RUNNING HEAD: SEVERITY OF ADOLESCENT ONSET OF AUD BY GENDER

Tables: 2

Figures: 4

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The trajectory of psychiatric problems following an adolescent vs. young adult onset of alcohol
use disorder

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Acknowledgement: This work was supported by the National Institute on Alcohol Abuse and Alcoholism grants (F31AA023121, Foster; R01AA009367, McGue) and the National Institute on Drug Abuse grants (R37 DA005147, Iacono; R01DA034606, Hicks).

Abstract

BACKGROUND: Alcohol use disorder (AUD) most often onsets in young adulthood (YAO), but prospective studies are needed to determine whether an onset in adolescence (AO) confers a more severe trajectory of psychiatric problems (e.g., depression, antisocial behavior, and other substance use) alongside AUD in men and women.

METHODS: Using a prospective approach, we compared the trajectories of psychiatric problems for men and women with an AO, a YAO, and no history of AUD from ages 17 to 29 years old.

RESULTS: Both gender and AUD onset moderated linear and non-linear changes in problems from adolescence to adulthood. AO conferred the poorest adolescent and young adult adjustment relative to the same-gender control and YAO groups. Critically, onset groups were more distinct among men (i.e., $AO > YAO > \text{no AUD}$) than women (i.e., $AO = YAO > \text{no AUD}$).

CONCLUSIONS: Adolescent onset of alcohol problems portends severe, broad spread problems for both men and women into adulthood. Critically, adolescent onset yields the worst psychiatric problems among men (vs. YAO) while women experience severe, persistent problems across domains irrespective of onset timing. For both genders, mitigating the long-term, cascade of problems that accompany AUD will require special attention to heterogeneity in the timing of its onset and acceleration of psychiatric problems thereafter.

KEYWORDS: alcohol use disorder; adolescence; young adulthood; onset; gender

1. Introduction

Alcohol use disorder (AUD) is among the most prevalent and disabling psychiatric problems worldwide (World Health Organization, 2015). Increasingly, AUD is conceptualized as a developmental disorder understood in the context of the broader life course. Developmentally, alcohol use first emerges in middle to late adolescence, escalate through young adulthood, and then decline through middle and later adulthood (Chassin et al., 2004; Chen and Kandel, 1995; Johnstone et al., 1996). While an adolescent onset (AO) of AUD may emerge as early as age 13 (Babor et al., 1992; Clark et al., 1998; Cloninger, 1987; Zucker, 1994), systematic study of early risks and consequences for AUD is limited by low cumulative prevalence until later adolescence (i.e., cumulative prevalence of 12.2% by age 17; Costello et al., 2003). Despite its low prevalence during adolescence, an AO of AUD has been used as a typological marker for severe subtype accompanied by multiple psychiatric problems (Babor et al., 1992; Cloninger, 1987; Hicks et al., 2010; Rohde et al., 2001; Skogen et al., 2015; Zucker, 1994). However, the developmental trajectory of psychiatric problems associated with AO has not been clearly differentiated from that of a young adulthood onset of AUD (YAO) in both genders, obscuring the relative prognostic value that can be attributed to each onset type. Previous work has linked retrospective report of early onset with more severe problems, but few studies apply a longitudinal approach that tracks individuals across development as problems unfold.

1.1 Differentiating Adult Outcomes of AUD by Timing of Onset

Relative to YAO, AO may be associated with more severe psychiatric problems for several reasons. More initial risk exposure may be required for the disorder to emerge at a younger age, potentiating problems across numerous other domains of psychosocial functioning (Caspi et al., 1995; Kim et al., 2017; Krueger et al., 2002; Maggs et al., 2008; Masse and

Tremblay, 1997; Moffitt and Caspi, 2001; Rutledge and Sher, 2001; Slutske et al., 2002).

Concomitantly, the toxicity of heavy alcohol exposure poses a threat to psychosocial skill development and neurological maturation in adolescence (Patrick and Schulenberg, 2013; Squeglia et al., 2015). Children who are disinhibited, aggressive, and have attention problems and poor social skills may experience high levels of rejection from pro-social peers and harsh treatment from socializing agents like teachers and parents (Dishion et al., 1991; Granic and Patterson, 2006; Tangney et al., 2004). As these negative experiences accumulate, deviant peer affiliation increases (Kim et al., 2017; Owens and Bergman, 2010), introducing both positive and negative social reinforcement for alcohol use and perpetuating risk for heavy alcohol use and physiological dependence. Importantly, adolescent AUD may disrupt the acquisition of social and emotional regulation skills, perpetuating social alienation, deviant peer affiliation, and negative affect. Consequently, adolescents with AUD face diminished psychological resources and lack pro-social influences, resulting in the emergence and persistence of psychiatric problems (e.g., depressive symptoms; Skogen et al., 2015).

In contrast, a YAO of AUD may confer less risk for long-term psychiatric problems. First, those with a YAO may have experienced limited risk exposures relative to AO during childhood and adolescence (Hicks et al., 2010; Rutledge and Sher, 2001; Schuckit and Smith, 2011). Second, more time has elapsed prior to AUD onset for neurological and psychosocial maturation to occur that can help buffer the negative effects of AUD. Finally, the timeframe for accumulating consequences of AUD before adulthood (e.g., by age 30) is substantially narrowed. Alternatively, YAO may be associated with more psychiatric problems in adulthood due the greater recency of acute symptoms. Few prospective studies have modeled these effects, thus it is necessary to compare initial adolescent risk exposure and adult consequences to determine the

relative severity of AUD onset for these developmental periods.

