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Assessing Cross-lagged Associations between Depression, Anxiety, and Binge Drinking in the National Consortium on Alcohol and Neurodevelopment in Adolescence (NCANDA) study

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Abstract

Background: Between 20 and 30 percent of teens suffer from depression or anxiety before reaching adulthood, and up to half also use or misuse alcohol. Although theories suggest bidirectional links between harmful alcohol use (e.g., binge drinking) and internalizing symptoms (i.e., depression and anxiety), empirical evidence to-date has been mixed. Systematic reviews have attributed mixed findings to limitations in study design, such as the utilization of between-person analyses and the focus on unidirectional effects. The goal of this study was to address these limitations by assessing bidirectional within-person associations between internalizing symptoms and binge drinking over the course of 5 years in the National Consortium on Alcohol and Neurodevelopment in Adolescence (NCANDA) sample, a large cohort recruited at ages 12–21 and followed annually on substance use and psychiatric functioning.

Methods: We used latent curve models with structured residuals to examine within-person lagged associations between depression, anxiety, and past month counts of binge drinking using NCANDA data (N=831). Analyses were supplemented with post-hoc power simulations.

Results: We found marginal evidence linking binge drinking with subsequent depression symptoms one year later among females. We found no evidence that depression or anxiety predicted subsequent binge drinking despite sufficient power.

Conclusions: Social and cognitive consequences of binge drinking may predict later depression symptoms in adolescence and young adulthood for young women, though there was little evidence

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Conflict of Interest

The authors declare that they have no conflict of interest.

AM generated the idea for the study. AM and CM wrote the initial draft of the manuscript, and SB and TB edited the manuscript. Analyses were conducted by CM. SB and TB provided data used for the current study. All authors approved the final version of the submitted manuscript.

favoring self-medication models for binge drinking. We note several moderating variables and common factor mechanisms that may better explain this link.

Keywords

binge drinking; depression; anxiety; adolescence; longitudinal

Introduction

Seventeen percent of 12th graders reported past 2-week binge alcohol use in 2020 (Johnston et al., 2021), defined as five or more drinks on the same occasion on at least 1 day in the past 30 days in males (four or more drinks in females). Adolescents tend to drink more alcohol per occasion, yet less frequently than adults (“Report to Congress on the Prevention and Reduction of Underage Drinking,” 2018). Binge drinking may have serious consequences on adolescent health, including overdose, fatal injuries, and motor vehicle accidents, and long term impacts on families, other students, and the general community (Hedden et al., 2014; Hingson and White, 2014). In addition, binge drinking has potential detrimental impacts on brain development, cognition, mood, and school performance (Meruelo et al., 2018).

One in five teens suffer from depression, over 30% suffer anxiety symptoms, and up to half of those endorsing internalizing symptoms also endorse comorbid substance use, including alcohol (Kaminer et al., 2007; Merikangas et al., 2010). Understanding youth binge drinking and its relation with co-morbid internalizing symptoms is therefore a critical problem that may affect adolescents throughout development. Persistent binge drinking, depression, and anxiety are associated with a variety of poor health outcomes (myocardial infarctions, obesity, and diabetes among others) that ultimately affect both quality and quantity of life (Baliunas et al., 2009; Egede, 2004; Egede et al., 2005; Everson-Rose and Lewis, 2005; Lim et al., 2012; Rehm et al., 2014, 2010). Rates of adolescents with depressive and/or anxiety symptoms in the United States have sharply increased since 2012 (Bitsko et al., 2018), and have coincided with decreases in alcohol consumption (Keyes et al., 2020). As such, understanding the evolving relation between adolescent internalizing symptoms and developing binge drinking behaviors remains crucial in determining developmentally informed targets for prevention and intervention of substance-related health risks among youth.

Theory has suggested bidirectional links between depression/anxiety and alcohol behaviors throughout adolescence (Garey et al., 2020). For instance, the *self-medication model* for negative affect and alcohol use proposes that because both anxiety and depressed mood produce aversive negative mood states, adolescents may develop coping motives for alcohol use via attempts to reduce negative affect symptoms through drinking. Over the long term, this behavior may lead to development of increasingly heavier use and delayed-onset alcohol use disorder by means of negative reinforcement. This model has been conceptually shared by several explanatory models for the development of alcoholism (Conger, 1956; Khantzian, 1985; Quitkin et al., 1972; Sher and Levenson, 1982) and has been supported by evidence including patients self-reporting drinking as a way of coping with their anxiety (ranging from 50–97% of participants), especially in those suffering from phobias (Bibb and

Chambless, 1986; Smail et al., 1984; Thomas et al., 2003; Turner et al., 1986). On the other hand, *substance-induced negative affect models* propose that anxiety and depression develop because of persistent, heavy alcohol use (Lev-Ran et al., 2014; Rao, 2006; Stewart and Conrod, 2008). Alcohol misuse can lead to several work, school, and relationship-related difficulties, and internalizing symptoms can result from difficulties in each of these areas. The development of alcohol use disorder occurs over the course of many recurring episodes of excessive and frequent drinking, and withdrawal may cause neural changes that lead to and/or exacerbate negative mood states. Over time, repeated recurring episodes may result in increased neural adaptation that may make a person who drinks alcohol more vulnerable to developing internalizing symptoms (Breese et al., 2005). A number of clinical studies have demonstrated that people who drink alcohol heavily that have recently stopped drinking experience an increase in anxiety, panic, and/or low mood, as well as symptoms of autonomic hyperactivity (e.g., increased heart rate, faster and shallower breathing) during an extended withdrawal period (Schuckit and Hesselbrock, 1994). However, there have also been a number of recent studies that suggest that it is possible there are no significant associations between anxiety, depression, and binge drinking (Bell and Britton, 2015; Farmer et al., 2016; Rhew et al., 2017; Ruggles et al., 2017).

