A longitudinal study of the association between internalizing problems during early adolescence and alcohol and cannabis use disorder at age 18 in a community sample

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Abstract

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Introduction: Substance use disorders, such as alcohol use disorder (AUD) and cannabis use disorder (CUD), in young adults are an important public health concern. AUD and CUD may have deleterious impacts on the ongoing maturation of the brain and lead to impaired thinking, memory, emotional, and learning functions. Research on how internalizing problems among adolescents are associated with subsequent substance use disorders is limited and understanding these potential links may provide important insights as the prevalence of internalizing disorders has increased in the young adult population. This study assessed the longitudinal association between general internalizing problems in eighth grade and AUD and CUD at 18 years of age, as

well as the unique associations of eighth grade depressive symptoms, physical symptoms of anxiety, and social anxiety symptoms with AUD and CUD at 18 years of age.

Methods: This analysis used data from a community sample of 521 adolescents recruited from Seattle public middle schools. We characterized general internalizing problems in eighth grade as a latent factor indicated by depressive symptoms, physical symptoms of anxiety, and social anxiety symptoms. Using structural equation modeling with a probit link, we examined the association between the latent factor and AUD and CUD at age 18. Unique associations of the three internalizing indicators with AUD and CUD independent of the internalizing problems latent factor were examined in separate models. All models adjusted for sex, highest level of parent/caregiver education, and previous substance use in the past six months at the 8^{th} grade visit.

Results: We did not find evidence of an association between the internalizing problems latent factor and AUD or CUD in unadjusted (AUD: $\beta = -0.049$, 95% CI: -0.21, 0.12; CUD: $\beta = 0.073$, 95% CI: -0.095, 0.24) or adjusted (AUD: $\beta = -0.017$, 95% CI: -0.19, 0.16; CUD: $\beta = 0.078$, 95% CI: -0.095, 0.25) models. Nor did we find evidence of a unique association between any of the three individual internalizing indicators and AUD or CUD in adjusted models independent of the internalizing problems latent factor.

Conclusions: Our study found that internalizing problems and individual indicators of internalizing problems in eighth grade were not associated with AUD and CUD in early adulthood. Despite the lack of associations, a contribution of this study is the latent characterization of internalizing problems comprised of depressive symptoms and anxiety symptoms indicators. Future studies can investigate if there are associations between

internalizing problems during high school and substance use disorder outcomes to better understand the effect of internalizing problems when it is observed closer in time to the outcome.

Background and Significance:

Substance use and misuse during the transition to adulthood remain an important public health concern. According to the 2019 National Survey on Drug Use and Health (NSDUH), 10.1% and 5.5% of young adults ages 18 to 25 in the United States met past year diagnostic criteria for alcohol use disorder (AUD) and cannabis use disorder (CUD), respectively (SAMHSA, 2020). Further, in the past decade, CUD prevalence in particular has been increasing as cannabis use has becoming increasingly acceptable (Hasin et al., 2019) and as legalization of nonmedical use of cannabis has expanded (Jones and Claster, 2001). Use of substances increases in frequency and prevalence over development, typically reaching its peak during young adulthood, often defined as ages 18-25 (Arnett, 2005). This developmental period is often viewed as a period of preparation for adulthood in society. As individuals in this age group gain more independence by entering the workforce, furthering education, or moving away from parental supervision, this can be a challenging time of adapting to new freedoms and responsibilities. This period is also a time in which social environments for these individuals are shifting to ones that tend to have a greater access to and tolerance of the use of substances, such as the military, certain occupations, and college campuses (Ames et al., 2009; Staff et al., 2010; Schulenberg et al., 1997)

Increased alcohol and cannabis use during adolescence and young adulthood may be particularly deleterious to the ongoing maturation of the brain and greater reward-sensitivity during development (Levine et al., 2017). Consistent with this, research suggests that increased alcohol and cannabis use during young adulthood may impair thinking, memory, and cognitive functions well into adulthood (Meier et al., 2012; Zeigler, 2005). Further, there may be elevated risk for acute consequences such as unintentional injuries, intoxicated driving, absenteeism from

school or work; as well as longer-term consequences such as cirrhosis, colorectal cancer, and continued problematic substance use into adulthood (Gil et al., 2004; Hingson et al., 2006; King et al., 2006; Schulte and Hser, 2014; Rehm et al., 2009). There is also some evidence that heavy alcohol and cannabis use during young adulthood increases risk of psychological problems, including major depression (more evident with alcohol use), anxiety, suicidal behaviors, and psychosis (more evident with cannabis use) (Colder et al., 2019; Gobbi et al., 2019; Leadbeater et al., 2019). To guide intervention strategies, it is crucial to understand factors related to the development of problematic substance use during the transition to adulthood.

