)	0.62 (0.63)	0.00–3.00	0.62 [0.56, 0.66]	0.78 [0.73, 0.84]
	Impulsivity (TR; age 12)	0.67 (0.71)	0.00–3.00	0.43 [0.35, 0.51]	0.93 [0.88, 0.98]
INT	Factor 1 (*SR Internalizing*)				
	Depression (SR; age 14)	0.64 (0.40)	0.00–3.00	0.25 [0.16, 0.33]	0.74 [0.68, 0.80]
	Depressive symptoms (SR; age 14)	34.69 (4.46)	28–62	0.31 [0.23, 0.39]	0.69 [0.63, 0.76]
	Self-esteem (SR; age 14)	30.32 (5.28)	10–40	0.39 [0.31, 0.46]	−0.59 [−0.66, −0.53]
	Social anxiety (SR; age 14)	0.89 (0.54)	0.00–3.00	0.29 [0.20, 0.37]	0.58 [0.52, 0.65]
	Factor 2 (*CR Internalizing*)				
	Depression (CR; age 14)	0.60 (0.41)	0.00–2.20	0.18 [0.09, 0.27]	0.73 [0.65, 0.81]
	Social anxiety (CR; age 14)	0.82 (0.61)	0.00–3.00	0.10 [0.00, 0.18]	0.70 [0.63, 0.78]
	Factor 3 (*FR Internalizing*)				
	Depression (FR; age 12)	10.73 (10.79)	0.00–95.00	0.48 [0.41, 0.54]	0.60 [0.51, 0.69]
	Social anxiety (FR; age 12)	11.07 (13.47)	0.00–100.00	0.56 [0.50, 0.61]	0.98 [0.85, 1.10]
	Factor 4 (*PR Internalizing*)				
	Depression (PR; age 12)	0.76 (0.43)	0.00–2.40	0.38 [0.31, 0.45]	0.63 [0.55, 0.71]
	Social anxiety (PR; age 12)	0.79 (0.59)	0.00–3.00	0.41 [0.34, 0.48]	0.80 [0.71, 0.89]
EXEC	Inhibition	24.76 (13.23)	2.00–93.00	0.24 [0.11, 0.35]	–
	Set-shifting	53.45 (28.64)	0.06–99.94	0.36 [0.28, 0.44]	–
	Visuospatial ability	25.20 (3.13)	0.00–30.00	0.28 [0.20, 0.35]	–
PEER ENV	Factor 1 (*Leisure Time Activities*)				
	Leisure time activities (age 12)	33.86 (20.93)	0–90	0.62 [0.56, 0.66]	0.46 [0.35, 0.56]
	Leisure time activities (age 14)	32.44 (22.82)	0–90	0.60 [0.55, 0.65]	1.05 [0.84, 1.25]

(*Continued*)

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Table 3. (*Continued*)

		Mean (*SD*)	Range	ICC [95% CI]	λ [95% CI]
	Factor 2 (*Peer Deviance*)				
	Peer deviance	7.79 (3.12)	4–16	0.62 [0.56, 0.67]	1.09 [1.06, 1.13]
	Peer drinking	2.39 (1.22)	1–4	0.53 [0.46, 0.58]	0.75 [0.70, 0.80]
	Peer drug use	1.34 (0.70)	1–4	0.48 [0.41, 0.54]	0.61 [0.57, 0.66]
	Peer smoking	2.42 (1.21)	1–4	0.56 [0.50, 0.61]	0.77 [0.73, 0.82]
	Factor 3 (*Social Adjustment*)				
	Adjustment (CR; age 14)	1.70 (0.43)	0.08–3.00	0.31 [0.23, 0.39]	0.50 [0.43, 0.57]
	Adjustment (FR; age 12)	20.98 (13.38)	0.00–78.86	0.57 [0.51, 0.62]	0.59 [0.53, 0.66]
	Adjustment (PR; age 12)	2.06 (0.39)	0.67–3.00	0.62 [0.57, 0.67]	0.45 [0.39, 0.52]
	Adjustment (SR; age 14)	1.78 (0.35)	0.67–2.83	0.28 [0.19, 0.36]	0.39 [0.31, 0.46]
	Adjustment (TR; age 12)	1.89 (0.56)	0.22–3.00	0.58 [0.53, 0.63]	0.66 [0.59, 0.72]
	Adjustment (TR; age 14)	1.84 (0.49)	0.36–2.92	0.47 [0.39, 0.54]	0.56 [0.49, 0.64]
HEA	Self-rated health	4.35 (0.67)	1–5	0.29 [0.21, 0.36]	–
	Physical activity	13.28 (10.12)	0–30	0.42 [0.34, 0.48]	–
	Age 12 sleeping difficulties	6.76 (11.24)	0–30	0.19 [0.10, 0.27]	–
	Age 14 sleeping difficulties	9.45 (12.32)	0–30	0.11 [0.02, 0.19]	–
PARENTS	Factor 1 (*Age 12 Relationship Quality*)				
	Autonomy granting (age 12)	13.43 (1.95)	4–16	0.58 [0.52, 0.63]	0.79 [0.73, 0.85]
	Monitoring (age 12)	10.75 (1.39)	3–12	0.46 [0.39, 0.52]	0.51 [0.45, 0.57]
	Tension (age 12)	5.17 (2.01)	3–15	0.47 [0.41, 0.53]	−0.51 [−0.57, −0.45]
	Warmth (age 12)	17.56 (2.23)	4–20	0.47 [0.41, 0.54]	0.75 [0.70, 0.81]
	Factor 2 (*Age 14 Relationship Quality*)				
	Autonomy granting (age 14)	13.17 (2.15)	4–16	0.51 [0.44, 0.57]	0.77 [0.72, 0.82]
	Monitoring (age 14)	10.25 (1.57)	4–12	0.48 [0.41, 0.54]	0.54 [0.48, 0.60]
	Tension (age 14)	5.42 (1.87)	3–14	0.39 [0.31, 0.45]	−0.65 [−0.70, −0.59]
	Warmth (age 14)	16.59 (2.62)	5–20	0.54 [0.48, 0.60]	0.88 [0.83, 0.93]
UNCAT	Age 12 alcohol expectancies	19.90 (3.49)	12–29	0.37 [0.12, 0.54]	–
	Age 14 alcohol expectancies	21.76 (2.99)	12–31	0.44 [0.23, 0.59]	–
	Difficulty of life events	1.94 (0.89)	1–4	0.45 [0.37, 0.52]	–
	Life events	2.69 (1.72)	0–9	0.58 [0.53, 0.63]	–
	Age 12 pubertal development	0.01 (0.98)	−1.64–3.46	0.52 [0.46, 0.58]	–
	Age 14 pubertal development	0.04 (0.99)	−3.51–2.46	0.46 [0.39, 0.52]	–
AD	YA Alcohol dependence symptoms	1.44 (1.28)	0–7	0.26 [0.15, 0.36]	–

