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Gender Differences in the Structure of Risk for Alcohol Use Disorder in Adolescence and Young Adulthood

Katherine T. Foster, M.S.[1], **Brian M. Hicks, Ph.D.**[2], **William G. Iacono, Ph.D.**[3], and **Matt McGue, Ph.D.**[3]

[1]Department of Psychology, University of Michigan

[2]Department of Psychiatry, University of Michigan

[3]Department of Psychology, University of Minnesota

Abstract

Background—Gender differences in the prevalence of alcohol use disorder (AUD) have motivated the separate study of its risk factors and consequences in men and women. However, leveraging gender as a third variable to help account for the association between risk factors and consequences for AUD could elucidate etiological mechanisms and clinical outcomes.

Method—Using data from a large, community sample followed longitudinally from ages 17 to 29, we tested for gender differences in psychosocial risk factors and consequences in adolescence and adulthood after controlling for gender differences in the base rates of AUD and the psychosocial factor. Psychosocial factors included alcohol use, other drug use, externalizing and internalizing symptoms, deviant peer affiliation, family adversity, academic problems, attitudes and use of substances by a romantic partner, and adult socio-economic status.

Results—At both ages 17 and 29, mean-levels of psychosocial risks and consequences were higher in men and those with AUD. However, the amount of risk exposure in adolescence was more predictive of AUD in women than men. By adulthood, AUD consequences were larger in women than men and internalizing risk had a stronger relationship with AUD in women at both ages.

Conclusion—Despite higher mean-levels of risk exposure in men overall, AUD appears to be a more severe disorder in women characterized by higher levels of adolescent risk factors and a greater magnitude of the AUD consequences among women than men. Furthermore, internalizing symptoms appear to be a gender specific risk factor for AUD in women.

Relative to women, men consume alcohol more frequently and in greater quantities, and so have higher rates of alcohol use disorder (AUD) (DSM-IV abuse, 24.6%; dependence, 17.4%) than women (abuse, 11.5%; dependence, 8.0%) (Keyes *et al*., 2008). These differences have encouraged the separate study of risk exposure and outcomes in men and

Corresponding Author: Katherine T. Foster *East Hall* 530 Church Street Ann Arbor, MI 48109 Phone: 719.964.1908 ktfoster@umich.edu.

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women; however, leveraging gender as a third variable to help account for the association between psychosocial factors and AUD may advance understanding of etiological mechanisms and clinical outcomes (Rutter *et al*., 2003).

Two types of gender effects—mean-level and structural—help to organize our understanding of the links among gender, AUD, and important psychosocial variables. *Mean-level* gender effects (i.e., the main effect of gender) refer to the absolute amount or severity of risk exposure experienced by men and women with AUD (e.g., a risk factor may occur at a higher rate in men than women). Another important source of gender differences are *structural* effects or the strength of the association between a risk factor and AUD within each gender. In particular, gender differences in both AUD and a psychosocial variable can obscure gender's moderating effects (i.e., interaction effects). For instance, a psychosocial variable could have a stronger association with AUD in one gender than the other, irrespective of mean-level gender differences for that variable. Risk factors with strong structural effects on AUD may be more potent in one gender and, consequently, require a lower mean-level of exposure to produce AUD. By controlling for the mean-level effect of gender, the strength of the association between AUD and each psychosocial variable (i.e., interaction effects) can be estimated directly.

Delineating the mean-level and structural effects of gender for multiple psychosocial variables can increase insight regarding the accumulation of impairment across different domains that may comprise gender-specific pathways for AUD. Further, evaluating mean-level and structural effects at key developmental periods for AUD will help identify patterns of psychosocial impairment that contribute to the onset and persistence of AUD. Specifically, late adolescence (when early onset AUD cases emerge) and young adulthood (when drinking reduces and serious consequences accumulate if AUD persists) are particularly informative periods to examine how gender differences in early risk factors and consequences of AUD underlie gender difference in its prevalence.

Common Risk Factors and Outcomes for AUD

AUD represents the end point in a long history of biological, psychosocial, and environmental risk factors interacting and accumulating over the course of development (Blazei *et al*., 2006; Zucker, 2006; Caspi *et al*., 1995, 1996; Masse & Tremblay 1997; Wong *et al*., 2006). Importantly, these variables may exhibit gender differences in their mean-level and structural associations with AUD. For example, behavioral disinhibition—a heritable cluster of disinhibited personality traits and externalizing disorders (Moffitt *et al*., 2001; Rutledge & Sher, 2001; Krueger *et al*., 2002; Slutske *et al*., 2002, Kendler *et al*., 2003)—increases the odds of early onset AUD and other problem behaviors (e.g., drug use, delinquency, precocious sexual behavior; Iacono *et al*., 2008; Hawkins *et al*., 1992; Iacono *et al*., 2008). A cycle of coercive parent-child interactions, conflict with socializing agents (e.g., teachers and prosocial peers) and affiliation with deviant peers (Dishion *et al*., 1991; Tangney *et al*., 1996; Patterson & Yoerger, 1997, 1999; Granic & Patterson, 2006) also contributes to AUD and related adult impairment (e.g., unemployment, romantic partnership problems, and life satisfaction; Cranford *et al*., 2011). Other non-specific risk factors for AUD include internalizing disorders and exposure to traumatic life events like physical and