One common self-reported reason for use and escalation of use of alcohol and/or cannabis in adolescents and young adults is as a strategy to cope with psychological distress or stress in general (Fox et al., 2011; Prince et al., 2015), which is often referred to as self-medication (Khantzian, 1997). This theory might suggest that adolescents with mental health problems, such as depression and forms of anxiety, may turn to alcohol or cannabis use as an emotion regulation strategy, which could subsequently increase the likelihood of heavy use and AUD or CUD (Kelly et al., 2015; Weinberger et al., 2019).

However, research in this area has been mixed, which may be related to differences in the specific form of psychological distress that is being considered. For example, although not entirely consistent, multiple studies have shown longitudinal associations between adolescent depression and alcohol and cannabis misuse (Brière et al., 2014; McCarty et al., 2013; Rhew et al., 2017). Different forms of anxiety disorders have shown differential associations with substance use. For example, a German study of 2,548 adolescents found that social anxiety as well as panic disorder, but not generalized anxiety disorder, showed independent associations with hazardous alcohol use (Zimmerman et al., 2003). Further, a 14-year longitudinal study

showed an association between social anxiety and alcohol and cannabis dependence, independent of other anxiety disorders (Buckner et al., 2008). This may suggest that beyond that of other internalizing problems, social anxiety may play an especially important role in the development of problematic alcohol or cannabis use.

Numerous studies have shown strong correlations among depression, generalized anxiety, and social anxiety, suggesting that there may be shared phenotypic qualities across these forms of psychopathology. This has led some to suggest that these forms of internalizing problems may be appropriately characterized by an overarching general internalizing problems factor (Caspi, et al. 2014; Zahn–Waxler et al., 2000). Understanding if there is a relationship between a general internalizing problems factor and AUD and CUD, as well as if there are unique associations of depression, generalized anxiety, and social anxiety with AUD and CUD can be helpful in identifying adolescent groups that are at higher risk for these outcomes.

Using data from a prospective study of youth, this study examined whether general internalizing problems—characterized as a latent factor indicated by depressive symptoms, physical symptoms of anxiety, and social anxiety symptoms in eighth grade—is associated with likelihood of meeting diagnostic criteria for alcohol and cannabis use disorder at approximately 18 years of age. We hypothesized that adolescents with higher levels of internalizing problems in eighth grade will have a greater likelihood of AUD and CUD at age 18. This study also examined whether there are unique associations of the three specific indicators of internalizing problems with AUD and CUD. We hypothesized that social anxiety symptoms would show a unique association with AUD and CUD.

Methods:

Study setting, subjects, and design

This study used data from the Developmental Pathways Project (DPP). DPP study participants were recruited as 6th graders from four middle schools in the Seattle Public School District in four consecutive annual cohorts from 2001 to 2004. Schools were chosen to reflect the varied geographic areas and demographic diversity of the school district (Vander Stoep et al., 2011). A two-stage sampling approach was used for this cohort study. First, a universal screening of all students in the four middle schools (N = 2,190) was conducted and, second, a sample of students who completed the screening were identified and recruited into the cohort study. For the screening, research team members administered two questionnaires: the Mood and Feelings Questionnaire (MFQ) to assess depressive symptoms and the Youth Self-Report (YSR) externalizing subscale to assess disruptive behavior problems. These screening questionnaires were administered during a class period at school (Vander Stoep, et al., 2005). To identify potential participants for the longitudinal study, students completing the screen were randomly selected from four risk groups. Risk groups were assigned based on whether or not students scored 0.5 standard deviations above the screening sample mean on the MFQ and/or YSR scales. The four groups were characterized as: (1) comorbid high depressive symptom and high conduct problem score, (2) high depressive symptom and low conduct problem score, (3) low depressive symptom and high conduct problem score, and (4) low depressive symptom and low conduct problem score (McCarty et al., 2007). The ratio of these groups in the original screening sample was 1: 1: 1: 4. For recruitment, however, these four groups were sampled in a ratio of 1: 1: 1: 2 to increase the likelihood of observing elevated levels of psychopathology and related outcomes during the course of the longitudinal study (McCarty et al., 2007). Of 811 eligible students, 521

(64.2%) students and their parents provided informed consent and were enrolled in the longitudinal study (Vander Stoep et al., 2005).

