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Between and within person associations between negative life events and alcohol outcomes in adolescents with ADHD

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These hypotheses and analyses have not been presented in any form prior to this manuscript.

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Abstract

Escalations in alcohol use during adolescence may be linked with exposure to negative life events, but most of this research has focused on between person associations. Moreover, adolescents with ADHD may be an especially vulnerable population, reporting more life events, alcohol involvement, and may even be more sensitive to the effects of life events on alcohol outcomes compared to those without ADHD. We tested the between and within person effects of the number and perceptions of negative life events on the development of alcohol use outcomes from age 14 to 17 in 259 adolescents with and without ADHD using generalized estimating equations. Between person differences in exposure to negative life events across adolescence, but not the perception of those events, were associated with a higher likelihood of alcohol use and drunkenness at age 17. Within person differences in life events was associated with alcohol use above and beyond that predicted by an adolescents' typical trajectory over time. Parent and teacher-reported ADHD symptoms were associated with more negative perceptions of life events, and with greater alcohol use and drunkenness at age 17, but symptoms did not moderate the life event-alcohol association. Interventions should consider the variables that produce vulnerability to life events as well as the immediate impact of life events. That the accumulation of life events, rather than their perceived negativity, was associated with alcohol outcomes, indicates that interventions targeting the reduction of negative events, rather than emotional response, may be more protective against alcohol use in adolescence.

Keywords: between-within individual differences; adolescent alcohol involvement; ADHD; generalized estimating equations; zero-inflated count models

Alcohol use disorder is most prevalent between ages 18 and 29 (B. F. Grant et al., 2015), but the development (e.g. the initiation of use and the first appearance of problems) of these disorders begins earlier in adolescence (Meich, Johnston, O'Malley, Bachman, & Schulenberg, 2015). As the average quantity and frequency of alcohol use increases in the general population from adolescence into young adulthood, variability in alcohol use also steadily increases with age, with some adolescents escalating rapidly into heavy drinking and eventually problems (e.g., Hussong, Bauer, & Chassin, 2008), while others remain light or moderate drinkers. Only a fraction of those who begin drinking in adolescence eventually develop an alcohol use disorder, with estimates of the past year prevalence of any alcohol use disorder between ages 18 and 29 at approximately 26% (B. F. Grant et al., 2015) . As such, understanding what influences the developmental trajectories of alcohol involvement across adolescent development remains a priority of research.

Although a large literature has outlined the pathways by which externalizing behaviors may influence the development of adolescent alcohol involvement (see review by Chassin, Colder, Hussong, & Sher, 2016), emerging evidence suggests that exposure to negative life events may independently shape alcohol use trajectories and presage worsening outcomes (Keyes, Hatzenbuehler, Grant, & Hasin, 2012). Negative life events predict higher levels of alcohol use, alcohol related problems, and alcohol use disorders among adolescents and young adults (Cerbone & Larison, 2000; King & Chassin, 2008; Wills, Sandy, & Yaeger, 2002). Prospective studies that have focused on change over time in alcohol use suggested that exposure to negative life events was associated with escalating trajectories of alcohol use during adolescence (King, Molina, & Chassin, 2009; Wills, Sandy, Yaeger, Cleary, & Shinar, 2001).

This prior research on the negative life event-alcohol use association focused on between-person associations, where those who report more negative life events at an earlier time point exhibited, on average, higher levels or greater increases in alcohol use and problems over time. However, most hypotheses about the role of negative life events in alcohol use focus on within-person processes, hypothesizing that alcohol use occurs when an individual is both exposed to negative life events and utilizes maladaptive coping strategies in the face of those negative life events (Chassin et al., 2016; Sher, Grekin, & Williams, 2005). Some individuals are more likely to experience negative life events, either because of contextual or individual factors such as parenting, temperament, or socio-economic status (King, Molina, & Chassin, 2008). Thus it is important to disaggregate the between individual effects of exposure, which may reflect more stable individual differences in the propensity to experience negative life events, from the within individual effects of the life events themselves, which may better represent the process of stress adaptation, as well as other time-varying factors that influence both stress and drinking (Curran & Bauer, 2011).

To date, one study showed that time-varying differences in negative life events were related to time specific increases (i.e. those not accounted for by an adolescent's average trajectory of use) in alcohol use and binge drinking during adolescence (Aseltine Jr. & Gore, 2000), but that study did not explicitly separate the within and between person associations of life events with alcohol use (Enders & Tofighi, 2007). Using a latent growth curve modeling framework, a second study showed that family life events were related to between and within person differences in alcohol use during adolescence (King et al., 2009). However, more recent methodological studies have suggested that some of the methods of that study, such as binning ordinal measures of alcohol use frequency (McGinley & Curran, 2014) or failing to disaggregate

between from within-person variance as predictors in growth models (Curran, Howard, Bainter, Lane, & McGinley, 2014), may have inflated the time-varying associations in those models. Finally, neither prior study accounted for the heavily skewed and zero-inflated nature of adolescent alcohol use (Atkins, Baldwin, Zheng, Gallop, & Neighbors, 2012).

Attention Deficit Hyperactivity Disorder (ADHD), Negative Life Events, and Alcohol Use

Substantial evidence suggests that adolescents with ADHD are at heightened risk of experiencing negative life events: ADHD is associated with academic and social difficulties that may directly increase the likelihood of experiencing negative life events (e.g., getting bad grades, fighting with peers (Barkley, 2006). Moreover, many children with ADHD continue to meet diagnostic criteria in adolescence (e.g. Barkley, Murphy, & Fischer, 2008) and even more experience impairment despite sub-clinical levels of ADHD symptoms (Sibley et al., 2012). Continued ADHD-related impairments may also indirectly increase the experience of other negative life events (e.g., parental decisions to restrict activities or resources). Finally, children and adolescents with ADHD come from families where they are exposed to higher levels of negative life events, such as exposure to marital conflict, divorce, general family adversity, and parental alcoholism (Counts, Nigg, Stawicki, Rappley, & von Eye, 2005; Knopik et al., 2006; Wymbs et al., 2008). It may be that adolescents with a diagnosis of ADHD report higher levels of negative life events because of the downstream effects of early ADHD (such as diminished peer relations), the background variables associated with a diagnosis of ADHD (such as family problems), or the effects of continued impairment from ADHD.

