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## Binge Drinking in Adolescence Predicts An Atypical Cortisol Stress Response in Young Adulthood

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### Abstract

Adolescence is a sensitive developmental period in which substance use can exert long-term effects on important biological systems. Emerging cross-sectional research indicates that problematic alcohol consumption may be associated with dysregulated neuroendocrine system functioning. The current study evaluated the prospective effects of binge drinking in adolescence on cortisol stress reactivity in young adulthood among individuals who had experienced parental divorce in childhood (N=160; Mean age = 25.55, SD = 1.22; 46.9% Female; 88.8% White Non-

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Author Declarations

Declarations of interest:

Sharlene A. Wolchik and Irwin Sandler declare the following competing financial interest: Partnership in Family Transitions—Programs That Work LLC, which trains and supports providers to deliver the New Beginnings Program. All other authors declare no competing interests.

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M. Hagan: Conceptualization; Formal analysis; Writing-Original, Review, and Editing; Final Approval; K. Modecki: Methodology; Formal analysis; Software; Writing-Original, Review, and Editing; Final Approval; L. Luecken: Conceptualization; Methodology; Funding Acquisition; Writing-Review and Editing; Final Approval; L. Moctezuma: Interpretation; Writing-Original Manuscript; Final Approval; S. Wolchik: Conceptualization; Supervision; Funding Acquisition; Writing-Review and Editing; Final Approval; I. Sandler: Methodology; Funding Acquisition; Final Approval.

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Hispanic). Youth completed validated measures of problematic drinking during adolescence (aged 15-19) and participated in a standardized social stress task nine years later in young adulthood. Latent growth modeling was conducted within a structural equation modeling framework. Greater binge drinking during adolescence was associated with a significantly lower cortisol stress response in young adulthood, controlling for young adult drinking, sex, childhood externalizing problems, and socioeconomic status. Findings suggest problematic alcohol consumption during mid-late adolescence may have important effects on the neuroendocrine stress response system at subsequent developmental stages.

## Keywords

cortisol; adolescence; young adulthood; alcohol; binge drinking

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## 1. Introduction

Alcohol is the most commonly abused substance among youth (Johnston et al., 2018). The rate of binge drinking (defined as the consumption of at least 5 drinks for males and 4 drinks for females in a 2-hour period) is alarmingly high in adolescence, with as many as 18% of youth reporting at least one binge drinking episode in a 30-day period (Kann et al., 2015). For adolescents who experience family disruption, such as parental divorce, the rate of problematic alcohol consumption is even higher (Barrett and Turner, 2006; Pilowsky et al., 2009). For example, parental divorce has been associated with an earlier age of onset of adolescent drinking (Jackson et al., 2016) and an increased risk for later alcohol abuse (Arkes, 2013). Adolescence is a developmental period of intense biological change. Problematic alcohol consumption during this sensitive period has been associated with abnormal brain development and emotion regulation deficits (Jones et al., 2016; Trantham-Davidson et al., 2017). The hypothalamic-pituitary-adrenal (HPA) axis is a prime mediator of the effects of alcohol on the body in the short-term and a potential pathway by which alcohol might exert long-term effects on biological systems; however, the lasting impact of problematic alcohol use on neuroendocrine functioning among youth has not been examined.

The HPA axis is the primary arm of the neuroendocrine stress system and is activated by both ascending (from the brainstem) and descending (from limbic structures) inputs (Herman et al., 2005). Superimposed on a diurnal rhythm, the stress-related activation of the HPA axis initiates a hormonal cascade that results in accelerated synthesis and secretion of cortisol. During stress, cortisol facilitates an increase in cardiovascular activity, alterations in cognitive and sensory thresholds, an increase in alertness, promotion of stress-induced analgesia, suppression of nonessential functions (e.g., growth, digestion, and reproduction), and the processing and consolidation of emotionally-laden memory (Ulrich-Lai and Herman, 2009). High levels of cortisol then trigger a negative feedback cycle in which the subsequent release of hormones is inhibited, ultimately leading to a decrease in cortisol to basal levels and a return to a pre-stress state (Tsigos and Chrousos, 2002). Thus, a typical cortisol response to stress involves a period of reactivity (a rise in cortisol levels that are sustained for an appropriate amount of time to meet the demands of the situation) and a period of

recovery (a decline in cortisol levels back to baseline). Dysregulation of this typical response is observed when cortisol reactivity continues when no longer needed or, conversely, is not of sufficient magnitude to meet the demands of the situation (McEwen, 2007).