sexual abuse and assault (Cutler & Nolen-Hoeksema, 1991; Widom *et al*., 1995; Wilsnack *et al*., 1997; Kilpatrick *et al*., 2000; Nolen-Hoeksema & Hilt, 2006). While these patterns of risk and consequences are generally associated with AUD, there may be gender differences in their mean-level and the strength of their association with AUD (i.e., structural effects). Examining the nature of gender differences in risk factors and consequences can help explain the prevalence, etiological course, and relative severity of AUD.

Gender Differences in Mean-levels of Risk Factors for AUD

The greater prevalence of AUD in men suggests that men experience higher mean-levels of risk exposure than women (i.e., between-gender differences in those with AUD). To express AUD, then, a woman must be more deviant relative to the norm for her gender (i.e., within-gender mean-level effects) than a man. Therefore, elucidating gender differences in the risks and consequences for AUD requires comparing men and women with alcohol use problems to those of the same gender that do not (e.g., AUD women vs non-AUD women). However, risk factors are often studied individually using between-gender comparisons of mean-level effects, making it difficult to discern their relative contributions to the development of AUD in men and women (Labouvie & McGee, 1986; Waldeck & Miller, 1997; Moffitt *et al*., 2001; Petry *et al*., 2002). For example, though mean-levels of behavioral disinhibition and sexual trauma vary significantly by gender, both are equally predictive of AUD in boys and girls (Moffit *et al*., 2001; Iacono *et al*., 2008; Stein *et al*., 1988; Cutler & Nolen-Hoeksema, 1991). Studies conducting between-gender comparisons of a single factor are not well-equipped to test the etiological importance of these factors as gender-specific pathways to AUD. Within-gender comparisons of mean-levels of risk between those with and without AUD estimates the importance of a risk factor on AUD separately for men and women. These comparisons are vital for identifying which risk factors are more predictive of AUD in men relative to women.

Gender Differences in Structural Associations between AUD Risk Factors and Consequences

An additional cause of gender differences in AUD is that psychosocial factors may have different structural associations with AUD in men and women. Notably, the association (e.g., correlation) between AUD and several psychosocial factors differs across gender. For example, alcohol's rewarding effects have been linked with AUD in men (Schuckit, 1994; Wilhelmsen *et al*., 2003) while, the lower threshold for alcohol-related impairment and toxicity in women has been conceptualized as a deterrent of heavy drinking (Klassen & Wilsnack, 1986; Niaura *et al*., 1987; Nixon, 1994; Blume & Russell, 2001). Also, internalizing disorders may play a more prominent role in the development of AUD among women (Nolen-Hoeksema, 2004). For example, even after controlling for higher rates of depression in women relative to men, depressive symptoms have been prospectively associated with AUD in women (Kendler *et al*., 1997; Brady & Randall, 1999; Sannibale & Hall, 2001). Finally, even among those who desist by young adulthood, a greater proportion of women than men exhibit enduring consequences of AUD, including prolonged polysubstance abuse, psychiatric problems, and poor psychosocial adjustment (Hicks *et al*., 2010; Foster *et al*., 2014). As such, AUD may be less prevalent in women because it is a

more extreme form of psychopathology, requiring a greater loading of risk before the disorder is expressed. These findings suggest then that gender-specific associations between AUD and its risk factors may contribute to gender differences in the prevalence of AUD.

Leveraging Gender Differences to Study the Etiology of AUD

Research on AUD has often been constrained within gender under the assumption that the link between AUD and its risks and consequences differs by gender. Consequently, few studies have compared the relative effects of multiple risk factors and outcomes for AUD in men and women in the same study. Without such tests, it is unclear if psychosocial risks and outcomes are simply more prevalent in one gender, or if gender-specific influences increase their association with AUD in one gender more than the other. To examine the potential moderating role of gender, we directly compared the effects of several well-replicated risk factors for and outcomes of AUD in a large, community sample of men and women at ages 17 and 29. Specifically, separately for men and women, we first estimated the odds of developing AUD by age 29 given the mean level of risk evident for each age-17 risk factor after controlling for gender differences in the average amount of exposure to the risk factor within each gender. We then estimated the association between AUD and several psychosocial outcomes at age 29, after adjusting for gender differences in the base rates of AUD and the psychosocial outcome. We hypothesized that mean-level but not structural gender effects would be present across risk factors. One exception, however, was internalizing disorders for which we predicted a stronger association with AUD in women relative to men.