Adolescents with ADHD may not only report greater exposure to negative life events, but they may also be especially sensitive to their effects. Their diminished skills for coping with distress (Hampel, Manhal, Roos, & Desman, 2008; Molina, Marshal, Pelham, & Wirth, 2005),

among other vulnerability characteristics such as weak executive function and generally increased impulsivity, support this hypothesis. One study from our group found a stronger cross-sectional association between academic life events (e.g., "doing poorly on an exam") and problem alcohol use for adolescents with, versus without, ADHD histories (Marshal, Molina, Pelham, & Cheong, 2007). Relatedly, other widely studied environmental factors, such as peer alcohol use (Marshal, Molina, & Pelham, 2003) and parental monitoring (Walther et al., 2012), have been shown to be more strongly related to alcohol use for those with ADHD compared to those without ADHD. Understanding the potential for stress vulnerability in ADHD is particularly important given the increased risk for alcohol use disorder that characterizes this population in adulthood (e.g. Lee, Humphreys, Flory, Liu, & Glass, 2011).

While much prior research on negative life event exposure and alcohol use has utilized simple count measures of life events (which require an adolescent to report whether or not an event occurred), research on negative life events highlights the importance of considering individuals' perception of events (K. E. Grant et al., 2003). For example, Davis and Compas (Davis & Compas, 1986) found that the desirability of a life event (whether rated as negative or positive) was positively related to students' perception that they could cope with events ($r = .84$). Moreover, the mere number of stressors and how stressors are perceived may explain different variation in psychopathology (Duggal et al., 2000). Classic models of stress and psychopathology argue that stressors should be perceived as a challenge or threat to the individual (Lazarus & Folkman, 1984), although reviews of the stress literature show that both counts of stressors and an individuals' perception of those stressors can be useful (K. E. Grant et al., 2004). To date, most research has relied on counts of stressors, and has not considered whether an adolescent's perception of stressors explains variance in alcohol use. Adolescents

with ADHD are known to over-estimate their competence and underestimate their impairment across a number of life domains (Evangelista, Owens, Golden, & Pelham, 2008; Hoza et al., 2004). It may be that adolescents with ADHD report a higher number of life events, but (due to cognitive biases) report that they are less impactful or upsetting, and that their perception of events differentially alters the relation between negative life events and alcohol outcomes.

Current Study

The current study extends prior research by examining the between and within person associations of negative life events and alcohol outcomes in a sample of adolescents with and without a well-established diagnosis of ADHD during childhood, using statistical methods that better account for the skewed and zero inflated nature of those outcomes. The main goal of the current study was to replicate prior work while attempting to explicitly address the methodological challenges raised in recent studies, as well as extending these models to a new high risk sample, adolescents with ADHD. We hypothesized that both between and within individual differences in exposure to negative life events would be associated with alcohol use. The second goal of the current study was to test whether children diagnosed with ADHD reported greater numbers of negative life events during adolescence, and to examine the contribution of concurrent ADHD symptoms to negative life events. Third, we aimed to test whether adolescents with ADHD showed stronger associations between life events and alcohol behaviors during adolescence. We hypothesized that ADHD history would predict the experience of negative life events and, most importantly, strengthen the association between life events and alcohol outcomes. Finally, we compared simple counts of negative life events with the adolescent's perception of the negativity of those events.

Method

Participants

More detailed information on recruitment of the Pittsburgh ADHD Longitudinal Study (PALS) may be found in (Molina et al., 2012).

ADHD group. Participants with childhood ADHD were diagnosed with DSM-III-R or DSM-IV ADHD in childhood, at an average age of 9.40 years old (*SD* = 2.27). Participants with ADHD were selected for longitudinal follow-up with annual interviews due to their diagnosis of ADHD and participation in a summer treatment program (STP) for children with ADHD, an 8-week intervention that included behavioral modification, parent training, and psychoactive medication trials where indicated (Pelham Jr. & Hoza, 1996).

Participants with ADHD were assessed in childhood using standardized parent and teacher DSM-III-R and DSM-IV disruptive behavior disorder symptom rating scales (Pelham Jr., Gnagy, Greenslade, & Milich, 1992) and a standardized semi-structured diagnostic interview administered to parents by a Ph.D. level clinician. Two Ph.D. level clinicians independently reviewed all ratings and interviews to confirm DSM diagnoses and when disagreement occurred, a third clinician reviewed the file and the majority decision was used. Exclusion criteria for follow-up was assessed in childhood and included a full-scale IQ < 80, a history of seizures or other neurological problems, and/or a history of pervasive developmental disorder, schizophrenia, or other psychotic or organic mental disorders. At the first PALS follow-up interview, which occurred on a rolling basis between 1999 and 2003, the mean age was 17.75 years (*SD* = 3.39 years, range = 11 to 25).

NonADHD group. Adolescents without ADHD were recruited into the PALS when those with ADHD were recruited for follow-up. NonADHD comparison participants were recruited on a rolling basis to ensure demographic similarity to the ADHD group (age within one year, sex,

race, highest parental education), and were recruited from the same regional area as the participants with ADHD. Individuals who met DSM-III-R criteria for ADHD (presence of 8 or more symptoms reported by either the parent or young adult participant), currently or historically, were excluded. NonADHD comparison participants with subthreshold ADHD symptomatology, or with other psychiatric disorders, were retained.

Procedure

Interviews for the PALS were conducted annually in adolescence. Interviews were conducted in the ADD Program offices by post-baccalaureate research staff. Informed consent was obtained and all participants were assured confidentiality of all disclosed material except in cases of impending danger or harm to self or others (reinforced with a DHHS Certificate of Confidentiality). In cases where distance prevented participant travel to the research offices, information was collected through a combination of mailed and telephone correspondence; home visits were offered as need dictated. Self-report questionnaires were completed either with paper and pencil or web-based versions on a closed circuit internet page. All procedures were approved by the Institutional Review Board of Western Psychiatric Institute and Clinic.

Selection of the Current Sample

Data were selected from the first four annual interviews of adolescents based on procedures used elsewhere to test longitudinal hypotheses about adolescent functioning (Molina et al., 2012). Participants were selected if they were interviewed one or more times between the ages of 14 and 17. Because multilevel modeling and generalized estimating equations make use of all available data at Level 1 (Raudenbush & Bryk, 2002), participants were only excluded if they were not interviewed between ages 14 and 17. For the resulting subsample (n = 259), there were no statistically significant differences between the ADHD (n = 146) and nonADHD (n =

113) groups on sex or ethnic/racial minority, but a statistically significant difference for highest parental education and household income (lower in the ADHD group). For analysis, data were organized by age at interview to allow modeling of life events and alcohol use longitudinally by age (Bollen & Curran, 2006). This provided data for life events and alcohol use at one (n = 43), two (n = 79), three (n = 86), or four (n = 51) occasions. Participants provided data at ages 14 (n = 114), 15 (n = 158), 16 (n = 166), and 17 (n = 167). To estimate between person associations, we had data from 259 participants with 756 observations. To estimate within person associations, we had data from 216 participants (with 689 repeated observations), 129 of those participants (with 388 observations) reported any alcohol use. Table 1 provides descriptive statistics for the current sample.

