Comparing the Potential Causal Influence of Two Indicators of Early Alcohol Use on Later Alcohol Use Disorder Symptoms

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**General Scientific Summary:** This study suggests that early initiation of regular drinking may be a better predictor of risk for developing alcohol use disorder than is age of first drink. Additionally, low levels of agreeableness and persistent adolescent marijuana use were causally associated with increased alcohol use disorder symptoms in adulthood.
Abstract

Age of first drink (AFD) has repeatedly been found to be associated with alcohol use disorders (AUD); however, some studies suggest this is a noncausal effect that may be due to childhood risk factors or familial influences. In contrast to indicators of any early alcohol use, such as AFD, indicators of a pattern of repeated drinking may be more likely to be causally associated with later problematic alcohol use. The current study examined AFD and age of initiation of regular drinking (ARD; defined as drinking at least once a month for six or more months) as quasi-causal predictors of lifetime AUD symptoms. Participants were 3,005 adult Australian twins who reported having been regular drinkers in their lifetime. Semi-structured interviews were conducted to assess AFD, ARD, AUD, and other substance use. Externalizing symptomatology and personality traits were assessed via questionnaire. Unadjusted and adjusted multilevel discordant twin models were conducted; the adjusted models included socioeconomic status, personality, conduct disorder, and adolescent initiation of regular smoking and marijuana use as covariates. Results from fully adjusted models controlling for familial confounds provided evidence for a potentially causal influence of ARD on AUD symptoms, whereby twins with an earlier age of regular drinking than their cotwin had more lifetime AUD symptoms. AFD did not significantly predict AUD symptoms in similar analyses. These results suggest that early patterns of alcohol use may be more important for understanding risk for future problems than simply initiation of any use.

Keywords: age of regular drinking, age of first drink, alcohol use disorder, multilevel model, cotwin control, discordant twin design
Introduction

Individuals vary considerably in their age of onset of alcohol use as well as their early patterns of use, and this might be important for understanding risk for developing an alcohol use disorder (AUD) and other alcohol-related harms. Age of first drink (AFD) has been repeatedly found to be associated with AUD and other problematic alcohol use behaviors (Aiken et al., 2018; DeWit et al., 2000; McGue et al., 2001). However, it is unclear whether this is a causal relationship, with some research suggesting that early onset of drinking is not associated with risk after controlling for childhood conduct problems or taking into account familial influences (Prescott & Kendler, 1999; Rossow & Kuntsche, 2013; Sartor et al, 2009). For example, recent research found minimal evidence of a causal effect of AFD on later substance use, mental health, and antisocial behavior after accounting for childhood risk factors (Waldron et al., 2018). Instead, the researchers concluded that the link between age of onset of drinking and later negative outcomes could be explained largely by genes and shared environment (Waldron et al., 2018). Together these findings suggest that the effects of AFD on alcohol use outcomes might be due to familial effects or other confounding factors. If this is the case and AFD’s impact on AUD is non-causal, this would suggest that efforts to discourage early initiation of alcohol use might not yield tangible benefits and that researchers and practitioners should instead focus their efforts on other indicators of risk.

Researchers have indeed begun to question the value of AFD as an indicator of alcohol-related risks (Kuntsche et al., 2016; Ward, Snow, & Aroni, 2010). Although AFD indicates onset of alcohol use to some degree, individuals may have just one drink of alcohol at a young age and then not have another drink for a number of years or may never proceed to a regular pattern of
drinking. An additional consideration is that of family and cultural/religious norms, as having a glass of alcohol at a young age might not be indicative of risk at all for some individuals.

Instead, indicators of more involved patterns of alcohol use may be more strongly associated with later hazardous substance use than initiation of any use (Baggio et al., 2013; Woodcock et al., 2015). For example, age of onset of drunkenness is a better predictor of progression to “hard” drug use (e.g., heroin, crystal methamphetamine) than onset of any alcohol use (Baggio et al., 2013). Similarly, in a sample of over five hundred heroin users the best predictor of progression to regular heroin use, accounting for 8.1% of the variance in onset, was age of initiation of regular alcohol and tobacco use (defined as using 3+ times per week; Woodcock et al., 2015). A potential explanation for this is that individuals who initiate regular alcohol use or intoxication early in adolescence or as children may disrupt critical social, psychological, and neurological developments that occur during this period (DeWit et al., 2000; Zeigler et al., 2005). These effects are likely to be a function of cumulative exposure, with greater use resulting in increased impairment compared to more limited or sporadic alcohol consumption. Although these studies did not assess alcohol-specific outcomes, they provided evidence that early, involved alcohol use may predict a variety of substance use outcomes better than early initiation.

Two studies have examined the effects of early regular drinking on later alcohol use outcomes. Using a sample of male Vietnam veteran twins, researchers conducted regression analyses of twin pairs discordant for early initiation of regular drinking (defined as drinking at least once a month for 6+ months) to determine whether this predicted adult substance use outcomes, including alcohol use and alcohol dependence, after accounting for genetic and shared environmental influences (Grant et al., 2006). There was evidence for a quasi-causal effect of
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early regular alcohol use on adult alcohol dependence, as well as marijuana and other drug abuse/dependence (Grant et al., 2006). Recent research using a sample of adolescents from the Minnesota Twin Family Study found some evidence for a causal effect of early intoxication on average number of drinks consumed in drinking episodes (Waldron et al., 2018). There was also evidence for the influence of a measure of adolescent consumption patterns on adult alcohol outcomes, including maximum drinks consumed, typical alcohol consumption in a drinking episode, and lifetime intoxications (Waldron et al., 2018). This line of research provides evidence for the importance of drinking patterns in adolescence on later problematic drinking.

The current study aimed to expand upon previous research by examining potential causal relationships between ARD, AFD, and lifetime AUD symptom counts using a multilevel discordant twin design. While causal influences of AFD and ARD have been examined separately within discordant twin analyses, these effects have not yet been directly compared within the same study. By examining both AFD and ARD as quasi-causal predictors of lifetime alcohol problems, the current study was able to make comparisons of the effects of these alcohol use onset phenotypes on the development of disordered drinking. The use of a genetically informative design provides a rigorous test of the potential causal relationship between these measures of alcohol initiation and lifetime AUD symptom counts. Additionally, the current study included a number of covariates associated with risk for alcohol use problems, including socioeconomic status, personality, conduct disorder, and adolescent initiation of regular smoking and marijuana use. Because multilevel discordant twin analyses can control for genetic and shared environmental influences, but not for other unique environmental influences that may affect both early alcohol use and lifetime AUD symptom counts, covariates were included in the
current analysis. Including these covariates allows for a more rigorous examination of causality and helps avoid incorrect causal inferences (McGue, Osler, & Christensen, 2010).