As part of the study, interviewers visited participants' homes to conduct study interviews with the student and a parent every six months throughout middle school. These students were further followed-up in three extensions of the original study when they were in 9th grade, again when they were approximately 18 years old (12th grade, if they were still enrolled in school), and once more when they were 22 years of age. For this current study, we used data collected during the fall of eighth grade and at the age 18 assessment. The DPP methods and data have been approved by the University of Washington's Human Subjects Research Division.

Measures

Depressive symptoms at eighth grade: The self-report Mood and Feelings Questionnaire (MFQ) was used to assess depressive symptoms for the longitudinal study. Questions within the MFQ are derived from the Diagnostic and Statistical Manual (DSM) and International Classification of Diseases (ICD) criteria for major depressive disorder and dysthymic disorder. The MFQ consists of 33 items related to how a respondent has been acting or feeling in the past two weeks. Participants were presented with a list of statements about how they felt during the past two weeks and for each statement they were asked to indicate whether statements were 'not true' (0), 'somewhat true' (1), or 'true' (2). Example statements included "I felt miserable and unhappy," "I didn't want to see my friends," "I ate more than usual," and "I thought that life wasn't worth living" (Angold et al., 1995). The total MFQ score was derived from the sum of the item scores where all items were weighted equally. The Cronbach's alpha in this study was 0.89 for adolescents aged 13 to 17, indicating strong internal consistency. The MFQ has shown strong criterion validity against clinician-based diagnoses of major depressive disorder in non-clinical

samples of children (Burleson Daviss et al., 2006; Sund et al., 2001). MFQ scores are also strongly correlated with scores from the Beck's Children's Depression Inventory, Child Behavior Checklist's Anxious/Depressed scale and the Children's Depressive Rating Scale.

Physical Symptoms of Anxiety and Social Anxiety at eighth grade: Physical symptoms of anxiety and social anxiety symptoms were assessed using subscales from the Multidimensional Anxiety Scale for Children (MASC), a 39-item inventory that asks questions about four domains of childhood anxiety. The MASC was developed for identifying anxiety symptoms in children and adolescents (March et al., 1997). The physical symptoms subscale contains 12 items related to the bodily responses to stress such as "I feel tense or uptight" or "I get shaky or jittery" (March et al., 1997). The social anxiety symptoms subscale contains 9 items related to the fears of humiliation, rejection, or poor performance, such as "I worry about doing something stupid or embarrassing" or "I worry about other people laughing at me" (March et al., 1997). All responses for both subscales were coded on a 4-point Likert scale from 0 (never true about me) to 3 (often true about me). Subscale scores were derived by summing the scores for items within the physical symptoms and social anxiety subdomains separately. The Cronbach alpha for physical symptoms of anxiety and social anxiety in eighth grade were 0.85 and 0.87, respectively, indicating strong internal consistency. Compared to the social anxiety subscale, the physical symptoms subscale showed a stronger correlation with the clinician-rated Hamilton Anxiety Rating Scale (HAM-A), which was developed to capture psychic anxiety (mental agitation and psychological distress) and somatic anxiety (physical complaints related to anxiety) (Rynn et al., 2006). The social anxiety subscale has shown positive correlations with scales specifically developed to assess social anxiety symptomology like the Social Phobia and Anxiety Inventory for Children and the Social Anxiety Scale for Adolescents (Anderson et al., 2009).

Alcohol and Cannabis Use Disorder Diagnosis at age 18: Diagnostic criteria for alcohol and cannabis use disorder within the past year were assessed at the age 18 study visit using the Voice-Diagnostic Interview Schedule for Children (V-DISC). The majority of interviews at age 18 were conducted at the participant's home and a smaller number at the research study site. The V-DISC is a computer-assisted survey, where participants wear headphones to listen to audio instructions from the computer and enter responses to questions themselves. Using an algorithm that analyzes the pattern of responses, the V-DISC can yield diagnoses for various psychiatric disorders, including AUD and CUD, based on DSM-IV criteria (Wasserman et al., 2002). Psychiatric disorder diagnoses based on the V-DISC have been well-validated when compared to clinical diagnosis as the criterion standard (Wasserman et al., 2002). Participants meeting DSM-IV criteria for past year abuse, dependence, or both were classified as having a use disorder (e.g., those meeting criteria for alcohol abuse or dependence were classified as meeting criteria for an alcohol use disorder).

Covariates: Observed potential covariates included demographic characteristics reported at grade 6: sex, race/ethnicity, highest level of educational attainment of parents/caregivers, and annual household income; and those reported at grade 8: self-reported age, total number of stressful life events in the past 6 months, and substance use in the past 6 months. Stressful life events were measured using the Life Events Checklist (LEC), a self-report inventory that asks respondents about 30 stressful events since the time they were last interviewed—in this case, six months (Greene et al., 1985). Examples of items include "you were teased or bullied by another student or a neighbor," "one of your parents/guardians lost his/her job" and "you were the victim of a crime" (Greene et al., 1985). Race/ethnicity was included as a potential covariate not because of alleged genetically determined biologic factors, but to disentangle important social

dimensions that influence health, such as discrimination and racism, from the associations of interest.