Measures

Background Variables: Parental characteristics, sex, and race

Because they have been shown to influence the occurrence of life events, alcohol use, or both, for all analyses we initially controlled for the baseline presence of a parental alcohol use disorder, parental antisociality, maternal depressive symptoms, parental divorce, sex and race. Parental alcohol use disorder was coded as present if either parent met criteria on the SCID-NP (Spitzer, Williams, Gibbon, & First, 1990) by their own report or was reported by the other parent on the Michigan Alcoholism Screening Test (MAST-S: (Selzer, Vinokur, & Rooijen, 1975). The MAST-S focuses on consequences from problematic drinking and a score of 3 or higher was coded as having an alcohol use disorder. These two assessments were combined and coded as 1: either parent met criteria based on self/other-report vs. zero: neither parent met criteria based on self/other-report. Parental antisociality was coded as present if either parent met criteria on the SCID-NP (Spitzer et al., 1990). Maternal depressive symptoms were assessed by

maternal self-report on the 21-item Beck Depression Inventory (Beck, Steer, & Carbin, 1988). Sex was self-reported (0 = female, 1 = male), as was race (0 = White, 1 = Non-White).

Negative life events. Negative life events in the past year were assessed annually with 120 items from the Adolescent Perceived Events Scale (APES; Compas, Davis, Forsythe, & Wagner, 1987). The APES has been used extensively in prior research, and has been shown to predict both internalizing and externalizing symptoms in adolescents (K. E. Grant et al., 2003; McMahon, Grant, Compas, Thurm, & Ey, 2003). For each item, adolescents indicated whether or not an event occurred and, using a 9 point scale, the degree to which it was experienced as negative or positive (1= "Extremely Bad" to 9 = "Extremely Good"). Example life events were "Parents getting divorced," "Parent loses a job," "Having few or no friends," "Not getting along with parents of friends," "Doing poorly on an exam or paper," "Problems or arguments with teachers or principal," "Getting in trouble or being suspended from school," "Death of a family member," "Change in the health of a friend" and "Hospitalization of a family member or relative." We excluded 31 items from the original scale that assessed minor life events (such as going to church/synagogue or helping other people), psychological symptoms, bereavement/illness (which also occurred very rarely), substance use, or ADHD diagnosis or treatment, leaving 89 total negative life events. Following prior work with this scale (Wagner & Compas, 1990), we computed both a count of negative life events and a score reflecting the subjective evaluation of those negative events. Prior research has indicated that both the accumulation of life events as well as the adolescent's perception of them are independent predictors of psychopathology (K. E. Grant, Compas, Thurm, McMahon, & Gipson, 2004). The count was comprised of all items rated by the adolescent as at least "Slightly bad" (4) to "Extremely bad" (1). The subjective evaluation score was computed as the mean of the

adolescent's ratings of all events that were rated as at least "slightly bad" after reverse-scoring the ratings (e.g., "extremely bad" = 4). Across age, these two scores were correlated very weakly $r = .18$, $p < .001$).

Table 1 provides descriptive statistics for negative life events. On average, adolescents reported approximately 11 different negative life events in the past year (range = 0-58), and reported an average perception of 2.36, which represents a response of "Somewhat bad."

ADHD Symptoms. Childhood diagnosis of ADHD is described above. At each wave, ADHD symptoms were measured using parent and teacher report of 18 DSM-IV ADHD symptoms (Pelham Jr. et al., 1992), scored on a 0 (not at all) to 3 (very much) scale. We then took the maximum score across the two raters for each symptom and computed a mean across all symptoms at each age.

Alcohol Use

Alcohol use was assessed at each annual interview with a structured paper-and-pencil substance use questionnaire (SUQ; Molina & Pelham, 2003; Molina, Pelham, Gnagy, Thompson, & Marshal, 2007). The SUQ is an adaptation of existing measures, including the Health Behavior Questionnaire (Jessor, R., Donovan, J. E., & Costa, 1989) and the National Household Survey on Drug Abuse interview (The Substance Abuse and Mental Health Services Administration., 1992) and includes both lifetime exposure questions (e.g., have you ever had a drink, age of first drink) and quantity/frequency questions for alcohol and other substances. The current study utilized two items that assessed frequency of use and drunkenness over the past 12 months. Items used a 12 point scale (from "Never" to "Several times a day". We tested alcohol outcomes separately because there are concerns in the literature about combining across alcohol

outcomes and/or converting them to pseudo-count variables (as we did previously, King et al., 2009), particularly when they are measured with an ordinal scale (McGinley & Curran, 2014).

Analytic Strategy

We were interested in predicting between person differences in negative life events during adolescence from childhood and adolescent ADHD symptoms, and in predicting within and between person differences in alcohol outcomes during adolescence from life events and ADHD. However, our alcohol outcomes were heavily skewed and zero-inflated, in that many adolescents did not report drinking, and when they did, most reported fairly low levels. This produces non-normality in the residuals, violating the assumptions of MLMs, and can produce bad parameter estimates and misleading inferences (Atkins et al., 2012). Thus, to predict alcohol outcomes, we used Generalized Estimation Equations (Zeger, Liang, & Albert, 1988), GEE readily allows the estimation of zero-inflated and hurdle count models (such as zero inflated Poisson or hurdle negative binomial models) which may better estimate the response generation process for these variables, while also accounting for the effects of clustering within the individual. MLMs and GEEs were well suited as analytic approaches because both estimate parameters using the available Level 1 data (i.e., repeated observations of individuals across age), do not require all Level 2 observations (i.e., participants) to have identical or balanced observations at Level 1, and readily allow the separation of between and within components of variance in predictors and outcomes (Raudenbush & Bryk, 2002).

We tested our hypotheses in R 3.2.3 using the nlme and pscl packages with the maximum likelihood estimator (ML). We used MLMs to predict negative life events across adolescence and GEEs to predict alcohol outcomes. To estimate GEEs, we estimated generalized linear models with the appropriate link function (such as negative binomial or hurdle negative

binomial) using the r package pscl (Zeileis, Kleiber, & Jackman, 2008), and used a custom sandwich estimator to correct model standard errors for clustering (Hu, *personal communication*). This corrects the standard errors of the fixed effects for the effects of clustering while avoiding the problems that can arise from trying to model the random covariance structure (i.e. slope and intercept variability) of complex distributions such as zero inflated count distributions. Because our hypotheses were related to fixed effects only (such as estimating the associations between ADHD and the slope of alcohol use), rather than on obtaining a population level estimate of individual differences in slopes, GEEs were an appropriate choice to test the current hypotheses.