Methods

Participants

The sample consisted of members of a cohort of adult twins from the Australian Twin Registry (ATR). The data for the current study were collected by computer-assisted telephone interviews conducted between 2005 and 2009. Participants were also mailed a questionnaire following completion of the phone interview to assess personality traits. Of the 3,877 individuals in the ATR, 563 siblings were excluded, as well as 22 individuals missing zygosity information. Individuals who did not report being regular drinkers (e.g. drinking at least once a month for six months or more) at some point in their lifetime were also not included (n = 287). The resulting sample for the current study consisted of 3,005 individual twins: 863 monozygotic female (MZF), 447 monozygotic male (MZM), 657 dizygotic female (DZF), 349 dizygotic male (DZM), and 689 dizygotic opposite sex (DZOS) twins. Participants were between the ages of 27 and 37 at the time of data collection, with a mean age of 31.84 years (SD = 2.45). 63.9% of the sample identified as female. For additional details regarding sample recruitment and characteristics, see Lynskey et al. (2012).

Measures

The interview was based on the Australian version of the Semi-Structured Assessment of the Genetics of Alcoholism (SSAGA-OZ; Bucholz et al., 1994) and included assessments of drinking behaviors, alcohol-related consequences, conduct disorder symptoms, use of other substances, and demographic characteristics. Participants also completed a self-report questionnaire that assessed personality traits.
Age of First Drink. To assess initiation of drinking, respondents were asked, “How old were you the first time you had a full drink of beer, wine or spirits?” In order to reduce the potential influence of outlying values, individuals who reported ages of less than 5 years were equated to 5 years.

Age of Initiation of Regular Drinking. To assess the age of initiation of regular drinking, respondents were asked, “At what age did you start to drink regularly—that is, drinking at least once a month for 6 months or more?” This question was used to restrict the sample for the current study to only regular drinkers. Participants reported initiating regular drinking on average at 18.21 years old (SD = 2.67).

While most of the original sample (and all of those included in analyses) progressed from initiation of alcohol use to regular use, 7.62% (n = 248) of ever drinkers did not become regular drinkers. These individuals first drank alcohol around 17 – 18 years on average (M = 17.66, SD = 2.73) and ranged in ages of initiation from 5 – 28 years. On the other hand, users who progressed to regular drinking initiated use around age 16 (M = 15.70, SD = 2.22) and reported an initiation range of 5 – 32 years old. Of never regular drinkers, 15.75% had first used alcohol by age 15.

Lifetime Alcohol Use Disorder Symptoms. AUD symptom counts were based on participants’ responses to questions pertaining to the DSM-IV-TR (American Psychiatric Association, 2000) diagnostic criteria for alcohol abuse and dependence. Participants’ lifetime symptom count scores were summed across abuse and dependence criteria. The resulting lifetime AUD symptom count score demonstrated high internal reliability (α = 0.76).

Income. Participants were asked, “What is your current combined household gross income, that is before tax?” The eleven response options ranged from ‘AU$0-9,999/year’ to
‘AU$150,000 or more/year’. Participants reported a median household income of AU$75,000–AU$99,999/year. This estimate is representative of the general Australian population, with the Australian Bureau of Statistics (2017) reporting a mean household income of $89,076/year around the time of data collection.

**Educational Attainment.** Participants were asked “What is the highest educational level you have completed?” Response options ranged from not completing primary school to obtaining a post-graduate degree. Responses were coded into a five level variable, where scores of ‘1’ indicated that a participant did not complete Year 12 (equivalent to not completing high school in the United States), ‘2’ indicated completion of Year 12 (high school diploma), ‘3’ indicated completion of technical college (similar to community college), ‘4’ indicated obtaining an undergraduate degree, and ‘5’ indicated obtaining post-graduate education.

**Conduct Disorder Symptomatology.** The interview assessed each of the 15 DSM-IV-TR (American Psychiatric Association, 2000) criteria for conduct disorder (CD). Participants were asked to only consider those behaviors that occurred prior to age 18. Criteria for CD includes symptoms within four broad domains: 1) aggression to people and animals, 2) destruction of property, 3) deceitfulness or theft, and 4) serious violations of rules. Criteria were summed across the four domains, with the resulting CD symptom count score having acceptable internal reliability (α = 0.67).

**Early Regular Smoking.** To assess early regular smoking, participants were first asked, “Was there ever a time in your life when you smoked cigarettes at least once a week for at least two months in a row?” Participants who endorsed having smoked regularly during their lifetime were then asked the age at which they first began smoking regularly. Age of initiation of regular
smoking ranged from 7 – 33 years in the current sample. Those who reported being regular smokers by age 18 were coded as ‘1’, while those who were not were coded as ‘0’.

** Persistent Adolescent Marijuana Use.** Participants were first categorized according to whether they had tried marijuana before age 18. Following this, participants who reported using marijuana in their lifetime were asked, “How soon after you first tried marijuana did you try it again?” In an attempt to capture a repeated pattern of use beyond mere initiation, participants who reported never using marijuana and those who only used marijuana once and never tried it again were coded as ‘0’, regardless of their age of initiation of marijuana use. Those who reported using marijuana at age 18 or younger who continued to use were coded as ‘1’. Therefore, this measure indexes repeated marijuana use that began in adolescence.

** Personality Traits.** Participants completed an adapted NEO PI-R (Costa & McCrae, 1992; Few et al., 2014) that assessed Big Five personality traits (neuroticism, extraversion, openness to experience, agreeableness, and conscientiousness) using 74 items. Responses were coded on a ‘1’ (strongly disagree) to ‘5’ (strongly agree) scale. Scale scores were the average of all responses for a particular personality trait and also ranged from ‘1’ to ‘5’. Each scale demonstrated high internal reliability, with alphas for the scales ranging from 0.77 - 0.89.

**Analytic Plan**

All analyses were conducted with SAS version 9.4 (SAS Institute, 2013). Descriptive analyses were conducted to examine sample characteristics. Correlations between study variables were calculated using survey analysis procedures to account for clustering in twin pair data. To examine the effect of AFD and ARD on lifetime AUD symptoms, two-level generalized linear mixed models (GLMMs) were run using PROC GLIMMIX. GLMMs are a statistical procedure used for the analysis of clustered data with non-normally distributed outcome variables (Hedeker, 2005). Twin data are clustered, with individual twins (level 1) nested within a twin
pair (level 2). Within the analyses, both level 1 and level 2 variances were estimated, along with a random intercept. A negative binomial distribution and log link function were used due to the skewness of the lifetime AUD symptom count variable, with about a third of respondents (34.43%) reporting zero lifetime symptoms. Coefficients produced from the multilevel models were exponentiated to produce incidence rate ratios (IRRs), which index relative risk.