1.2 Gender Differences in Proximal and Distal Outcomes for AUD

There are known gender differences in AUD and its associated problems, foregrounding the importance of gender comparisons in the study of AUD severity. Namely, although women exhibit a lower prevalence of AUD overall (Keyes et al., 2008), women who do exhibit major risk factors for AUD (e.g., heavy alcohol and substance use, externalizing problems; Foster et al., 2015) are at increased risk for developing AUD compared to men (Sannibale and Hall, 2001). Furthermore, despite typically later onset of drinking, some evidence suggests that women who develop AUD experience a more rapid and severe course of the disorder compared to men (i.e., telescoping; Hernandez-Avila et al., 2004; Randall et al., 1999) and some refutes the presence of this effect in the general population (Keyes et al., 2010). Consequently, features of the disorder – like onset age – may have uncertain or relatively less prognostic value for predicting AUD severity in women than men. Additionally, some risks appear to be gender-specific such that AUD has a stronger association with some psychosocial problems in women than men (e.g., internalizing problems; Foster et al., 2015; Pedrelli et al., 2016). Though gender differences in AUD are well-documented, no study has examined whether gender moderates AUD onset differences (i.e., AO vs. YAO) in the developmental course of psychiatric problems.

1.3 Gender Differences in Proximal and Distal Outcomes for AUD

We tested whether alcohol problems (i.e., AO of AUD) that develop during adolescence are associated with a more severe trajectory of psychiatric problems in the decade that follows. Additionally, we test whether this adolescent marker for adult problems differs in prognostic value for adolescent boys and girls. To address this, we used an individual differences framework to compare the trajectory of psychiatric problems from age 17 to 29 years old among

men and women with an AO vs. YAO to same-gender controls with no AUD history. Age-related changes in alcohol use, other drug use problems, depression symptoms, and antisocial behavior were modeled between onset groups during this developmental period to capture the aggregation of risk across these groups from earliest onset of AUD, through its peak prevalence in the early 20s, and into young adulthood, when risks typically stabilize and the rates of AUD decline (Chassin et al., 2004; Chen and Kandel, 1995; Johnstone et al., 1996). We hypothesized that AO would be a greater risk factor for adult impairment than a more recent onset (i.e., YAO). That is, we expected age-related changes in psychiatric problems for the AO group to deviate more from same-gender controls than the YAO group. Compared to men, we hypothesized that women in both AUD onset groups would exhibit a faster remission of psychiatric problems from age 17 to age 29 but continue to exhibit significantly higher levels of impairment when compared to same-gender controls.

2. Materials and Methods

2.1 Sample

Participants were male ($n=578$) and female ($n=674$) twins of the Minnesota Twin Family Study (MTFS), a prospective, community sample designed to map the etiology of substance use disorders (Iacono et al., 1999). Following Institutional Review Board approval, twin pairs born between the years of 1972 and 1979 were identified via Minnesota public birth records. Of the 90% of families located, 83% completed the in-person laboratory assessment at the University of Minnesota. Participants predominately reported non-Hispanic White (96%) ethnicity and race and were similar to non-participating families on parental occupation, education, and history of psychological treatment.

2.2 Assessment

Participants were assessed for lifetime alcohol and other substance use disorders along with several other psychiatric, psychosocial, and environmental variables at age 17. Follow-up assessments were conducted every 3-5 years at the target ages of 20 ($n=1110$, 89% retention rate, 83% of men and 93% of women), 24 ($n=1159$, 92% retention rate, 94% of men and 91% of women) and 29 years old ($n=1164$, 93% retention rate, 91% of men and 94% of women). Each assessment covered the time period since the last assessment and the same measures of mental health were used at each assessment.

2.2.1 AUD Diagnosis and Onset

Using DSM-III-R and later DSM-IV criteria, AUD status was assessed using the Substance Abuse Module (SAM; Cottler et al., 1989) of the Composite International Diagnostic Interview (Robins, 1988) at the target ages of 17, 20, 24 and 29 years old. Consistent with the current DSM-5 criteria, two or more alcohol abuse or dependence symptoms were coded as a positive AUD diagnosis for each assessment through age 29 (lifetime AUD: males, $n=316$; females, $n=155$). While these lifetime prevalence rates exceed those typically for epidemiological surveys, they reflect the advantages of using multiple, prospective assessments for capturing the lifetime prevalence of psychiatric problems (Hamdi and Iacono, 2014). Furthermore, multiple studies using the MTF sample have demonstrated the validity of this approach (Elkins et al., 2004, 2006, 2007).

Those with AUD at age 17 were classified as an AO and those who met criteria for the first time at either ages 20 or 24 were classified as YAO (Foster et al., 2014; Hicks et al., 2010). Of those with any onset of AUD by age 24, 40% were classified as AO. YAO was the more common onset type for both genders (i.e., 56% of women and 70% of men with AUD had YAO) and AO was more common in women than men (i.e., 44% of women and 30% of men with AUD

had AO). Each AUD onset group was compared to a same-gender control group that exhibited fewer than two symptoms of AUD at each assessment.

