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Tests of the Effects of Adolescent Early Alcohol Exposures on Adult Outcomes

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Abstract

Aims—To determine whether early adolescent alcohol use contributes to adult alcohol use, misuse, and other adult substance-related and social outcomes.

Design—In a longitudinal study of twins assessed at target ages 11, 14, and 24, two techniques adjusted for confounding factors: a propensity score (PS) adjusting for the effects of measured background covariates, and cotwin control (CTC) adjusting for confounding by unmeasured (including genetic) factors shared within early alcohol exposure-discordant pairs.

Setting—The community-based Minnesota Twin Family Study.

Participants—1512 (760 female, 752 male) twins.

Measurements—Early adolescent alcohol exposures, adult substance-related and social outcomes, and background variables reflecting behavioral, familial, and environmental characteristics.

Findings—Background covariates unbalanced between those with and without early alcohol exposure were balanced through PS-based weighting, leaving several adult outcomes related to substance use or social functioning remaining significantly associated with early alcohol exposure.Likewise, the within-pair individual-level component of a CTC indicated that early alcohol-exposed twins had higher risk than their non-exposed cotwins for several, but not all, of the same adult outcomes. For example, early alcohol use was associated with an adult index of alcohol use in both PS-weighted ($\beta = 0.57$, $p < 0.001$) and CTC ($\beta = 0.21$, $p = 0.031$) analyses.

Conclusions—Early alcohol exposures predict adult alcohol problems and related outcomes, despite stringent adjustment for measured and non-measured sources of potential confounding using PS and CTC. Contrasting the methods indicated that exposure effect estimates from PS application were likely biased by unmeasured confounding factors.

Introduction

Measures of early alcohol use have frequently been associated with adult psychopathology, maladaptive behaviors, and negative outcomes. Early alcohol use is related to higher prevalence of alcohol abuse and dependence through young adulthood [1, 2], and adult use

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and abuse of other psychoactive substances, as well as antisocial behaviors [3-5]. The perception that early alcohol exposure contributes to later alcohol problems and other negative outcomes has fueled policy and community-based efforts to prevent adolescent alcohol use [6]. A number of mechanisms might credibly mediate a causal effect of early use on adult outcomes, including social feedback loops as a result of affiliation with peers who are themselves intoxicated or encouraging of alcohol use [7], or neurocognitive adaptation or neurotoxicity [8] that could lead to cognitive deficits, elevated addiction risk, or higher disinhibition in general. Another possibility, however, is that the association between early alcohol exposure and adult problems is attributable to confounding common causal influences. In particular, analyses in twins have suggested that the association between age at first drink and the later development of alcohol use disorders is strongly influenced by an underlying genetic liability [9, 10], which, further, likely evinces a more general genetically mediated relationship between externalizing behavior in early adolescence and a variety of forms of adult psychopathology [11]. Similarly, several studies have found that links between early alcohol use and adult alcohol problems became non-significant after adjusting for risk factors including externalizing behaviors and parental alcohol use[12-14], raising additional doubts about the potential for the association to be causal in nature.

Ethical and practical considerations make it impossible to conduct a randomized experimental study of the effects of adolescent alcohol exposures. This complicates efforts to determine whether the adult correlates of early exposure are due to a causal effect, or rather to a more general genetically-influenced predisposition to behavioral disinhibition.One alternative approach involves adjusting for factors that may confound the relationship between adolescent substance use and the outcomes that potentially arise from it by making use of the propensity score (PS), which is the probability of receiving the exposure conditional on a set of observed, potentially confounding, variables. After PS adjustment, if theoretical assumptions hold (most notably the assumption that there exist no confounding variables apart from those included in the propensity score model) the relationship between an exposure and later outcomes associated with it may have a causal interpretation [15]. One study, using propensity scores estimated from a variety of personal and familial background covariates to match participants who had used alcohol or illicit drugs before age 15 with those who had not, found that after propensity score matching, early adolescent substance use retained its associations with several negative adult outcomes, including substance dependence and number of criminal convictions, among others [16].