Despite supporting theory, evidence demonstrating links between internalizing symptoms and alcohol use has been mixed, with several systematic reviews demonstrating modest associations between depression and alcohol use and minimal-to-no relation between anxiety and use (Dyer et al., 2019; Groenman et al., 2017; Hussong et al., 2017; Myers et al., 2003). For instance, Hussong and colleagues (2017) provided a systematic review of longitudinal studies testing the relation between negative affect symptoms and substance use controlling for externalizing factors. They found that while there is some consistent evidence of a link between depression and substance use, only 5 out of 61 studies reviewed found a positive unique association between anxiety and use, 6 found a *negative* association, and the remaining 52 found no relation. A more recent meta-analysis examined 97 associations across 51 studies testing the link between anxiety and alcohol use disorders. They found inconsistent evidence of this link for binge drinking or drinking frequency/quantity and no clear association between generalized anxiety and alcohol use disorder (Dyer et al., 2019).

In light of this mixed evidence, methodological considerations have been noted that may clarify the relation between internalizing symptoms and binge drinking in adolescence (Dyer et al., 2019). First, because this relation may be confounded by other between-person factors characterizing risk, within-person designs better accounting for these factors that may reduce bias in estimating the link between internalizing symptoms and binge drinking (Smith and Randall, 2012). For instance, the common-factor model of anxiety and alcohol use disorders hypothesizes that no direct relations exist between these two conditions, and may instead be explained by confounding variables (Goodwin et al., 2004; Smith and Randall, 2012). Studies that have modeled such variables explicitly have shown that the internalizing-alcohol use link may be explained by environmental contexts [e.g., childhood and family factors, prior substance dependence, comorbid depression, and peer affiliations; (Goodwin et al., 2004)], trait-level sensitivity to anxiety (DeHaas et al., 2001; DeMartini and Carey, 2011; Schmidt et al., 2007), and genetic contributors (Stein et al., 1999; Stewart and Conrod, 2007). While these studies have controlled for common factors at the between-person level,

alternative approaches can distinguish between- from within-person effects by relegating the influence of these factors to random-effects components of a statistical model (Grimm et al., 2021). Utilizing such methods to explicate between- versus within-person effects may help partition the influence of these common factors from the link between internalizing symptoms and binge behaviors at the individual level. Relatedly, few have assessed bi-directional links between internalizing and binge drinking factors (Dyer et al., 2019). Because substance use may lead to increased risk of internalizing symptoms, assessing these associations bi-directionally will provide tests of self-medication and substance-induced negative affect models simultaneously (Stewart and Conrod, 2008). Finally, few studies to-date have addressed the concern of power in detecting these effects, which meta-analyses have suggested are relatively small in magnitude (Dyer et al., 2019; Hussong et al., 2017). Well-designed studies utilizing appropriate statistical methods may be better able to detect these effects if they are present, and conversely, increase confidence in null results when these effects are not found.

The goal of the present study was to examine the extent to which adolescent and young adult depression and anxiety predict binge drinking (and vice versa) using a within-person analytic approach. Aims were pursued in the large, diverse, prospectively followed National Consortium on Alcohol and Neurodevelopment in Adolescence cohort (Brown et al., 2015) (NCANDA, N=831) from age 17 to age 21. Similar to controlling for between-person common factors (Goodwin et al., 2004; Smith and Randall, 2012), utilization of within-person designs can account for between-person factors by allowing statistical models to partition between-person variation from person-level effects. Further, analyses focused on temporally lagged effects, allowing these factors to be appropriately sequenced in time (e.g., internalizing factors predicting later binge behaviors and vice versa) and were supplemented by post-hoc power analyses to increase confidence in the presence or absence of effects. As such, the NCANDA cohort and analyses conducted in this sample may be ideal for clarifying competing hypotheses regarding the association between internalizing symptoms and binge drinking. Given extant evidence favors the self-medication model of binge drinking risk, we hypothesized that adolescent depression, and to a lesser degree anxiety, would predict adolescent binge drinking over a 5-year period for participants from the NCANDA study. Observing no within-person links between these constructs may suggest common factors observed at the between-person level may instead be driving these associations.

Materials and Methods

Participants

Data were from the nationally representative National Consortium on Alcohol and Neurodevelopment in Adolescence (NCANDA.org) cohort. Participants were recruited between 12 and 21 years of age at project entry from 5 site locations (University of California San Diego, SRI International, Duke, University of Pittsburgh, and Oregon Health & Science University) in 2013–2014. NCANDA is following these individuals through adolescence and into young adulthood (Brown et al., 2015). After 2548 participants were screened, 1110 were excluded based on criteria that included MRI contraindications,