Data analysis

Structural equation modeling (SEM) was used to examine associations of a latent factor for internalizing problems (as indicated by depressive symptoms, physical symptoms of anxiety, and social anxiety) with AUD and CUD, and unique associations of the three internalizing problems indicators with AUD and CUD above and beyond the latent factor. As a first step in the modeling approach, we conducted a confirmatory factor analysis (CFA) to examine whether covariance among the indicators could be explained reasonably by a single common factor, which would reflect unidimensionality. Specifying a one-factor solution, we examined the factor loadings of the indicators which describe the correlation of each indicator with the latent variable. Because the latent factor was comprised of only three indicators, common model fit indices, such as the comparative fit index (CFI) and Tucker-Lewis index (TLI), could not be assessed. Next, we examined the association between the latent factor and AUD and CUD, separately. A probit form of the model was used that estimates the inverse standard normal distribution of the probability as a linear combination of the covariates. Probit coefficients describe the change in z-score for the distribution of the probability associated with a one unit change in the covariate. Standardized coefficients were estimated that describe change in z-score for every one standard deviation increase in the internalizing problems latent factor. To aid in interpretability, we calculated model-predicted prevalence estimates of AUD and CUD for several values of the latent variable (at the mean, one standard deviation above the mean, and one standard deviation below the mean) when all adjustment covariates are at their mean. We first ran unadjusted models for the association between the latent internalizing variable and AUD

and CUD, separately. Then, we further included sex, highest level of parent/caregiver education, and previous substance use in the past six months as additional covariates. Although additional covariates were considered, this final set of covariates was determined based on *a priori* theory and comparisons of model fit with different covariates. For analyses, we windsorized the most extreme values (over 3 SD from the mean) for age, MFQ scores and MASC physical symptom scores to reduce the impact of possibly spurious outliers on our results. MASC social anxiety symptom scores did not show values over 3 SD above the mean.

After examining the association between the overall latent factor and AUD and CUD, we examined the extent to which each of the three indicators were associated with AUD and CUD above and beyond the internalizing problems latent factor. Three additional models for each outcome were run where each of the three indicators were included separately as an additional covariate. In these models, the standardized coefficient for the internalizing problem indicator represents the change in z-score for every one standard deviation change in the specific internalizing problem indicator above and beyond the overall internalizing problems latent factor.

As post-hoc analyses, we explored whether associations between the latent internalizing problems factor and AUD and CUD differed by sex by running the SEM analyses for males and females separately.

For all SEM analyses, weighted least squared mean and variance (WLSMV) estimation was used. WLSMV is a robust estimator that does not assume normally distributed variables and provides the best option for modeling categorical or ordered data (Brown, 2006). We included all 521 participants in analyses despite missingness of mental health indicators and outcomes by specifying covariances of covariates with one another. In total, 73 participants were missing

MFQ data (14.0%) and 75 participants were missing MASC data (14.6%). Similar levels of missingness were seen in the outcomes: 61 (11.7%) were missing AUD status, and 59 (11.3%) were missing CUD status. In analyses, we specified the estimation of covariances of model covariates with one another, which allowed estimation of models using all participants given that they are not missing all covariates or outcomes (all participants in this study had available data on sex and highest level of parent/caregiver education). Under the assumption that the data was missing at random (MAR), results should be unbiased with respect to missingness using WLSMV estimation.

As recommended by Bentler (1980), we examined several goodness-of-fit indices for SEM models including the Comparative Fit Index (CFI); Tucker-Lewis Index (TLI); and the Root Mean Square Error of Approximation (RMSEA). Better fitting models have high CFI and TLI, with .90 indicating a relatively good fit (Kline, 2005). Contrastingly, lower RMSEA scores indicate better fit and RMSEA values of $\leq$.05 are thought to indicate acceptable fit (Browne and Cudeck, 1992).

To account for oversampling of students with elevated depressive symptoms and conduct problems in the DPP study as well as demographic differences between the study sample and the broader Seattle public middle school population, study sampling weights were applied to the analyses. All SEM analyses were run using Mplus version 8.7 (Muthén and Muthén, 2017).