Another approach to estimating the effects of specific environmental exposures, the cotwin control (CTC)method, is a natural experimental design involving using the genetic similarity and shared rearing environment of twins discordant for exposure to an environmental risk factor to control for variables that might confound the association between the exposure and an outcome [17]. Unlike methods that use PS adjustment, this method can be used to control for unknown genetic and shared environmental confounders, without having to measure or explicitly account for the potentially confounding variables. Earlier twin pair analysis had suggested that the association between age at first drink and later development of alcohol dependence was non-causal and likely attributable largely to common genetic effects [9]. However, more recent studies using CTC have found that the relationship between earlier

alcohol use and measures of adult alcohol involvement [18], adult alcohol dependence, and the use and abuse of other substances [19], may not be entirely attributable to familial factors shared between twins. Instead, they are likely to also be significantly, though less strongly, influenced by factors not shared by twins discordant for early alcohol use or age at first drink. Such findings may reflect an effect of earlier alcohol use mediated by environmental factors unique to each member of a twin pair.

We sought to determine whether early alcohol use is directly implicated in the adult presentation of alcohol and other substance abuse and negative life outcomes, rather than simply co-occurring as a result of common causal factors. In a community-based, prospective study of twins assessed through adolescence and into adulthood, we conducted both PS-adjusted and CTC analyses. If there is a causal effect of early alcohol exposure on adult outcomes, we expected that 1) measures of early alcohol exposure would be associated with adult outcomes after PS adjustment, and 2) in twin pairs discordant for measures of early alcohol exposure, twins exposed to alcohol in early adolescence would, as adults, be more likely than their non-exposed cotwins to abuse alcohol, and experience other negative outcomes. By comparing the results of the two methods, each can be used to address the other's limitations. PS adjustment may help identify potentially confounding imbalance in the distributions of measured variables not shared between discordant twins in CTC analyses. In turn, CTC analysis may indicate whether the PS-adjusted exposure effect estimate is biased by unmeasured shared genetic or environmental confounders.

Methods

Participants

The Minnesota Twin Family Study (MTFS) is a population-based, longitudinal study of twins born in Minnesota and their families [20, 21]. The current study includes same-sex twin pairs from a twin cohort born 1977 to 1984, first assessed at a target age of 11, then followed up with assessments at intervals of three or four years. This study uses measurements from the initial assessment (Intake (IN)) at target age 11 (age M(SD) = 11.72(0.43); N = 1512, 50.3% female), second assessment (Follow-up one (FU1)) at target age 14 (age M(SD) = 14.8(0.53); N = 1404, 50.6% female), and fifth assessment (Follow-up four (FU4)) at target age 24 (age M(SD) = 25.29(0.74); N = 1328, 51.4% female). Of the total sample, MZ twins numbered 972 (64%) and DZ twins numbered 540 (36%).

Measures

Background Covariate Measures for Propensity Score Estimation Model at Target Age 11—We included in the PS model a number of variables reflecting behavioral and demographic characteristics of the twin participants, their parents, and their familial environment, especially externalizing behaviors that might contribute to risk for early alcohol exposures, reflecting the potentially confounding pathway of externalizing psychopathology. The PS was therefore derived from a model which included as predictors 29 variables measured at the initial (IN) assessment (listed in Table S1, and described in supplementary material). These reflect either individual twin measurements (unique to each

twin in a pair), or parental and familial measurements (holding the same value across both twins in a pair).

Early Adolescent Alcohol Exposure Measures at Target Age 14—Early alcohol exposure was indicated by two self-reported dichotomous measures: ever having had an alcoholic drink (without parental permission) by FU1 (N = 505 exposed, 36% of total sample), and ever having been intoxicated by FU1 (N = 212 exposed, 15% of total sample). Rates of early use and intoxication approximated national rates for adolescents of similar cohort and age [22]. Early alcohol use did not differ by zygosity ($X^2(1) = 0.192$, $p = 0.66$), nor did early intoxication ($X^2(1) = 0.691$, $p = 0.41$). Discordance for early alcohol use among MZ pairs was 20%, while among DZ pairs discordance was 26%. Discordance for early intoxication among MZ pairs was 9%, while among DZ pairs discordance was 12%.