Note: *SD*, standard deviation; ICC, sibling intra-class correlation coefficient; CI, confidence interval; ACA, Academic Achievement; SUB, Early Adolescent Substance Use; EXT, Externalizing Problems; INT, Internalizing Problems; EXEC, Executive Functioning; PEER ENV, Peer Environment; HEA, Physical Health; PARENTS, Relationship with Parents; UNCAT, Uncategorized Predictors; AD, Alcohol Dependence Outcome; CR, co-twin-reported; FR, peer-reported; PR, parent-reported; SR, self-reported; TR, teacher-reported; YA, young adult.

second split-half sample with the first two latent factors and exhibited satisfactory model fit (CFI = 0.914, SRMR = 0.053). We did not further modify the model before conducting CFA in the full sample (CFI = 0.932, SRMR = 0.047). Indicators included in the computation of factor scores are shown in Table 3.

Individual-Level and Co-Twin Comparison Analyses

Because individual-level and co-twin comparison analyses employed a Poisson distribution, we first evaluated evidence for overdispersion. The dispersion ratio ranged from 0.663 to 0.823 across the models tested, suggesting that a Poisson model provided an appropriate fit to the data. Results for individual-level and co-twin Poisson regression analyses are shown by domain in Table 4, and statistically significant effects from individual-level analyses are reviewed in Figure 1. In individual-level analyses, adolescents with higher levels of substance use, teacher-reported externalizing problems at age 12, externalizing problems at age 14, self- and co-twin-reported internalizing problems, peer deviance, and perceived difficulty of life events reported more symptoms of AD in young adulthood. Conversely, individuals with higher academic achievement, social adjustment, self-rated health, and parent–child relationship quality at ages 12 and 14 met fewer AD clinical criteria. Peer- and parent-reported externalizing problems, peer- and parent-reported internalizing problems, inhibition, set-shifting, visuospatial ability, leisure time activities,

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Table 4. Results for individual-level and co-twin comparison analyses