Results:

As shown in Table 1, at the eighth grade study visit, participants were on average 14.1 years old (SD: 0.44; range: 13-16 years). The sample showed a relatively even distribution with regard to sex, household income, and highest educational attainment of parent/caregiver. There

was also good racial/ethnic diversity with 44.9% of non-Hispanic White race, 27.7% non-Hispanic Black, 17.2% non-Hispanic Asian, and 10.2% other race/ethnicity (Native American and Hispanic). On average at eighth grade, the mean MFQ score was 7.90 (SD: 6.99, range: 0-43), the mean MASC physical symptom score was 6.54 (SD: 5.53, range: 0-28), and the mean MASC social anxiety score was 8.90 (SD: 5.82, range 0-25). With regard to past six month substance use, 10% reported using alcohol, and 6% reported cannabis at the grade 8 study visit.

Correlations among the internalizing problems indicators are shown in Table 2. Generally, there was moderate-to-strong correlation among the variables with a Pearson coefficient of 0.57 for the correlation between depressive symptoms and physical symptoms of anxiety, 0.45 for the correlation between depressive symptoms and social anxiety symptoms, and 0.52 for the correlation between physical symptoms of anxiety and social anxiety symptoms (Table 2). We then assessed the appropriateness of a single latent internalizing problems factor indicated by these three variables using CFA. The factor loadings for each internalizing problems indicator were high (0.75 for depressive symptoms, 0.78 for physical symptoms of anxiety, 0.62 for social anxiety symptoms), which suggests that each of the indicators contribute meaningfully to the latent variable.

We next examined the associations between the latent internalizing problems factor and AUD and CUD using SEM. In regression modeling, we did not find evidence of an association between the internalizing problems latent variable and AUD or CUD in unadjusted (AUD: β = -0.05, 95% CI: -0.21, 0.12, CFI: 0.760, TLI: 0.703, RMSEA: 0.018; CUD: β = 0.07, 95% CI: -0.10, 0.24, CFI: 0.741, TLI: 0.680, RMSEA: 0.009) or adjusted (AUD: β = -0.02, 95% CI: -0.19, 0.16, CFI: 0.933, TLI: 0.843, RMSEA: 0.371; CUD: β = 0.08, 95% CI: -0.10, 0.25, CFI: 0.932, TLI: 0.842, RMSEA: 0.368) models (Table 3). To aid in interpretation, model-predicted

prevalence estimates of AUD and CUD at different levels of the latent factor are shown in Table 4. The predicted prevalence of AUD was 20.7% at one standard deviation below the mean of the latent internalizing problems factor, 20.2% at the mean, and 19.7% at one standard deviation above the mean level. The predicted prevalence of CUD in the adjusted model was 19.4% at one standard deviation below the mean of the latent internalizing problems factor, 21.6%, at the mean, and 24.0% at one standard deviation above the mean. Thus, consistent with the modeling results, there was little difference in age 18 AUD or CUD prevalence across eighth grade levels of internalizing problems.

Next, when further adding the specific internalizing problems indicators as covariates in separate models, we did not find evidence of a unique association of depressive symptoms (AUD: $\beta = 0.21$, 95% CI: -0.13, 0.55, CFI: 0.934, TLI: 0.826, RMSEA: 0.314; CUD: $\beta = -0.03$, 95% CI: -0.31, 0.24, CFI: 0.931, TLI: 0.818, RMSEA: 0.290), physical symptoms of anxiety symptoms (AUD: $\beta = -0.04$, 95% CI: -0.37, 0.28, CFI: 0.931, TLI: 0.818, RMSEA: 0.288; CUD: $\beta = 0.20$, 95% CI: -0.16, 0.56, CFI: 0.934, TLI: 0.828, RMSEA: 0.320), and social anxiety symptoms (AUD: $\beta = -0.14$, 95% CI: -0.34, 0.07, CFI: 0.935, TLI: 0.829, RMSEA: 0.325; CUD: $\beta = -0.12$, 95% CI: -0.32, 0.09, CFI: 0.933, TLI: 0.825, RMSEA: 0.312) with age 18 AUD or CUD (Table 3).

As exploratory analyses, we also did not find evidence of an association between the internalizing problems latent variable and the outcomes in either males (AUD: $\beta = -0.04$, 95% CI: -0.26, 0.18, CFI: 1.00, TLI: 1.00, RMSEA: 0.958; CUD: $\beta = 0.02$, 95% CI: -0.20, 0.25, CFI: 0.994, TLI: 0.981, RMSEA: 0.490) or females (AUD: $\beta = 0.06$, 95% CI: -0.19, 0.31, CFI: 0.940,

TLI: 0.819, RMSEA: 0.136; CUD: β = 0.25, 95% CI: -0.01, 0.50, CFI: 0.985, TLI: 0.956, RMSEA: 0.398).