Associations between alcohol consumption and cortisol activity are complex. In a non-stress context, consumption of alcohol has a stimulating effect on the HPA axis, resulting in an initial increase in cortisol output (Magrys et al., 2013). However, many experimental studies have shown that when alcohol is consumed immediately prior to or following a discrete psychosocial stressor it can have an attenuating effect among some individuals such that cortisol reactivity is much lower than expected or does not appear at all (Balodis et al., 2011; Dai et al., 2002; Schrieke et al., 2016).

Emerging cross-sectional literature documents associations between alcohol use outside of the experimental context and alterations to the expected cortisol stress response profile (e.g., Orio et al., 2017). Only one study to our knowledge has prospectively examined alcohol use and biological stress system functioning. In an examination of a community sample of youth, it was found that a flattened diurnal cortisol rhythm at age 11 predicted greater alcohol use between ages 15-18, and heavier alcohol use predicted further flattening of the diurnal rhythm six months later (Ruttle et al., 2015). No study to our knowledge has evaluated the association between excessive alcohol consumption at one developmental stage and cortisol reactivity to social stress at a subsequent developmental stage. This is a critical oversight given that problematic substance use earlier in life is likely to have pervasive and enduring consequences for central nervous system functioning. The long-term detrimental effects of alcohol consumption may be especially likely to occur when consumption takes place during adolescence – a period when the neurobiological stress system undergoes critical developmental alterations (Casey and Jones, 2010). Consistent with this idea, animal models show that alcohol exposure during this developmental period alters the neural circuitry underlying the activation of the stress response (specifically the functioning of the paraventricular nucleus) resulting in a blunted stress response later in life (Allen et al., 2011).

With one exception (e.g., Jones et al., 2013), cross-sectional studies with humans have shown an attenuation of the neuroendocrine response to stress (i.e., a decrease in levels across an acute stressor) among adults who report binge drinking or other forms of heavy alcohol use (Lovallo et al., 2000; Orio et al., 2017). Atypical patterns of cortisol reactivity, such as a blunted response, have been associated with a wide range of physical and mental health problems (for a review, see Phillips et al., 2013). For example, attenuated cortisol reactivity may have implications for the development of and recovery from substance use disorders (Back et al., 2010; Blaine and Sinha, 2017) and different forms of psychopathology (Petrowski et al., 2013; Scott et al., 2013). As such, the potential prospective effects of adolescent binge drinking on later neuroendocrine system functioning may have a number of consequences. Yet, little is known about the relation between problematic drinking in adolescence and stress reactivity in young adulthood, especially with regard to individuals who experienced parental divorce in childhood. To address this critical gap in the literature, the current study tested the hypothesis that greater binge

drinking during adolescence (ages 15-19) would predict an attenuated cortisol response to social stress (i.e., lower cortisol reactivity) in young adulthood among individuals who experienced parental divorce in childhood, even after statistically adjusting for a range of covariates known to be associated with cortisol reactivity, including participant sex, smoking, family socioeconomic status, childhood externalizing problems, and binge drinking in young adulthood.

## 2. Materials and Methods

### 2.1. Participants

Participants were a subsample of families who were part of a longitudinal study of divorced families that participated in a randomized trial of a prevention intervention. Participant recruitment and eligibility are described in detail by Wolchik and colleagues (Wolchik et al., 2000) and only briefly reviewed here. Potential participants were identified by reviewing randomly selected divorce decrees (divorced within 2 years prior to baseline assessment) of families with children between ages 9 and 12. Families were recruited through letters and telephone calls; 20% of the sample was recruited through supplemental methods (e.g., media, referrals). The primary eligibility criteria were: primary residential parent was female, neither child nor mother was in treatment for mental health problems, mother had not remarried, and custody arrangements were anticipated to be stable. Families were excluded and referred for treatment if the child scored above 17 on the Children's Depression Inventory or 97<sup>th</sup> percentile on the Externalizing subscale of the Child Behavior Checklist or endorsed suicidal ideation.