Adult Outcome Measures at Target Age 24—FU4 measures of adult twin alcohol and drug use, adult antisocial behavior, dependent stressful life events, family and interpersonal relationships, social engagement, and adult independence are described in supplementary material.

Statistical Analyses

Propensity Score Estimation, Weighting, and Exposure Effect Estimation—We estimated the PS using logistic regression of each early alcohol exposure on 29 variables reflecting intake assessment measurements (Table S1). The estimated PSs for each individual were that individual's model-fitted values from these logistic regression models —the predicted probability of having experienced each of the two early alcohol use exposures, separately, conditional on the model covariates. Because we are primarily interested in the effects of early alcohol exposure, rather than other covariates, the PS balances covariates across exposed and non-exposed groups [23], and provides a means to more clearly demonstrate covariate balance (Tables 1A and 1B) than traditional multiple regression.

PS adjustment involved inverse probability weighting. That is, exposed individuals were weighted by 1/PS , while non-exposed individuals received the weight 1/(1-PS) [24]. Models were fit using generalized estimating equations (GEE) to obtain standard errors robust to twin-pair clustered observations. An advantage of weighting is that, if the variables in the PS include all sources of confounding, then the weighted sample represents a pseudo-population in which confounding is eliminated, allowing for an unbiased estimate of the average effect of the exposure on the outcomes [25]. Cotwin Control Application and Exposure Effect Estimation

We implemented a CTC analysis by decomposing the effects of exposure into between-pair, or family-level effects, which are represented in the model by the pair mean value for the exposure, and within-pair, or individual-level effects, which are represented by the difference between each individual twin's exposure value and the pair mean [26]. We were interested in the coefficient reflecting individual-level, within-pair effects—the association between the exposure and the outcome arising only from influences that are not shared between members of a twin pair, and consequently free from the potentially confounding

effects of both shared environmental influences and either 50% (in DZ twin pairs) or 100% (in MZ twin pairs) of genetic influences. For CTC analysis, we again used GEE. If there are no additional environmental confounders unshared within twin pairs then the within-pair effects are consistent with an interpretation as the causal effect of the exposure on the outcome [27].

We conducted separate CTC analyses first for all twins without consideration of zygosity, then with zygosity entered as a potential moderator of between- and within-pair effects. If genetic influences contribute to the differences between members of the same twin pair in the association between exposures and outcomes, within-pair coefficients for DZ twins will be expected to exceed those for MZ twins. Additional statistical and data-related considerations are addressed in the supplementary material.

Results

Propensity Score and Inverse Probability of Treatment Weights

Tables 1A and 1B show the standardized difference (mean difference divided by pooled standard deviation) between the exposed and non-exposed groups for early alcohol use (Table 1A) and early intoxication (Table 1B) across the background variables used to predict the PSs upon which the inverse probability of treatment weights were based. Standardized differences less than 0.25 suggest that the distribution of the variable is reasonably balanced across exposed and non-exposed groups [24].

In the full unweighted sample, of the 29 variables included in the PS model, 13 exceeded the standardized difference criterion threshold of 0.25 between those who had used alcohol by FU1 and those who had not, while 19 exceeded the criterion threshold between those who had been intoxicated by FU1 and those who had not. In the unweighted sample, the mean of the absolute values of the standardized differences of the background variables between those who had ever had a drink by FU1 and those who had not was 0.23, while the equivalent value in the weighted sample was reduced to 0.03. Likewise, the mean of the absolute values of the standardized differences comparing those who had ever been intoxicated by FU1 and those who had not decreased from 0.29 in the unweighted sample, to 0.07 in the weighted sample. Weights based on PS models for both early alcohol exposure measures therefore achieve balance across exposed and non-exposed individuals for all included covariates below the standardized difference criterion threshold of 0.25.

Tables 1A and 1B also show standardized differences for the subset of the variables included in the PS model that were individually varying—that is, variables which could take different values between the two members of a given twin pair—calculated between members of twin pairs discordant for early alcohol use and early intoxication. All individual level variables are adequately balanced across discordant twin pairs, with the sole exception that the members of DZ twin pairs who had ever been intoxicated by FU1 reported experiencing a greater number of physical signs of puberty compared to their cotwins who had not been intoxicated by FU1.