Models were initially run at the individual level taking into account non-independence of twin-pair observations. Base models were fit including sex, zygosity, and AFD or ARD as predictors of lifetime AUD symptoms. Evidence for sex differences was evaluated by including an ARD or AFD-by-sex interaction term; if significant, this interaction term was carried forward into subsequent analyses. Fully adjusted models were fit including all additional covariates (income, education, personality traits, CD symptoms, early regular smoking, and persistent adolescent marijuana use). These individual level analyses examine evidence for an overall effect of early drinking, as indicators are not decomposed into within- and between-twin pair sources of variance; these analyses approximate analyses conducted using unrelated individuals.

Following this, co-twin control models were fit in an attempt to identify potential sources of confounding that might contribute to the overall effect (McGue et al., 2010). Compared to analysis of unrelated individuals, the discordant twin analysis controls for familial environmental and genetic factors (partially for dizygotic and completely for monozygotic twins), permitting stronger causal inference regarding environmental exposures. If between-twin pair effects are significant, this suggests that genetic or shared environmental factors associated with the predictor contribute to lifetime AUD symptom development. On the other hand, if within-twin pair effects are significant, this suggests that the associated environmental exposure (such as ARD or AFD) may causally contribute to AUD symptom development. The current design
provides a more stringent test of the causal effect of the environment compared to other designs that do not account for familial effects of an environmental variable on the outcome of interest.

All predictor variables were centered using group mean centering (Enders & Tofighi, 2007). Using this method, the level 1 and level 2 predictor coefficients represent the direct within-twin pair (compared against the co-twin) and between-twin pair (compared against other twin pairs) effects (Begg & Parides, 2003), respectively. Models were conducted that were limited to either DZ (n = 1695) or MZ (n = 1310) twins. Base and fully adjusted models were fit for these zygosity-limited samples, wherein the ARD or AFD indicator was decomposed into two variables indexing within-twin pair and between-twin pair sources of variance. Models including only MZ twins allow for a stronger causal interpretation, whereby a predictor may be isolated as having a unique environmental effect on lifetime AUD symptomatology.

**Results**

**Sample Characteristics**

With respect to education, 10.37% of the sample reported not completing Year 12, 13.86% completed Year 12, 28.22% completed technical college, 28.05% completed an undergraduate program, and 19.51% completed post-graduate education. Approximately two-thirds (65.57%) of the sample reported at least one AUD symptom in their lifetime, and just under half (42.54%) met criteria for lifetime AUD based on endorsing two or more lifetime AUD symptoms. On average, participants reported 1.76 lifetime AUD symptoms (SD = 2.02). Additionally, almost half (45.49%) of participants endorsed at least one CD symptom, and 9.61% endorsed three or more CD symptoms, the number of symptoms required for a lifetime CD diagnosis.

Participants reported a mean age of first drink of 15.70 (SD = 2.22), with ages of initiation ranging from 5 – 32 years. 15.33% of twins in the sample were concordant for AFD.
On average, participants became regular drinkers around age 18 ($M = 18.21; SD = 2.67$), and 18.08% of twins were concordant for ARD. Participants reported being on average 17.85 years old ($SD = 3.33$) when they first used marijuana and quite a bit younger when they first used tobacco ($M = 14.29, SD = 3.55$). About half (50.48%) had tried marijuana by age 18 and most of these (46.93%) were classified as persistent adolescent marijuana users. A substantial majority of participants (81.46%) reported smoking tobacco by age 18. However, just 37.54% of these users progressed to regular smoking and were classified as early regular smokers for the current study.

**Correlations between Study Variables**

ARD and lifetime AUD symptoms were significantly negatively correlated ($r = -0.33, p < .0001$), such that those with a lower ARD had significantly more lifetime AUD symptoms. AFD was also negatively correlated with AUD symptoms ($r = -0.31, p < .0001$). Lower income and less educational attainment were associated with endorsing more lifetime AUD symptoms (see Table 1). Higher levels of neuroticism were associated with more AUD symptoms, as were lower levels of agreeableness, extroversion, and conscientiousness. CD symptoms, early regular smoking, and persistent adolescent marijuana use were all associated with AUD symptoms.

Many covariates that were associated with AUD, such as the personality traits of neuroticism, agreeableness, extroversion, and conscientiousness, CD symptoms, early regular smoking, and persistent adolescent marijuana use were also correlated with ARD and AFD (see Table 1). Individuals higher in extroversion and openness and lower in agreeableness and conscientiousness were more likely to have earlier ages of alcohol use. Additionally, early regular smoking, persistent adolescent marijuana use, and CD symptoms were associated with lower ages of alcohol use initiation. Although associated with AUD, indicators of SES (income and educational attainment) were not associated with ARD and AFD.

[insert Table 1 here]
**Multilevel Models**

**Age of Initiation of Regular Drinking.** The base GLMM run at the individual level indicated that ARD significantly predicted AUD symptoms (IRR = 0.89 [0.87 – 0.90]; see Figure 1), indicating that each additional year of age at which regular drinking was initiated was associated with an 11% decrease in the expected AUD symptom count. Sex was a significant predictor of lifetime AUD symptoms in this base individual level model, as well as all additional models, with men having higher rates of lifetime AUD symptoms. There was no evidence for a significant sex-by-ARD interaction (IRR = 1.02 [0.98 – 1.05]). After adjusting for covariates, the protective effect of later initiation of regular drinking remained (IRR = 0.93 [0.91 – 0.94]). Additionally, all personality traits except openness predicted AUD symptoms in the fully adjusted individual-level model. CD symptoms (IRR = 1.12 [1.08 – 1.15]), regular smoking (IRR = 1.12 [1.02 – 1.22]), and persistent adolescent marijuana use (IRR = 1.29 [1.18 – 1.40]) were also associated with AUD symptoms.