Method

Sample

Participants were male (n=578) and female (n=674) twins of the Minnesota Twin and Family Study (MTFS), a prospective, community-based study designed to investigate the etiology of substance use disorders (for extensive details on study design see Iacono *et al*., 1999). Twin pairs born between the years of 1972 and 1979 were recruited from Minnesota public birth records at age 17. Of the 90% of families located, 83% completed the in-person laboratory assessment at the University of Minnesota. Nearly all participants were of European American ancestry (96%) and were similar to non-participating families in parental occupation, education, and history of mental health treatment.

Assessment

At the age 17 assessment, multiple informants (twins, parents, and teachers) provided information on alcohol and other substance use along with psychiatric, psychosocial, and environmental functioning. Follow-up assessments occurred 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). The current report focused on risk factors and domains of psychosocial functioning at ages 17 and 29 (Hicks *et al*., 2009, 2010) to

assess both risk and outcomes for lifetime AUD by age 29. More comprehensive descriptions of the measures are provided elsewhere (Hicks *et al*., 2009, 2010).

AUD Diagnosis

Trained staff administered the Substance Abuse Module (SAM; Robins *et al*., 1987) of the Composite International Diagnostic Interview (Robins *et al*., 1988) to determine lifetime AUD status at age 17. Subsequent evaluations assessed AUD symptoms since the last assessment. Consistent with DSM-5, AUD was defined as 2 or more symptoms of alcohol abuse or dependence for at least one assessment by age 29 (men, n=316; women, n=155). Multiple studies using the MTFS sample have demonstrated the validity of this approach (Elkins *et al*., 2004; McGue & Iacono, 2005; Elkins *et al*., 2006; Elkins *et al*. 2007). For each gender, an AUD group was compared with a non-AUD group (i.e., no more than one AUD symptom at any assessment; men, n=226; women, n=449) on the risk factors and outcomes.

Measures of Risk and Impairment

Prior studies using the MTFS sample have linked several measures of risk and consequences with AUD in both genders (Hicks *et al*., 2010; Foster *et al*., 2014). Using principal components analysis and theoretical considerations, we combined variables into composites (i.e., mean z-score across constituent variables) to assess critical domains of AUD risk exposure and impairment at age 17 and age 29. Whenever possible, the same measures were used to assess each factor at ages 17 and 29. However, certain domains were age-specific including family adversity and academic problems in adolescence (age 17 only) and romantic partner relationships and socio-economic status in adulthood (age 29 only).

Alcohol, nicotine and illicit substance use—Alcohol use was assessed using past year average quantity and the maximum number of drinks consumed in 24 hours. Nicotine and illicit drug use were estimated using DSM-IV symptoms of nicotine dependence and abuse/dependence for illicit drugs, along with quantity and frequency of use and the number of drug classes tried. Substances assessed included nicotine, amphetamine, cannabis, cocaine, hallucinogen, inhalant, opioid, PCP, and sedatives. The illicit drug class with the greatest number of reported symptoms was used for each participant's drug abuse/ dependence variable.

Externalizing symptoms—At age 17, symptoms of adult antisocial behavior were assessed using a structured interview similar to the SCID-II module for antisocial personality disorder. Personality traits of disinhibition were assessed using the behavioral constraint (i.e., inclination toward planning, traditional social values, and caution) factor of the Multidimensional Personality Questionnaire (MPQ; Tellegen & Waller, 2008). At age 29, symptoms of adult antisocial behavior over the past 6-years were assessed in conjunction with behavioral constraint.

Internalizing distress—Internalizing distress was assessed using lifetime symptoms of major depressive disorder, negative emotionality, and significant mental health problems (i.e., prior suicide attempts, mental health treatment, or psychiatric hospitalization).

Symptoms of major depression were assessed using the Structured Clinical Interview for DSM-III-R. Trait negative emotionality (i.e., propensity toward breakdown under stress and a suspicious, aggressive interpersonal style) was assessed using the MPQ. Mental health problems were assessed using the Lifetime Events Interview (Bemmels et al., 2008). At age 29, the same variables were used to estimate internalizing distress (i.e., major depression symptoms, mental health problems over the past 6 years, and negative emotionality scores).

Deviant peer group affiliation—Adolescent peer groups were assessed for antisocial (α = 0.82; e.g., my friends enjoy getting drunk, get into fights, can't seem to hold a job) and prosocial behaviors (α = 0.60; e.g., my friends work hard, do volunteer work, have a regular job) using a teacher rating form (5-items each; Walden *et al*., 2004). At age 29, participants reported antisocial (coded positive) and prosocial (coded negative) qualities of their own peer group (27-item questionnaire).