Zero-inflated hurdle models. Although alcohol outcomes were measured on an ordinal scale, we utilized models for count data as they best fit the distributions of the alcohol variables. Across all alcohol outcomes, model fit indices (BIC and AIC) suggested that zero-inflated or hurdle negative binomial models best fit the data; we chose hurdle negative binomial models because they best fit our interpretation of adolescent's actual behavior. Hurdle negative binomial models separately model the presence or absence of the outcome (i.e. the "hurdle", or likelihood) and, among those with any level of the outcome, the count (or level) of the outcome as a negative binomial distribution, which has a variance which is greater than its mean (Hilbe, 2011). Thus for each outcome, coefficients predicting the likelihood of the outcome occurring (i.e. whether or not an adolescent reported drinking in the past year) may be transformed into an odds ratio (OR), which predicts the relative odds of an event occurring. Coefficients predicting the level of an outcome are converted to a rate ratio (RR), which predicts the number of events (such as the number of drinks in the past year that an adolescent may report).

Centering of life events. To disaggregate the between and within person associations of negative life events with alcohol outcomes, we used a combination of centering within cluster at Level 1 and grand-mean centering at level 2 (Enders & Tofighi, 2007), which perfectly separates variation in a given predictor into within and between person variability. Centering within cluster (CWC) is achieved by subtracting a participant-level mean across observations from each participant's score at each time point. This provides a time-specific score that only reflects within person variance, and observations at each time point essentially become a deviation score, representing that person's deviation *from their own average* at that time point. The participant's mean score across observations may be grand-mean-centered (GMC) by subtracting each participant's mean from the sample average of all participant means, which can then be entered as their "between person" variable. This score represents a participant's average deviation from the sample mean, and reflects their average level of life event exposure across adolescence. These resulting CWC and GMC scores are perfectly *uncorrelated* ($r = 0.00$), as they partial within and between person variance in life event exposure over time. In this way, a multilevel model may be utilized to address state-trait questions by a simple centering scheme.

Model fitting approach. We followed a standardized approach to model fitting. For all model comparisons, we relied on AIC and BIC as tests of relative model fit (Raftery, 1995) prior to applying the GEE correction to account for clustering within subjects. We first tested for the general shape of change for both alcohol outcomes, comparing linear and quadratic models. Because there was little variability in alcohol outcomes at Age 14, we used age 17 as the intercept, and estimating growth from age 14 to 17, as in our previous research (Molina et al., 2012). To ensure that the main hypothesis tests were not biased by un-modeled dependencies in the data, we tested all covariate by predictor interactions as well as the between by within person

effects of both count and perceptions of life events. This is recommended as best practice for model building in regression models (Allison, 1977), and simulations have shown that *not* including or estimating interactions that exist in models can induce substantial bias in the main effects coefficients (Vatcheva, Lee, McCormick, & Rahbar, 2015). To balance the risk of alpha inflation against model mis-specification, we used an a-priori threshold of $p < .01$ to retain significant covariate by predictor interactions and refrained from interpreting any interactions we did retain to avoid speculation about non-hypothesized interactions. Then we examined the main effects of between and within person negative life events on each outcome. Next, we tested whether childhood ADHD was associated with life events during adolescence, and compared those models with ones measuring the effects of concurrent ADHD symptoms. Finally, we tested whether childhood diagnosis and concurrent symptoms of ADHD moderated the between and within person associations of life events with each alcohol outcome. Again, because we only had general hypotheses about this effect (i.e. that life events would have a stronger relation for those with ADHD or more ADHD symptoms), we used the Benjamini-Hochberg correction (Benjamini & Hochberg, 1995) to control for the false discovery rate. We initially controlled for parental alcoholism, antisociality and depression in all analyses, but controlling for them did not change the magnitude of the coefficients or inferences from the final models, so we dropped them for the sake of parsimony. Thus the final models controlled for sex, race, and parental divorce to control for baseline differences.

Results

Descriptive statistics

Adolescents with and without childhood diagnoses of ADHD reported similar counts and perceptions of life events (all $t(277) < 1.28$, $p > .20$), averaging around 11 negative life events

and reporting them to be "somewhat bad" on average. Among those with a childhood ADHD diagnosis, the average ADHD symptom score from age 14 to 17 was 1.51 (SD = .63), while the average ADHD symptom score for those without a childhood diagnosis was lower (M = .48, SD = .37), t(277) = -15.42, $p < .001$.

Only two covariate-by-predictor interactions were significant at our a-priori threshold of $p < .01$. A significant interaction of race (White vs. Non-White) by divorce (Non-divorced vs. Divorced parents) ($p = .0022$) suggested that the effects of parental divorce on the likelihood of any alcohol use were smaller for Non-White (OR = .05) adolescents than for White adolescents (OR = .60). Because these interactions were not hypothesized, we do not interpret them further, but we did include them in all further models to reduce model mis-fit and to improve coefficient estimation.

Unconditional models of alcohol involvement

We illustrate the unconditional growth models in Figure 1 to aid interpretation. For all alcohol outcomes, a linear effect of time best fit the data, with all fit indices for the quadratic model greater than those for the linear models, suggesting the linear model of time fit better than the quadratic. Unconditional model results, with estimates of intercepts and slopes, are presented in Table 2. Generally, the likelihood of alcohol involvement across each outcome increased over time, with the odds of reporting any alcohol use or drunkenness increasing by 1.7 – 1.9 per year from age 14 to 17. In other words, for every year that passed, the likelihood of any alcohol use or drunkenness nearly doubled. For example, the probability of reporting any alcohol use rose from less than 20% at age 14 to over 50% by age 17, while the probability of reporting any drunkenness rose from less than 10% to around 35%.

There were also linear increases in the frequency of alcohol use over time, with drinking increasing by 18% - 19% per year (controlling for the influence of the covariates) among those who reported any alcohol use. On the other hand, those who reported any drunkenness exhibited no increases in the level over time, even as other adolescents became more likely to drink in that manner.

Negative Life Events and Alcohol Involvement

We then examined the between and within person associations of negative life events with alcohol use during adolescence, predicting the likelihood and level of alcohol outcomes from between and within person variability in the number and perception of life events.