[insert Figure 1 here]

Zygosity-limited cotwin-control analyses were then conducted (see Table 2). First, the sample was restricted to DZ twins only. There was no evidence for a significant sex-by-ARD-within twin pair interaction (IRR = 0.93), so this interaction term was not included in the fully adjusted model. In the fully adjusted model, the within-twin pair effect indexing the quasi-causal influence of ARD was significant (IRR = 0.95). Additional significant within-twin pair predictors included neuroticism (IRR = 1.38), extroversion (IRR = 1.40), and CD symptoms (IRR = 1.14). Between-twin pair, or familial level, influences of regular drinking (IRR = 0.92), neuroticism (IRR = 1.42), extroversion (IRR = 1.45), CD symptoms (IRR = 1.12), and persistent adolescent marijuana use (IRR = 1.47) were also significant.
Restricting the sample to MZ twins produced similar results, with just a few differences. Notably, the quasi-causal within-twin pair effect of ARD remained significant in this most stringent model (IRR = 0.94). However, within-twin pair effects of neuroticism and extroversion were no longer significant. Instead, within-twin pair effects of agreeableness (IRR = 0.76) and persistent adolescent marijuana use (IRR = 1.39) were significant. Between-twin pair effects were similar to those in the DZ-limited sample, with the exception that the between-twin pair effect of regular smoking was significant (IRR = 1.37).

**Age of First Drink**. Analyses at the individual level indicated significant effects of AFD on lifetime AUD symptoms in the base (IRR = 0.89 [0.87 – 0.91]) and fully adjusted models (IRR = 0.94 [0.92 – 0.96]; see Figure 1). Sex was also a significant predictor in the base model (IRR = 1.73 [1.59 – 1.88]) and all other models; however, there was no evidence for a significant sex-by-AFD interaction (IRR = 1.04 [1.00 – 1.08]). In the fully adjusted model, all personality traits except openness were predictors of lifetime AUD symptoms (neuroticism [IRR = 1.35 (1.26 – 1.44)], extroversion [IRR = 1.28 (1.17 – 1.38)], agreeableness [IRR = 0.80 (0.73 – 0.87)], conscientiousness [IRR = 0.87 (0.80 – 0.94)]). CD symptoms (IRR = 1.12 [1.08 – 1.15]), early regular smoking (IRR = 1.13 [1.03 – 1.24]), and persistent adolescent marijuana use (IRR = 1.32 [1.21 – 1.44]) were also significant predictors, while SES indicators (income and education) were not associated with lifetime AUD symptoms.

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1 Analyses were also conducted including individuals who initiated drinking but did not progress to regular drinking (see supplemental materials). Results were nearly identical to those obtained among the regular drinking subsample (base models: individual [IRR = 0.87 (0.86 – 0.89)], DZ [IRR = 0.92 (0.88 – 0.96)], MZ [IRR = 0.98 (0.94 – 1.03)]; fully-adjusted models: individual [IRR = 0.90 (0.87 – 0.92)], DZ [IRR = 0.93 (0.89 – 0.98)], MZ [IRR = 0.95 (0.89 – 1.01)]).
Models limited to DZ twin pairs produced similar results to those presented above. Within- and between-twin pair effects of AFD were significant in the DZ limited base model (within-twin: IRR = 0.93; between-twin: IRR = 0.85) and remained significant after including all covariates (see Table 2). SES predictors were nonsignificant, both at the within- and between-twin pair levels. There were, however, within-twin pair effects of personality, with neuroticism (IRR = 1.40) and extroversion (IRR = 1.38) predicting lifetime AUD symptoms. Within-twin pair effects of CD symptoms were also significant (IRR = 1.14), while within-twin pair effects of early regular smoking and persistent adolescent marijuana use were not. Between-twin pair, or familial, influences of CD symptoms (IRR = 1.12) and persistent adolescent marijuana use (IRR = 1.51) were associated with AUD.

In the base model restricted to MZ twins, the quasi-causal within-twin pair effect of AFD was nonsignificant (IRR = 0.99 [0.94 – 1.03]), while the between-twin pair effect remained significant (IRR = 0.86 [0.82 – 0.90]). Upon adding the interaction term, there was evidence for a significant sex-by-within-twin pair effect of AFD, such that the effect of AFD was stronger among women than men (IRR = 1.14 [1.04 – 1.25]; additional information exploring this interaction can be found in supplemental materials). After adjusting for covariates, both within- and between-twin pair effects of AFD became nonsignificant (see Table 2), suggesting absence of a causal association between AFD and lifetime AUD symptoms after accounting for familial confounds. The sex-by-within-twin pair AFD interaction retained significance (IRR = 1.14). Just two other within-twin pair effects remained significant: agreeableness (IRR = 0.74) and persistent adolescent marijuana use (IRR = 1.47).

Discussion
This study compared the effects of ARD and AFD on lifetime AUD symptom counts using a genetically informed research design. The cotwin control design can be used to determine whether an effect is truly environmental and even potentially causal. The results of the current study suggest that ARD may have an important causal effect on lifetime AUD symptoms, with the twin who began to regularly drink earlier than their cotwin going on to experience more symptoms of AUD. These effects persisted even after controlling for the effects of SES, personality, CD symptomatology, and regular tobacco and marijuana use.

Developing a pattern of alcohol use in adolescence, which is a time associated with a number of developmental and social milestones, may be indicative of poor coping skills or stress management. For example, research suggests those who begin substance use during this stressful life period are more likely to continue using alcohol frequently as a way to cope with problems (Buchmann et al., 2010; McCubbin, Needle, & Wilson, 1985). Drinking to cope has been found to be associated with alcohol problems (Carpenter & Hasin, 1999; Holahan et al., 2001), and adolescents who begin drinking during this period may be more likely to develop an association between drinking and removal of negative affect than those who begin in later years. This is in line with the social learning theory of alcohol use, which suggests that those who go on to develop alcohol problems differ from healthy drinkers in their ability to cope with stressful life events and their expectancies of alcohol use (Abrams & Niaura, 1987). If this is the case, drinking to cope may partially or completely explain the effect of ARD on lifetime AUD symptoms. A formal mediation analysis should support an indirect effect of within-twin pair ARD on AUD via drinking to cope. Because the current study did not assess drinking motives, this remains an important direction for future research.
An additional possibility is that of dose-dependent effects of alcohol on the brain, which may help explain why early regular use is more hazardous and more likely to be causally related to lifetime AUD development compared to initiation or experimental use of alcohol. Research using animal models indeed suggests there are dose- and age-dependent effects of alcohol on brain functioning, such that repeated or binge exposure to alcohol during adolescence is associated with greater susceptibility to alcohol’s memory-impairing effects (Crews et al., 2000). Research with human samples has supported these conclusions; accelerated declines in frontal and temporal cortical volumes were found among heavy adolescent drinkers compared to light/nondrinkers (Squeglia et al., 2015). These impairments may be critical to risk for developing AUD, as learning and memory play important roles in the development of addiction (Torregrossa & Taylor, 2016). Therefore, indices of a pattern of regular drinking during adolescence may have greater implications than initiation for understanding adolescents’ risk for experiencing the harmful cognitive effects of alcohol, including impairments in memory formation and unhealthy habit development.