Discussion:

We used data from a prospective study of youth to examine whether general internalizing problems in eighth grade—characterized as a latent factor indicated by depressive symptoms, physical symptoms of anxiety, and social anxiety symptoms—was associated with AUD and CUD at 18 years of age. We also studied whether there were unique associations of the three specific forms of internalizing problems with AUD and CUD above and beyond the general internalizing problems factor. Our study found no evidence of an association between internalizing problems assessed in early adolescence and AUD or CUD assessed at age 18 in the full sample or when stratifying by sex. In addition, we found no evidence of unique associations of depressive symptoms, physical symptoms of anxiety, or social anxiety with AUD or CUD above and beyond the latent internalizing problems factor.

There may be a variety of explanations for why we did not observe associations consistent with our hypotheses. First, internalizing problems are difficult to characterize in length and pattern. Depressive symptoms, for example, can be episodic. In our study, we only assessed depressive symptoms at a single time point and the particular measure, MFQ, captures depressive symptoms in the two weeks prior to the time of the interview. Our study, therefore, was only able to assess depressive symptoms during a relatively brief time window. This also applies to the anxiety measures. Thus, our internalizing problems measures may not have adequately captured individuals with more elevated, severe, and/or sustained depression and anxiety, as well as individuals that may have had depressive or anxious symptoms that subsided prior to the interview period. In one study using the same study sample, youth with more chronic

or severe forms of depression have elevated risk for CUD at age 18, suggesting that the cumulative experience of mental health problems may be important to consider beyond a single point-in-time assessment (Rhew et al., 2017).

A second explanation may be related to the lengthy four-year span between the eighth grade assessment of internalizing problems and age 18 assessment of AUD and CUD. It may be that the more relevant timing of the association is more proximal. Also, this gap between assessments occurs during a development period when adolescents are experiencing significant shifts in social interactions. For example, during high school ages, students are more likely to find themselves in social situations such as parties and gatherings that simultaneously make substances more available and exacerbate the desire to cope or fit-in by using substances (Patrick et al., 2011; Patrick et al., 2014). When we look at students that may feel unprepared to handle these new social situations in high school, we may discover different relationships between internalizing problems and substance use outcomes.

A third explanation for the lack of an association between the overall latent internalizing factor and AUD and CUD is that although depression and anxiety are often co-occurring, they may result in different coping mechanisms that affect risk of substance use disorder. Adolescents that have more depressive symptoms may be drawn to substances to cope but those with more anxiety symptoms may be more risk averse, choosing to avoid discomforting effects by not drinking or using cannabis (Crum and Pratt, 2001). These different motivators can also exist within the same individuals at differing moments (Hall and Queener., 2007; Leshner, 1999). When these multiple forms of mental health problems are considered together in an internalizing problems latent factor, they may become obfuscated by the differences in directionality, resulting in null results. However, in our study, this is likely not the case. When we tested the unique

association of each indicator on the outcomes, our results suggest that the individual indicators in eighth grade also were not associated with AUD or CUD at 18 years of age. Further examination of this using study samples with larger sample sizes may be informative.

When considering analyses of unique associations of the specific mental health indicators, we observed a high factor loading for depressive symptoms compared to the factor loadings for physical symptoms of anxiety or social anxiety symptoms. Thus, there may have been potential collinearity between depression and the latent internalizing factor, which would make it challenging to disentangle the effect of depressive symptoms from the overall latent internalizing problems factor. This may also be reflected in the large shift in the coefficient for internalizing problems upon adjustment for depression.

Despite the lack of associations shown, a contribution of this study to current knowledge is the characterization of internalizing problems comprised of multiple indicators: depressive symptoms, physical anxiety symptoms, and social anxiety symptoms. Thirty years since Khantzian's original theory for self-medication, most studies have only looked at forms of psychopathology, such as antisocial personality, depression, and anxiety separately as potential risk factors for substance use and misuse. However, there remains debate regarding the distinctions between some mental disorders, especially depression and anxiety (Caspi et al., 2014; Hankin et al., 2016; Snyder et al., 2017). Indeed, depression and anxiety disorders are often comorbid and, thus, treating them as distinct mental health problems may miss the ways in which their shared root etiology may contribute to risk for outcomes such as substance use disorder (Hirschfeld, 2001). To address this, our study used a latent variable approach to characterize an overall internalizing problems factor using three indicators in adolescence. This is aligned with recent literature exploring dimensional nosology of mental health conditions,

which have found two core underlying psychopathological processes: an internalizing dimension generally comprised of mood and anxiety disorders, such as depression and anxiety, and an externalizing dimension comprised of substance use disorders and antisocial and other externalizing disorders (Caspi, et al. 2014).