The most consistent effect we observed was that between person differences in the average count of negative life events over time were associated with higher age 17 likelihoods of alcohol use (OR = 1.10) and drunkenness (OR = 1.069). Additionally, within person variance in the number of negative life events was related to an increased likelihood of drunkenness (OR = 1.045), and a higher level (RR = 1.035) of alcohol use, meaning that in any given year, reporting more negative life events than expected were related to higher likelihoods of reporting drunkenness and more frequent alcohol use than what would be predicted by that adolescent's own trajectory of use. Moreover, after correction for the false discovery rate, we observed an association of within person variance in the number of negative life events and the *likelihood* of any alcohol use (OR = 1.033, $p = .06$).

On the other hand, the adolescent's perception of those life events was not related to either drinking outcome at either the between or within person level.

Predicting trait negative life events from ADHD

We next tested whether childhood ADHD predicted a larger number or worse perception of negative life events during adolescence using MLM. There was substantial between (54%) and within-person (46%) variability in adolescents' report of both the number and perception of negative life events. None of the covariates were related to the perception or number of negative life events across adolescence. Moreover, only the effect of ADHD on the perception of negative life events approached significance (b = .152, SE = 0.082, p = .063), which suggested that adolescents with ADHD reported marginally more negative perceptions of negative life events from age 14 to 17, but did not report any more or less negative life events relative to adolescents without ADHD.

This effect seemed to be confirmed in separate models using adolescent ADHD symptoms as a predictor of life events: the average level of ADHD symptoms across adolescence was associated with reporting more negative perceptions (but not higher numbers) of negative life events (b = .12, S.E. = .05, p = .035). In other words, higher levels of average ADHD symptoms across adolescence were related to more negative perceptions of life events on average.

Does ADHD moderate the effects of life events on alcohol involvement across adolescence?

Finally, we tested whether the relation between counts or perceptions of negative life events on alcohol use differed depending on childhood ADHD diagnosis or adolescent ADHD symptoms. Table 3 presents these final results. We tested this hypothesis by including ADHD diagnosis or adolescent ADHD symptoms (in separate models) as predictors of level and change in alcohol involvement, and as moderator(s) of the between and within person effects of life events described above. There were no main effects of childhood ADHD, nor moderation of life events by childhood ADHD that survived correction for the false-discovery rate. This suggested

that there was little support for the notion that childhood ADHD moderated the effects of life events on alcohol use.

Between person differences in ADHD symptoms during adolescence were associated with higher levels of alcohol use frequency (RR = 1.31) and drunkenness (RR = 1.53) at age 17. Among those who reported average or high levels of average ADHD symptoms across adolescence, the level of alcohol outcomes rose accordingly. There were no other main effects of ADHD symptoms during adolescence, nor did ADHD symptoms moderate the effects of life events on alcohol outcomes. Moreover, the associations between life events and alcohol use were largely unchanged with the inclusion of ADHD symptoms.

Discussion

The goals of the current study were to extend prior research on the between and within person associations between negative life events and alcohol involvement during adolescence in a high risk sample using a broad measure of life events and statistical models that better accounted for between and within person variability in life events as well as the non-normal distributions of alcohol outcomes in adolescence. We tested whether ADHD was associated with heightened vulnerability to negative life event exposure, and whether ADHD predicted a stronger association between negative life event exposure and alcohol involvement. Overall our results largely suggested that the number, but not the perception, of negative life events was associated with both between and within person changes in the level or likelihood of alcohol involvement during adolescence. Only ADHD symptoms that persisted across adolescence were associated with more negative perceptions of life events (but not the number of life events), as well as with higher levels of alcohol use and drunkenness. Neither childhood diagnosis of

ADHD nor persistence of ADHD symptoms strengthened the association between life event exposure and alcohol involvement.

Previous work (King et al., 2009) suggested that both between and within person exposure to uncontrollable stressors (familial life events) were related to trajectories of alcohol use. We partially replicated and extended this finding, showing that between person differences in the number of negative life events were associated with an increased likelihood of alcohol involvement. Specifically, adolescents who reported an average number of negative life events that was 1 SD above the mean across adolescence also reported a likelihood of any drinking that was nearly twice as high (OR = 1.96; obtained by multiplying the model coefficient by the SD of between person count of life events and then exponentiating) and a likelihood of getting drunk that was over one and a half times as high (OR = 1.61) as an adolescent at the mean number of life events. Conversely, adolescents whose *perceptions* of life events were 1 SD more negative than average were no more likely to drink (OR = 1.04) or report getting drunk (OR = 1.05) than those whose perceptions were at the sample average. One interpretation of this finding is a third–variable explanation: adolescents who are prone to experience negative life events, such as those with high levels of personality risk, or those in environmental contexts that expose them to high levels of adversity over time, are also more likely to drink and get drunk. Alternately, these findings may suggest that negative life events may be impactful because of their occurrence, rather than by their perception by the adolescent (Duggal et al., 2000). Altering appraisals of negative life events may be less effective than interventions that might seek to either reduce the number of negative life events themselves (by reducing controllable negative life events, such as by improving social skills), or by providing environmental supports that may counter the effects of uncontrollable negative life events whether or not an adolescent perceives them to be negative

(e.g., increasing involvement in prosocial activities). Interestingly, most research and theory on interventions to address stress among youth emphasize improved individual's coping or emotion regulation skills (Izard, 2002), but our findings lead us to speculate that supplementary approaches that counters the loss of resources that accompany accumulated negative life events (e.g., transportation to extramural activities needed after parental job loss; tutoring to raise poor grades) might be especially helpful. A growing literature on interventions that directly address ADHD-related impairments in adolescence is also relevant (Sibley et al., 2016). Future studies contrasting these approaches, and their associations with alcohol and other health risk behaviors, are warranted.

We also observed a relatively consistent within person association: above and beyond the variance explained by age, when adolescents reported more negative life events than what was typical for them, in that same year they had higher likelihoods of drunkenness and higher levels of alcohol use that were not explained by their developmental trajectories of alcohol involvement (the association with the likelihood of alcohol use approached significance). Adolescents who reported life events in a year that were 1 SD above the average number of life events they reported across the study also reported 15% higher levels (RR = 1.15) of alcohol use, and 1.20 times the odds (OR = 1.20) of reporting drunkenness in that year, relative to the expected level and likelihood at their average number of life events. On the other hand, the relative associations of within person fluctuations in perceptions with the level of alcohol use and the likelihood of drunkenness were much smaller and not significant (RR = .91, OR = .89, respectively). This finding extends our previous work (King et al., 2009) by showing that the associations of a broader range of negative life events beyond the relatively narrow range of family related life events captured by that earlier study are related to increased risk. Future

interventions/preventions may directly benefit from these results. For example, alcohol prevention/intervention efforts could focus on adolescents who report a recent life event (e.g., such as parental divorce or school transitions), as this may be a time when alcohol use will subsequently increase. Moreover, our findings suggest that it is the events themselves, not the adolescents' perception of them, which explain the within-person associations of negative life events with alcohol outcomes. Future research should explore the degree to which these state associations generalize to other forms of externalizing and internalizing psychopathology, and whether other time varying factors (such as social support or coping skills) may moderate the associations of life events with psychopathology to guide the target of intervention. However, we should also caution that these within-person associations, which represent retrospective associations at the yearly level, cannot determine the true direction of effect; studies with a more time sensitive design can bring us closer to an understanding of the connections between stress and alcohol use in the moment.