		Analysis type	$\hat{\beta}$ [95% CI]	*p*
ACA	Academic achievement	Individual	−0.146 [−0.260, −0.032]	.012*
		Co-twin	0.099 [−0.212, 0.409]	.532
SUB	Adolescent substance use	Individual	0.065 [0.003, 0.128]	.041*
		Co-twin	0.010 [−0.159, 0.179]	.904
EXT	Age 14 externalizing	Individual	0.115 [0.046, 0.184]	.001*
		Co-twin	0.003 [−0.142, 0.148]	.968
	FR externalizing	Individual	0.022 [−0.044, 0.088]	.516
		Co-twin	0.022 [−0.120, 0.164]	.763
	PR externalizing	Individual	0.014 [−0.052, 0.080]	.683
		Co-twin	−0.018 [−0.146, 0.110]	.781
	TR externalizing	Individual	0.071 [0.003, 0.139]	.041*
		Co-twin	0.037 [−0.122, 0.195]	.652
INT	SR internalizing	Individual	0.167 [0.092, 0.243]	1.48×10^{-05}*
		Co-twin	0.011 [−0.136, 0.158]	.882
	CR internalizing	Individual	0.081 [0.002, 0.161]	.044*
		Co-twin	0.031 [−0.107, 0.169]	.663
	FR internalizing	Individual	0.008 [−0.061, 0.077]	.824
		Co-twin	0.020 [−0.127, 0.166]	.789
	PR internalizing	Individual	0.060 [−0.016, 0.136]	.120
		Co-twin	0.061 [−0.094, 0.216]	.441
EXEC	Inhibition	Individual	−0.008 [−0.102, 0.085]	.862
		Co-twin	0.022 [−0.157, 0.200]	.813
	Set-shifting	Individual	−0.048 [−0.114, 0.017]	.146
		Co-twin	0.074 [−0.060, 0.209]	.280
	Visuospatial ability	Individual	−0.023 [−0.086, 0.040]	.469
		Co-twin	−0.060 [−0.175, 0.054]	.303
PEER ENV	Leisure time activities	Individual	0.025 [−0.037, 0.086]	.432
		Co-twin	0.020 [−0.113, 0.152]	.770
	Peer deviance	Individual	0.049 [0.001, 0.097]	.044*
		Co-twin	0.010 [−0.096, 0.116]	.849
	Social adjustment	Individual	−0.117 [−0.194, −0.040]	.003*
		Co-twin	0.062 [−0.125, 0.249]	.515
HEA	Self-rated health	Individual	−0.101 [−0.162, −0.040]	.001*
		Co-twin	−0.112 [−0.227, 0.003]	.056
	Physical activity	Individual	−0.011 [−0.076, 0.053]	.731
		Co-twin	0.017 [−0.117, 0.150]	.806
	Age 12 sleeping difficulties	Individual	0.044 [−0.020, 0.108]	.177
		Co-twin	0.044 [−0.070, 0.158]	.451
	Age 14 sleeping difficulties	Individual	0.028 [−0.034, 0.090]	.383
		Co-twin	0.029 [−0.075, 0.132]	.586
PARENTS	Age 12 relationship quality	Individual	−0.080 [−0.149, −0.010]	.024*
		Co-twin	0.034 [−0.157, 0.225]	.727
	Age 14 relationship quality	Individual	−0.104 [−0.170, −0.038]	.002*
		Co-twin	0.008 [−0.164, 0.180]	.927

(*Continued*)

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Table 4. (*Continued*)

		Analysis type	$\hat{\beta}$ [95% CI]	*p*
UNCAT	Age 12 alcohol expectancies	Individual	−0.009 [−0.114, 0.095]	.859
		Co-twin	−0.047 [−0.321, 0.228]	.738
	Age 14 alcohol expectancies	Individual	−0.023 [−0.133, 0.087]	.681
		Co-twin	0.125 [−0.244, 0.495]	.506
	Difficulty of life events	Individual	0.111 [0.043, 0.180]	.001*
		Co-twin	−0.018 [−0.171, 0.135]	.822
	Life events	Individual	0.056 [−0.007, 0.119]	.081
		Co-twin	0.040 [−0.113, 0.193]	.608
	Age 12 pubertal development	Individual	0.002 [−0.066, 0.070]	.949
		Co-twin	0.049 [−0.097, 0.196]	.507
	Age 14 pubertal development	Individual	−0.010 [−0.074, 0.054]	.756
		Co-twin	0.011 [−0.124, 0.145]	.874

Note: ACA, Academic Achievement; SUB, Early Adolescent Substance Use; EXT, Externalizing Problems; INT, Internalizing Problems; EXEC, Executive Functioning; PEER ENV, Peer Environment; HEA, Physical Health; PARENTS, Relationship with Parents; UNCAT, Uncategorized Predictors; CR, co-twin-reported; FR, peer-reported; PR, parent-reported; SR, self-reported; TR, teacher-reported; *$p < .05$.