Estimated Effects of Early Alcohol Exposures on Adult Outcomes

Results of regression-based effect estimation are shown on Tables 2A and 2B. In the unweighted sample, all measures of the use and abuse of alcohol and other substances, as well as symptoms of adult antisocial behavior and dependent stressful life events, were substantially elevated among both those who had had a drink before FU1 and those who had been intoxicated before FU1. Measures of social functioning (family relationships, interpersonal problems, social engagement), and adult independence were not as distinct, varying only slightly or not at all between those exposed and those not exposed to alcohol in early adolescence. After weighting the sample by the PS-based inverse probability of treatment weights, the magnitude of the effects of both early alcohol use measures on substance related, antisocial, and dependent stressful life event FU4 outcomes were somewhat reduced, but largely still strongly significant. Effects of early alcohol exposure on adult independence and interpersonal problems, while nominally significant in the unweighted sample, fell to insignificance in the weighted sample.

In CTC analyses among all discordant pairs without consideration of zygosity (Tables 2A and 2B), within-pair effects for both measures of early alcohol exposure were attenuated relative to exposure effects in both the full unweighted and weighted sample, but were still significant to at least the $p < 0.05$ level for alcohol and substance use variables, antisocial behavior, and dependent stressful life events, except early intoxication no longer significantly predicted symptoms of adult antisocial behavior. Zygosity did not significantly moderate within-pair effects of either early alcohol use or early intoxication on any FU4 adult outcomes, although within-pair effects for several substance-related measures were significant among discordant DZ twins but not among discordant MZ twins.

Discussion

We studied the relationship between alcohol use and intoxication before target age 14 and adult outcomes related to alcohol, other substances, antisocial behavior, dependent stressful life events, social functioning, and independent adult functioning, measured at target age 24. We addressed competing models: that early alcohol use has a causal role in the development of alcohol use, substance use, and other adult outcomes, or that common factors influence both early alcohol use and adult outcomes, confounding their association. Results suggest that, despite extensive adjustment for potential sources of confounding from genetic, shared environmental, and non-shared environmental influences, early exposures to alcohol and early intoxication retain associations consistent with a causal effect upon measures of adult substance use and abuse, as well as other forms of adult externalizing.

In order to bolster the possibility for an interpretation of the association between early alcohol exposures and adult outcomes as being consistent with a causal effect, we adjusted for the effects of potentially confounding influences on the association between early alcohol exposures and adult outcomes using two complementary approaches: PS-based weighting and the CTC, or discordant-twin design. In keeping with earlier research [1-4], in both unweighted and weighted analyses using the full sample, early adolescent exposures to alcohol were associated with greater use and abuse of both alcohol and other substances in adulthood, as well as antisocial symptomatology. Early alcohol exposures also suggested

elevated risk for stressful life events dependent on the individual's own behavior. There was little evidence for impairment in measures of adult social functioning among those exposed to alcohol in early adolescence. Although both early alcohol use and early intoxication were related to a significant increase in functioning as an independent adult in the unweighted sample, this effect became non-significant in the weighted sample, suggesting that it was attributable to confounding.

Unweighted estimates of the effect of early alcohol exposure were shown to be potentially biased, since many of the background variables used to estimate the PSs were substantially unbalanced between those who used alcohol or had been intoxicated in early adolescence and those who had not. However, we showed that application of weights based on the PS, which is the estimated probability of exposure conditional on the background variables, successfully balanced the covariates, allowing a causal interpretation of the subsequently estimated effects of early alcohol exposures, assuming no unmeasured sources of confounding.

Yet CTC analyses showed that confounding factors other than those included in the PS model were in fact also likely to exist. Within-pair effects estimated among twin pairs discordant for early alcohol exposures reflect only the influence of factors not shared between members of each twin pair, and thus provide an estimate free from potential confounders in the shared environment, and genetic influences, depending on the zygosity of the pair . That within-pair estimates of the effects of early alcohol exposure in the entire set of discordant pairs (ignoring zygosity) were substantially attenuated relative to the estimates from the weighted sample indicates the presence of unmeasured confounders that were not included in the PS model, highlighting the value of comparing PS-based estimates to those from CTC analyses. However, random measurement error of the exposure may also produce a reduction in the relative magnitude of within-pair estimates to unpaired estimates (see Frisell, 2012 [27] for additional details).