2.2.2 Psychiatric problems

We modeled differences in age-related change across several psychiatric domains. First, an alcohol use composite was calculated using average quantity consumed over the past year and the maximum number of drinks consumed in 24 hours. A composite for drug use problems included DSM-III-R and -IV criteria for both nicotine dependence and abuse/dependence for illicit drugs across the drug classes of amphetamines, cannabis, cocaine, hallucinogen, inhalant, opioid, PCP, and sedatives. The illicit drug class with the highest number of symptoms endorsed was used to quantify each participant's abuse/dependence status for illicit substances. Other indicators of drug use problems included frequency of marijuana use and the number of different drug classes tried. Composites were computed as the mean z-score across the constituent variables and then converted to age-centered T-scores to facilitate interpretation. Other psychiatric variables included counts of DSM-IV symptoms of major depression and the adult criteria for antisocial personality disorder.

2.3 Statistical Analysis

Multilevel modeling (MLM) was used to estimate the degree to which gender, AUD onset, and their interaction accounted for variability in age-related change for each of the four variables from age 17 to age 29. For the current analyses, three levels of data were represented in the MLM equation: repeated observations (level-1) were nested within individuals (level-2) who were also nested within families (level-3). MLM has been identified as particularly useful for adjustment of standard errors and *p*-values when data have a nested structure (Hox, 2010; Raudenbush and Bryk, 2002).

For each dependent variable, we fit an MLM using HLM 7.0 software. Alcohol and drug composites were modeled via normal distribution since their residuals were normally distributed and count distribution models were used to account for zero-inflation in psychiatric symptom data. Each model estimated parameters for the linear and quadratic effects of age (i.e., change in the variable since the age 17, baseline assessment) along with the independent and moderating fixed effects of explanatory variables at level-2 (i.e., gender and AUD onset) on variability in the longitudinal observations at level-1 (i.e., intercept, age, and age²). Including actual age as an effect in the MLM models controlled for individual differences in age at each assessment. In addition to gender (i.e., coded as 0 for women and 1 for men), AUD group differences were estimated through inclusion of two orthogonal contrasts (i.e., dummy-coded variables) comparing control versus YAO groups (coded as 0 for those in the AO group, -1 for control, + 1 for YAO) and the AO versus YAO groups (coded as 0 for the control group, -1 for YAO, and +1 for AO). Interactions between the dummy codes for gender and AUD onset group contrasts were then added to estimate their effects on variability in the linear and quadratic effects of age for the dependent variable. A random effect for the intercept was also included to account for variation between families at level-3 of the model.

3. Results

Means and standard deviations by AUD onset group and gender are presented for each outcome at each in Table 1. Parameter estimates for the MLM models are presented in Table 2. Figures 1-4 plot the model-predicted effects by gender and AUD onset. In Table 2, Level-1 parameters (i.e., age effects) are presented on the left and level-2 parameters (i.e., main effects and interactions of Gender and AUD onset group) are presented on the right. Level-2 parameter effects are split into 3 columns. The “predicting intercept” column provides the effect of the

level-2 parameter while the subsequent two columns present estimates of each level-2 parameter's influence on the linear (i.e., "predicting age") and quadratic (i.e., "predicting age²") effects of age. For each model, we begin with a review of the linear and quadratic effects of age and then discuss the pattern of effects for gender, AUD onset group contrasts, and their interactions. Effects from the table are also reported in the discussion of the first variable to facilitate clear use of the table for interpreting results.

3.1 Alcohol use

Model estimated effects for alcohol use are presented in Figure 1 with parameter coefficients, standard error, and significance noted in Table 2. Alcohol use increased with age ($\beta=2.25, p<0.001$) and decelerated ($\beta=-0.16, p<0.001$) significantly between age 17 and age 29. Within each gender, mean-levels of alcohol use followed a pattern of Control < YAO < AO. At age 17, alcohol use was significantly higher in men than women ($\beta=1.11, p<0.01$) with subsequent increases ($\beta=0.79, p<0.001$) and deceleration ($\beta=-0.16, p<0.001$) in alcohol use also significantly faster for men than women. With respect to AUD onset, alcohol use followed a similar pattern (i.e., Control < YAO < AO; control vs. YAO: $\beta=8.48, p<0.001$; AO vs. YAO: $\beta=11.46, p<0.001$). Increases in alcohol use with age were similar between the YAO and control groups ($\beta=0.15, p>0.05$). Compared to the AO group, the YAO group exhibited faster age-related increases ($\beta=1.67, p<0.001$) and deceleration ($\beta=0.09, p<0.001$) in alcohol use.

Gender significantly moderated the effect of AUD onset on both the intercept and age-related change in alcohol use through young adulthood. Compared to women, group differences in the intercept at age 17 between the YAO-control groups ($\beta=1.83, p<0.001$) and AO-YAO groups ($\beta=2.78, p<0.001$) were greater in men. Additionally, differences in the linear increases ($\beta=0.32, p<0.05$) and quadratic ($\beta=-0.03, p<0.05$) decreases between YAO and control groups

were greater for men than women. Gender did not moderate AO-YAO group differences in the rate of change ($\beta=0.02$, $p>0.05$) or deceleration of alcohol use ($\beta=-0.01$, $p>0.05$).