Family adversity—At age 17, family adversity was indexed by socioeconomic status for the family of origin, quality of the parent-child relationship, and parental externalizing disorder symptoms. Socio-economic status was defined as the mean z-score for each parent's years of education, occupational status (Hollingshead Index) and annual income. The Parent Environment Questionnaire (PEQ; Elkins *et al*., 1997) measured quality of the parent-child relationship from each parent and adolescent (mean z-score of the three informant ratings for the first principle component of the PEQ scales; Hicks *et al*., 2009). Parental externalizing disorders were indexed using the symptoms of antisocial personality disorder and alcohol, nicotine, and drug abuse/dependence.

Academic problems—At age 17, difficulties in school were assessed using the Academic History Questionnaire (Johnson *et al*., 2006) that queried mother and child for cumulative grade point average and positive engagement with academics (7-items; α = 0.83).

Adult romantic partner drug use—Participants in a current romantic relationship (i.e., married, cohabiting, or consistently dating the same person for 3 months or more) at age 29 reported their partner's past year drinking patterns including the frequency, quantity and proportion of intoxicating drinking episodes and attitudes toward substance use (e.g., “my spouse/partner would be upset if he knew I was smoking”; “my spouse/partner would purchase alcohol if I asked him to”; “my spouse's/partner's friends use marijuana”) using an 11-item scale (α = 0.84).

Adult socio-economic status—Measures of educational attainment, a Hollingshead rating of current occupational status, and annual income all reported in the Life Events Interview and the Social Adjustment Inventory were used to create a composite for socio-economic status.

Statistical Analysis

A series of hierarchical linear models were fit to estimate the associations between AUD, Gender and the risk factors assessed at age 17. Generalized estimating equations were used

to model the associations between adolescent risk exposure and the odds of developing AUD by age 29 in men and women using the following model:

$$AUD_{ij}=\gamma 00+\gamma 10^{*}GENDER_{ij}+\gamma 20^{*}RISK_{ij}+\gamma 30^{*}GENDER^{*}RISK_{ij}+\mu 0_{j}$$

Data for this model were mean-centered within each gender to facilitate interpretation as follows. The main effect of gender (**γ*10***) was the increase in the odds of AUD by age 29 given gender status and an average level of risk exposure for that gender (e.g., increase in odds for men compared to women, given average levels of risk within men and women). The main effect for the risk factor (**γ*20***) was estimated as the increase in the odds of AUD by age 29 given a 1 SD increase in risk exposure. The Gender x Risk interaction term (**γ*30***) tested whether the association between AUD and the risk factor was moderated by gender. Models were fit using the Bernoulli option in HLM 7.0 specifically designed to predict binary outcomes (i.e., AUD or non-AUD by age 29 in this case). Data were nested within families (**γ*00***) to adjust for the non-independence of the twin data and any non-normal distributions for the risk factor variables. A residual term was also included (**$\mu 0_j$**) to account for variation in the outcome not accounted for by the predictor variables.

At age 29, we estimated the associations between lifetime AUD, gender, and several psychosocial consequences using the following model:

$$OUTCOME_{ij}=\gamma 00+\gamma 10^{*}GENDER_{ij}+\gamma 20^{*}AUD_{ij}+\gamma 30^{*}GENDER^{*}AUD_{ij}+\mu 0_{j}$$

This model included the main effects of gender (**γ*10***) and AUD status (**γ*20***) and the Gender x AUD interaction (**γ*30***) in the prediction of each psychosocial outcome at age 29. Parameters were adjusted for other variables in the model so that the effect of gender on the outcome was adjusted for AUD vs. non-AUD group differences in outcome, while the effect of AUD was adjusted for gender differences on the outcome. The Gender x AUD interaction term tested whether gender moderated the association between AUD and the adult outcome. Models for age 29 outcome variables were fit using the cluster option and the MLR estimator in Mplus 5.0 that is appropriate for continuous outcomes (i.e., degree of the risk outcome). All standard errors and p-values were adjusted for the non-independence of the family-level data (i.e., nested by **γ*00***) and any non-normal distributions for risk factor variables. A residual term was also included (**$\mu 0_j$**) to account for variance in the outcome independent of gender, AUD, and their interaction.

Results

Over a third of the sample (n=471, 37.6%) reported 2 or more symptoms of AUD at one or more assessments by age 29. In our sample, lifetime AUD was more prevalent among men than women (Odds Ratio [OR]: 2.37, 95% Confidence Interval [CI]: 1.90–2.90).