Using the CTC design, discordant MZ twin pairs provide the clearest estimate of the effect of non-shared factors between exposed and non-exposed twins. In our sample, estimates from MZ and DZ twins did not differ significantly from each other. However, that several within-pair estimates of adult alcohol and drug-related outcomes were higher among discordant DZ pairs than among discordant MZ pairs suggests that the association between adolescent alcohol exposures and those adult outcomes among exposure-discordant DZ twin pairs is partially attributable to confounding by genetic factors. This would be in line with previous studies that have indicated that genetic factors substantially influence the relationship between early adolescent externalizing problems (including early alcohol use) and the later development of adult externalizing behaviors in general, including the use and abuse of alcohol and other substances as well as other disinhibited behaviors [11].

A primary limitation of the CTC method is its inability to distinguish true causal effects from confounding influences that are not shared between exposure-discordant twins. In the present study, nearly all individually-varying predictors of early alcohol exposures included in the PS model were also adequately balanced across exposed and non-exposed members of discordant twin pairs. However, in other contexts, discordant twins may systematically

differ on variables antedating the exposure for which they are discordant[28]. In such cases, when the application of CTC methodology can be shown to have not achieved adequate balance across potentially confounding measured variables, adjustment with the PS might be used to achieve balance. Conversely, as previously described, comparison of effects estimated in CTC designs to those estimated in PS-adjusted models may act as a form of sensitivity analysis against the assumption that variables that were not observed or not included in the PS model do not confound the relationship between the exposure and associated outcomes. An extra-rigorous form of simultaneous adjustment for both individually-varying measured variables (via PS application) and non-measured shared environmental and genetic variables (via CTC) has already been successfully applied [29], although this approach was not necessary in the present study, since nearly all individual level variables included in the PS were balanced across exposure-discordant twin pairs (Tables 1A, 1B).

Our analyses support a causal effect of early alcohol use on adult functioning; they do not necessarily identify causal mechanisms. Apart from confounding with externalizing psychopathology, several hypotheses have been advanced to account for the effects of early alcohol exposure. One hypothesis is that alcohol, especially when exposure is early and heavy in adolescence, might influence brain development [8]. Alternatively, some have hypothesized that adolescent drinking impacts the course of adolescent social development, increasing the likelihood of negative adult outcomes [30]. Although we cannot unequivocally resolve these two possibilities, it is notable that we found no evidence that early alcohol use influenced a diverse set of social outcomes (e.g., social engagement, adult independence), which might run counter to expectations under the second hypothesis.

To conclude, these analyses suggest that early alcohol use and intoxication may be causally linked to increased adult alcohol and drug related outcomes, antisocial behavior, and dependent stressful life events, but only in the absence of confounding due to unmeasured variables (in the case of PS-based analyses) or non-shared genetic and environmental factors other than early alcohol exposure (in the case of CTC analyses). However, we observed no reliable evidence for effects of early alcohol exposures on measures of adult social functioning or adult independence. By comparison with CTC-based estimates, we found that PS adjustment was biased by unmeasured confounders, despite PSs being based on a rich set of exposure-pertinent background covariates. Additional research is required to determine whether these apparent causal effects are authentic, and the mechanisms by which they might be mediated.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1A

Standardized Differences Between Alcohol Exposed and Non-exposed Groups in the Means of Propensity Score Model Covariate at Target Age 11 (Intake Assessment)