Although not the subject of the current study, the larger project included a randomized controlled trial of a preventive intervention, the New Beginnings Program, which was designed to reduce children's post-divorce mental health problems. The original trial included 240 families, a sample size selected so that small to medium effects of the program could be detected with power equal to or greater than .80. Of the original 240 offspring enrolled in the trial, 194 participated in the 15-year follow-up. The current study is based on participants in the 15-year follow-up who supplied saliva samples, across intervention group assignment. Of the 194 individuals in the 15-year follow-up, 12 did not participate in the stressor task or provide saliva samples, and two had a cortisol concentration that was outside normal physiological parameters ( $>50$  nmol/L; Nicolson, 2008), indicating assay interference. Of the remaining 180 participants, 20 were excluded a priori due to pregnancy or breast-feeding ( $n = 9$ ), use of steroidal medications or chronic health conditions ( $n = 9$ ), violation of protocol by smoking within 30 minutes of the first saliva sample ( $n = 1$ ), or only one viable saliva sample ( $n = 1$ ). Thus, the final sample included 160 offspring (53.1% male; 88.8% White Non-Hispanic) between ages 24 and 28 ( $M = 25.55$ ,  $SD = 1.22$ ). By the 15-year follow-up, 40.2% of young adults had completed at least some college education. Young adults' median pre-tax annual household income was \$59,500.

### 2.2. Procedures

The current study comprises families who were randomized to participate in a literature control or an intervention (mother-only program and mother-plus child program version of a

preventive intervention for divorced families) (Wolchik et al., 2013, 2000). Because neither intervention condition was shown to have direct effects on cortisol, intervention and control groups were combined and intervention condition was included as a covariate in all analyses. Because previous analyses reported an age x intervention effect on cortisol reactivity in this sample (Luecken et al., 2015), analyses were repeated with this interaction term. However, the interaction was not significant in relation to cortisol and model fit deteriorated, thus the more parsimonious model is presented here.

All procedures and measures were approved by the Arizona State University Institutional Review Board. Six waves of assessment were conducted: baseline, post-test, 3-months later, 6-months later, 6 years later and 15 years later. In the current study, only data from the baseline, 6-year and 15-year follow-up assessments were used. All assessments were conducted by trained staff in participants' homes. At each assessment, confidentiality was explained, and mothers signed consent forms; offspring younger than 18 signed assent forms and offspring 18 or older signed consent forms. Families received \$45 compensation for participating in the interviews at baseline and young adults received \$225 and parents received \$50 at the 15-year follow-up.

## 2.3 Measures

**2.3.1 Adolescent binge drinking.**—During adolescence, binge drinking was measured using one item from the Monitoring the Future Scale (MFS; Johnston et al., 1995). The item read “Think back over the last two weeks. How many times have you had five or more drinks in a row (a “drink” is a glass of wine, a bottle of beer, a shot glass of liquor, or a mixed drink)?” Responses were measured on a six-point scale, from 1 = None to 6 = Ten or more times. The MFS was administered as part of a self-administered battery. Importantly, research has shown that survey administration procedures (i.e., anonymous vs. confidential) do not affect adolescent self-report responses to the MFS (O’Malley et al., 2000). The MFS has been used with high school and college students to assess national drug, alcohol and smoking trends and has been shown to have adequate construct validity (Johnston et al., 1995). Within our sample, 44.5% of adolescents reported having drunk alcohol in the last month and 20.5% reported binge drinking in the last two weeks.

**2.3.2 Young adult binge drinking.**—Binge drinking was measured at the 15-year follow-up with the same item used in the assessment in adolescence. During young adulthood, 87.4% of the sample reported having drunk alcohol in the last month and 44.4% reported binge drinking in the last two weeks.

**2.3.3 Social stress task and salivary cortisol collection.**—At the 15-year follow-up, young adults participated in a modified Trier Social Stress Task (TSST), which consisted of a mental arithmetic and a video-recorded speech task. The three-minute mental arithmetic task involved serial subtraction problems performed out loud with a new starting number provided each minute and adjusted for difficulty based on performance. It was conducted under time pressure, with prompting from the interviewer. Immediately following this portion of the task, participants were given 4 minutes to prepare a speech describing their personal strengths and weaknesses and 4 minutes to perform the speech. The interviewer

was present during the performance, which was also video-recorded. Prior to the performance, the interviewer informed the participant that the video would be evaluated by a team of psychologists and verbally instructed the participant to look into the camera.