Risk Exposure at Age 17 and Lifetime AUD Outcomes by Gender

Results for the main effects of Gender, Risk factor, and the Gender x Risk factor interaction terms at age 17 are reported in Table 1. The average level of risk exposure common to boys

at age 17 significantly increased odds of developing AUD relative to the average level of risk exposure common to girls at 17. The significant main effects of risk exposure at age 17 indicated that higher levels of risk increased the odds of developing AUD by age 29. Within both men and women, a 1 SD increase in alcohol use, other drug use, externalizing problems, deviant peers, family adversity and academic problems increased the odds of AUD. Internalizing distress at age 17 was associated with increased odds of AUD in women (OR: 1.55, 95% CI: 1.30–1.85, $p < 0.001$) but not men (OR: 1.23, 95% CI: 0.96–1.57, $p = 0.098$), suggesting a gender-specific risk factor for AUD. Finally, the association between each risk exposure and AUD was stronger for women except for family adversity, suggesting that similar increases in risk for both genders are linked with more severe consequences in women compared to men (see Figure 1). For instance, a 1 SD increase in drug use was associated with a greater increase in the odds of AUD in women (OR: 2.59, 95% CI: 2.02–3.32) compared to men (OR: 1.78, 95% CI: 1.36–2.32). Consequently, we detected Gender x Risk factor interactions for alcohol use, other substance use, deviant peers, and academic problems, such that greater risk exposure on these variables had a significantly stronger association with AUD in women relative to men.

Consequences of AUD at Age 29

Results for the main effects for Gender, AUD, and the Gender x AUD interactions for the age 29 outcomes are reported in Table 2. Lifetime AUD predicted greater alcohol consumption, nicotine and illicit drug use, internalizing distress, externalizing problems, deviant peer affiliation and substance use by a romantic partner at age 29. Men exhibited significantly greater alcohol use, other substance use, externalizing symptoms, deviant peer affiliation, and socioeconomic status. Women reported greater partner substance use. Although mean-level comparisons at age 29 suggest men with AUD were more impaired than women with AUD, the difference in psychosocial outcome between non-AUD and AUD groups was larger among women than men for alcohol use, drug use, internalizing, deviant peers, and romantic partner drug use. That is, AUD coincided with greater overall decrements in functioning among women than men compared to those of the same gender without the disorder (see Figure 2). For example, the effect size of AUD on other drug use was larger in women ($d = 1.00$) relative to men ($d = 0.65$). We also detected a Gender x AUD interaction for internalizing distress, such that the differences between AUD and non-AUD groups was greater among women than men.

Discussion

The higher prevalence of AUD in men relative to women suggests that mean-levels of risk exposure for AUD are either greater in men or that certain risk factors have differential effects across gender. To test the moderating role of gender, we estimated the strength of the association between AUD and several established risk factors and negative outcomes after adjusting for gender differences in their prevalence. Our results confirmed the hypothesis that women with AUD have a greater loading of risk at age 17 and that AUD increases mean-levels of psychosocial impairment in young adulthood for both men and women, but that internalizing distress has a stronger structural relationship with AUD for women than men.

Greater exposure to each risk factor was associated with increased the odds of AUD by age 29. Further, men tended to have higher mean-levels of risk exposure that contributed to a higher prevalence of AUD in men relative to women. Despite the higher level of absolute risk in men, AUD in women was associated with an especially high level of risk exposure during adolescence relative to their gender norm, and a higher level of risk exposure was necessary for women to exhibit AUD relative to men. Gender variation in the psychosocial consequences of AUD during young adulthood followed a similar pattern. That is, the magnitude of the difference between AUD and non-AUD impairment levels at age 29 (i.e., effect size) was larger in women than men for most variables. Compared to their gender norm, women with AUD tended to experience both higher risk exposure in adolescence and more negative outcomes in young adulthood relative to men with AUD. Consequently, AUD appears to be a more severe form of psychopathology in women, with a risk structure that is present early in development (i.e., at least by adolescence).

We detected several interactions between gender and adolescent risk factors, such that increases in alcohol use, other substance use, deviant peer relationships and academic problems increased odds of developing AUD more dramatically in women compared to men. Notably, these risks are not necessarily associated with concurrent AUD, as our AUD groups were derived using lifetime diagnoses by age 29. That is, the risk structure for AUD appears to emerge by adolescence, irrespective of the onset and chronicity of alcohol problems. The higher levels of adolescent risk exposure and young adult consequences associated with AUD in women provides further evidence that it is a more severe and debilitating disorder in women than men. While psychosocial problems in young adulthood may be consequences of AUD they may, alternatively, also reflect the persistence of the high loading of risk present in adolescence for women with AUD. Studies aiming to understand the etiology of AUD in women would benefit from examining risk structure at even earlier ages to track how risk exposure relates to the onset and persistence of AUD and psychosocial problems.