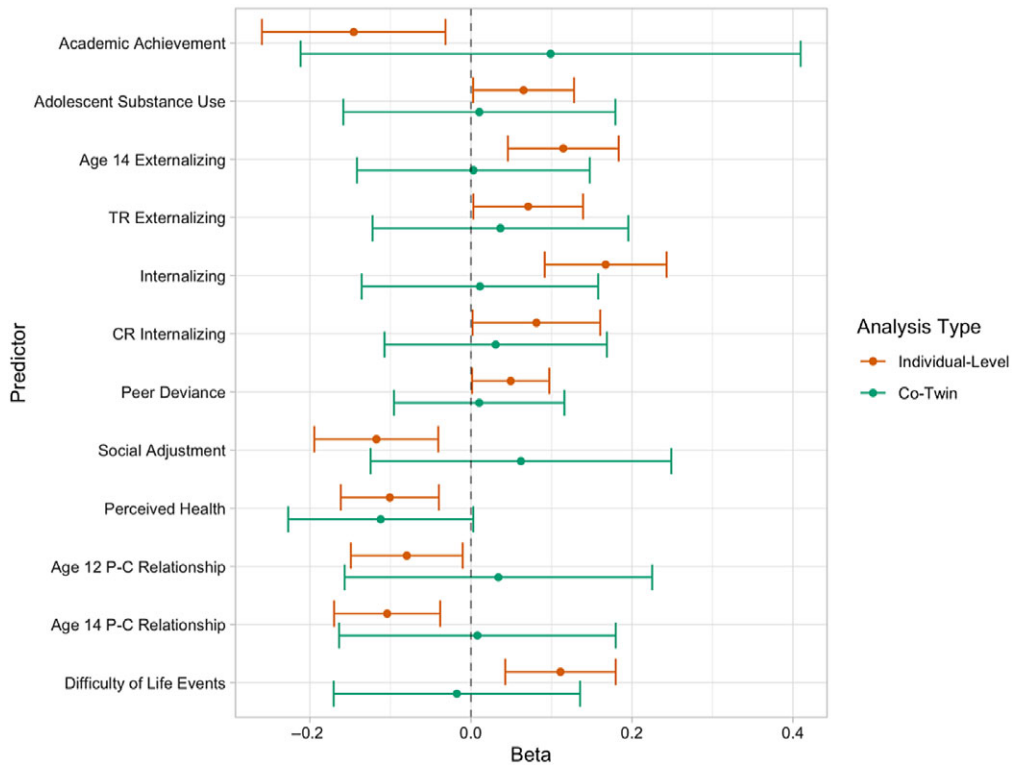

Fig. 1. Examining adolescent predictors of AD symptoms in individual-level and co-twin analyses
Note: Error bars denote 95% confidence intervals of estimates. TR, teacher-reported; CR, co-twin-reported; P–C, parent–child.

physical activity, sleeping difficulties, alcohol expectancies, pubertal development, and stressful life events in adolescence were not related to lifetime AD clinical criterion count.

When statistically significant predictors from individual-level analyses were examined within the co-twin comparison design, the CIs for these associations were larger and included zero (Table 4). To evaluate whether individual-level estimates were substantially attenuated within the co-twin comparison design, we first considered whether the co-twin comparison estimate was contained within the 95% CI of the individual-level estimate and, second, conducted a series of *z* tests to empirically examine whether these nominal differences were statistically significant ($p < 0.05$). As shown in Figure 1, point estimates appeared to be attenuated for academic achievement ($z = 1.45$, $p = .07$), age 14 externalizing problems ($z = 1.37$, $p = .09$), self-reported internalizing problems ($z = 1.85$, $p = .03$), social adjustment ($z = 1.74$, $p = .04$), parent–child relationship characteristics at ages 12 ($z = 1.10$, $p = .14$) and 14 ($z = 1.19$, $p = .12$), and perceived

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difficulty of life events ($z = 1.50$, $p = .07$), as the beta estimates from co-twin comparison analyses were not contained within the 95% CIs of the individual-level estimates. However, z tests, which account for larger standard errors within the co-twin comparison design, demonstrated that individual-level associations were significantly reduced for self-reported internalizing problems and social adjustment only. Conversely, the beta estimates from co-twin comparisons of adolescent substance use ($z = 0.60$, $p = .28$), teacher-reported externalizing problems ($z = 0.39$, $p = .35$), co-twin-reported internalizing problems ($z = 0.62$, $p = .27$), peer deviance ($z = 0.66$, $p = .25$), and self-rated health ($z = 0.17$, $p = .57$) were contained within the 95% CIs of the individual-level estimates. The corresponding z tests similarly indicated no statistically significant differences between the estimates from the individual-level and co-twin comparison analyses.

Discussion

The current study used a co-twin comparison design to evaluate prospective predictors of AD symptoms. In individual-level analyses, we replicated many well-known adolescent correlates of later AD. Specifically, we found that higher levels of adolescent substance use, teacher-reported externalizing problems at age 12, externalizing problems at age 14, self- and co-twin-reported internalizing problems, peer deviance, and perceived difficulty of life events were associated with more AD symptoms by young adulthood. On the other hand, individuals with higher academic achievement, social adjustment, self-rated health, and parent–child relationship quality met fewer AD clinical criteria. These findings are consistent with prior studies demonstrating the relevance of individual characteristics, features of the parent–child relationship, and characteristics of the social environment to the development of alcohol problems by young adulthood (Edwards et al., 2016; Maggs et al., 2008; Merline et al., 2008).