The current study also found evidence for a familial, or between-twin pair, effect of regular drinking initiation on later AUD symptoms, suggesting that genetic or shared environmental factors confer risk for early regular drinking initiation and AUD symptom development. This is consistent with work finding overlapping genetic influences on onset of drinking and alcohol dependence and AUD (Grant et al., 2006; Ystrom, Kendler, & Reichborn-Kjennerud, 2014) and suggests that the relationship between onset of regular drinking and later alcohol-use problems is complex and cannot be explained solely by a causal effect.

Unlike the results for ARD, within-twin pair effects of AFD did not remain significant in the fully adjusted MZ-only analyses, which fully control for genetic and shared environmental
influences. While the associations of AFD and ARD with AUD symptoms were of similar magnitude ($r_s = -0.31$ and $-0.33$, respectively), the powerful co-twin control design revealed only ARD as a causal contributor to risk for lifetime AUD symptoms. Rather than a causal environmental effect, the influence of AFD on risk for AUD may operate through familial influences, with AFD being a marker of genetic liability for AUD. For example, research has shown that the overlap between AFD and alcohol dependence and AUD is due largely to genetic factors, with almost no evidence for overlap of nonshared environmental influences, indicating the absence of a causal environmental mechanism (Sartor et al., 2009; Ystrom et al., 2014).

Another possibility is that the causal association between AFD and AUD is weaker than the association between ARD and AUD because AFD is a more distal predictor. Effects of AFD may be mediated through several other steps on the causal pathway, including ARD. Previous research found a quasi-causal effect of AFD on age of first AUD symptom; however, part of the association between AFD and age of first AUD symptom appeared to be mediated through ARD (Deutsch et al., 2017). AFD, therefore, may be a distal, somewhat noisy indicator of the true causal factor—ARD.

Two of the covariates, low agreeableness and persistent adolescent marijuana use, were consistently found to be quasi-causally associated with lifetime AUD symptoms. Notably, agreeableness was the only personality trait with significant within-twin pair effects in the fully adjusted analyses restricted to MZ twins. A number of hypotheses for the relationship between personality traits and AUD have been proposed (Littlefield & Sher, 2010). One theory posits that certain personality traits increase risk for alcohol use and abuse, and research does show that personality in adolescence predicts later alcohol use (Sher, Bartholow, & Wood, 2000). However, an alternative model suggests instead that alcohol use alters personality development
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(White et al., 2011). Research has shown that initiation of alcohol use leads to increases in aggression and alienation (Blonigen et al., 2015), measures from the Multidimensional Personality Questionnaire (MPQ; Tellegen & Waller, 2008) which are roughly equivalent to the Big Five dimension of agreeableness. These two seemingly opposing theories likely operate together to influence one’s risk for AUD and highlight the importance of personality in understanding alcohol use.

Persistent adolescent marijuana use was the other predictor quasi-causally associated with lifetime AUD symptoms in the fully adjusted MZ only analyses. This is in line with prior research, as at least two studies have made use of the discordant twin design to examine the extent to which early marijuana use predicts later substance use and abuse/dependence (Grant et al., 2010; Lynskey et al., 2003). In the first of these studies (Lynskey et al., 2003), even after controlling for a variety of risk factors, early initiation of marijuana was associated with increased risk of alcohol dependence compared to a cotwin who did not endorse early initiation. Similar results were obtained in the second study (Grant et al., 2010). These findings may be due to cumulative effects of alcohol and marijuana use on the brain during developmentally sensitive periods. For example, research suggests that marijuana, too, has deleterious effects on areas of the brain associated with memory formation (Chan et al., 1998), which may play a critical role in habit development. Additionally, there is some evidence that these effects on learning and memory are heightened for adolescent users of marijuana (Cha et al., 2006; Pope et al., 2003). Due to these effects, frequent use of marijuana in adolescence may increase the risk of developing risky alcohol use behaviors, including an AUD.

Limitations
While the current study was able to provide evidence for the importance of age of initiation of regular drinking as a causal environmental influence on lifetime AUD symptoms, there were also a number of limitations. Participants’ reports of lifetime AUD symptoms as well as the ARD and AFD were retrospective, and are, therefore, subject to a number of biases. Prospective reports of such behaviors would have been preferable. Another limitation is related to inconsistencies in the literature in how “regular drinking” is defined. For the current project, regular drinking was defined as drinking at least once a month for six or more months, as has been used in a previous twin study (Grant et al., 2006). Other definitions of regular drinking that have been used in the literature, including drinking about once a week (Reifman et al., 1998), would have likely resulted in reports of different ages of initiation for some respondents. Another limitation is the use of an Australian, mostly white sample. It is unclear whether the findings of the current study would generalize to those of other nationalities or ethnicities. For example, research shows that Australia is a particularly heavy drinking country, ranking in the top twenty countries for alcohol consumption based on data from the Organization for Economic Cooperation and Development (OECD, 2018).

The cross-sectional nature of the current study did not allow for the establishment of temporal precedence for all covariates included in analyses. However, these covariates were included to provide a more rigorous test of the quasi-causal effect of early drinking on AUD symptoms by accounting for potential third variables associated with AUD that may have also played a role in discordance for onset of drinking and onset of regular drinking. As discussed earlier, some research indicates that initiation of alcohol use is associated with changes in typical patterns of personality maturation (Blonigen et al., 2015). The cross-sectional nature of the current study does not allow for an assessment of whether pre-existing personality traits
influenced risk for alcohol use or if alcohol use facilitated changes in personality instead. Similar issues exist with interpreting the effect of educational attainment. Measures of early educational achievement, including math and reading performance in elementary school, have been found to predict onset of alcohol use (Crum et al., 2006; Hill et al., 2000). However, early drinking has also been found to increase risk for dropping out of high school (Yamada, Kendix, & Yamada, 1996), and alcohol might similarly reduce completion rates at other levels of education. As the current study was cross-sectional, such bi-directional relationships cannot be ruled out.

While regular drinking was found to be causally associated with lifetime AUD symptoms, the current study did not assess contextual factors related to adolescents’ drinking. Importantly, drinking safely with adults has been found to reduce risk of problematic drinking (Bellis et al., 2007; Foley et al., 2004; Strunin et al., 2010). In fact, research with adolescents and young adults in Italy indicates that having early alcohol experiences in the context of family dinners may be protective against later alcohol use problems, including binge drinking (Strunin et al., 2010). Research in the United States and England has obtained similar results (Bellis et al., 2007; Foley et al., 2004). This suggests that early regular drinking might not always increase risk for AUD. Future research should incorporate contextual information beyond whether or not regular drinking is occurring in order to better understand risk for AUD.