3.2 Drug use problems

Model estimated effects for drug use problems are presented in Figure 2 with parameter coefficients, standard error, and significance noted in Table 2. Drug use problems increased and decelerated significantly between age 17 and age 29. Within each gender, the magnitude of drug use problems generally followed a similar pattern to alcohol use of Control < YAO < AO. At age 17, drug use problems were significantly higher in women than men with subsequent increases and deceleration in drug use problems significantly faster for men than women. With respect to AUD onset, drug use problems similarly increased and decelerated at a faster rate for the YAO than the control group. Drug use problems increased at a similar rate for the YAO and AO groups, but problems reduced at a faster rate for the AO than the YAO group.

Gender significantly moderated the effect of AUD onset on both the intercept and age-related change in drug use problems through young adulthood. At age 17, women exhibited larger YAO-control group differences in drug problems compared to men but AO-YAO group differences were similar for men and women. However, both AUD onset groups exhibited more distinct age-related change in drug problems (vs. control) in men than in women.

3.3 Major depression symptoms

Model estimated effects for depression symptoms are presented in Figure 3 with parameter coefficients, standard error, and significance noted in Table 2. There was a non-linear increase in depression symptoms with age. For women, the magnitude of depression symptoms generally followed a pattern of Control = YAO < AO. By contrast, AUD onset did not appear to differentiate levels of depression in men. At age 17, depression symptoms were significantly

higher in women than men, but these initial differences were not accompanied by gender differences in age-related change. With respect to AUD onset, depression symptoms were higher in the AO than YAO group at age 17, but these differences were not accompanied by subsequent differences in age-related change. In contrast to the other outcomes measured, gender did not significantly moderate the effect of AUD onset on either the intercept at age 17 or age-related change in depression symptoms through young adulthood.

3.4 Adult antisocial behavior symptoms

Model estimated effects for antisocial behavior symptoms are presented in Figure 4 with parameter coefficients, standard error, and significance noted in Table 2. Antisocial behavior increased from age 17 to the mid-20's and then declined to age 29. Within each gender, mean-levels of antisocial behavior followed a pattern of Control < YAO < AO. At age 17, antisocial behavior was significantly higher in men than women, but these initial differences were not accompanied by gender differences in age-related change in antisocial behavior. With respect to AUD onset, significant differences in symptoms followed a pattern of Control < YAO < AO. Age-related linear increases in antisocial behavior followed a similar pattern wherein the YAO group had significantly faster increases in symptoms than the control group, and the AO group had significantly faster increases in symptoms than the YAO group. Rates of deceleration in antisocial behavior were similar between the YAO and control groups while significantly faster decline in symptoms was observed in the YAO as compared to the AO group.

4. Discussion

We tested whether an AO vs YAO of AUD and gender influenced trajectories of psychiatric and substance use problems from age 17 to 29 years old. Alcohol use was consistently higher among men than women across nearly all groups at each age assessed.

Despite being associated with lower risk for AUD than AO, a YAO was still preceded by significantly elevated psychiatric problems even though AUD would not onset for another 3-7 years. Among men, psychiatric and substance use problems typically followed a pattern of $\text{Control} < \text{YAO} < \text{AO}$. Importantly, these patterns link AO with uniquely high risk for psychiatric problems that persist through adulthood, even relative to cases of YAO that developed more proximally to adult problems. Despite a generally lower absolute peak on nearly all variables relative to men (except for depression symptoms), women typically exhibited a pattern of $\text{Control} < \text{YAO} = \text{AO}$ through young adulthood, wherein longer-term psychiatric problems were equally likely for AO and YAO. Depression symptoms were uniquely elevated for women with AUD while all other groups reported no elevation or age-related increases in this factor.

Following adolescence, psychiatric symptoms tended to decline from age 24 to age 29, with the fastest rates of ostensible decline in problems observed for women and those with an AO. However, these rates should be carefully interpreted. First, initially higher levels of adolescent problems for the AO group (vs. YAO) required a larger overall reduction of problems to return to levels comparable to controls. For men and women, AO was linked with the persistence of psychiatric problems into adulthood. Second, while women also exhibited relatively faster rates of recovery during this period, AO and YAO conferred similar levels of impairment for young adult women relative to same-gender controls. Taken together, these findings caution solely using improvement in alcohol and substance use or psychiatric problems as an index of recovery since these metrics omit key information about the relative severity of the disorder that is associated with its onset.

While AUD onset appeared to have less prognostic value in women due to generally more uniform severity of AO and YAO groups of women (vs. Controls), depression appears to exhibit a unique relationship with AUD in women. Women with AUD exhibited significant, sustained elevation in depression relative to gender-matched controls, suggesting that depression symptoms are both an early risk and long-term consequence for AUD in this group. Further, depression symptoms were highest among women with an AO (e.g., control < YAO < AO). By contrast, depression was only elevated for men among those with an AO suggesting that depression may be a distinguishing feature of early AUD symptoms in men, despite its lower overall base rate among men relative to women. While the causal relationship between depression symptoms and AUD in women remains unclear, the current results reflect a gender-specific association between depression symptoms and AUD in women consistent with previous research on binge drinking (Dir et al., 2017). Importantly, gender-specific heterogeneity in the presence and nature of this effect may explain why prior work evaluating the link between internalizing problems and AUD onset in gender mixed samples has been mixed (Farmer et al., 2016).