Consistent with previous reports (Nolen-Hoeksema, 2004; Foster *et al*., 2014), internalizing distress exhibited a unique structural relationship with AUD in women compared to men, suggesting it may be a gender-specific risk factor for AUD. In women, increases in internalizing distress significantly increased the odds of AUD during adolescence and also had a significant relationship with AUD in young adulthood. In contrast, AUD had a near zero association with internalizing distress in men at both ages, suggesting it is neither a risk for or a consequence of AUD in men. While previous literature has documented that women develop internalizing symptoms at a higher rate than men, our results suggest that, even after controlling for gender differences in their prevalence, internalizing symptoms likely play a role in the development of AUD in women but not men. The early emergence of internalizing symptoms in girls may potentiate alcohol use problems later in life through a developmental cascade. For example, symptoms of depression and anxiety that are more common in girls than boys during adolescence may be commonly associated with difficulties in school, work, and peer relationships during puberty and catalyze alcohol use problems as a method of coping with negative emotions. As a result, alcohol use may

exacerbate internalizing distress indirectly through its negative influence on psychosocial development.

The temporal relationship between internalizing distress and alcohol problems, however, remains unclear. Another possibility is that girls may engage in early and heavy use of alcohol independent of internalizing distress. Heavy alcohol use by adolescent girls has been shown to impair neurocognitive functioning (Squeglia *et al.*, 2010, 2011) and may increase isolation, disrupt social relationships, and hinder academic engagement. A lack of stability in social support and academic success may substantially diminish girls' self-esteem and efficacy for coping with negative emotions in adaptive and prosocial ways (Lopez & DuBois, 2005). Subsequently, internalizing symptoms may emerge during young adulthood. Directly testing the temporal relationship between internalizing distress and alcohol problems using longitudinal methods will be vital for explicating this aspect of women's vulnerability to AUDs.

Overall, we provided evidence that AUD is a more severe disorder in women and that internalizing distress may play a gender-specific role in AUD symptoms among women. As only a few studies of gender differences have directly compared men and women in the association between multiple risk variables and the development of AUD at multiple time points, this research represents an important advancement of current research. However, these findings are limited in a number of ways. First, the same associations between each risk factor and AUD may not apply to more diverse samples of men and women. Replication among a more racially and ethnically diverse sample are needed to determine the generalizability of our findings. Second, the associations between risk factors and AUD may be better explained by a third variable that also varies by gender. Third, the use of multiple comparisons is not ideal but allowed for the comparison of the relative contributions of a number of risks to identify candidates for causal pathways that should be validated through future replication of this work and other investigations of individual risk factors. Finally, our analyses do not address the co-development between each risk exposure and AUD. Future work in these areas will be important for determining the etiological role of these for AUD and its clinical features (i.e., onset and course).

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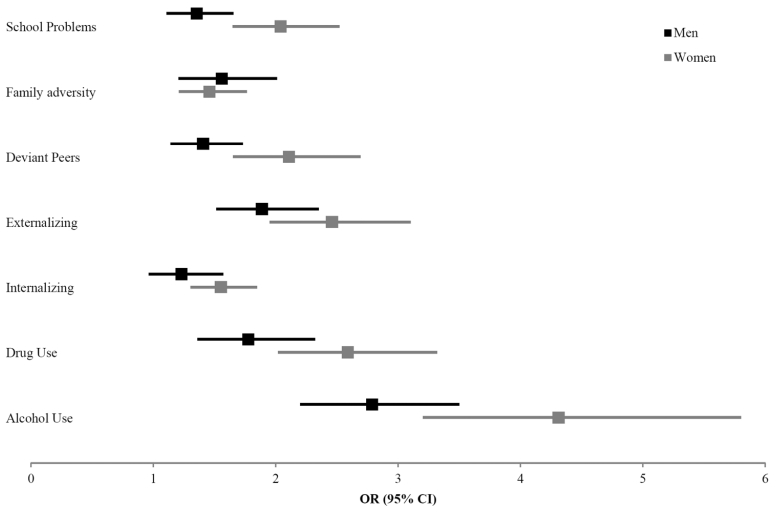

Figure 1.

Odds of developing AUD by age 29 for each one SD increase from average level of risk exposure for a person of that gender at age 17.