In addition to individual-level analyses, we also examined the contribution of each adolescent factor to young adult AD using the co-twin comparison design, which evaluates whether differences between twins in adolescence predict differences in their young adult AD symptoms after accounting for genetic and environmental influences that twin siblings share. Though a number of adolescent factors were associated with AD symptoms in individual-level analyses, we found that differences between twins in adolescence were not related to within-pair differences in AD symptoms. One possible explanation for this pattern of statistically nonsignificant associations within the co-twin comparison design is that relations between adolescent factors and later alcohol problems are confounded by factors that vary between families, such as SES, neighborhood characteristics, or familial genetic load. However, it is also plausible that we did not have sufficient power to detect significant associations in co-twin comparison analyses. Indeed, though point estimates were reduced after controlling for genetic and environmental influences that twin siblings share, the individual-level beta estimates for adolescent substance use, externalizing problems, co-twin-reported internalizing problems, peer deviance, perceived difficulty of life events, academic achievement, self-rated health, and parent–child relationship quality were not statistically significantly attenuated within the co-twin comparison design. Furthermore, the magnitude of the association between self-rated health and AD symptoms was larger within the co-twin comparison design than in individual-level analyses, though the point estimate had a larger standard error within co-twin comparisons, which use the twin pair as the unit of analysis. This suggests that associations with each of these adolescent factors may remain relevant after accounting for family-level influences, though they did not reach conventional significance thresholds.

These results should be considered in light of several limitations. First, the co-twin comparison design controls for genetic and environmental influences that twin siblings share but does not account for potential confounding by unmeasured individual-level characteristics (e.g., one co-twin's affiliation with a deviant peer group). Second, co-twin comparisons compound measurement error (McGue et al., 2010) and effectively reduce sample size using the twin pair as the unit of analysis (Boardman & Fletcher, 2015), which yields increased risk for Type II error when compared to individual-level analyses. For this reason, we focused our inferences on whether the magnitude of the effect sizes changed across the individual-level and co-twin comparison methods rather than on statistical significance within the co-twin design.

Our study has some notable strengths, as well. We assessed a population-based sample of all twins born over a 5-year period in Finland, with no selection based on sociodemographic factors or place of residence. Only Swedish-speaking families were excluded from this intensively studied cohort, given the extra cost of translation and interviewer training in a second language. Data were gathered from multiple reporters, including co-twins, parents, peers and teachers, as well as from the twins themselves. Finally, the longitudinal nature of the study is a notable strength: we collected information on social, behavioral, and psychiatric factors at ages 12 and 14 when alcohol-related problems are quite rare and infrequent.

In summary, the current study illustrates the utility of co-twin comparisons for understanding pathways to alcohol problems by young adulthood. The co-twin comparison design controls for genetic and environmental influences that twin siblings share; thus, relative to a study of singletons, co-twin comparisons strengthen inferences about whether purported adolescent risk factors are predictive above and beyond these confounding familial factors. Our findings highlight academic achievement, externalizing and internalizing problems, substance use, parent–child relationship characteristics, self-rated health, and features of the peer environment as predictors of AD. Moreover, the associations between adolescent substance use, teacher-reported externalizing problems, co-twin-reported internalizing problems, peer deviance, self-rated health, and AD symptoms were of a similar magnitude in co-twin comparisons. Ultimately, we hope that results from this study can inform preventive intervention efforts by refining our understanding of the nature of associations between a host of commonly studied risk factors and the development of alcohol problems.

Supplementary Material. To view supplementary material for this article, please visit https://doi.org/10.1017/thg.2021.36.

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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.

References

Bates, T. C., Maes, H., & Neale, M. C. (2019). umx: Twin and path-based structural equation modeling in R. *Twin Research and Human Genetics*, *22*, 27–41.

Benner, A. D., Kretsch, N., Harden, K. P., & Crosnoe, R. (2014). Academic achievement as a moderator of genetic influences on alcohol use in adolescence. *Developmental Psychology*, *50*, 1170–1178.

Boardman, J. D., & Fletcher, J. M. (2015). To cause or not to cause? That is the question, but identical twins might not have all of the answers. *Social Science & Medicine*, *127*, 198–200.

Boardman, J. D., Alexander, K. B., & Stallings, M. C. (2011). Stressful life events and depression among adolescent twin pairs. *Biodemography and Social Biology*, *57*, 53–66.

Brooks, M. E., Kristensen, K., Benthem, K. J. van, Magnusson, A., Berg, C. W., Nielsen, A., Skaug, H. J., Mächler, M., & Bolker, B. M. (2017). GlmmTMB balances speed and flexibility among packages for zero-inflated generalized linear mixed modeling. *The R Journal*, *9*, 378–400.

Bucholz, K. K., Cadoret, R., Cloninger, C. R., Dinwiddie, S. H., Hesselbrock, V. M., Nurnberger, J. I., Reich, T., Schmidt, I., & Schuckit, M. A. (1994). A new, semi-structured psychiatric interview for use in genetic linkage studies: A report on the reliability of the SSAGA. *Journal of Studies on Alcohol*, *55,* 149–158.