Certain limitations temper the impact of our findings. For example, findings in our predominately White sample may not extend to other racial or ethnic groups. We were not able to establish causality in the present analyses; preexisting problems may potentiate a particular AUD onset, which may then undergird the subsequent trajectory of psychiatric problems. However, our findings provide evidence of between-person variation in the aggregation of problems and these trajectories provide clinically meaningful information about both the proximal and distal implications of various psychiatric problems in adolescence.

5. Conclusions

The current study advances prior literature in the following ways. First, we characterized proximal and distal developmental consequences of an adolescent vs. young adult onset of AUD in men and women. While prior reports have identified risks specific to adolescents, no study to date has tracked these consequences prospectively to compare the severity of adult outcomes for AUD in men and women that are uniquely associated with an AO. Despite the closer temporal proximity of YAO to adulthood, an AO of AUD was associated with a more severe trajectory of psychiatric problems in the transition to adulthood in men and women, signaling the significant and unique long-term costs associated with alcohol problems during early development. Second, our approach leverages person-specific developmental differences (i.e., the timing of AUD onset) to account for differences in AUD severity. Results support differences in prognosis and treatment needs in the decade following adolescence. Given the well-documented heterogeneity of AUD subtypes, these findings may assist in guiding person-centered clinical decision-making to increase the efficacy of AUD interventions.

References

- Babor, T., Hofmann, M., Delboca, F., Hesselbrock, V., Meyer, R., Dolinsky, Z., and Rounsaville, B. (1992). Types of Alcoholics. 1. Evidence for an empirically derived typology base on indicators of vulnerability and severity. *Archives of General Psychiatry*, 49(8), 599–608.
- Caspi, A., Henry, B., McGee, R. O., Moffitt, T. E., and Silva, P. A. (1995). Temperamental Origins of Child and Adolescent Behavior Problems: From Age Three to Age Fifteen. *Child Development*, 66(1), 55–68. doi: 10.1111/j.1467-8624.1995.tb00855.x
- Chassin, L., Flora, D., and King, K. (2004). Trajectories of alcohol and drug use and dependence from adolescence to adulthood: the effect of familial alcoholism and personality. *Journal of Abnormal Psychology*, 113, 483–498.
- Chen, K., and Kandel, D. B. (1995). The natural history of drug use from adolescence to the mid-thirties in a general population sample. *American Journal of Public Health*, 85(1), 41–47. doi: 10.2105/AJPH.85.1.41
- Clark, D. B., Kirisci, L., and Tarter, R. E. (1998). Adolescent versus adult onset and the development of substance use disorders in males. *Drug and Alcohol Dependence*, 49(2), 115–121. doi: 10.1016/S0376-8716(97)00154-3
- Cloninger, C. R. (1987). Neurogenetic adaptive mechanisms in alcoholism. *Science*, 236(4800), 410–416.
- Costello, E. J., Mustillo, S., Erkanli, A., Keeler, G., and Angold, A. (2003). Prevalence and Development of Psychiatric Disorders in Childhood and Adolescence. *Archives of General Psychiatry*, 60(8), 837–844. doi: 10.1001/archpsyc.60.8.837

- Cottler, L., Robins, L., and Helzer, J. (1989). The Reliability of the CIDI-SAM: a comprehensive substance abuse interview. *Addiction*, 84(7), 801–814. doi: 10.1111/j.1360-0443.1989.tb03060.x
- Dir, A. L., Bell, R. L., Adams, Z. W., and Hulvershorn, L. A. (2017). Gender Differences in Risk Factors for Adolescent Binge Drinking and Implications for Intervention and Prevention. *Frontiers in Psychiatry*, 8, 289. Frontiers Media SA. doi: 10.3389/fpsyt.2017.00289
- Dishion, T. J., Patterson, G. R., Stoolmiller, M., and Skinner, M. L. (1991). Family, school, and behavioral antecedents to early adolescent involvement with antisocial peers. *Developmental Psychology*, 27(1), 172–180. doi: 10.1037/0012-1649.27.1.172
- Elkins, I. J., King, S. M., McGue, M., and Iacono, W. G. (2006). Personality traits and the development of nicotine, alcohol, and illicit drug disorders: Prospective links from adolescence to young adulthood. *Journal of Abnormal Psychology*, 115(1), 26–39. doi: 10.1037/0021-843X.115.1.26
- Elkins, I. J., McGue, M., and Iacono, W. G. (2007). Prospective effects of attention-deficit/hyperactivity disorder, conduct disorder, and sex on adolescent substance use and abuse. *Archives of General Psychiatry*, 64(10), 1145–52. doi: 10.1001/archpsyc.64.10.1145
- Elkins, I. J., McGue, M., Malone, S., and Iacono, W. G. (2004). The effect of parental alcohol and drug disorders on adolescent personality. *The American Journal of Psychiatry*, 161(4), 670–6.
- Farmer, R. F., Gau, J. M., Seeley, J. R., Kosty, D. B., Sher, K. J., and Lewinsohn, P. M. (2016). Internalizing and externalizing disorders as predictors of alcohol use disorder onset during three developmental periods. *Drug and Alcohol Dependence*, 164, 38–46. doi:

10.1016/j.drugalcdep.2016.04.021

Foster, K. T., Hicks, B., Iacono, W., and McGue, M. (2014). Alcohol Use Disorder in Women : Risks and Consequences of an Adolescent Onset and Persistent Course. *Psychology of Addictive Behaviors*, 28(1). doi: 10.1037/a0035488