The challenge task began approximately 30 minutes after arrival at the home. Participants provided four samples of cortisol throughout the task at baseline (T1), post-task (T2), 20 minutes later (T3) and 40 minutes later (T4). Participants were instructed not to eat, drink, smoke, or exercise during the two hours prior to the first saliva sample. Saliva was collected with a Salivette sampling device (Sarstedt, Rommelsdorf, Germany) held against the participant's inner cheek for 2 minutes. Saliva samples were then frozen at 20°C and mailed overnight to Salimetrics, Inc. where they were assayed for cortisol using a high-sensitive enzyme immunoassay. This immunoassay test has a range of sensitivity from .007 to 1.8, and average intra- and inter-assay coefficients of variation of 4.13% and 8.89%, respectively. Notably, although there was a decrease in cortisol, on average, across the task, there was significant variability in reactivity and a significant task-related increase in negative affect across the sample (Hagan, Luecken, Modecki, Sandler, & Wolchik, 2016).

**2.3.4 Covariates.**—A number of demographic and health factors known to influence cortisol were evaluated as potential covariates, including sex, family income during childhood, smoking status, and time of day<sup>1</sup>. Per capita income was assessed by maternal report at baseline. At the 15-year follow-up participants reported on their smoking status (“Do you currently smoke cigarettes or cigars?; 0 = No, 1 = Yes). Given the circadian rhythm of cortisol, time of day of saliva sampling was taken into account. Time of day was calculated by taking the number of minutes between midnight and the time at which the baseline cortisol sample was taken; minutes were transformed to hours to aid in model convergence.

To assess whether adolescent binge drinking prospectively predicted cortisol reactivity in young adulthood, adjusted for childhood externalizing or related characteristics that might also contribute to cortisol responses, child report of externalizing problems at baseline was included as a covariate, given its relation with young adult binge drinking (Englund et al., 2008). Externalizing problems were measured via the 27-item Divorce Adjustment Project Externalizing Scale (Program for Prevention Research, 1985; Cronbach's alpha = .87, unpublished manual).

## 2.4 Data Analysis

All analyses were run in Mplus v. 8 with Full Information Likelihood Estimation and robust standard errors to account for potential non-normality of study variables. Correlations among study variables are provided in Table A.1. In conditional models of growth curves, all predictors were grand mean centered, in-line with best practice (Curran et al., 2004).

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<sup>1</sup>We also tested models with either childhood or adolescent reports of life stress as covariates and all results were substantively the same. Hence, the more parsimonious models are presented here.

### 3. Results

#### 3.1 Examining and modeling unconditional trajectory of cortisol change over time.

First, we visually examined the individual values of (log-transformed) cortisol change over time, and these generally showed a pattern of decreasing cortisol over the first three time points, as well as indication of both linear and curvilinear change. Between-person variation was particularly evident for the last time sample. Next, we statistically modeled the nature of the trajectory of cortisol change over time (e.g. Felt et al., 2017). Modelling the unconditional trajectory of cortisol, the intercept was centred at the pre-task sample (T1) and specified fixed intervals associated with mean time elapsed for each repeated measure relative to T1 (e.g. 0, 1, 2.5, 3.5), with fixed time residual variances (e.g. Yeung et al., 2016). A likelihood ratio test was used to compare fit of linear versus quadratic models:  $-2LL \Delta (4) = 14.79$ ,  $p = .002$ , indicating the fit of the quadratic model was significantly better. Two models were then fit with the last cortisol sample fixed versus freed:  $-2LL \Delta (2) = 12.72$ ,  $p = .032$ , indicating that the specification with the last time sample free to vary was a significantly better fit. Here, the intercept reflects the pre-task sample (baseline cortisol) and the linear and quadratic slopes represent linear and non-linear change in cortisol across the task (often interpreted in terms of early and later change, respectively; e.g. Dawes et al., 2015). Hence, the linear slope relates to cortisol reactivity and the quadratic to cortisol recovery.

Fit indices indicated data fit the model well,  $\chi^2 = 2.83 (2) = .24$ ; RMSEA = .05; CFI = .99; SRMR = .05. As expected, on average, baseline cortisol was significantly different from zero (intercept  $b = -2.55$ ,  $p < .001$ ). There were significant decreases in cortisol across the initial time samples (i.e., “reactivity”; linear slope  $b = -.067$ ,  $p = .028$ ), followed by subsequent trend-level increases over the later time samples (i.e. “recovery”; quadratic slope  $b = .02$ ,  $p = .096$ ). There was also significant variation in baseline cortisol levels (intercept,  $b = .46$ ,  $p = .007$ ) and cortisol reactivity (linear slope,  $b = .016$ ,  $p = .039$ ). There was no significant variation in cortisol recovery (quadratic slope,  $b = .001$ ,  $p = .495$ ). However, this does not preclude regressing predictors on the quadratic slope, as significant covariates can still subsequently predict variation (e.g. Dawes et al., 2015).