This study had several limitations. First, during the analysis, several additional covariates were considered for adjustment including age, parental income, and stressful life events. However, due to unexpectedly having fairly low correlations among them, inclusion of these covariates reduced model fit appreciably and were thus removed from the model. Second, data for this study were collected before legalization of nonmedical (or "recreational") use, possession, and sales of cannabis in Washington State, and therefore this study may not be generalizable to a post-legalization setting. It should be noted, however, that the prevalence of CUD in this sample was higher than the national average which may alleviate some concerns regarding generalizability to a setting where cannabis use is more common and acceptable. The sample also consisted of students from the Seattle public school system and therefore our study results may not generalize to students from other educational settings and other geographical areas.

In closing, internalizing problems in eighth grade, characterized as a latent factor indicated by depressive symptoms, physical symptoms of anxiety, and social anxiety, did not show associations with AUD and CUD, nor were unique associations of the mental health indicators with AUD and CUD observed. The manifestation and motivation for alcohol use disorder and cannabis use disorder in young adulthood is multifaceted. Future studies can explore measuring chronic depression and anxiety by aggregating or analyzing data from multiple visits, creating a latent variable of internalizing problems that includes domains of

depression and anxiety that were not investigated here, and looking at exposures more proximal to age 18. Because of the increasing prevalence of AUD and CUD among young adults, further investigations into the etiology of these disorders are necessary.

Table 1. Characteristics of the Sample

Characteristic	Mean (SD) / n (%)	Missing n (%)
Age at eighth grade visit	14.1 (0.4)	46 (9.8)
Race/ethnicity		0 (0)
Non-Hispanic White	211 (44.9)	
Non-Hispanic Black	130 (27.7)	
Non-Hispanic Asian	81 (17.2)	
Non-Hispanic Native American	5 (1.1)	
Hispanic, any race	43 (9.1)	
Sex		0 (0)
Male	244 (51.9)	
Female	226 (48.1)	
Annual Household Income, $		0 (0)
<25,000	123 (26.2)	
25,000-50,000	107 (22.8)	
50,000-75,000	88 (18.7)	
75,000-100,000	61 (13.0)	
>100,000	91 (19.4)	
Highest level of parent/caregiver education		0 (0)
High school or less	82 (17.4)	
Some college or associate degree	115 (24.5)	
Bachelors degree	121 (25.7)	
Masters/professional school/doctoral degree	152 (32.3)	
Number of stressful life events in past 6 months	3.1 (3.1)*	0 (0)
Eighth grade MFQ	8.0 (7.0)	
Eighth grade MASC		
Physical symptoms	6.7 (5.6)	53 (11.3)
Social anxiety	9.0 (5.8)	53 (11.3)
Eighth grade any alcohol use in past 6 months	47 (9.8)	
Eighth grade any cannabis use in past 6 months	27 (5.6)	
Alcohol Use Disorder in past year at age 18	102 (21.7)	61 (11.7)
Cannabis Use Disorder in past year at age 18	98 (20.9)	58 (11.3)

*Based on a summation of unit scores (with each event weighted 1)

Table 2. Correlations among Latent Variable Indicators

	Depressive symptoms	**Physical symptoms of anxiety**	**Social anxiety symptoms**
Depressive symptoms	1	-	-
Physical symptoms of anxiety	0.567	1	-
Social anxiety symptoms	0.451	0.518	1

Table 3. Unadjusted and Adjusted Structural Equation Model Results for Associations of Internalizing Problems (as a latent factor and specific indicators) on AUD and CUD