Foster, K. T., Hicks, B. M., Iacono, W. G., and McGue, M. (2015). Gender differences in the structure of risk for alcohol use disorder in adolescence and young adulthood. *Psychological Medicine*, 45(14), 3047–3058. doi: 10.1017/S0033291715001014

Granic, I., and Patterson, G. R. (2006). Toward a comprehensive model of antisocial development: a dynamic systems approach. *Psychological Review*, 113(1), 101–31. doi: 10.1037/0033-295X.113.1.101

Hamdi, N. R., and Iacono, W. G. (2014). Lifetime prevalence and co-morbidity of externalizing disorders and depression in prospective assessment. *Psychological Medicine*, 44(2), 315–24. doi: 10.1017/S0033291713000627

Hernandez-Avila, C. A., Rounsaville, B. J., and Kranzler, H. R. (2004). Opioid-, cannabis- and alcohol-dependent women show more rapid progression to substance abuse treatment. *Drug and Alcohol Dependence*, 74(3), 265–72. doi: 10.1016/j.drugalcdep.2004.02.001

Hicks, B. M., Iacono, W. G., and McGue, M. (2010). Consequences of an Adolescent Onset and Persistent Course of Alcohol Dependence in Men : Adolescent Risk Factors and Adult Outcomes. *Alcoholism: Clinical & Experimental Research*, 34(5), 819–833. doi: 10.1111/j.1530-0277.2010.01154.x

Hox, J. J. (2010). *Multilevel analysis: Techniques and applications* (2nd ed.). New York: Routledge.

- Iacono, W. G., Carlson, S. R., Taylor, J., Elkins, I. J., and McGue, M. (1999). Behavioral disinhibition and the development of substance-use disorders: findings from the Minnesota Twin Family Study. *Development and Psychopathology*, *11*(4), 869–900.
- Johnstone, B., Leino, E., Ager, C., Ferrer, H., and Fillmore, K. (1996). Determinants of life-course variation in the frequency of alcohol consumption: meta-analysis of studies from the Collaborative Alcohol-Related Longitudinal Project. *Journal of Studies on Alcohol*, *57*, 494–506.
- Keyes, K. M., Grant, B. F., and Hasin, D. S. (2008). Evidence for a closing gender gap in alcohol use, abuse, and dependence in the United States population. *Drug and Alcohol Dependence*, *93*(1–2), 21–9. doi: 10.1016/j.drugaldep.2007.08.017
- Keyes, K. M., Martins, S. S., Blanco, C., and Hasin, D. S. (2010). Telescoping and gender differences in alcohol dependence: new evidence from two national surveys. Keyes, K.M. et al., 2010. Telescoping and gender differences in alcohol dependence: new evidence from two national surveys. *The American journal of psychiatry*. *The American journal of psychiatry*, *167*(8), 969–76. AMER PSYCHIATRIC PUBLISHING, INC, 1000 WILSON BOULEVARD, STE 1825, ARLINGTON, VA 22209-3901 USA. doi: 10.1176/appi.ajp.2009.09081161
- Kim, M. J., Mason, W. A., Herrenkohl, T. I., Catalano, R. F., Toumbourou, J. W., and Hemphill, S. A. (2017). Influence of Early Onset of Alcohol Use on the Development of Adolescent Alcohol Problems: a Longitudinal Binational Study. *Prevention Science*, *18*(1), 1–11. Springer New York LLC. doi: 10.1007/s11121-016-0710-z
- Krueger, R. F., Hicks, B. M., Patrick, C. J., Carlson, S. R., Iacono, W. G., and McGue, M.

- (2002). Etiologic connections among substance dependence, antisocial behavior and personality: Modeling the externalizing spectrum. *Journal of Abnormal Psychology*, 111(3), 411–424. doi: 10.1037//0021-843X.111.3.411
- Maggs, J. L., Patrick, M. E., and Feinstein, L. (2008). Childhood and adolescent predictors of alcohol use and problems in adolescence and adulthood in the National Child Development Study. *Addiction*, 103(s1), 7–22. doi: 10.1111/j.1360-0443.2008.02173.x
- Masse, L., and Tremblay, R. (1997). Behavior of boys in kindergarten and the onset of substance use during adolescence. *Archives of General Psychiatry*, 54(1), 62–68.
- Moffitt, T. E., and Caspi, A. (2001). Childhood predictors differentiate life-course persistent and adolescence-limited antisocial pathways among males and females. *Development and Psychopathology*, 13(2), 355–75.
- Owens, M. R., and Bergman, A. (2010). Alcohol use and antisocial behavior in late adolescence: Characteristics of a sample attending a GED program. *Journal of Child & Adolescent Substance Abuse*, 19(1), 78–98. doi: <http://dx.doi.org/10.1080/10678280903400768>
- Patrick, M. E., and Schulenberg, J. (2013). Prevalence and predictors of adolescent alcohol use and binge drinking in the United States. *Alcohol Research: Current Reviews*, 35(2), 193–200.
- Pedrelli, P., Shapero, B., Archibald, A., and Dale, C. (2016, March 1). Alcohol use and Depression During Adolescence and Young Adulthood: a Summary and Interpretation of Mixed Findings. *Current Addiction Reports*. Springer. doi: 10.1007/s40429-016-0084-0
- Randall, C., Roberts, J., Del Boca, F., Carroll, K., Connors, G., and Mattson, M. (1999). Telescoping of landmark events associated with drinking: A gender comparison. *Journal of*

Studies on Alcohol, 60(2), 252–260.