#### 3.2 Conditional model of cortisol trajectory of change over time.

Once the best-fitting unconditional model of cortisol change was specified, we ran a conditional model in which cortisol intercept, linear, and quadratic slopes were regressed onto study covariates and adolescent binge drinking. Smoking status, time of day, participant sex, intervention condition, family income during childhood, childhood externalizing, and adolescent binge drinking were included as predictors of cortisol. In the conditional model, the only significant covariate that emerged was time of day (cortisol intercept,  $b = -.13$ ,  $p < .001$ ), such that earlier time of day was associated with higher cortisol starting values. Notably, participants sex was not a significant predictor of cortisol within our models. As hypothesized, adolescent binge drinking was a significant predictor of cortisol reactivity (on linear slope,  $b = -.023$ ,  $p = .043$ ), though not recovery (on quadratic slope,  $b = .01$ ,  $p = .73$ ). For illustration purposes, predicted estimates from this conditional

model were used to plot the effect of different patterns of adolescent binge drinking on cortisol trajectories (see Figure A.1).

### 3.3 Modeling SEM with Cortisol and Young Adult Binge Drinking as Outcomes.

Next, we added young adult binge drinking as a second dependent variable within the model, so that young adult cortisol indices (intercept, linear slope, and quadratic slope) were allowed to correlate with young adult binge drinking. Young adult binge drinking was also regressed on sex, intervention status, family income during childhood, childhood externalizing, and adolescent binge drinking. Thus, in this final model, the relation between adolescent binge drinking and young adult cortisol reactivity accounts for concurrent relations with young adult binge drinking, as well as parallel effects of key covariates. Fit indices indicated that the final SEM fit the data well,  $\chi^2(24) = 34.22$ ,  $p = .081$ ; RMSEA = .05; CFI = .983; SRMR = .045. Significant paths are shown in Figure B.1.

## 4. Discussion

The current study tested the prospective effects of adolescents' binge drinking on their neuroendocrine stress response during young adulthood among individuals at increased risk for problematic alcohol use by virtue of experiencing a stressful event—parental divorce—during childhood. Importantly, adolescents who reported greater binge drinking exhibited significantly lower cortisol reactivity to a standardized social stress task (i.e., greater, more rapid decreases in cortisol immediately following the task) nine years later compared to those who reported either no binge drinking or low levels of binge drinking. This association was not accounted for by other factors likely to impact both alcohol use and cortisol activity, including participant sex, childhood externalizing problems, family-of-origin socioeconomic status, or binge drinking in young adulthood.

Prior to discussion of the implications of these findings, the strengths of the study design are worth noting. First, unlike previous research on binge drinking and cortisol responses to stress (e.g., Orio et al., 2017), the current investigation used a prospective design, thereby establishing temporal precedence. This is critical given that the relation between alcohol and cortisol is likely bidirectional, with cortisol reactivity affecting alcohol consumption and alcohol drinking patterns influencing cortisol reactivity (Childs et al., 2011). Second, the study focused on adolescents who experienced parental divorce during late childhood or early adolescence, a group that is at elevated risk for problematic alcohol use (Pilowsky et al., 2009). Scholarly attention towards adolescents at risk for problematic alcohol use is particularly important given hypotheses that adversity experienced during the pre-pubertal period increases the risk of alcohol dependence in young adulthood via greater problematic drinking in adolescence (Dragan and Hardt, 2016). Third, the current investigation employed advanced statistical methods, and used a latent growth curve to model within-person indices of the cortisol stress response (e.g., Felt et al., 2017) and accounted for a number of known factors related to both problematic alcohol consumption and cortisol dysregulation. Fourth, the analyses took into account recent drinking patterns, placing cortisol response in the context of a path model, thereby minimizing the possibility that associations with stress reactivity could be attributable to recent drinking, rather than the use of alcohol at an earlier developmental stage.