physical limitations, lack of parental consent, substance use disorders, medication use, prenatal exposure to substances and learning disorders at baseline (i.e., the remaining 1438 were identified as eligible). To test NCANDA's primary aims and ensure our sample was optimized to detect changes over time that pertain to one's alcohol intake, we excluded youth with a range of other factors or conditions that could obscure our ability to do so, including those with prenatal exposure to substances. Recruitment was designed to oversample individuals at higher risk for substance use issues based on endorsement of externalizing symptoms, internalizing symptoms, and family history of alcohol or substance use disorders (Brown et al., 2015). The majority (85%) of the sample at baseline had limited or no exposure to alcohol or other drugs as determined by the age and sex-based guidelines from the National Institute on Alcohol Abuse and Alcoholism (NIAAA), indicative of misuse based on the Center for Disease Control surveillance. The study's cohort sequential design recruited adolescents in three groups (12–14, 15–17, and 18–21 years), facilitating investigation of a wide developmental span due to between-subject variance in starting age. Before entering the study, most participants had not participated in binge drinking (n=121). Participants at risk for increased drinking were identified based on screening for early experimentation with alcohol, positive family history for substance use disorder, and externalizing/internalizing symptoms; these participants were over-recruited and consisted of 50% of participants at study entry (Brown et al., 2015). An accelerated longitudinal design allows recruitment of all ages in the cohort starting during the baseline year; 15% of the cohort were selected for enrichment of alcohol and drug use based on NIAAA guidelines for normative drinking in community sample, which was possible due to later age of recruitment at baseline.

Of the 831 enrolled participants, 139 were people who drink alcohol and 692 were people who do not drink alcohol at study entry. People who do not drink alcohol were defined as those with fewer than 1–4 drinks once a year or 1–2 drinks once a month (Squeglia et al., 2017). People who drink alcohol were those that exceeded these thresholds (Squeglia et al., 2017). Adult participants provided voluntary informed consent, while minors provided assent in addition to the informed consent of a parent or legal guardian.

Measures

Depression and anxiety symptoms were assessed annually from the Diagnostic and Statistical Manual (DSM)-5 oriented scales of the Youth Self-Report (YSR; < 18 years) and Adult Self-Report [ASR; >18 years; (Achenbach and Rescorla, 2001)]. DSM-V oriented depressive symptoms were assessed with questions including, 'There is very little I enjoy,' 'I cry a lot,' 'I deliberately try to hurt or kill myself,' 'I don't eat as well as I should,' 'I feel worthless or inferior,' 'I feel too guilty,' 'I feel overtired without good reason,' 'I sleep less than most kids,' 'I sleep more than most kids during day and/or night,' 'I think about killing myself,' 'I have trouble sleeping,' 'I don't have much energy,' 'I am unhappy, sad, or depressed,' 'I feel that I can't succeed.' DSM-V oriented anxiety symptoms were assessed with questions including, 'I am afraid of certain animals, situations, or places, other than school,' 'I am afraid of going to school,' 'I am afraid I might think or do something bad,' 'I am nervous or tense,' 'I have nightmares,' 'I feel too fearful or anxious,' 'I am

self-conscious or easily embarrassed,' 'I worry a lot,' 'I worry about my family,' 'I worry about my future.' T-scores for each measure were derived and used in analyses.

Alcohol and other substance use history was assessed annually with the Customary Drinking and Drug Use Record (Brown et al., 1998) to follow use of alcohol, tobacco, cannabis, illicit drugs, and misuse of prescription medications. The CDDR is an interviewer-administered questionnaire, designed for use with adolescents and young adults, that probes recent (past 3 months) and lifetime use of alcohol, tobacco, cannabis, illicit drugs, and misuse of prescription medications. It has been found to be internally consistent and reliable over time and across interviewers, in addition to being able to differentiate between abusing and non-abusing adolescents, and with excellent diagnostic specificity compared to other standard instruments. Past year binge drinking (also known as heavy episodic drinking or HED) was assessed using the item "during the past year, how many times have you consumed 4+ (females) / 5+ (males) drinks within an occasion? (0–365)". Endorsement of binge drinking in the sample increased from baseline (14.1%) to year 5 of data collection (61.3%). People who drink alcohol (defined in Participants section above) endorsed using higher amounts of alcohol, cigarette, and cannabis use compared to people who do not drink alcohol, and using higher amounts of other drugs (Brown et al., 2015). Consistent with prior work conducted using the CDDR in this sample, HED was transformed into an ordinal scale using percentile-based cutoffs, such that 0 = "0 episodes," 1 = "1 – 2 episodes," 2 = "3 – 5 episodes," 3 = "6 – 17 episodes," and 4 = "18 or more episodes" (for more detail, see McCabe et al., 2021).

Socioeconomic status was assessed with a modified version of the MacArthur Sociodemographic Questionnaire (Giatti et al., 2012). This reflected parental family income except if the youth was living independently, in which case it reflected the youth's own socioeconomic status. Twenty percent of parents endorsed education below a college degree, twenty-seven percent with at least one parent completing college, and fifty-three percent with at least one parent with education beyond a college degree for the full sample. Annual family income ranged from below \$12,000 to greater than \$200,000. A total of 18% of the sample reported income below \$50,000 per year. While the median income in the United States at the time of study entry (2013) was \$52,250, median incomes ranged from \$50,988 to \$90,786 across NCANDA data collection sites. Eleven percent of the sample did not know or declined to provide income data (Brown et al., 2015).

Reliability across sites and training for assessments was ensured through the development of training manuals, developed by doctoral-level senior staff members, mock and practice sessions, observations, and annual visits to check for interviewer drift and confirmation of training of new staff members (Brown et al., 2015).