Raudenbush, S. W., and Bryk, A. S. (2002). *Hierarchical linear models : applications and data analysis methods*. SAGE Publications, Los Angeles, CA.

Robins, L. N. (1988). The Composite International Diagnostic Interview. *Archives of General Psychiatry*, 45(12), 1069–1077. doi: 10.1001/archpsyc.1988.01800360017003

Rohde, P., Lewinsohn, P. M., Kahler, C. W., Seeley, J. R., and Brown, R. A. (2001). Natural course of alcohol use disorders from adolescence to young adulthood. *Journal of the American Academy of Child and Adolescent Psychiatry*, 40(1), 83–90. doi: 10.1097/00004583-200101000-00020

Rutledge, P., and Sher, K. (2001). Heavy drinking from the freshman year into early young adulthood: The roles of stress, tension-reduction drinking motives, gender and personality. *Journal of Studies on Alcohol*, 62(4), 457–466.

Sannibale, C., and Hall, W. (2001). Gender-related symptoms and correlates of alcohol dependence among men and women with a lifetime diagnosis of alcohol use disorders. *Drug and Alcohol Review*, 20(4), 369–383. doi: 10.1080/09595230120092779

Schuckit, M. a., and Smith, T. L. (2011). Onset and course of alcoholism over 25 years in middle class men. *Drug and Alcohol Dependence*, 113(1), 21–28. doi: 10.1016/j.drugalcdep.2010.06.017

Skogen, J. C., Knudsen, A. K., Hysing, M., Wold, B., and Sivertsen, B. (2015). Trajectories of alcohol use and association with symptoms of depression from early to late adolescence: The Norwegian Longitudinal Health Behaviour Study. *Drug and Alcohol Review*, (May), n/a-n/a. doi: 10.1111/dar.12350

Slutske, W. S., Heath, A. C., Madden, P. a F., Bucholz, K. K., Statham, D. J., and Martin, N. G.

(2002). Personality and the genetic risk for alcohol dependence. *Journal of Abnormal Psychology*, 111(1), 124–133. doi: 10.1037/0021-843X.111.1.124

Squeglia, L. M., Tapert, S. F., Sullivan, E. V., Jacobus, J., Meloy, M. J., Rohlfing, T., and

Pfefferbaum, A. (2015). Brain Development in Heavy-Drinking Adolescents. *American Journal of Psychiatry*, 172(6), 531–542.

Tangney, J. P., Baumeister, R. F., and Boone, A. L. (2004). High self-control predicts good

adjustment, less pathology, better grades, and interpersonal success. *Journal of Personality*, 72(2), 271–324. doi: 10.1111/j.0022-3506.2004.00263.x

World Health Organization. (2015). *World health statistics: 2015*. Geneva, Switzerland.

Zucker, R. (1994). Pathways to alcohol problems and alcoholism: A developmental account of the

evidence for multiple alcoholisms and for contextual contributions to risk. In R. A. Zucker, G. M. Boyd, and J. Howard (Eds.), *The development of alcohol problems : exploring the biopsychosocial matrix of risk* (pp. 255–289). NIAAA Research Monograph 26.

Department of Health and Human Services.