In the current study, adolescents who reported heavy binge drinking exhibited a steeper decline in cortisol during a social stress task in young adulthood compared to adolescents who reported lower or no binge drinking. This rapid decline among heavy adolescent drinkers may appear counter intuitive given the known excitatory effects of alcohol use on cortisol activity immediately following consumption. However, previous research indicates that over time, problematic alcohol use can indeed result in a dampening of HPA axis activity (e.g., Orio et al., 2017). The steeper decline in cortisol observed here is concerning given the important role the cortisol stress response plays in meeting the neurobiological challenges inherent in stressful social situations. The activation and subsequent deactivation of the HPA axis and the associated release of cortisol is an integral part of the human stress response, with cortisol facilitating a number of psychophysiological functions including but not limited to increased cardiovascular activity, alterations to sensory thresholds, and sharpened cognition (Sapolsky et al., 2000). Although exaggerated cortisol reactivity has been historically regarded as synonymous with poor physical and psychological health, there is extensive research showing that attenuated reactivity, like the pattern observed here, is also associated with increased risk of a number of physical and mental health problems (for a review, see Phillips et al., 2013). Indeed, attenuated cortisol reactivity may have implications for the development of and recovery from substance use disorders. Previous research suggests that alcohol-associated alterations to HPA axis activity during stress may be a key pathway to the development of alcohol use disorders (Blaine and Sinha, 2017). In addition, attenuated cortisol reactivity has been associated with a higher rate of relapse among cocaine dependent subjects (Back et al., 2010), suggesting that neuroendocrine dysregulation may further complicate recovery from substance use disorders. Finally, a blunted cortisol stress response has also been associated with greater risk for different types of psychopathology (Petrowski et al., 2013; Scott et al., 2013), greater risk of developing post-traumatic stress disorder following a traumatic event (Stuedte-Schmiedgen et al., 2015), poor executive functioning (Blair et al., 2005), and chronic fatigue or chronic pain (Fries et al., 2005).

Our findings are also notable in the study's focus on adolescent predictors of later cortisol stress responses. That is, there is burgeoning clinical and research interest in adolescence as a time when individual trajectories related to both competence and psychopathology become more firmly established, as well as a time in which behavioral problems are increasingly likely to appear (Romer and Walker, 2007). It is also during this developmental period that adolescents and young adults make critical behavioral choices in multiple life spheres (Schulenberg et al., 2004), and neurobiological systems undergo critical developmental changes during adolescence (Casey and Jones, 2010). Despite legal restrictions on underage drinking, however, youth are more likely than adults to consume excessive amounts of alcohol in a short period of time (Windle, 2016). Perhaps owing to the continued developmental fine-tuning to the central nervous system, adolescents experience attenuated sensitivity to alcohol's negative effects (i.e., less drowsiness and motor impairment) as well as hypersensitivity to positive effects (i.e., motivation and reward processes) relative to adults (Spear and Swartzwelder, 2014; Varlinskaya and Spear, 2004). These developmental features render alcohol consumption particularly rewarding for adolescents in the short-term, but binge drinking during this period may be especially problematic for long-term mental

and physical health outcomes. Indeed, findings from the current study suggest potential negative consequences from adolescent drinking for stress system functioning in young adulthood.

Interestingly, relations between binge drinking and the indices of the cortisol stress response varied depending on developmental stage. In contrast to adolescent binge drinking, which was related to greater decreases in cortisol across time but was not associated with pre-task cortisol in young adulthood, greater binge drinking in young adulthood was associated with *higher* pre-task cortisol, but not to cortisol change during the stressor. Cross-sectional and longitudinal studies of alcohol use and the cortisol stress response have primarily examined cortisol reactivity in the context of acute alcohol administration, making it difficult to compare the present results with previous reports. The findings reported here, if replicated, suggest that previous and concurrent drinking patterns may differentially relate to pre-task cortisol and the cortisol stress response, highlighting the importance of examining components of the cortisol stress response profile separately.