Statistical analyses

NCANDA uses a cohort sequential design (Duncan et al., 2006; Miyazaki and Raudenbush, 2000), in which participants spanned a large range of ages at baseline then were assessed annually thereafter. Because participants were enrolled across multiple ages at baseline and provided data in up to five subsequent waves, data resulted in a pattern of planned missingness that can be considered completely at random (Baraldi and Enders, 2010;

McCabe et al., 2021). We therefore used full information maximum likelihood as an estimator in our structural model to accommodate this design (Baraldi and Enders, 2010). Missingness was 21.7%, 23.8%, 25.9%, 29.1%, and 29.0% on outcome variables across waves 2 through 6, respectively. We examined correlations between number of observations provided by each participant and all other study variables to assess whether attrition across waves was associated with levels of any of our study variables of interest. While socioeconomic status was correlated with greater retention in the sample ($r = 0.12$, $p < 0.01$), no other study variables were associated with attrition across waves. Data were structured treating age (versus wave) as time, and were analyzed in the 5-year span from age 17 to age 21.¹ Moreover, noting positive skew in our binge drinking outcome, we further employed robust estimator (i.e., maximum likelihood with robust standard errors) that provided more accurate and robust parameter estimation for models of non-normal data compared to the standard maximum likelihood estimation and alternatives (Mindrila, 2010; Rhemtulla et al., 2012; Schumacker and Beyerlein, 2000).

Latent curve models with structured residuals (LCM-SRs) were used to address primary hypotheses (Curran et al., 2014; Grimm et al., 2021) and were conducted separately for depression and anxiety. A schematic of the LCM-SRs employed are provided in Figure 1. LCM-SRs are an integration of random effects and cross-lagged panel models aimed at estimating lagged effects in longitudinal panel data at the within-person level. In contrast to standard cross-lagged methodologies, LCM-SRs can estimate temporally lagged associations between depression and binge drinking that are partitioned of between-person differences in these associations. This is achieved by specifying a latent curve model to account for between-person differences in level and change in longitudinal data while estimating auto-regressive and cross-lagged effects of time-dependent residuals, which have a purely within-person interpretation. In these models, we evaluated model fit using the adjusted χ^2 difference test, where a non-significant result was an indication of adequate model fit. We supplemented this test with a number of alternative fit indices (Chen, 2007; Cheung and Rensvold, 2002; Meade et al., 2008), including scaled variants of the comparative fit index (CFI) and root mean square error of approximation (RMSEA). Evaluation of model fit was guided by approximate recommendations offered in prior work (Chen, 2007; Hu and Bentler, 1999; Yu, 2002). We included socioeconomic status and sex at baseline as covariates to control for between-person demographic factors that may be influencing levels of internalizing symptoms and binge drinking. Socioeconomic status was measured using a modified version of the MacArthur Sociodemographic Questionnaire (Giatti et al., 2012). In sensitivity analyses, we replicated each LCM-SR separately for males and females to explore whether effects differed across sexes.² All analyses were conducted in R (R Core Team, 2017) using 'lavaan' (Rosseel, 2012). A significance threshold of 0.05 or better was required across analyses.

¹Though a window of up to 6 ages could be represented given this design, covariances between the first and last timepoints (i.e., ages 16 and 21) reflected fewer than 10% of the observations in the sample. Data from age 16 was therefore omitted from analysis due to low covariance coverage.

²Multigroup LCM-SRs were attempted to test moderation of autoregressive and cross-lagged parameters by sex. However, these models failed to converge.

Analyses were supplemented with post-hoc power simulations conducted using the pwrSEM application (Wang and Rhemtulla, 2021) to determine whether LCM-SRs employed were sufficiently powered to detect targeted autoregressive and cross-lagged effects. Power was computed using the Monte Carlo method following steps provided in Wang and Rhemtulla, 2021 and Hancock and French, 2013. Namely, we specified a population LCM-SR based on the standardized variances and covariances between variables included within our model. Assuming this covariance structure, we modified effect sizes for target parameters (i.e., autoregressive and cross-lagged effects) within these models across a range of magnitudes (e.g., 0.1, 0.2, and 0.3) to assess the minimum effect size needed to detect each target parameter. Then, we generated 1,000 samples assuming 831 observations for this model, fit our LCM-SR to each, and recorded the proportions in which the target parameters were different from 0 based on a significance threshold of $\alpha = 0.05$.

Data used here are from the data release NCANDA_PUBLIC_4Y_STRUCTURAL_V01 (<https://dx.doi.org/10.7303/syn22216457>)(Zhao et al., 2021) and NCANDA_PUBLIC_4Y_REDCAP_V02 (<https://dx.doi.org/10.7303/syn24226662>) distributed to the public according to the NCANDA Data Distribution agreement: “www.niaaa.nih.gov/research/major-initiatives/national-consortium-alcohol-and-neurodevelopment-adolescence/ncanda-data.”

Results

In total, 4.1% and 3.3% of participants reported borderline or higher ($T > 64$) clinically-significant levels of depression and anxiety at baseline, respectively, with 17.8% and 13.4% reporting clinically-significant levels at least once throughout the study period. Moderate to high correlations were observed between years in internalizing symptoms and binge drinking, separately, but not generally with each other.