Table 1. Means and Standard Deviations by AUD Group and Gender

	Overall			Men			Women		
	Control	YAO	AO	Control	YAO	AO	Control	YAO	AO
Alcohol Use Problems									
<i>Age 17</i>	45.66 (5.41)	51.50 (9.27)	66.83 (10.5)	44.52 (4.67)	51.75 (9.89)	70.14 (9.88)	46.06 (5.60)	50.83 (7.31)	62.09 (9.74)
<i>Age 20</i>	52.33 (6.88)	67.54 (10.3)	69.48 (12.7)	53.81 (9.23)	69.76 (10.4)	75.35 (11.4)	51.88 (5.93)	62.17 (8.21)	61.41 (9.91)
<i>Age 24</i>	51.56 (4.82)	64.07 (9.35)	66.05 (12.2)	52.83 (6.18)	66.42 (9.39)	71.17 (12.3)	51.15 (4.21)	58.39 (6.36)	59.15 (7.87)
<i>Age 29</i>	49.61 (4.50)	58.81 (8.68)	62.30 (10.6)	51.00 (5.53)	60.15 (9.03)	65.10 (10.8)	49.20 (4.06)	55.14 (6.40)	58.54 (9.09)
Substance Use Problems									
<i>Age 17</i>	47.53 (4.88)	49.29 (7.07)	61.59 (18.7)	46.41 (2.26)	48.39 (6.28)	59.77 (17.6)	47.93 (5.46)	51.69 (8.41)	64.24 (20.0)
<i>Age 20</i>	49.09 (6.73)	63.16 (23.9)	75.58 (29.7)	47.71 (5.50)	62.04 (21.4)	83.26 (33.1)	49.56 (7.05)	65.87 (29.0)	65.23 (20.6)
<i>Age 24</i>	48.98 (6.39)	62.71 (28.4)	70.42 (32.8)	48.23 (5.95)	63.98 (31.3)	75.91 (39.2)	49.24 (6.53)	59.35 (18.5)	62.74 (18.7)
<i>Age 29</i>	48.30 (4.84)	55.98 (13.2)	62.47 (17.5)	48.25 (5.88)	56.80 (14.6)	66.28 (19.9)	48.31 (4.44)	53.74 (8.13)	57.29 (12.0)
Depression Symptoms									
<i>Age 17</i>	0.94 (2.13)	0.68 (1.70)	1.90 (2.85)	0.69 (1.76)	0.50 (1.31)	1.21 (2.27)	1.03 (2.24)	1.19 (2.43)	2.91 (3.30)
<i>Age 20</i>	0.68 (1.84)	0.96 (2.17)	1.12 (2.36)	0.90 (2.15)	0.80 (1.94)	0.89 (2.22)	0.61 (1.72)	1.34 (2.63)	1.43 (2.52)
<i>Age 24</i>	0.79 (1.99)	0.83 (2.03)	1.59 (2.78)	0.44 (1.56)	0.51 (1.56)	0.77 (1.88)	0.91 (2.11)	1.65 (2.75)	2.77 (3.38)
<i>Age 29</i>	1.10 (2.35)	0.92 (2.15)	1.60 (2.87)	1.22 (2.45)	0.66 (1.80)	1.13 (2.46)	1.06 (2.32)	1.61 (2.80)	2.23 (3.25)
Adult Antisocial Behavior Symptoms									
<i>Age 17</i>	0.25 (0.59)	0.72 (0.99)	2.31 (1.76)	0.32 (0.53)	0.77 (1.01)	2.45 (1.72)	0.22 (0.60)	0.58 (0.93)	2.10 (1.81)
<i>Age 20</i>	0.35 (0.70)	1.47 (1.22)	2.10 (1.47)	0.54 (0.92)	1.59 (1.27)	2.53 (1.46)	0.29 (0.59)	1.20 (1.04)	1.48 (1.27)
<i>Age 24</i>	0.52 (0.69)	1.59 (1.12)	2.34 (1.55)	0.64 (0.90)	1.77 (1.18)	2.73 (1.59)	0.47 (0.60)	1.12 (0.76)	1.78 (1.32)
<i>Age 29</i>	0.34 (0.50)	1.12 (0.97)	1.28 (1.08)	0.45 (0.57)	1.22 (1.01)	1.56 (1.20)	0.31 (0.47)	0.84 (0.78)	0.91 (0.78)

Table 2. Multilevel model analyses for mental health factors

Factor	Level-1 Parameters			Level-2 Parameters		
	Intercept	Age	Age ²	Predicting Intercept	Predicting Age	Predicting Age ²
Alcohol Use	53.88 (0.38)***	2.25 (0.14)***	-0.16 (0.01)***	Gender	1.11 (0.38)**	0.79 (0.14)***
				YAO (vs. Control)	8.48 (0.42)***	0.15 (0.16)
				AO (vs. YAO)	11.46 (0.62)***	-1.67 (0.24)***
				Gender x YAO (vs. Control)	1.83 (0.42)***	0.32 (0.16)*
				Gender x AO (vs. YAO)	2.78 (0.62)***	0.02 (0.24)
						-0.01 (0.02)
Drug Use Problems	52.46 (0.65)***	2.75 (0.32)***	-0.20 (0.02)***	Gender	-1.96 (0.65)**	1.21 (0.32)***
				YAO (vs. Control)	4.77 (0.67)***	2.28 (0.33)***
				AO (vs. YAO)	7.84 (1.26)***	0.80 (0.53)
				Gender x YAO (vs. Control)	-1.37 (0.67)*	1.22 (0.33)***
				Gender x AO (vs. YAO)	-0.34 (1.26)	1.69 (0.53)**
						-0.12 (0.04)**
Depression Symptoms	-0.38 (0.09)***	-0.04 (0.03)	0.004 (0.002)*	Gender	-0.29 (0.09)***	-0.03 (0.03)
				YAO (vs. Control)	0.22 (0.13)	0.05 (0.04)
				AO (vs. YAO)	0.62 (0.13)***	-0.07 (0.04)
				Gender x YAO (vs. Control)	-0.18 (0.13)	-0.03 (0.04)
				Gender x AO (vs. YAO)	-0.11 (0.13)	-0.03 (0.04)
						0.00 (0.00)
Adult Antisocial Behavior	-0.53 (0.06)***	0.16 (0.01)***	-0.01 (0.001)***	Gender	0.16 (0.06)**	0.02 (0.01)
				YAO (vs. Control)	1.06 (0.09)***	-0.05 (0.02)*
				AO (vs. YAO)	1.09 (0.07)***	-0.12 (0.02)***
				Gender x YAO (vs. Control)	-0.08 (0.09)	0.02 (0.02)
				Gender x AO (vs. YAO)	-0.02 (0.07)	0.01 (0.02)
						0.00 (0.00)

Intercept values reflect scores at age 17 years. Gender coded as 0 for women and 1 for men. Random effects are estimated for the intercept; all other parameters were fixed. *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$

Figure 1. Model-predicted Alcohol Use by Gender and AUD Onset

Figure 2. Model-predicted Drug Use Problems by Gender and AUD Onset

Figure 3. Model-predicted Depression Symptoms by Gender and AUD Onset

Figure 4. Model-predicted Antisocial Behavior Symptoms by Gender and AUD Onset