These findings must be considered in the context of the study's limitations. First, we did not assess cortisol reactivity during adolescence, and it is possible that the observed blunted cortisol reactivity was present even earlier in development. Second, it was necessary for the study that the social stress task be administered at people's homes, as part of full assessment battery, and the level of cortisol response was perhaps consequently lower than responses to the task found in lab-based studies. In addition, although time of day was taken into account in the cortisol analyses, participant wake time was not assessed, and this was an important limitation given the influence of wake time on diurnal patterns of cortisol release. Third, binge drinking was assessed using self-report on a single item from a widely-used measure of risky behavior. It is possible that participants under-reported their use of alcohol on this index. If this is the case, however, we could expect study findings to be conservative. Fourth, participant sex was statistically adjusted for (and exploratory analyses tested for potential interaction effects between alcohol and sex on cortisol stress response, which were non-significant); however, it is possible that alcohol consumption differs in its effects on neuroendocrine activity across sex. Given known sex difference in cortisol responses to stress and substance use patterns, it will be important for future studies with larger prospective samples to examine whether the current findings occur in both males and females. Fifth, associations between alcohol use and cortisol activity may be affected by a family history of alcohol use disorder, and this was not assessed in the current study. Future research should explore whether prospective relations between problematic alcohol use and cortisol reactivity to stress is moderated by family history of alcohol use disorders. Finally, the participants in the current study were predominately white, healthy (i.e., no clinical psychiatric disorder at enrollment) and all had experienced parental divorce in childhood. As such, the findings may not necessarily generalize to other populations of young adults, such as individuals from two-parent or never-married families or other at-risk individuals (i.e., persons diagnosed with a psychiatric disorder or other forms of family disruption).

The present findings highlight a number of potentially productive directions for future research. Here, we explored the effect of adolescent binge drinking on later neuroendocrine stress responses among individuals who experienced parental divorce during childhood, and

it would be important to ascertain this effect in other populations experiencing stressful childhood circumstances. Further, establishing potential differences in this relation among those who have experienced early stressful circumstances and those who have not, might better elucidate mechanisms of stress effects on later neuroendocrine functioning. Likewise, greater attention to the developmental timing of heavy drinking and the perimeters for especially sensitive periods that are disruptive for neuroendocrine activity is needed. It is also unknown whether the associations between adolescent binge drinking and young adult cortisol activity have implications for other relevant developmental outcomes, such as risk-taking behavior or depression. Given other evidence that alcohol-associated neuroendocrine alterations might increase the risk of substance use disorders, it will be important to examine whether this may be the case over the long-term.

#### 4.1 Conclusions.

The biological consequences of risky health behaviors can be long-standing and especially insidious when they occur during a sensitive developmental period. Notably, during adolescence, the neuroendocrine stress response continues to undergo calibration as the human hormonal profile shifts from pre-puberty to post-puberty. This shift may render adolescence an especially vulnerable time for adverse effects on the stress response system. We found a significant prospective association between binge drinking during adolescence and cortisol reactivity to psychosocial stress in young adulthood. Individuals who reported high levels of binge drinking exhibited a more rapid decline in cortisol than those reporting lower levels of binge drinking. These findings indicate that problematic drinking in adolescence may lead to neuroendocrine dysregulation in young adulthood.