Croissant, Y., & Millo, G. (2018). *Panel data econometrics with R*. John Wiley & Sons.

Dick, D. M., Meyers, J. L., Rose, R. J., Kaprio, J., & Kendler, K. S. (2011). Measures of current alcohol consumption and problems: Two independent twin studies suggest a complex genetic architecture. *Alcoholism, Clinical and Experimental Research*, *35*, 2152–2161.

Dick, D. M., Pagan, J. L., Viken, R., Purcell, S., Kaprio, J., Pulkkinen, L., & Rose, R. J. (2007). Changing environmental influences on substance use across development. *Twin Research and Human Genetics*, *10*, 315–326.

Do, E. K., Prom-Wormley, E. C., Eaves, L. J., Silberg, J. L., Miles, D. R., & Maes, H. H. (2015). Genetic and environmental influences on smoking behavior across adolescence and young adulthood in the Virginia Twin Study of Adolescent Behavioral Development and the transitions to substance abuse follow-up. *Twin Research and Human Genetics*, *18,* 43–51.

Donaldson, C. D., Handren, L. M., & Crano, W. D. (2016). The enduring impact of parents' monitoring, warmth, expectancies, and alcohol use on their children's future binge drinking and arrests: A longitudinal analysis. *Prevention Science*, *17*, 606–614.

Edwards, A. C., & Kendler, K. S. (2012). Twin study of the relationship between adolescent attention-deficit/hyperactivity disorder and adult alcohol dependence. *Journal of Studies on Alcohol and Drugs*, *73*, 185–194.

Edwards, A. C., Gardner, C. O., Hickman, M., & Kendler, K. S. (2016). A prospective longitudinal model predicting early adult alcohol problems: Evidence for a robust externalizing pathway. *Psychological Medicine*, *46*, 957–968.

Edwards, A. C., Maesr, H. H., Prescott, C. A., & Kendler, K. S. (2015). Multiple mechanisms influencing the relationship between alcohol consumption and peer alcohol use. *Alcoholism, Clinical and Experimental Research*, *39*, 324–332.

Ehringer, M. A., Rhee, S. H., Young, S., Corley, R., & Hewitt, J. K. (2006). Genetic and environmental contributions to common psychopathologies of childhood and adolescence: A study of twins and their siblings. *Journal of Abnormal Child Psychology*, *34*, 1–17.

Esser, M. B., Hedden, S. L., Kanny, D., Brewer, R. D., Gfroerer, J. C., & Naimi, T. S. (2014). Prevalence of alcohol dependence among US adult drinkers, 2009–2011. *Preventing Chronic Disease*, *11*, E206.

Fitzmaurice, G., Laird, N., & Ware, J. (2011). *Applied longitudinal analysis* (2nd ed.). John Wiley & Sons.

Friedman, N. P., Miyake, A., Altamirano, L. J., Corley, R. P., Young, S. E., Rhea, S. A., & Hewitt, J. K. (2016). Stability and change in executive function abilities from late adolescence to early adulthood: A longitudinal twin study. *Developmental Psychology*, *52,* 326–340.

Galea, S., Nandi, A., & Vlahov, D. (2004). The social epidemiology of substance use. *Epidemiologic Reviews*, *26*, 36–52.

Grant, B. F., Goldstein, R. B., Saha, T. D., Chou, S. P., Jung, J., Zhang, H., Pickering, R. P., Ruan, W. J., Smith, S. M., Huang, B., & Hasin, D. S. (2015). Epidemiology of DSM-5 Alcohol Use Disorder: Results from the National Epidemiologic Survey on Alcohol and Related Conditions III. *JAMA Psychiatry*, *72*, 757–766.

Guo, J., Hawkins, J. D., Hill, K. G., & Abbott, R. D. (2001). Childhood and adolescent predictors of alcohol abuse and dependence in young adulthood. *Journal of Studies on Alcohol*, *62*, 754–762.

Haber, J. R., Harris-Olenak, B., Burroughs, T., & Jacob, T. (2016). Residual effects: Young adult diagnostic drinking predicts late-life health outcomes. *Journal of Studies on Alcohol and Drugs*, *77*, 859–867.

Homack, S., & Riccio, C. A. (2004). A meta-analysis of the sensitivity and specificity of the Stroop Color and Word Test with children. *Archives of Clinical Neuropsychology*, *19,* 725–743.

Horn, J. L. (1965). A rationale and test for the number of factors in factor analysis. *Psychometrika*, *30*, 179–185.

Hu, L., & Bentler, P. M. (1999). Cutoff criteria for fit indexes in covariance structure analysis: Conventional criteria versus new alternatives. *Structural Equation Modeling*, *6*, 1–55.

Huurre, T., Lintonen, T., Kaprio, J., Pelkonen, M., Marttunen, M., & Aro, H. (2010). Adolescent risk factors for excessive alcohol use at age 32 years. A 16-year prospective follow-up study. *Social Psychiatry and Psychiatric Epidemiology*, *45*, 125–134.