Research has also suggested that cultural norms influence the alcohol socialization process, and these cultural factors are important for understanding risk associated with early drinking (Rolando et al., 2012). Contextual factors associated with early drinking may differ across a number of cultural identities, including nationality and gender. This relationship should be considered in a number of different populations, as cultural differences in the experience and
meaning of drinking among adolescents from various backgrounds may influence the
generalizability of these findings to other groups.

Conclusions

Despite the limitations of the current study, it represents a rigorous attempt to detect
causal influences of age of onset of regular drinking and age of first drink on lifetime AUD
symptoms. Age of first drink did not withstand stringent, fully adjusted models controlling for
the effects of genetic and shared environmental influences, suggesting that instead of serving as a
causal predictor of later AUD, age of first drink might be a marker of familial risk. Inconsistent
results regarding causal effects of age of first drink may be due to its correlation with regular
drinking initiation, which instead may be the key risk factor for later problem drinking, for which
age of first drink may serve as a proxy. As age of onset of regular drinking appears to be a causal
environmental influence on AUD symptom development, the findings suggest that interventions
targeting postponing the onset of regular drinking might be effective at reducing later harms
from alcohol use. Additionally, adolescent marijuana use was found to be a predictor of later
AUD, suggesting that efforts to target reductions in alcohol use could benefit from focusing on
adolescent substance use more generally.
References


Table 1.

Correlation matrix and means of study variables.

<table>
<thead>
<tr>
<th></th>
<th>1.</th>
<th>2.</th>
<th>3.</th>
<th>4.</th>
<th>5.</th>
<th>6.</th>
<th>7.</th>
<th>8.</th>
<th>9.</th>
<th>10.</th>
<th>11.</th>
<th>12.</th>
<th>13.</th>
<th>14.</th>
<th>M (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>31.86 (2.48)</td>
</tr>
<tr>
<td>2. Sex⁰</td>
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<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.64 (0.48)</td>
</tr>
<tr>
<td>3. AFD</td>
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<td>0.23</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>15.70 (2.22)</td>
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<tr>
<td>4. ARD</td>
<td>0.05</td>
<td>0.15</td>
<td>0.61</td>
<td>-</td>
<td></td>
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<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>18.21 (2.68)</td>
</tr>
<tr>
<td>5. AUD symptoms</td>
<td>-0.03</td>
<td>-0.36</td>
<td>-0.31</td>
<td>-0.33</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.76 (2.02)</td>
</tr>
<tr>
<td>6. Income</td>
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<td>-0.09</td>
<td>-0.03</td>
<td>-0.03</td>
<td>-0.05</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>8.73 (2.02)</td>
</tr>
<tr>
<td>7. Education</td>
<td>0.03</td>
<td>0.11</td>
<td>0.03</td>
<td>0.04</td>
<td>-0.17</td>
<td>0.28</td>
<td>-</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>3.32 (1.23)</td>
</tr>
<tr>
<td>8. Neuroticism</td>
<td>-0.06</td>
<td>0.16</td>
<td>0.02</td>
<td>0.00</td>
<td>0.22</td>
<td>-0.23</td>
<td>-0.10</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.60 (0.73)</td>
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<td>9. Extroversion</td>
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<td>0.02</td>
<td>-0.06</td>
<td>-0.05</td>
<td>-0.06</td>
<td>0.22</td>
<td>0.14</td>
<td>-0.53</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.54 (0.55)</td>
</tr>
<tr>
<td>10. Agreeableness</td>
<td>0.05</td>
<td>0.31</td>
<td>0.11</td>
<td>0.12</td>
<td>-0.27</td>
<td>0.02</td>
<td>0.12</td>
<td>-0.35</td>
<td>0.28</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
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<td>3.75 (0.47)</td>
</tr>
<tr>
<td>11. Openness</td>
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<td>0.06</td>
<td>-0.10</td>
<td>-0.07</td>
<td>0.03</td>
<td>0.02</td>
<td>0.27</td>
<td>0.06</td>
<td>0.13</td>
<td>0.07</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td>3.31 (0.47)</td>
</tr>
<tr>
<td>12. Conscientiousness</td>
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<td>0.17</td>
<td>0.09</td>
<td>0.07</td>
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<td>0.16</td>
<td>0.17</td>
<td>-0.42</td>
<td>0.31</td>
<td>0.27</td>
<td>-0.04</td>
<td>-</td>
<td></td>
<td></td>
<td>3.84 (0.54)</td>
</tr>
<tr>
<td>13. Regular smoking</td>
<td>0.00</td>
<td>-0.08</td>
<td>-0.29</td>
<td>-0.32</td>
<td>0.31</td>
<td>-0.16</td>
<td>-0.37</td>
<td>0.14</td>
<td>-0.10</td>
<td>-0.17</td>
<td>-0.03</td>
<td>-0.16</td>
<td>-</td>
<td></td>
<td>0.31 (0.46)</td>
</tr>
<tr>
<td>14. Marijuana use</td>
<td>-0.11</td>
<td>-0.19</td>
<td>-0.49</td>
<td>-0.50</td>
<td>0.37</td>
<td>-0.03</td>
<td>-0.19</td>
<td>0.08</td>
<td>-0.07</td>
<td>-0.17</td>
<td>0.14</td>
<td>-0.18</td>
<td>0.62</td>
<td>-</td>
<td>0.47 (0.50)</td>
</tr>
<tr>
<td>15. CD symptoms</td>
<td>-0.05</td>
<td>-0.30</td>
<td>-0.37</td>
<td>-0.34</td>
<td>0.43</td>
<td>-0.10</td>
<td>-0.29</td>
<td>0.12</td>
<td>-0.07</td>
<td>-0.28</td>
<td>0.03</td>
<td>-0.20</td>
<td>0.50</td>
<td>0.48</td>
<td>0.88 (1.35)</td>
</tr>
</tbody>
</table>

Note: AFD = age of first drink; ARD = age of initiation of regular drinking; AUD = alcohol use disorder symptoms; CD = conduct disorder, M = mean, SD = standard deviation. Bold indicates significance (p < 0.05).

⁰ = coded as ‘0’ = male, ‘1’ = female
Table 2.