		Full sample		Estimates with twin pairs discordant on exposure		
Individual level variables		**Unweighted sample**	**Weighted sample**	**All twins**	**MZ twins**	**DZ twins**
1	Twin IQ	−0.09	0.00	0.09	0.12	0.06
2	Twin menarche[1]	0.10	0.01	−0.04	−0.02	−0.09
3	Twin puberty measure	**0.25**	0.01	0.07	0.03	0.13
4	Twin GPA	−0.21	−0.02	0.05	0.02	0.11
5	Twin academic problems	**0.31**	0.01	0.10	0.13	0.05
6	Twin academic motivation	**−0.38**	−0.01	−0.10	−0.04	−0.18
7	Twin externalizing disorder symptoms	**0.33**	0.00	0.20	0.19	0.21
8	Twin delinquent behaviors	**0.51**	0.04	0.06	0.05	0.05
9	Conflict between twin and parents	**0.29**	0.01	0.05	0.09	−0.02
	Absolute mean of individual level variables	**0.27**	0.01	0.08	0.08	0.10
Family level variables						
10	Twin sex[2]	−0.13	−0.03			
11	Twin age	**0.28**	0.02			
12	Twin ethnicity[3]	0.15	0.00			
13	Parent age	0.00	−0.02			
14	Parent IQ	−0.15	−0.04			
15	Parent years of education	−0.21	−0.01			
16	Parent occupational status	−0.14	−0.01			
17	Family income	−0.09	−0.02			
18	Family history of externalizing	0.14	0.01			
19	Parent delinquent behaviors	**0.32**	0.04			
20	Parent externalizing disorder symptoms	**0.29**	0.02			
21	Parent alcohol abuse or dependence symptoms	0.21	0.03			
22	Parent drug abuse or dependence symptoms	0.24	0.05			
23	Parent alcohol use quantity and frequency index	**0.39**	0.04			
24	Parent tobacco use quantity and frequency index	**0.45**	0.03			
25	Parent ever used marijuana	**0.25**	0.07			
26	Parent number of times used marijuana	0.24	0.06			
27	Parent number of drug classes ever used	**0.30**	0.06			
28	Parents ever separated or divorced	0.24	0.01			
29	Immediate family member of twins ever died	0.05	−0.01			
	Absolute mean of all variables	0.23	0.03			

Positive standardized differences indicate that the value of a covariate was higher, on average, among early-exposed participants than those without early exposure, while negative standardized differences indicate that the value of a covariate was higher among those without early exposure to

alcohol than those who experienced early exposure. Values in bold indicate standardized differences greater than 0.25. The “weighted sample” is the sample after application of the propensity score as sample weights, as described in text. Standardized difference is calculated as $(M_{exposed} - Mn_{onexposed}) / \sqrt{[(\sigma^2_{exposed} + \sigma^2_{nonexposed}) /2]}$. [1] Applies to females only, variable is a binary indicator of menarche status. [2] Sex is coded Male = 0, Female = 1. [3] Ethnicity coded White = 0, Any other ethnicity = 1.

Table 1B

Standardized Differences Between Early Intoxicated and Non-intoxicated Groups in the Means of Propensity Score Model Covariates at Target Age 11 (Intake Assessment)

		Full sample		Estimates with twin pairs discordant on exposure		
Individual level variables		**Unweighted sample**	**Weighted sample**	**All twins**	**MZ twins**	**DZ twins**
1	Twin IQ	−0.14	−0.07	0.06	0.02	0.13
2	Twin menarche[1]	0.11	0.04	0.01	0.06	−0.01
3	Twin puberty measure	**0.31**	0.02	0.16	0.05	**0.31**
4	Twin GPA	**−0.37**	−0.07	−0.03	−0.08	0.05
5	Twin academic problems	**0.46**	0.11	0.11	0.15	0.06
6	Twin academic motivation	**−0.46**	0.00	−0.10	−0.06	−0.14
7	Twin externalizing disorder symptoms	**0.44**	0.04	0.15	0.13	0.14
8	Twin delinquent behaviors	**0.79**	0.05	0.16	0.16	0.12
9	Conflict between twin and parents	**0.34**	0.05	0.02	0.05	−0.05
	Absolute mean of individual level variables	**0.38**	0.05	0.09	0.08	0.11
Family level variables						
10	Twin sex[2]	−0.14	0.02			
11	Twin age	**0.31**	0.07			
12	Twin ethnicity[3]	0.22	0.00			
13	Parent age	−0.01	−0.08			
14	Parent IQ	−0.11	−0.12			
15	Parent years of education	**−0.30**	−0.14			
16	Parent occupational status	−0.22	−0.05			
17	Family income	−0.10	−0.02			
18	Family history of externalizing	0.16	−0.03			
19	Parent delinquent behaviors	**0.37**	0.05			
20	Parent externalizing disorder symptoms	**0.30**	0.10			
21	Parent alcohol abuse or dependence symptoms	**0.26**	0.08			
22	Parent drug abuse or dependence symptoms	**0.29**	0.07			
23	Parent alcohol use quantity and frequency index	**0.44**	0.13			
24	Parent tobacco use quantity and frequency index	**0.42**	0.09			
25	Parent ever used marijuana	**0.28**	0.11			
26	Parent number of times used marijuana	**0.29**	0.11			
27	Parent number of drug classes ever used	**0.39**	0.10			
28	Parents ever separated or divorced	**0.30**	0.01			
29	Immediate family member of twins ever died	0.02	−0.05			
	Absolute mean of all variables	**0.29**	0.07			