Irons, D. E., Iacono, W. G., & McGue, M. (2015). Tests of the effects of adolescent early alcohol exposures on adult outcomes. *Addiction*, *110*, 269–278.

Kendler, K. S., Ohlsson, H., Sundquist, J., & Sundquist, K. (2017). School achievement, IQ, and risk of alcohol use disorder: A prospective, co-relative analysis in a Swedish national cohort. *Journal of Studies on Alcohol and Drugs*, *78*, 186–194.

Kezer, F., & Arik, R. S. (2012). An examination and comparison of the revisions of the Wechsler Intelligence Scale for Children. *Procedia — Social and Behavioral Sciences*, *46*, 2104–2110.

Korhonen, T., Kujala, U. M., Rose, R. J., & Kaprio, J. (2009). Physical activity in adolescence as a predictor of alcohol and illicit drug use in early adulthood: A longitudinal population based twin study. *Twin Research and Human Genetics*, *12*, 261–268.

Kovacs, M. (1992). *Children's Depression Inventory*. Multi-health Systems.

Kristenson, H., & Trell, E. (1982). Indicators of alcohol consumption: Comparisons between a questionnaire (Mm-MAST), interviews and Serum Glutamyl Transferase (GGT) in a health survey of middle-aged males. *British Journal of Addiction*, *77,* 297–304.

Latendresse, S. J., Rose, R. J., Viken, R. J., Pulkkinen, L., Kaprio, J., & Dick, D. M. (2010). Examining the etiology of associations between perceived parenting and adolescents' alcohol use: Common genetic and/or environmental liabilities? *Journal of Studies on Alcohol and Drugs*, *71*, 313–325.

Latvala, A., Castaneda, A. E., Perälä, J., Saarni, S. I., Aalto-Setälä, T., Lönnqvist, J., Kaprio, J., Suvisaari, J., & Tuulio-Henriksson, A. (2009). Cognitive functioning in substance abuse and dependence: A population-based study of young adults. *Addiction*, *104*, 1558–1568.

Latvala, A., Tuulio-Henriksson, A., Dick, D. M., Vuoksimaa, E., Viken, R. J., Suvisaari, J., Kaprio, J., & Rose, R. J. (2011). Genetic origins of the association between verbal ability and alcohol dependence symptoms in young adulthood. *Psychological Medicine*, *41*, 641–651.

Lippa, S. M., & Davis, R. N. (2010). Inhibition/switching is not necessarily harder than inhibition: An analysis of the D-KEFS Color-Word Interference Test. *Archives of Clinical Neuropsychology*, *25*, 146–152.

Liu, M., Jiang, Y., Wedow, R., Li, Y., Brazel, D. M., Chen, F., Datta, G., Davila-Velderrain, J., McGuire, D., Tian, C., Zhan, X., Choquet, H., Docherty, A. R., Faul, J. D., Foerster, J. R., Fritsche, L. G., Gabrielsen, M. E., Gordon, S. D., Haessler, J., ... **Vrieze, S.** (2019). Association studies of up to 1.2 million individuals yield new insights into the genetic etiology of tobacco and alcohol use. *Nature Genetics*, *51*, 237.

https://doi.org/10.1017/thg.2021.36 Published online by Cambridge University Press

Maggs, J. L., Patrick, M. E., & Feinstein, L. (2008). Childhood and adolescent predictors of alcohol use and problems in adolescence and adulthood in the National Child Development Study. *Addiction*, *103*, 7–22.

Mahmood, O. M., Goldenberg, D., Thayer, R., Migliorini, R., Simmons, A. N., & Tapert, S. F. (2013). Adolescents' fMRI activation to a response inhibition task predicts future substance use. *Addictive Behaviors*, *38*, 1435–1441.

Marmorstein, N. R. (2009). Longitudinal associations between alcohol problems and depressive symptoms: Early adolescence through early adulthood. *Alcoholism, Clinical and Experimental Research*, *33*, 49–59.

McGue, M., Osler, M., & Christensen, K. (2010). Causal inference and observational research: The utility of twins. *Perspectives on Psychological Science*, *5*, 546–556.

Merline, A., Jager, J., & Schulenberg, J. E. (2008). Adolescent risk factors for adult alcohol use and abuse: Stability and change of predictive value across early and middle adulthood. *Addiction*, *103*, 84–99.

National Institute on Alcohol Abuse and Alcoholism. (2016). *Alcohol use disorder: A comparison between DSM-IV and DSM-5.*

Nosek, B. A., Ebersole, C. R., DeHaven, A. C., & Mellor, D. T. (2018). The preregistration revolution. *Proceedings of the National Academy of Sciences of the United States of America*, *115*, 2600–2606.

Petersen, A. C., Crockett, L., Richards, M., & Boxer, A. (1988). A self-report measure of pubertal status: Reliability, validity, and initial norms. *Journal of Youth and Adolescence*, *17*, 117–133.