Results from zyosity-limited fully adjusted multilevel models predicting alcohol use disorder symptoms.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Regular Drinking Initiation</th>
<th>Age of First Drink</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DZ</td>
<td>MZ</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WP ARD</td>
<td>0.95</td>
<td>0.94</td>
</tr>
<tr>
<td>BP ARD</td>
<td>0.92</td>
<td>0.93</td>
</tr>
<tr>
<td>WP AFD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BP AFD*Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WP Income</td>
<td>0.99</td>
<td>1.01</td>
</tr>
<tr>
<td>BP Income</td>
<td>0.98</td>
<td>0.98</td>
</tr>
<tr>
<td>WP Education</td>
<td>1.05</td>
<td>1.05</td>
</tr>
<tr>
<td>BP Education</td>
<td>0.93</td>
<td>1.02</td>
</tr>
<tr>
<td>WP Neuroticism</td>
<td>1.38</td>
<td>1.11</td>
</tr>
<tr>
<td>BP Neuroticism</td>
<td>1.42</td>
<td>1.54</td>
</tr>
<tr>
<td>WP Agreeableness</td>
<td>0.81</td>
<td>0.76</td>
</tr>
<tr>
<td>BP Agreeableness</td>
<td>0.81</td>
<td>0.95</td>
</tr>
<tr>
<td>WP Extroversion</td>
<td>1.40</td>
<td>1.17</td>
</tr>
<tr>
<td>BP Extroversion</td>
<td>1.45</td>
<td>1.23</td>
</tr>
<tr>
<td>WP Conscientiousness</td>
<td>0.90</td>
<td>0.93</td>
</tr>
<tr>
<td>BP Conscientiousness</td>
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<td>0.89</td>
</tr>
<tr>
<td>WP Openness</td>
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<td>0.86</td>
</tr>
<tr>
<td>BP Openness</td>
<td>0.98</td>
<td>0.89</td>
</tr>
<tr>
<td>WP CD Symptoms</td>
<td>1.14</td>
<td>1.03</td>
</tr>
<tr>
<td>BP CD Symptoms</td>
<td>1.12</td>
<td>1.03</td>
</tr>
<tr>
<td>WP Regular Smoking</td>
<td>1.08</td>
<td>0.88</td>
</tr>
<tr>
<td>BP Regular Smoking</td>
<td>1.11</td>
<td>0.88</td>
</tr>
<tr>
<td>WP Marijuana Use</td>
<td>1.10</td>
<td>1.10</td>
</tr>
<tr>
<td>BP Marijuana Use</td>
<td>1.47</td>
<td>1.10</td>
</tr>
</tbody>
</table>

Note: Bold indicates significance. WP = within-twin pair, BP = between-twin pair, ARD = age of regular drinking initiation, AFD = age of first drink, CD = conduct disorder.
Figure 1. Forest plots of models examining regular drinking initiation as a predictor of alcohol use disorder (AUD) symptoms (left) and age of first drink as a predictor of AUD symptoms (right). Adjusted models refer to fully adjusted models including all covariates. DZ = dizygotic twins, MZ = monozygotic twins, IRR = incident rate ratio. * indicates inclusion of within-twin pair x sex effect.
Supplemental Materials for
Comparing the Potential Causal Influence of Two Indicators of Early Alcohol Use on Later Alcohol Use Disorder Symptoms
Christal N. Davis, Wendy S. Slutske, Thomas M. Piasecki, Nicholas G. Martin, Arpana Agrawal, & Michael T. Lynskey

Contents:

1) Probing the significant sex-by-within-twin pair effect of age of first drink

2) Age of first drink analyses including all drinkers

3) Supplemental Figure S1. Forest plots of models examining age of first drink as a predictor of alcohol use disorder symptoms among males and females.

4) Supplemental Figure S2. Forest plots of models examining age of first drink as a predictor of alcohol use disorder symptoms among all ever drinkers and only regular drinkers.
Sex Differences in the Effects of Age of First Drink on Lifetime AUD Symptoms

Upon discovering evidence for a significant sex-by-within-twin pair age of first drink (AFD) interaction in the base model restricted to MZ twins, sex-specific analyses were conducted in a similar fashion as those in the main manuscript in order to probe this finding. Model results are presented in Supplemental Figure 1.

Individual Level Analyses

Among women, the base model run at the individual level indicated that AFD significantly predicted AUD symptoms, such that early AFD was associated with elevated symptoms (IRR = 0.88 [0.85 – 0.90]; see Figure S1). Similarly, among men an earlier AFD was associated with increased rates of AUD symptomatology (IRR = 0.91 [0.89 – 0.94]). After accounting for all covariates, this effect remained for women only (IRR = 0.92 [0.89 – 0.94]). Among men, there was no evidence for an effect of AFD on lifetime AUD symptoms (IRR = 0.97 [0.95 – 1.00]).

Cotwin Control Analyses

Cotwin control analyses were first conducted including only DZ twins. Base models provided evidence for a quasi-causal effect of AFD on lifetime AUD symptoms among men only (IRR = 0.92 [0.87 – 0.99]). Among women, this quasi-causal effect was not significant (IRR = 0.93 [0.86 – 1.00]). Between-twin pair, or familial level effects of AFD were significant for both men and women, however (men: IRR = 0.86 [0.81 – 0.91]; women: IRR = 0.85 [0.81 – 0.90]).

After adjusting for covariates, the within-twin pair effect of AFD was now significant only among women (IRR = 0.92 [0.86 – 0.99]). Neuroticism (IRR = 1.47 [1.16 – 1.85]), extroversion (IRR = 1.36 [1.05 – 1.76]), and conduct disorder symptoms (IRR = 1.17 [1.03 – 1.33]) also exhibited quasi-causal effects on lifetime AUD symptoms among women. A number
of familial level influences were also significant (neuroticism: \( \text{IRR} = 1.27 \ [1.04 \text{–} 1.55] \), extroversion: \( \text{IRR} = 1.42 \ [1.14 \text{–} 1.78] \), agreeableness: \( \text{IRR} = 0.72 \ [0.55 \text{–} 0.95] \), conscientiousness: \( \text{IRR} = 0.74 \ [0.58 \text{–} 0.93] \), regular smoking: \( \text{IRR} = 1.34 \ [1.01 \text{–} 1.77] \), and persistent adolescent marijuana use: \( \text{IRR} = 1.65 \ [1.25 \text{–} 2.18] \)). Between-twin pair effects of AFD were not significant, however (\( \text{IRR} = 0.95 \ [0.89 \text{–} 1.01] \)).