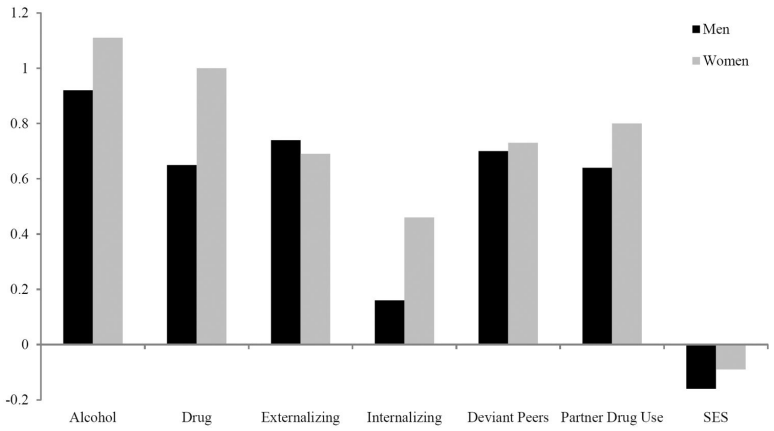

Figure 2.
Cohen's *d* effect sizes for the main effect of AUD within each gender at age 29.

Table 1

T-score means, standard deviations, Cohen's d, and results for the generalized estimating equation using risk factors at age 17 and gender to predict the odds of developing AUD by age 29.

		Gender Difference	AUD Status by Age 29			Risk Effect at age 17			Gender Effect (men vs. women)	Risk x Gender
Predictors at 17	**Overall**	***d*[a]**	**Control**	**AUD**	***d*[b]**	**β (SE)**	**OR**	**95% CI**	**β (SE)**	**p-value**
Alcohol Use										
Total	50.0 (10.0)		46.4 (6.2)	56.1 (12.0)	1.02					
Women	48.6 (7.9)		46.4 (5.6)	55.1 (9.9)	1.09	1.46 (0.15)	4.31**	3.20–5.80		
Men	52.3 (12.0)	0.36	46.3 (7.2)	56.5 (12.9)	0.98	1.02 (0.12)	2 79**	2.19–3.54	1.78 (0.16)**	0.025†
Other Drug Use										
Total	50.0 (10.0)		47.6 (6.3)	53.5 (13.0)	0.58					
Women	50.1 (9.8)		47.7 (5.7)	56.9 (14.9)	0.82	0.95 (0.12)	2.59**	2.02–3.32		
Men	50.0 (10.3)	−0.01	47.4 (7.3)	51.9 (11.6)	0.46	0.57 (0.13)	1.78**	1.36–2.32	1.51 (0.15)**	0.043†
Externalizing										
Total	50.0 (10.0)		47.2 (7.3)	54.7 (11.7)	0.77					
Women	48.0 (9.1)		46.1 (7.0)	53.5 (12.0)	0.76	0.90 (0.12)	2.46**	1.95–3.10		
Men	52.8 (10.5)	0.49**	49.3 (7.6)	55.2 (11.6)	0.61	0.63 (0.11)	1.89**	1.51–2.35	1.56 (0.15)**	0.112
Internalizing										
Total	50.0 (10.0)		48.8 (9.3)	51.5 (10.2)	0.28					
Women	50.0 (11.1)		48.9 (10.0)	54.7 (13.1)	0.51	0.43 (0.08)	1.55**	1.30–1.85		
Men	49.5 (8.0)	0.09	48.7 (7.7)	50.0 (8.1)	0.16	0.20 (0.12)	1.23	0.96–1.57	1.45 (0.15)**	0.129
Deviant Peers										
Total	50.0 (10.0)		48.1 (8.5)	52.5 (11.0)	0.45					
Women	49.8 (9.3)		48.2 (8.4)	54.8 (10.2)	0.71	0.74 (0.12)	2.11**	1.65–2.69		
Men	50.0 (10.4)	0.02	48.0 (8.7)	51.5 (11.2)	0.35	0.34 (0.10)	1.41*	1.14–1.73	1.55 (0.16)**	0.014†
Family Adversity										
Total	50.0 (10.0)		48.6 (9.6)	51.6 (9.9)	0.32					
Women	50.0 (11.0)		48.8 (10.6)	53.3 (11.6)	0.40	0.37 (0.09)	1.46**	1.21–1.76		
Men	49.7 (8.4)	−0.02	48.1 (7.4)	50.9 (8.9)	0.35	0.44 (0.12)	1.56*	1.21–2.01	1.45 (0.15)**	0.687

		Gender Difference	AUD Status by Age 29			Risk Effect at age 17			Gender Effect (men vs. women)	Risk x Gender
Predictors at 17	**Overall**	***d*[a]**	**Control**	**AUD**	***d*[b]**	**β (SE)**	**OR**	**95% CI**	**β (SE)**	**p-value**
Academic Problems										
Total	50.0 (10.0)		47.8 (9.0)	52.9 (10.5)	0.53					
Women	48.6 (9.7)		46.8 (8.9)	53.6 (10.1)	0.71	0.71 (0.10)	2.03**	1.65–2.52		
Men	51.4 (10.0)	0.28	49.6 (8.8)	52.6 (10.7)	0.30	0.30 (0.10)	1.35*	1.11–1.65	1.47 (0.15)**	0.006*