Piotrowska, P. J., Stride, C. B., Croft, S. E., & Rowe, R. (2015). Socioeconomic status and antisocial behaviour among children and adolescents: A systematic review and meta-analysis. *Clinical Psychology Review*, *35,* 47–55.

Pulkkinen, L., Kaprio, J., & Rose, R. J. (1999). Peers, teachers and parents as assessors of the behavioural and emotional problems of twins and their adjustment: The Multidimensional Peer Nomination Inventory. *Twin Research*, *2*, 274–285.

Rose, R. J., Salvatore, J. E., Aaltonen, S., Barr, P. B., Bogl, L. H., Byers, H. A., Heikkilä, K., Korhonen, T., Latvala, A., Palviainen, T., Ranjit, A., Whipp, A. M., Pulkkinen, L., Dick, D. M., & Kaprio, J. (2019). FinnTwin12 cohort: An updated review. *Twin Research and Human Genetics*, *22*, 302–311.

Rosenberg, M. (1965). *Society and the adolescent self-image.* Princeton University Press.

Rosseel, Y. (2012). lavaan: An R package for structural equation modeling. *Journal of Statistical Software*, *48*, 1–36.

Rubin, M. (2017). An evaluation of four solutions to the forking paths problem: Adjusted alpha, preregistration, sensitivity analyses, and abandoning the Neyman-Pearson approach. *Review of General Psychology*, *21,* 321–329.

Salvatore, J. E., Aliev, F., Edwards, A. C., Evans, D. M., Macleod, J., Hickman, M., Lewis, G., Kendler, K. S., Loukola, A., Korhonen, T., Latvala, A., Rose, R. J., Kaprio, J., & Dick, D. M. (2014). Polygenic scores predict alcohol problems in an independent sample and show moderation by the environment. *Genes*, *5*, 330–346.

Samek, D. R., Keyes, M. A., Iacono, W. G., & McGue, M. (2013). Peer deviance, alcohol expectancies, and adolescent alcohol use: Explaining shared and nonshared environmental effects using an adoptive sibling pair design. *Behavior Genetics*, *43,* 286–296.

Savage, J. E., Kaprio, J., Korhonen, T., Pulkkinen, L., Rose, R. J., Verhulst, B., & Dick, D. M. (2016). The effects of social anxiety on alcohol and cigarette use across adolescence: Results from a longitudinal twin study in Finland. *Psychology of Addictive Behaviors*, *30*, 462–474.

Savage, J. E., Rose, R. J., Pulkkinen, L., Silventoinen, K., Korhonen, T., Kaprio, J., Gillespie, N., & Dick, D. M. (2018). Early maturation and substance use across adolescence and young adulthood: A longitudinal study of Finnish twins. *Development and Psychopathology*, *30*, 79–92.

Silventoinen, K., Posthuma, D., Lahelma, E., Rose, R. J., & Kaprio, J. (2007). Genetic and environmental factors affecting self-rated health from age 16–25: A longitudinal study of Finnish twins. *Behavior Genetics*, *37*, 326–333.

Stephenson, M., Barr, P., Ksinan, A., Aliev, F., Latvala, A., Viken, R., Rose, R., Kaprio, J., Dick, D., & Salvatore, J. (2020). Which adolescent factors predict alcohol misuse in young adulthood? A co-twin comparisons study. *Addiction*, *115*, 877–887.

Tombaugh, T. N. (2004). Trail Making Test A and B: Normative data stratified by age and education. *Archives of Clinical Neuropsychology*, *19*, 203–214.

Verweij, K. J. H., Creemers, H. E., Korhonen, T., Latvala, A., Dick, D. M., Rose, R. J., Huizink, A. C., & Kaprio, J. (2016). Role of overlapping genetic and environmental factors in the relationship between early adolescent conduct problems and substance use in young adulthood. *Addiction (Abingdon, England)*, *111*, 1036–1045.

Walters, R. K., Polimanti, R., Johnson, E. C., McClintick, J. N., Adams, M. J., Adkins, A. E., Aliev, F., Bacanu, S.-A., Batzler, A., Bertelsen, S., Biernacka, J. M., Bigdeli, T. B., Chen, L.-S., Clarke, T.-K., Chou, Y.-L., Degenhardt, F., Docherty, A. R., Edwards, A. C., Fontanillas, P., … **Agrawal, A.** (2018). Transancestral GWAS of alcohol dependence reveals common genetic underpinnings with psychiatric disorders. *Nature Neuroscience*, *21*, 1656–1669.

Wong, M. M., Roberson, G., & Dyson, R. (2015). Prospective relationship between poor sleep and substance-related problems in a national sample of adolescents. *Alcoholism, Clinical and Experimental Research*, *39*, 355–362.

https://doi.org/10.1017/thg.2021.36 Published online by Cambridge University Press