When lagged parameters and residual variances were estimated freely, LCM-SR models failed to converge. Thus, we systematically fixed autoregressive and cross-lagged parameters, residual covariances, and residual variances of depression/anxiety and binge drinking to be invariant over time beyond the initial assessment (see, e.g., Grimm et al., 2021).³ We compared model fit indicators across these specifications to determine the best-fitting model that minimized constraints while remaining estimable. Results suggested that LCM-SRs with constrained cross-lagged and auto-regressive effects constituted the least-constrained model with adequate fit (see Supplemental Table 1). With these constraints in place, model fit was adequate for the LCM-SR of depression ($\chi^2_{46} = 110.62$, $p < 0.01$, RMSEA = 0.04, CFI = 0.94) and anxiety ($\chi^2_{46} = 123.53$, $p < 0.01$, RMSEA = 0.05, CFI = 0.92). Fit was comparable when analyzed separately by sex for depression (males: $\chi^2_{40} = 81.6$, $p < 0.01$, RMSEA = 0.05, CFI = 0.92, females: $\chi^2_{40} = 79.56$, $p < 0.01$, RMSEA = 0.05, CFI = 0.94) and anxiety (males: $\chi^2_{40} = 138.16$, $p < 0.01$, RMSEA = 0.08, CFI = 0.78, females: $\chi^2_{40} = 86.42$, $p < 0.01$, RMSEA = 0.05, CFI = 0.90).

³In exploratory sex difference analyses, depression and anxiety models each produced negative variance estimates for each estimated random intercept. These parameters were therefore fixed to zero in each model to facilitate estimation.

LCM-SR Results.

Results are summarized in Table 2. Between-person effects indicated socioeconomic status was associated with greater growth in HED over time, and that women reported higher depression and anxiety and more growth in HED than men. Autoregressive path parameters indicated that HED was positively associated with levels at the subsequent timepoint, indicating moderate year-to-year stability over the five-year study window. Addressing within-person effects, binge drinking marginally predicted depression among females ($\beta = 0.04$, $p = 0.08$). No other effects were significant. We note that confidence intervals for within-person effects were narrow for the associations between depression and anxiety symptoms and subsequent HED (see Tables 2 and 3), demonstrating high precision in these null associations in the sample.

Post-hoc Power Results.

For the depression LCM-SR, results suggested that power was at least sufficient for small effect sizes (0.15) for cross-lagged effects (binge_{t-1} → depression_t: $1 - \beta = 0.87$, depression_{t-1} → binge_t: $1 - \beta = 0.99$) and for autoregressive effects of depression (depression_{t-1} → depression_t: $1 - \beta = 1.0$), and for small-to-medium autoregressive effects (0.20) of binge drinking (binge_{t-1} → binge_t: $1 - \beta = 0.87$). For the anxiety LCM-SR, power was at least sufficient for small effect sizes (0.1) for cross-lagged effects (binge_{t-1} → anxiety_t: $1 - \beta = 1.00$, anxiety_{t-1} → binge_t: $1 - \beta = 1.00$) and anxiety autoregressive effects (anxiety_{t-1} → anxiety_t: $1 - \beta = 1.0$), and for small-to-moderate effect sizes (0.2) for autoregressive binge drinking effects (binge_{t-1} → binge_t: $1 - \beta = 0.98$). These results indicated that, assuming the conventional 0.80 level of acceptable power, the LCM-SR model specified was sufficiently powered to detect small to medium effect sizes across target effects of interest, were these effects present in the population.

Discussion

We examined lagged associations between adolescent binge drinking, anxiety, and depression symptoms over five years in a large, diverse, prospectively followed sample of participants from the NCANDA study. While the self-medication hypothesis suggested that binge drinking behaviors may follow the presence of internalizing symptoms as a means of coping with negative affect, other theories have suggested binge drinking may disrupt social and cognitive functioning and may serve as a metabolic insult that predisposes youth towards the occurrence of depression and anxiety. One underlying mechanism of the impact of binge drinking on the development of depression and anxiety has been explained in the literature as related to systemic and CNS inflammation that develops with increasing alcohol use and leads to subsequent psychiatric symptoms (Alho et al., 2004; Liukkonen et al., 2006). Alternatively, shared between-person factors, such as environmental and peer influences, may drive relations between these co-developing constructs. We used latent curve models with structured residuals to test these hypotheses concurrently. Given equivocal evidence that internalizing symptoms and binge behaviors are linked in adolescence, we supported our findings with post-hoc power analyses to determine whether the NCANDA sample was sufficiently powered to detect these effects if they were present in our target population. Results demonstrated trending evidence that binge drinking predicted

subsequent depression and anxiety among females, and no direct evidence that internalizing symptoms predicted later binge drinking. This suggests that although binge behaviors may increase later internalizing risk for females, it is likely that binge behaviors may develop largely independently from internalizing factors across this developmental period (e.g., Keyes et al., 2020).

Since we found a small and unidirectional relation between binge drinking and adolescent depressive or anxiety symptoms, results provided slight evidence favoring substance induced anxiety and depression models of internalizing risk (Rao, 2006; Stewart and Conrod, 2008). As such, results highlight that efforts aimed at preventing early initiation and hazardous or harmful alcohol use may have significant downstream effects on incidence of internalizing symptoms for females within the adolescent period. By contrast, we found little direct evidence of a self-medication model when analyzed at the within-person level. Though links between internalizing symptoms and binge drinking have been observed for adults (King et al., 2020), present findings may therefore indicate that early-onset internalizing symptoms represent a different developmental pathway unique from adult-onset symptoms that confer elevated substance use risk (Alpert et al., 1999; Harrington, 2001; Weissman et al., 1999), or relatedly, that stronger associations have been found with more severe levels or extended histories of substance use and internalizing disorder (Schuckit, 2006).