In general, adolescents with a childhood diagnosis of ADHD were no different in terms of their experience of the number or perception of negative life events between ages 14 and 17. However, between person differences in *current* ADHD symptoms (i.e. parent and teacher reported symptoms during adolescence) were associated with a more negative perception of negative life events. Although a proliferation of studies have shown that adolescents and young adults with ADHD histories perceive less symptomatology and impairment than reported by their peers or parents (e.g., Mrug, Hoza, & Bukowski, 2004), this positive self-perception bias may not fully extend to perception of negative life events as stressful. This finding does not rule out the possibility that adolescents with ADHD actually under-report the *occurrence* of negative life events, but perceive those that do occur as more negative. This differential finding may suggest

that it is inattention to event occurrence that explains positive biases. Both symptoms of and impairment from ADHD for many adolescents continue to persist into adolescence (Barkley et al., 2008; Sibley et al., 2012), and these impairments may contribute to the perception of negative life events as more negative or stressful, particularly in the familial, school, and social domains as adolescents navigate the challenges of developing autonomy and individuation from parents, increasingly challenging school and social demands (Bagwell, Molina, Pelham Jr., & Hoza, 2001; Kent et al., 2011). A number of studies have shown that symptom persistence in adolescence is associated with other externalizing problems such as oppositional defiant disorder and conduct disorder, (i.e. Costello & Maughan, 2015), emotion problems, suicidality and academic failure and dropout (Costello & Maughan, 2015; Kessler et al., 2014), as well as early adult substance use (Howard et al., 2015) including, in this sample, an association between ADHD symptom persistence, delinquency, and frequency of alcohol use (Molina et al., 2012, and replicated in the current study).

On the other hand, neither these life event perceptions, nor the experience of the negative life events themselves, were more strongly associated with alcohol outcomes for adolescents with a history of ADHD or with ongoing ADHD symptoms. These results conflict with prior work suggesting that adolescents with ADHD may be more susceptible to environmental conditions in regard to alcohol use (e.g., peer alcohol use, parenting factors, Belendiuk, Pedersen, King, Pelham, & Molina, 2016; Marshal et al., 2007; Walther et al., 2012). The differences between prior studies and the current one may reflect the longitudinal nature of the current study, the emphasis on the between and within individual differences in negative life events, or the treatment of alcohol use as a zero-inflated count outcome. It may also be important to consider additional dimensions of life event perception beyond positivity and negativity, such

as the impact a life event has on an adolescent, or how important an adolescent views the event itself. Further research utilizing multiple informants of life events (e.g., school records, parental report) would also be useful as a check on the role of positive self-perception bias on our findings. In addition, a direct comparison of the effects of parent-reported impairments from ADHD, with the most typical being academic, behavioral, and social (Barkley et al., 2008), to those of self-reported negative life events associated with the experience of these impairments, would further specify sources of alcohol use vulnerability for adolescents with ADHD. Mechanistic studies of negative affect, versus impairment-driven, pathways could follow (Molina & Pelham Jr., 2014).

It should also be considered that both our null and significant findings could have been influenced by low power to detect effects in the current study, particularly at the within-person level, and that lack of support for certain effects (especially interactions) may at best suggest that effects that do exist may be smaller than the significant effects we were able to detect. Those effects were only estimable using data from individuals with more than one time point (n = 216 participants with 689 repeated observations, and only 129 of those participants reported any alcohol use). It is not well understood what study or design factors influence statistical power in GEEs, especially for hurdle count GEEs, and there are no guidelines for standard measures of effect size for count models in terms of what constitutes a small, medium or large effect size. The relatively low variability in alcohol outcomes in the current study may have influenced our ability to detect associations, and thus the null effects we report may not be reliably ruled out unless they are replicated in other samples. Moreover, some studies have raised the concern that effect size estimates from smaller samples, even if statistically significant, may be unreliable (Kraemer, Mintz, Noda, Tinklenberg, & Yesavage, 2006). Although it is not clear whether 689

repeated observations should be considered "small" for a GEE with a hurdle negative binomial outcome, given the low variability in alcohol outcomes, this possibility should be considered, and it would be important to replicate the current findings to determine the degree to which the effect size estimates are reliable.

There are several strengths to the current study. First, we modeled our alcohol outcomes in a way that accounted for the heavily zero-inflated and skewed nature of the data, and avoided combining across outcomes when doing so has been shown to produce mis-estimation (McGinley & Curran, 2014). Our application of multiple methods (such as testing between and within-individual effects of negative life events, count and perceived life events, and childhood vs. concurrent ADHD) allowed a more nuanced examination of the current hypotheses. This is particularly important in light of the increasing awareness of p-hacking (Simmons, Nelson, & Simonsohn, 2011), practices which bias research studies toward presenting positive findings. As such we intentionally presented all of our findings across all operationalizations of predictors and outcomes, and used a relatively conservative approach to alpha correction with the Benjamini-Hochberg correction, in order to provide a clear and hopefully reliable picture of how and when ADHD and negative life events are associated with alcohol use.

At the same time, several limitations warrant acknowledgement. Moreover, while we utilized zero-inflated hurdle models to account for the non-normal distributions in alcohol outcomes, the alcohol items were ordinal in nature, and not true counts. It may be that ignoring this may have inflated the estimates of alcohol use in the current study. Secondly, our reliance on self-report, particularly of life events, may have resulted in an underreporting in these events, particularly by the ADHD group. Moreover, we collapsed multiple categories of negative life events (both major and minor, and life events of different sources). Although the goal here was

to measure a general sense of the negative life event load, it could be that more precise findings could be obtained by a more fine grained analysis of the effects of sub-categories of negative life events. Unfortunately there are few theoretically driven approaches to categorizing life events (but see Pillow, Barrera, & Chassin, 1998), and doing so for the current manuscript would have dramatically increased the risk of alpha inflation.

Despite these limitations, the current study adds significantly to the literature by examining negative life events with multiple different approaches over time. Specifically, these findings highlight the complexity of the negative life events-alcohol association and indicate the importance of examining both the number of life events as well as the perception of how negative these events are to the adolescent. Further, future efforts focused on decreasing alcohol use the year following a negative life event may help reduce the escalation of adolescent alcohol use. Lastly, understanding how negative life events relate to alcohol use for adolescents with ADHD underscores the possibility that targeting negative life events, acute as well as chronic, may ultimately decrease risk for alcohol use disorder in this at risk population.