Positive standardized differences indicate that the value of a covariate was higher, on average, among early-intoxicated participants than those without early intoxication, while negative standardized differences indicate that the value of a covariate was higher among those without early

alcohol intoxication than those who experienced early intoxication. Values in bold indicate standardized differences greater than 0.25. The "weighted sample" is the sample after application of the propensity score as sample weights, as described in text. Standardized difference is calculated as $(M_{exposed} - M_{nonexposed}) / \sqrt{[(\sigma^2_{exposed} + \sigma^2_{nonexposed}) /2]}$. [1] Applies to females only, variable is a binary indicator of menarche status. [2] Sex is coded Male = 0, Female = 1. [3] Ethnicity coded White = 0, Any other ethnicity = 1.

Table 2A

Standardized Estimates for the Effect of Early Alcohol Use on Adult Outcomes

Adult Outcomes	Unweighted Sample		Propensity score-based weighted sample		Cotwin control: All discordant pairs		Cotwin control: Discordant MZ pairs		Cotwin control: Discordant DZ pairs	
	β_{expos} (SE)	P-value	β_{expos} (SE)	P-value	β_w (SE)	P-value	β_w (SE)	P-value	β_w (SE)	P-value
Alcohol use quantity and frequency index	0.63 (0.06)	<0.001	0.57 (0.06)	<0.001	0.21 (0.09)	0.031	0.22 (0.10)	0.042	0.20 (0.14)	0.142
Alcohol abuse or dependence symptoms	0.46 (0.06)	<0.001	0.36 (0.07)	<0.001	0.24 (0.11)	0.035	0.17 (0.14)	0.185	0.34 (0.16)	0.044
Tobacco use quantity and frequency index	0.63 (0.06)	<0.001	0.49 (0.07)	<0.001	0.21 (0.09)	0.036	0.09 (0.12)	0.291	0.39 (0.16)	0.018
Number of times used marijuana	0.54 (0.06)	<0.001	0.43 (0.07)	<0.001	0.28 (0.10)	0.006	0.22 (0.11)	0.055	0.38 (0.18)	0.042
Number of drug classes ever used	0.73 (0.06)	<0.001	0.60 (0.07)	<0.001	0.44 (0.10)	<0.001	0.41 (0.12)	0.004	0.50 (0.17)	0.006
Drug abuse or dependence symptoms	0.51 (0.06)	<0.001	0.40 (0.07)	<0.001	0.27 (0.11)	0.018	0.18 (0.14)	0.168	0.42 (0.17)	0.016
Adult antisocial behavior symptoms	0.52 (0.07)	<0.001	0.38 (0.08)	<0.001	0.19 (0.09)	0.046	0.08 (0.11)	0.312	0.37 (0.17)	0.034
Dependent stressful life events	0.35 (0.07)	<0.001	0.26 (0.08)	0.002	0.26 (0.10)	0.010	0.26 (0.11)	0.030	0.26 (0.19)	0.145
Family relationships	−0.10 (0.07)	0.134	−0.05 (0.08)	0.320	−0.08 (0.11)	0.311	−0.07 (0.14)	0.357	−0.09 (0.22)	0.357
Interpersonal problems	0.15 (0.06)	0.029	0.08 (0.08)	0.242	0.03 (0.11)	0.386	0.10 (0.14)	0.307	−0.09 (0.21)	0.355
Social engagement	0.05 (0.06)	0.285	0.12 (0.07)	0.089	−0.06 (0.10)	0.332	−0.03 (0.13)	0.388	−0.12 (0.21)	0.335
Adult independence	0.16 (0.07)	0.033	0.15 (0.08)	0.063	0.00 (0.12)	0.396	−0.02 (0.15)	0.392	0.03 (0.17)	0.394