Alternatively, consistent with the common-factor model, the effect sizes observed in this study may also imply minimal direct relation between these two conditions, such that associations observed between internalizing symptoms and binge behaviors may be better explained by common factors giving rise to each. For instance, a number of groups including Goodwin *et al.* found that after controlling for confounding factors (e.g., childhood and family environmental conditions, prior substance dependence, comorbid depression, and peer affiliations), anxiety disorder was unrelated to all measures of substance use (Goodwin et al., 2004), and support by similar findings for confounding factors have been seen in a number of family and twin studies (Merikangas et al., 1998, 1996; Tambs et al., 1997). In addition, several groups have proposed that genetic contributors and anxiety sensitivity render individuals susceptible to co-occurring anxiety and alcohol misuse (Stein et al., 1999; Stewart and Conrod, 2007); similarly, common genetic factors have been identified as predisposing towards depression and alcohol dependence (Andersen et al., 2017; Zhou et al., 2017). While prior studies controlled for these between-person environmental and genetic factors directly, we analogously used a within-person design to partition factors that may be confounding associations. Employing this statistical approach provided evidence largely consistent with these prior findings, adding that we find only modest and unidirectional associations when sequenced (i.e., lagged) over time.

While the NCANDA study has major strengths of being a large, diverse, and prospectively followed sample, we note several limitations. First, episodic variation and measurement may be necessary to more accurately capture self-medication processes, such as in the application of weekly (e.g., Bekman et al., 2013) ecological momentary assessment methods (Bollen and Curran, 2004; Ferrer and McArdle, 2003); the CDDR monthly binge drinking and Achenbach depressive symptom metrics from NCANDA may not have had the temporal sensitivity to capture these nuanced levels of association. Relatedly, some evidence suggests

that while self-reported recall methods are reasonably accurate for adolescents and young adults at moderate levels (Hjorthøj et al., 2012; Williams and Nowatzki, 2005), younger populations may under-estimate their alcohol consumption at higher levels of consumption (Northcote and Livingston, 2011). Thus, the present findings may reflect an underestimation of true binge drinking in the sample (Northcote and Livingston, 2011) and may have tempered effect sizes observed in the present study. Second, it is also possible that other forms of substance use (e.g., marijuana or illicit drug use) might have stronger links with internalizing pathology across this developmental period. Though our analyses focused primarily on testing theories of alcohol misuse in adolescence and young adulthood, examination of these effects across a wider range of substance outcomes may be a crucial extension of this research. Third, we note that several constraints were imposed on the estimated LCM-SRs in this study, including fixing cross-lagged and autoregressive parameters to equivalence across time. As such, we encourage results to be replicated in future analyses, ideally in larger national samples of adolescent substance use such as the Adolescent Brain Cognitive Development (ABCD) Study (Lisdahl et al., 2018). Fourth, the Youth and Adult Self-Report (YSR/ASR) scales offer several advantages and limitations. Self-report intrinsically allows data to be gathered more easily since participants can describe their own symptoms, thus avoiding the need to meet or speak with a staff member. However, such reported symptoms can be less objective than reported symptoms from a trained, clinician staff member. Clinical scales such as the ASR/YSR capture a range of anxiety and depression symptoms that typically necessitate mental health intervention. This is both a strength and weakness in that we can capture lower level of symptoms, but are also gathering information on participants experiencing lesser symptoms than those having DSM-5 diagnostic criteria for a disorder such as major depressive disorder or generalized anxiety disorder. The ASR/YSR anxiety questionnaire as described in detail in the methods highlights that several different types of anxiety are probed in a mixed fashion, limiting generalizability and specificity to differentiate between types of anxiety disorders such as panic, specific phobias, separation, or generalized anxiety disorders using the results from this NCANDA study. Ferdinand et al. found that YSR anxiety scores predicted DSM-IV disorders only moderately while YSR depressive scores corresponded closely to DSM-IV major depressive disorder and dysthymia (Ferdinand, 2008). Finally, very limited data was available for the NCANDA study for the context of each episode of binge drinking (e.g., in college or community dwelling); given social drinking factors may play a large role in predicting binge drinking engagement (Catalano and Hawkins, 1996), drinking context could have an important impact on understanding our findings for the depression-binge drinking relationship.

Our work provides an investigation of the interrelation between depression or anxiety and binge drinking in the large, diverse, and prospectively followed NCANDA sample. Our work is in line with other studies that have found minimal associations between depression or anxiety and binge drinking (Keyes et al., 2020), and suggest that binge drinking may modestly predict later internalizing symptoms or that common factors may better explain links between these facets throughout adolescence. This may highlight the importance of simultaneous treatment of binge drinking and co-morbid depressive or anxiety disorders for