T-score means arranged by gender and AUD status (Women: n=155 AUD, 449 control; Men: n=316 AUD, 226 non-AUD) reflect mean-level of risk exposure for each group at age 17. Cohen's d effect sizes estimate the magnitude of the difference in the average level of risk between males and females overall (i.e., all Men vs. all Women; d^a). and the change in risk exposure coinciding with AUD in each gender (e.g., Control Women vs. AUD Women; d^b). The Risk Effect for each gender estimates the increased odds of developing AUD by age 29 as a result of a 1 SD increase in risk exposure for a person of that gender (i.e., potency of the risk). The Gender Effect estimates the increase in odds of developing AUD by age 29 in men compared to women given an average level of risk exposure within each gender. Positive β-value denotes higher odds in men compared to women. The Risk x Gender interaction effect tested if gender moderated the relationship between the risk factor and the AUD outcome.

** $p < 0.001$,

* $p < 0.01$,

† $p < 0.05$,

Table 2

T-Score means, standard deviations, Cohen's d, and β-value using AUD status and gender to predict psychosocial functioning at age 29.

		AUD Status by age 29		AUD Effect		Gender Effect		AUD x Gender
Criterion at age 29	**Overall**	**Control**	**AUD**	***d*[a]**	**β-value**	***d*[b]**	**β-value**	**β-value**
Alcohol Use								
Total	50.0 (10.0)	46.0 (6.9)	56.5 (10.7)	1.17**	0.43**	0.84**	0.24**	0.01
Women	46.6 (7.7)	44.4 (5.4)	53.2 (9.7)	1.11**				
Men	54.5 (10.8)	49.2 (8.5)	58.1 (10.8)	0.92**				
Other Drug Use								
Total	50.0 (10.0)	46.9 (6.8)	54.7 (12.0)	0.82**	0.40**	0.37†	0.08†	−0.05
Women	48.5 (8.0)	46.4 (5.8)	54.8 (10.0)	1.00**				
Men	51.7 (11.6)	47.8 (8.9)	54.7 (12.8)	0.65**				
Externalizing								
Total	50.0 (10.0)	46.8 (8.1)	55.0 (10.6)	0.87**	0.29**	0.75**	0.22**	0.06
Women	46.7 (8.4)	45.3 (7.4)	51.1 (9.5)	0.69**				
Men	53.8 (10.3)	49.7 (8.6)	56.9 (10.5)	0.74**				
Internalizing								
Total	50.0 (10.0)	48.9 (8.9)	51.4 (11.0)	0.26**	0.27**	−0.08	−0.02	−0.18*
Women	50.3 (10.6)	49.0 (9.3)	54.3 (13.3)	0.46**				
Men	49.5 (8.9)	48.7 (8.2)	50.1 (9.3)	0.16				
Deviant Peers								
Total	50.0 (10.0)	47.0 (8.8)	54.8 (9.7)	0.84**	0.32**	0.60**	0.17**	0.01
Women	47.5 (9.1)	45.9 (8.4)	52.4 (9.4)	0.73**				
Men	53.2 (10.1)	49.3 (9.3)	56.0 (9.7)	0.70**				
Romantic Partner Drug Use								
Total	50.0 (10.0)	48.2 (9.4)	52.9 (10.1)	0.48**	0.38**	−0.36**	−0.25**	−0.09
Women	51.5 (10.1)	49.3 (9.5)	57.5 (10.0)	0.80**				
Men	48.1 (9.3)	44.8 (8.5)	50.5 (9.2)	0.64**				
Socio-economic Status								
Total	50.0 (10.0)	50.2 (10.3)	49.7 (9.3)	−0.05	−0.05	0.20*	0.14*	−0.03
Women	49.1 (10.1)	49.3 (10.2)	48.4 (9.8)	−0.09				
Men	51.0 (9.6)	52.0 (10.3)	50.3 (8.9)	−0.16†				

T-score means arranged by gender and AUD status (Women: n=155 AUD, 449 control; Men: n=316 AUD, 226 non-AUD) reflect mean-level of consequences for each group at age 29. Cohen's d effect sizes estimate the magnitude of the change in consequence factor coinciding with AUD in each gender (i.e., Control Women vs. AUD women) and the difference in each mean-level consequence between men and women at age 29 (i.e., all Men vs. all Women; d^b). The AUD Effect estimates the level of consequences at age 29 associated with lifetime AUD status compared to control status. The Gender effect estimates the difference in consequences at age 29 for men compared to women. The AUD x Gender interaction effect tests if gender moderates the relationship between AUD and consequences at age 29.

** $p < 0.001$,

* $p < 0.01$,

† $p < 0.05$,