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Table 1. Demographics of Current Sample (n = 259)

	Total (*n* = 259)		**ADHD (*n* = 146)**		**Control (*n* = 113)**	
% Female	7.7		8.2		7.1	
% White	79.2		78.8		81.4	
	M	***SD***	***M***	***SD***	***M***	***SD***
Parental Education	7.27	1.61	7.09*	1.57	7.51*	1.64
Household Income (in thousands of dollars)	65.06	46.95	54.68***	40.37	78.45***	51.44
Age at Time 1	14.48	1.68	14.53	1.63	14.42	1.75
Grade Level at Time 1	8.86	1.74	8.86	1.67	8.87	1.83
Mean of negative life events across all ages						
	M	***SD***	***M***	***SD***	***M***	***SD***
Number of Negative Life Events	11.42	8.55	11.38	9.40	11.47	7.47
Perception of Events (1 = "Slightly Bad" to 4 = "Extremely Bad")	2.25	0.89	2.31	0.97	2.19	0.79
	M	SD	M	SD	M	SD
Alcohol Frequency	1.23	2.12	1.02	1.62	1.23	2.12
Frequency of Drunkenness	0.81	1.91	0.49**	1.19	0.81**	1.91
% with no Alcohol involvement	30.1%		29.9%		30.4%	

Difference is significant, p< .05; ** Difference is significant, p< .01; * Difference is significant, p< .001*

Table 2. Unconditional growth model

	Count			Likelihood		
Alcohol frequency	**b**	**SE**	**RR**	**b**	**SE**	**OR**
Intercept	**0.927**	0.140	2.527	0.166	0.125	1.180
Age	**0.175**	0.072	1.192	**0.556**	0.067	1.743
Frequency of drunkenness						
Intercept	**0.690**	0.373	1.994	**-0.617**	0.131	0.539
Age	0.080	0.097	1.083	**0.644**	0.088	1.904

**Note:* RR = Rate ratio, OR = Odds Ratio, SE = Standard Error. Bolded coefficients are significant at p < .05.

Table 3. Effects of negative life events and ADHD on alcohol involvement.

	Count			**Likelihood**		
Alcohol Frequency	RR	LCL	UCL	OR	LCL	UCL
Number of Negative Life Events (Within Person)	**1.03**	1.01	1.06	1.03	1.01	1.06
Perceived Negative Life Events (Within Person)	0.87	0.69	1.10	0.99	0.80	1.22
Number of Negative Life Events (Between Person)	1.01	0.99	1.03	**1.10**	1.04	1.15
Perceived Negative Life Events (Between Person)	0.97	0.77	1.22	1.07	0.68	1.68
Age X Number of Negative Life Events (Between Person)	1.00	0.98	1.02	1.02	0.99	1.04
Age X Perceived Negative Life Events (Between Person)	0.82	0.64	1.04	0.89	0.71	1.11
Childhood ADHD	1.21	0.91	1.62	0.74	0.43	1.27
Age X Childhood ADHD	0.94	0.72	1.22	0.85	0.64	1.13
Adolescent ADHD Symptoms (Within Person)	1.00	0.70	1.43	0.86	0.52	1.41
Adolescent ADHD Symptoms (Between Person)	**1.31**	1.08	1.59	1.01	0.70	1.46
Age X Adolescent ADHD Symptoms (Between Person)	1.10	0.94	1.30	0.91	0.76	1.10
Frequency of Drunkenness	RR	LCL	UCL	OR	LCL	UCL
Number of Negative Life Events (Within Person)	1.00	0.96	1.04	**1.04**	1.01	1.08
Perceived Negative Life Events (Within Person)	0.99	0.66	1.49	0.83	0.59	1.17
Number of Negative Life Events (Between Person)	1.01	0.98	1.04	**1.07**	1.02	1.12
Perceived Negative Life Events (Between Person)	0.98	0.70	1.37	1.08	0.68	1.73
Age X Number of Negative Life Events (Between Person)	1.01	0.99	1.03	1.00	0.97	1.03
Age X Perceived Negative Life Events (Between Person)	**0.68**	0.49	0.98	0.95	0.71	1.28
Childhood ADHD	1.66	1.08	2.56	0.91	0.51	1.62
Age X Childhood ADHD	1.09	0.74	1.60	0.80	0.54	1.18
Adolescent ADHD Symptoms (Within Person)	1.78	1.11	2.86	0.85	0.46	1.58
Adolescent ADHD Symptoms (Between Person)	**1.54**	1.15	2.06	1.22	0.82	1.81
Age X Adolescent ADHD Symptoms (Between Person)	1.37	1.02	1.83	0.92	0.73	1.17

* Childhood and Adolescent ADHD effects are reported from separate models; all other coefficients are from the Childhood ADHD models, and did not substantively differ from the Adolescent models. Bolded coefficients are significant at $p < .05$ following a Benjamini Hochberg correction for the False Discovery Rate. We controlled for gender, race, and parental divorce. RR = Rate ratio, OR = Odds Ratio, LCL = Lower Confidence Limit, UCL = Upper Confidence Limit, ADHD = Attention Deficit Hyperactivity Disorder.

Figure 1. Unconditional growth models of past year alcohol involvement.
Figure 1a. Frequency of use.

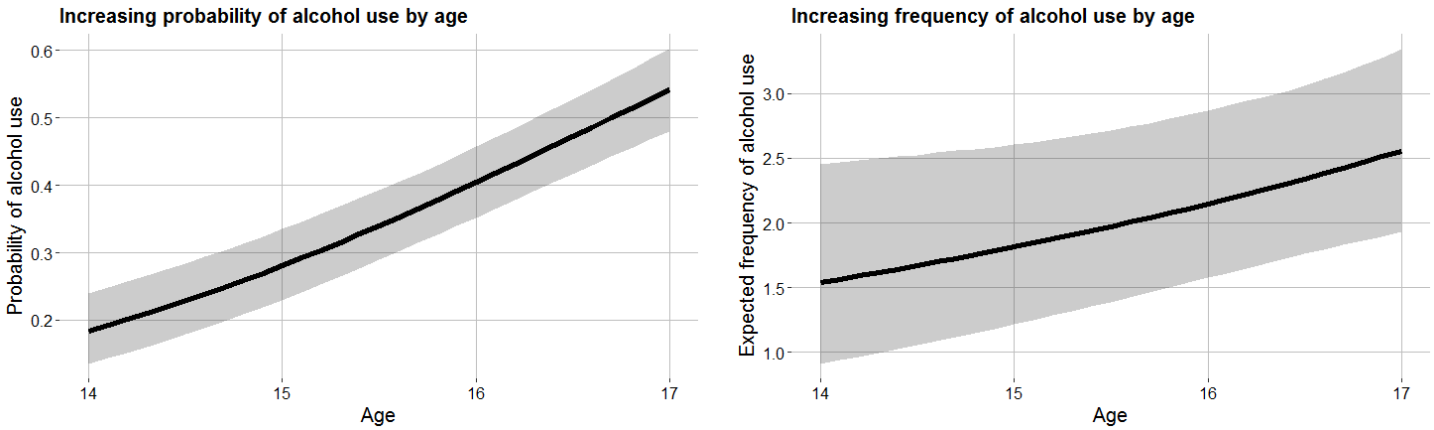

Figure 1b. Frequency of drunkenness.