both males and females. Future larger studies such as ABCD will be able to build on the early findings identified here.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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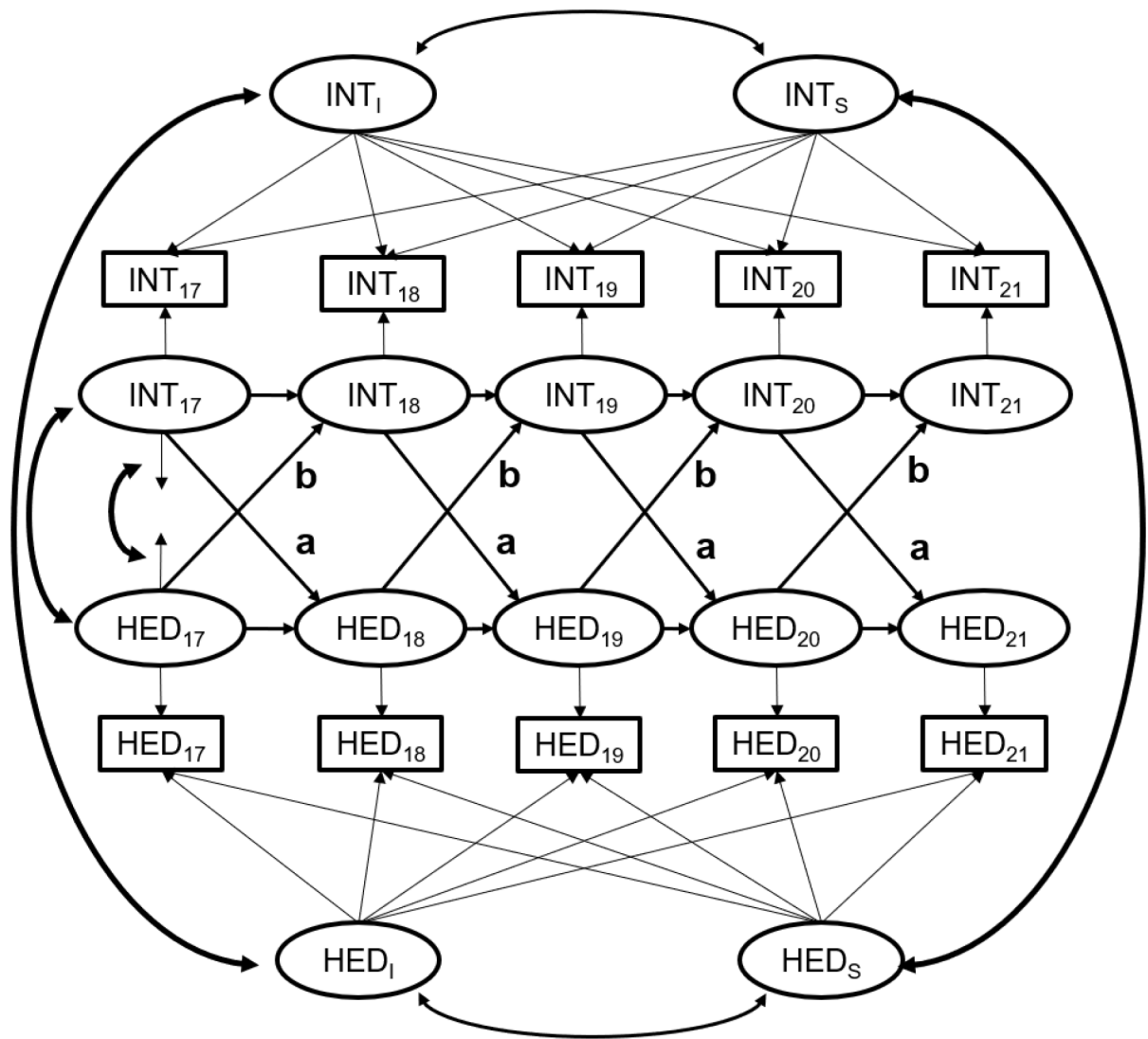


Figure 1.

Schematic of Latent Curve Model with Structured Residuals.

Note. INT = Internalizing Symptoms, BD = Binge Drinking. Path *a* refers to cross-lagged effect of depression or anxiety at time $t - 1$ predicting binge drinking at time t . Path *b* refers to binge drinking at time $t - 1$ predicting depression or anxiety at time t . (Co)variances (e.g., between HED intercept and INT slope and INT intercept and HED slope), residuals, and autoregressive path estimates are not displayed above for parsimony.

Table 1.

NCANDA sample study correlations and descriptive statistics.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
1. Socioeconomic Status		-0.05	0.02	0.01	0.04	0.02	-0.04	-0.02	-0.02	-0.03	0.02	-0.06	0.16	0.21	0.15	0.20	0.09
2. Sex (1 = Female)			0.13	0.08	0.07	0.02	-0.03	0.07	0.13	0.19	0.05	0.00	-0.03	-0.06	-0.09	-0.01	0.02
<i>Depression (T Score)</i>																	
3. Age 17				0.60	0.45	0.55	0.34	0.58	0.46	0.32	0.37	0.25	-0.01	0.02	-0.04	0.02	-0.04
4. Age 18					0.57	0.62	0.44	0.36	0.62	0.31	0.49	0.29	0.08	0.04	0.00	-0.07	-0.17
5. Age 19						0.58	0.53	0.27	0.35	0.52	0.48	0.35	0.06	0.09	0.07	0.01	0.01
6. Age 20							0.63	0.27	0.24	0.36	0.65	0.50	-0.07	-0.03	-0.03	-0.01	-0.03
7. Age 21								0.36	0.22	0.41	0.58	0.70	-0.08	0.02	-0.04	-0.03	-0.07
<i>Anxiety (T Score)</i>																	
8. Age 17									0.52	0.42	0.35	0.49	-0.03	-0.01	-0.05	0.00	-0.20
9. Age 18										0.46	0.39	0.33	0.07	0.00	-0.04	-0.08	-0.19
10. Age 19											0.66	0.51	0.04	0.03	0.02	0.03	-0.02
11. Age 20												0.67	0.00	0.01	-0.05	-0.05	-0.06
12. Age 21													-0.10	0.06	-0.03	-0.07	-0.03
<i>HED</i>																	
13. Age 17														0.63	0.46	0.39	0.36
14. Age 18															0.58	0.49	0.47
15. Age 19																0.68	0.68
16. Age 20																	0.75
17. Age 21																	
<i>Mean</i>	7.22	0.51	53.91	53.54	53.09	53.68	53.4	53.13	52.6	51.95	52.45	52.45	0.45	0.77	1.36	1.57	1.68
<i>SD</i>	3.06	0.50	5.66	5.54	5.48	6.41	5.89	5.16	4.57	3.91	4.73	5.06	0.97	1.23	1.54	1.62	1.56
<i>Skew</i>	-1.36	-0.04	1.69	2.20	2.24	2.22	2.36	2.26	2.48	2.83	2.45	2.99	2.22	1.42	0.60	0.42	0.33

Note. Bolded values indicate significant correlations at $p < 0.05$. HED = Heavy Episodic Drinking.