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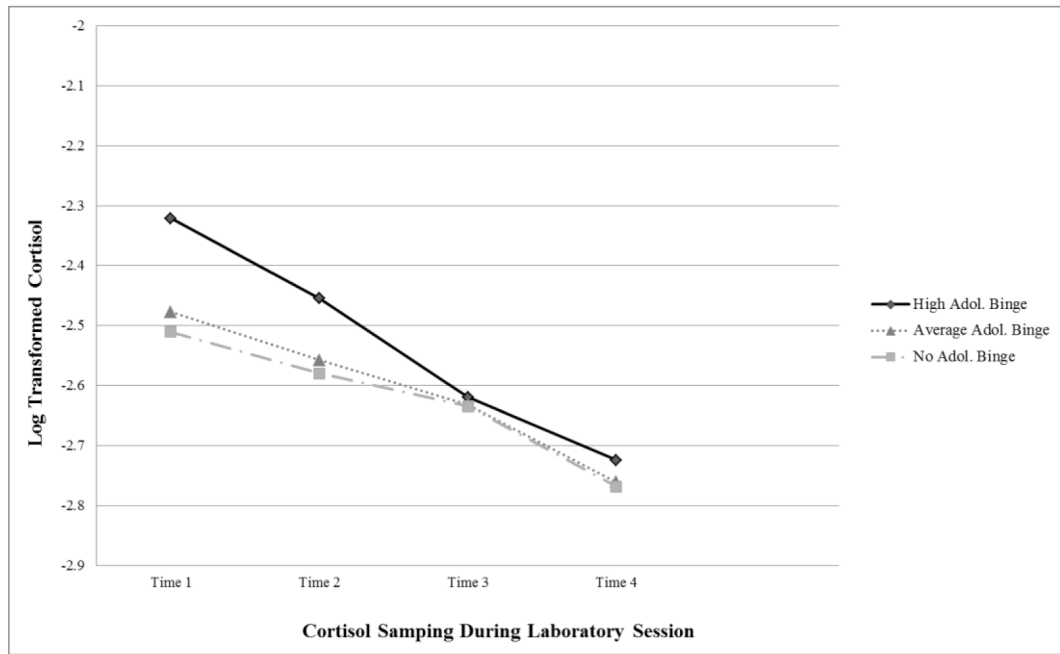
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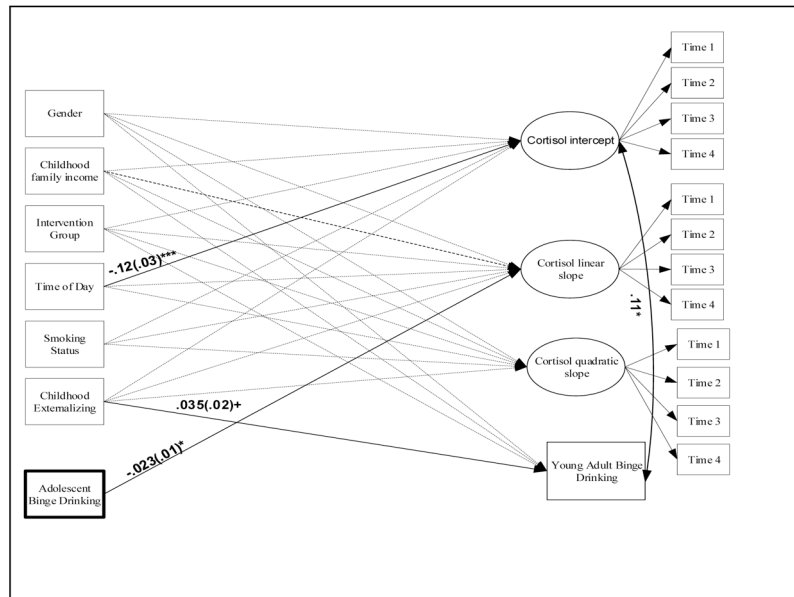
### Highlights

- Adolescent binge drinking predicts attenuated cortisol reactivity 9 years later
- Binge drinking in young adulthood is associated with higher pre-stress cortisol
- Problematic alcohol consumption relates to different aspects of the cortisol response



**Figure A.1.** Conditional model of young adult cortisol output during a standardized social stress task at no, mean, and high (2 SD above mean) adolescent binge drinking, controlling for all study covariates.





**Figure B.1.** Conditional path model, adolescent binge drinking predicting young adult cortisol trajectories and binge drinking.  
*Note.* Significant and trend paths shown +  $p < .10$ , \* $p < .05$ . \*\*\* $p < .001$ . Significant and trend paths denoted by solid lines with associated unstandardized betas and standard errors.

**Table A.1.**

Pairwise correlations between main study variables.

Variables	1	2	3	4	5	6	7	8	9	10
1. Sex	-									
2. Income	.14 <sup>+</sup>	-								
3. Smoking Status	-.11	-.05	-							
4. Extern	-.17 <sup>*</sup>	-.08	.06	-						
5. Adol Binge	-.11	.11	-.08	.17 <sup>*</sup>	-					
6. Adult Binge	-.11	.01	-.08	.19 <sup>*</sup>	.16 <sup>*</sup>	-				
7. Cortisol 1	.01	-.06	.02	.01	.05	.16 <sup>*</sup>	-			
8. Cortisol 2	-.01	-.09	.04	-.03	.06	.22 <sup>**</sup>	.89 <sup>***</sup>	-		
9. Cortisol 3	-.13	-.07	.03	-.01	.01	.22 <sup>**</sup>	.74 <sup>***</sup>	.84 <sup>***</sup>	-	
10. Cortisol 4	-.03	-.03	.01	-.05	-.04	.19 <sup>*</sup>	.73 <sup>***</sup>	.83 <sup>***</sup>	.87 <sup>***</sup>	-

Note. Sex: 0 = male, 1 = female; Income = childhood per capita income; Smoking Status: 0 = not currently smoker,

1 = current smoker; Extern = childhood extern.; Adol. Binge = adolescent binge drinking; Adult Binge = adult binge drinking.

<sup>+</sup>  $p < .10$ ;

<sup>\*</sup>  $p < .05$ ;

<sup>\*\*</sup>  $p < .01$ ;

<sup>\*\*\*</sup>  $p < .001$