β_{expos} is the coefficient for the effect of an FU1 alcohol exposure on an FU4 outcome.

β_W is the within-pair, individual-level coefficient for the effect of an FU1 alcohol exposure on an FU4 outcome in cotwin control analyses

Table 2B

Standardized Estimates for the Effect of Early Intoxication on Adult Outcomes

Adult Outcomes	Unweighted Sample		Propensity score-based weighted sample		Cotwin control: All discordant pairs		Cotwin control: Discordant MZ pairs		Cotwin control: Discordant DZ pairs	
	β_{expos} (SE)	P-value	β_{expos} (SE)	P-value	β_w (SE)	P-value	β_w (SE)	P-value	β_w (SE)	P-value
Alcohol use quantity and frequency index	0.62 (0.08)	<0.001	0.57 (0.08)	<0.001	0.37 (0.13)	0.009	0.26 (0.17)	0.127	0.54 (0.23)	0.024
Alcohol abuse or dependence symptoms	0.53 (0.10)	<0.001	0.31 (0.11)	0.010	0.29 (0.15)	0.061	0.15 (0.19)	0.286	0.51 (0.25)	0.046
Tobacco use quantity and frequency index	0.68 (0.07)	<0.001	0.50 (0.11)	<0.001	0.25 (0.12)	0.042	0.16 (0.15)	0.234	0.38 (0.17)	0.031
Number of times used marijuana	0.60 (0.10)	<0.001	0.31 (0.11)	0.006	0.43 (0.17)	0.022	0.27 (0.19)	0.139	0.66 (0.28)	0.025
Number of drug classes ever used	0.84 (0.09)	<0.001	0.62 (0.10)	<0.001	0.50 (0.16)	0.008	0.38 (0.15)	0.020	0.68 (0.28)	0.027
Drug abuse or dependence symptoms	0.68 (0.11)	<0.001	0.38 (0.14)	0.010	0.47 (0.16)	0.007	0.26 (0.21)	0.174	0.78 (0.24)	0.003
Adult antisocial behavior symptoms	0.60 (0.08)	<0.001	0.43 (0.11)	<0.001	0.18 (0.16)	0.197	0.08 (0.16)	0.354	0.35 (0.26)	0.163
Dependent stressful life events	0.47 (0.10)	<0.001	0.40 (0.13)	0.006	0.38 (0.15)	0.016	0.43 (0.18)	0.026	0.30 (0.21)	0.146
Family relationships	−0.08 (0.11)	0.304	0.05 (0.15)	0.376	0.07 (0.20)	0.366	0.09 (0.24)	0.363	0.03 (0.29)	0.391
Interpersonal problems	0.19 (0.10)	0.064	0.07 (0.13)	0.335	−0.07 (0.19)	0.370	−0.08 (0.25)	0.372	−0.05 (0.29)	0.390
Social engagement	−0.09 (0.09)	0.230	0.11 (0.12)	0.271	−0.06 (0.14)	0.368	0.07 (0.17)	0.362	−0.26 (0.25)	0.225
Adult independence	0.18 (0.09)	0.041	0.18 (0.11)	0.105	0.01 (0.15)	0.396	0.02 (0.19)	0.391	−0.02 (0.25)	0.397

β_{expos} is the coefficient for the effect of an FU1 alcohol exposure on an FU4 outcome.

β_w is the within-pair, individual-level coefficient for the effect of an FU1 alcohol exposure on an FU4 outcome in cotwin control analyses