Table 2.

Latent curve models with structured residuals describing associations between depression and heavy episodic drinking.

Effect	b	SE	95% CI	β
<i>Within-person Effects</i>				
Depression ($t-1$) \rightarrow Depression (t)	0.09	0.09	[-0.09, 0.27]	0.10
HED ($t-1$) \rightarrow HED (t)	0.24	0.11	[0.02, 0.47]	0.14
Depression ($t-1$) \rightarrow HED (t)	0.00	0.01	[-0.03, 0.03]	0.00
HED ($t-1$) \rightarrow Depression (t)	0.27	0.24	[-0.21, 0.75]	0.04
<i>Between-person Effects: HED</i>				
SES \rightarrow HED Intercept	0.02	0.01	[-0.01, 0.04]	0.07
SES \rightarrow HED Slope	0.04	0.00	[0.03, 0.04]	0.32
Female \rightarrow HED Intercept	-0.12	0.08	[-0.28, 0.04]	-0.07
Female \rightarrow HED slope	0.09	0.04	[0.01, 0.16]	0.12
<i>Between-person Effects: Depression</i>				
SES \rightarrow Depression Intercept	0.00	0.06	[-0.11, 0.12]	0.00
SES \rightarrow Depression Slope	0.01	0.01	[-0.01, 0.04]	0.04
Female \rightarrow Depression Intercept	1.08	0.42	[0.25, 1.91]	0.13
Female \rightarrow Depression Slope	-0.26	0.15	[-0.56, 0.04]	-0.11
<i>Slope-Intercept Correlations</i>				
Depression Intercept \Leftrightarrow Depression Slope	-0.84	1.01	[-2.83, 1.15]	-0.18
HED Intercept \Leftrightarrow HED Slope	-0.04	0.04	[-0.13, 0.05]	-0.15
Depression Intercept \Leftrightarrow HED Intercept	0.35	0.35	[-0.33, 1.04]	0.11
Depression Intercept \Leftrightarrow HED Slope	-0.18	0.15	[-0.47, 0.10]	-0.13
HED Intercept \Leftrightarrow Depression Slope	-0.10	0.10	[-0.30, 0.10]	-0.11
Depression Slope \Leftrightarrow HED Slope	0.01	0.05	[-0.10, 0.12]	0.03

Note: Heavy-episodic drinking (i.e., binge drinking) has been abbreviated as HED. Fixed parameter estimates, covariances, and residual variances are omitted for parsimony. Boldface type indicates significant fixed effects. b = unstandardized estimate; β = standardized estimate.

Table 3.

Latent curve models with structured residuals describing associations between anxiety and heavy episodic drinking.

Effect	b	SE	95% CI	β
<i>Within-person Effects</i>				
Anxiety ($t-1$) \rightarrow Anxiety (t)	0.19	0.15	[-0.10, 0.49]	0.23
HED ($t-1$) \rightarrow HED (t)	0.25	0.12	[0.02, 0.48]	0.15
Anxiety ($t-1$) \rightarrow HED (t)	-0.01	0.02	[-0.04, 0.02]	-0.07
HED ($t-1$) \rightarrow Anxiety (t)	-0.11	0.24	[-0.58, 0.37]	-0.01
<i>Between-person Effects: HED</i>				
SES \rightarrow HED Intercept	0.02	0.01	[-0.01, 0.04]	0.07
SES \rightarrow HED Slope	0.04	0.00	[0.03, 0.04]	0.32
Female \rightarrow HED Intercept	-0.14	0.08	[-0.30, 0.02]	-0.09
Female \rightarrow HED slope	0.09	0.04	[0.02, 0.17]	0.13
<i>Between-person Effects: Anxiety</i>				
SES \rightarrow Anxiety Intercept	-0.01	0.06	[-0.12, 0.10]	-0.02
SES \rightarrow Anxiety Slope	0.00	0.01	[-0.02, 0.03]	0.01
Female \rightarrow Anxiety Intercept	0.83	0.37	[0.11, 1.56]	0.18
Female \rightarrow Anxiety Slope	0.01	0.14	[-0.26, 0.29]	0.01
<i>Slope-Intercept Correlations</i>				
Anxiety Intercept \Leftrightarrow Anxiety Slope	0.82	2.09	[-3.28, 4.91]	0.52
HED Intercept \Leftrightarrow HED Slope	-0.04	0.05	[-0.12, 0.05]	-0.13
Anxiety Intercept \Leftrightarrow HED Intercept	0.54	0.44	[-0.33, 1.40]	0.30
Anxiety Intercept \Leftrightarrow HED Slope	-0.24	0.14	[-0.52, 0.04]	-0.32
HED Intercept \Leftrightarrow Anxiety Slope	-0.11	0.13	[-0.37, 0.15]	-0.20
Anxiety Slope \Leftrightarrow HED Slope	0.08	0.06	[-0.04, 0.19]	0.34

Note: Heavy-episodic drinking (i.e., binge drinking) has been abbreviated as HED. Fixed parameter estimates, covariances, and residual variances are omitted for parsimony. Boldface type indicates significant fixed effects. b = unstandardized estimate; β = standardized estimate.