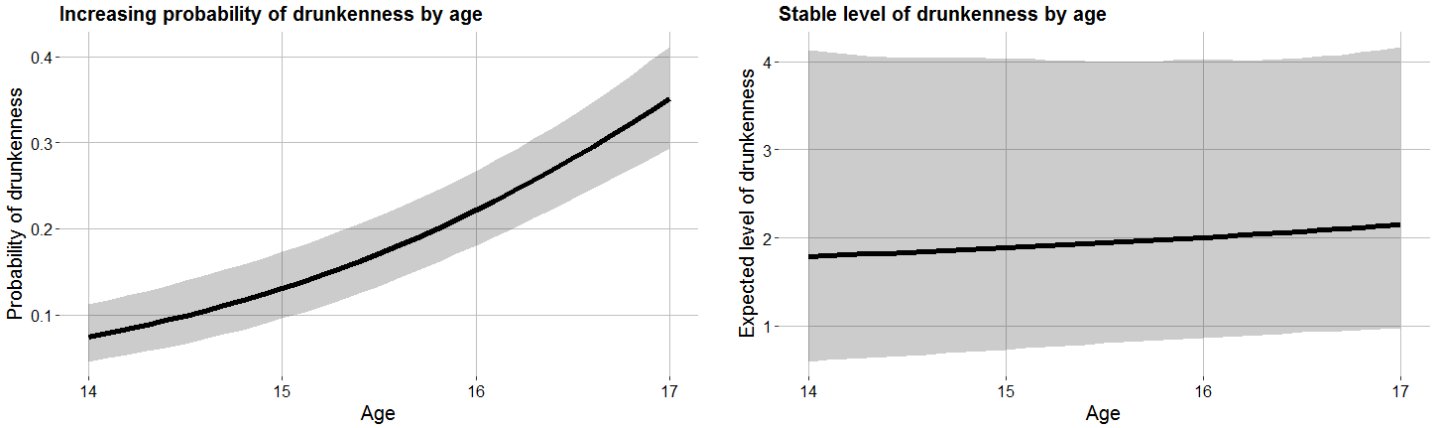

Figure Caption. *Model predicted probability and level of alcohol outcomes by age. Confidence intervals were simulated using the simcf package (Adolph, personal communication).*

Figure 2. Between person differences in life event exposure predicts heightened probability of alcohol use over time.

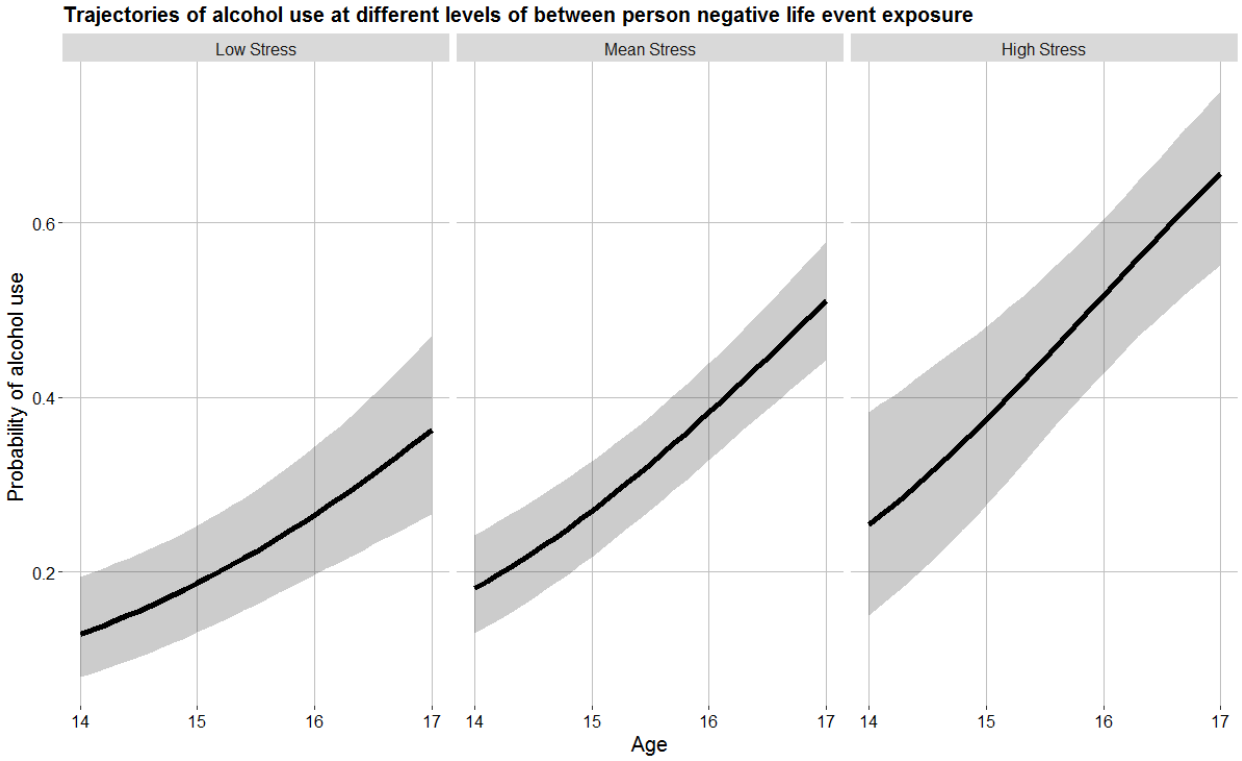

Figure Caption. *Model predicted probability of alcohol use by age at -1, mean and +1 SD of between person count life event exposure. Confidence intervals were simulated using the simcf package (Adolph, personal communication).*