Among men, neither within- or between-twin pair effects of AFD reached significance (within: \( \text{IRR} = 0.96 \ [0.90 \text{–} 1.03] \); between: \( \text{IRR} = 0.95 \ [0.88 \text{–} 1.01] \)). Instead, within-and between-twin pair effects of neuroticism (within: \( \text{IRR} = 1.39 \ [1.13 \text{–} 1.71] \); between: \( \text{IRR} = 1.67 \ [1.33 \text{–} 2.09] \)), extroversion (within: \( \text{IRR} = 1.50 \ [1.23 \text{–} 1.83] \); between: \( \text{IRR} = 1.44 \ [1.12 \text{–} 1.85] \)), and conduct disorder symptoms (within: \( \text{IRR} = 1.13 \ [1.02 \text{–} 1.25] \); between: \( \text{IRR} = 1.16 \ [1.06 \text{–} 1.27] \)) contributed to risk for development of AUD symptoms among men.

Finally, the sample was restricted to MZ twins only where a significant sex-by-within-twin AFD interaction was initially observed in mixed-sex analyses (see manuscript pg. 15). The quasi-causal effect of AFD on lifetime AUD symptoms was significant for women only in the base model (\( \text{IRR} = 0.92 \ [0.86 \text{–} 0.98] \)), with no evidence for a causal effect of AFD on development of AUD symptoms among men (\( \text{IRR} = 1.05 \ [0.99 \text{–} 1.12] \)). However, between-twin pair effects of AFD were significant for both men and women (men: \( \text{IRR} = 0.84 \ [0.77 \text{–} 0.92] \); women: \( \text{IRR} = 0.87 \ [0.81 \text{–} 0.93] \)). After controlling for all covariates, the quasi-causal effect of AFD on lifetime AUD symptoms became nonsignificant among women (\( \text{IRR} = 0.94 \ [0.88 \text{–} 1.01] \)) and remained nonsignificant among men (\( \text{IRR} = 1.07 \ [0.99 \text{–} 1.14] \)). There was also no evidence for familial level effects of AFD on AUD symptoms among men or women (men: \( \text{IRR} = 0.97 \ [0.89 \text{–} 1.06] \); women: \( \text{IRR} = 0.96 \ [0.90 \text{–} 1.02] \)). In the fully adjusted model, just one quasi-causal predictor remained significant among women: persistent adolescent marijuana use
Among men, agreeableness was the only predictor quasi-causally associated with lifetime AUD symptoms (IRR = 0.68 [0.51 – 0.91]).

**Discussion**

Sex specific analyses exploring a finding of a significant sex-by-within-twin pair AFD interaction suggested that AFD might be a more useful indicator of risk for AUD development among women compared to men. In the base model restricted to MZ twins, which controls for genetic and shared environmental influences that may potentially confound any effect, AFD only predicted AUD symptoms among women. However, even this effect diminished once additional covariates were included in analyses, providing no evidence for a causal effect of AFD on AUD among men or women. AFD may instead act as a more general marker of substance abuse susceptibility among women, for whom an early age of first drink may be more deviant as compared to men, who are subject to less restrictive social and cultural norms surrounding drinking (Schulte, Ramo, & Brown, 2009). If AFD were a marker of more general liability among women, this would explain why the inclusion of other predictors associated with substance abuse would render the effect of AFD nonsignificant among women.

While AFD was not a causal predictor of AUD symptoms among men or women, there was evidence for a causal effect of low agreeableness among men and persistent adolescent marijuana use among women. These predictors were also significant in the mixed-sex analyses; however, additional analyses limited to just men or just women revealed that sex-specific effects might drive these causal findings. Recent research has found that sex moderates the effects of alcohol use initiation on personality (Blonigen et al., 2015), and personality may also operate differently to influence risk for AUD in men and women. Among men, clinical interventions might seek to encourage adult roles that will facilitate changes in personality that have been
associated with “maturing out” from alcohol use (Littlefield, Sher, & Wood, 2009). For women, these results could also have practical implications for developing prevention and intervention strategies. Targeting delaying all substance use might lessen risk for developing AUD symptoms in the future. The sex-specific nature of these findings should be explored in future research, as personality characteristics may be more important for influencing risk for AUD among men, while early substance use may play a larger role in the development of alcohol problems among women.

**Age of First Drink Analyses Including All Drinkers**

Additional analyses were conducted including individuals who initiated drinking but had not progressed to regular drinking, with a resulting sample size of 3,258 individual twins (MZF = 963, MZM = 473, DZF = 729, DZM = 363, OS = 730). Models were ran in this full sample to determine whether restricting the sample to regular drinkers may have influenced findings on the effects of age of first drink (AFD). However, results from this full sample were nearly identical to those obtained among the regular drinking subsample.

Base models at the individual level indicated that those with a lower AFD had increased rates of AUD symptoms (IRR = 0.87 [0.86 – 0.89]). Similar to the sample restricted to regular drinkers, there was evidence for a significant interaction of AFD with sex, whereby there was evidence of an increased effect of early onset drinking among women (IRR = 1.05 [1.01 – 1.09]). After adjusting for all covariates, the effect of AFD remained (IRR = 0.90 [0.87 – 0.92]). Cotwin control analyses restricted to DZ twins also provided evidence for a quasi-causal effect of AFD on AUD symptom counts after accounting for covariates (IRR = 0.93 [0.89 – 0.98]). There was also evidence for a familial effect of AFD on AUD symptom counts (IRR = 0.92 [0.88 – 0.96]). Finally, after restricting the sample to MZ twins and adjusting for all covariates, there was no evidence for an effect of AFD on lifetime AUD symptom counts (IRR = 0.95 [0.89 – 1.01]).
However, the familial effect of AFD remained (IRR = 0.90 [0.86 – 0.95]). A graphical comparison of these results to those from the regular drinking subsample is presented in Supplemental Figure 2.

These results indicate that restricting the sample to regular drinkers only did not have significant effects on model findings. Even after including all ever drinkers, there was no evidence for a quasi-causal effect of AFD on lifetime AUD symptom counts in the most stringent model accounting for all genetic and shared environmental confounds.

References


Figure S1.

Forest plots of models examining age of first drink as a predictor of alcohol use disorder (AUD) symptoms among males (left) and females (right). Adjusted models refer to fully adjusted models including all covariates. DZ = dizygotic twins, MZ = monozygotic twins, IRR = incident rate ratio.
Forest plots of models examining age of first drink (AFD) as a predictor of alcohol use disorder (AUD) symptoms among all ever drinkers (left) and only regular drinkers (right). Adjusted models refer to fully adjusted models including all covariates. DZ = dizygotic twins, MZ = monozygotic twins, IRR = incident rate ratio. * indicates that a significant sex*AFD interaction was included.