	Unadjusted Model		Model 1		Model 2		Model 3		Model 4	
AUD as outcome	β	**95% CI**	β	**95% CI**	β	**95% CI**	β	**95% CI**	β	**95% CI**
Internalizing problems latent factor	-0.05	(-0.26, 0.17)	-0.02	(-0.19, 0.15)	-0.23	(-0.64, 0.18)	0.02	(-0.34, 0.39)	0.10	(-0.12, 0.32)
Depressive symptoms	-	-	-	-	0.21	(-0.13, 0.55)	-	-	-	-
Physical symptoms of anxiety	-	-	-	-	-	-	-0.04	(-0.37, 0.28)	-	-
Social anxiety symptoms	-	-	-	-	-	-	-	-	-0.14	(-0.34, 0.07)
Sex	-	-	0.24	(0.12, 0.35)	0.24	(0.12, 0.35)	0.24	(0.12, 0.35)	0.24	(0.12, 0.35)
Parent/Caregiver Education	-	-	-0.07	(-0.20, 0.05)	-0.07	(-0.20, 0.05)	-0.07	(-0.20, 0.05)	-0.07	(-0.20, 0.05)
Previous Alcohol/Cannabis Use	-	-	0.14	(0.04, 0.24)	0.14	(0.04, 0.24)	0.14	(0.04, 0.24)	0.14	(0.04, 0.24)
CUD as outcome	**β**	**95% CI**	**β**	**95% CI**	**β**	**95% CI**	**β**	**95% CI**	**β**	**95% CI**
Internalizing problems latent factor	0.07	(-0.10, 0.24)	0.08	(-0.10, 0.25)	0.11	(-0.23, 0.45)	-0.12	(-0.54, 0.30)	0.18	(-0.03, 0.39)
Depressive symptoms	-	-	-	-	-0.03	(-0.31, 0.24)	-	-	-	-
Physical symptoms of anxiety	-	-	-	-	-	-	0.20	(-0.16, 0.56)	-	-
Social anxiety symptoms	-	-	-	-	-	-	-	-	-0.12	(-0.32, 0.09)
Sex	-	-	0.24	(0.12, 0.35)	0.24	(0.12, 0.35)	0.24	(0.12, 0.35)	0.24	(0.12, 0.35)
Parent/Caregiver Education	-	-	-0.08	(-0.20, 0.05)	-0.08	(-0.20, 0.05)	-0.08	(-0.20, 0.05)	-0.07	(-0.20, 0.08)
Previous Alcohol/Cannabis Use	-	-	0.14	(0.04, 0.24)	0.14	(0.04, 0.24)	0.14	(0.04, 0.24)	0.14	(0.04, 0.24)

Notes:

Unadjusted model: Outcome on internalizing disorders without covariates

Model 1: Outcome on internalizing disorders + covariates

Model 2: Outcome on internalizing disorders + depressive symptom score + covariates

Model 3: Outcome on internalizing disorders + physical symptoms of anxiety + covariates

Model 4: Outcome on internalizing disorders + social anxiety + covariates

Table 4. Model-Predicted Probabilities for AUD and CUD at Different Levels of Internalizing Problems using Model 1

Level of internalizing problems	**Predicted probability of AUD**
1 SD below mean	0.21
Mean	0.20
1 SD above mean	0.20
Level of internalizing problems	**Predicted probability of CUD**
1 SD below mean	0.19
Mean	0.22
1 SD above mean	0.24

References:

Ames, G. M., Duke, M. R., Moore, R. S., & Cunradi, C. B. (2009). The impact of occupational culture on drinking behavior of young adults in the US Navy. *Journal of Mixed Methods Research*, *3*(2), 129-150.

Anderson, E. R., Jordan, J. A., Smith, A. J., & Inderbitzen-Nolan, H. M. (2009). An examination of the MASC social anxiety scalein a non-referred sample of adolescents. *Journal of Anxiety Disorders*, 23(8), 1098-1105.

Angold, A., Costello, J., Van Kämmen, W., & Stouthamer-Loeber, M. (1995). Development of a short questionnaire for use in epidemiological studies of depression in children and adolescents: factor composition and structure across development. *International Journal of Methods in Psychiatric Research 5*(4), 251–262).

Arnett, J. J. (2005). The developmental context of substance use in emerging adulthood. *Journal of drug issues*, *35*(2), 235-254.

Bentler, P. M., & Bonett, D. G. (1980). Significance tests and goodness of fit in the analysis of covariance structures. Psychological bulletin, 88(3), 588.

Brière, F. N., Rohde, P., Seeley, J. R., Klein, D., & Lewinsohn, P. M. (2014). Comorbidity between major depression and alcohol use disorder from adolescence to adulthood. *Comprehensive psychiatry*, *55*(3), 526-533.

Brown, T. A. (2006). Confirmatory factor analysis for applied research. New York: The Guilford Press.

Browne, M. W., & Cudeck, R. (1992). Alternative ways of assessing model fit. *Sociological methods & research*, *21*(2), 230-258.

Buckner, J. D., Schmidt, N. B., Lang, A. R., Small, J. W., Schlauch, R. C., & Lewinsohn, P. M. (2008). Specificity of social anxiety disorder as a risk factor for alcohol and cannabis dependence. *Journal of psychiatric research*, 42(3), 230-239.

Burleson Daviss, W., Birmaher, B., Melhem, N. A., Axelson, D. A., Michaels, S. M., & Brent, D. A. (2006). Criterion validity of the Mood and Feelings Questionnaire for depressive episodes in clinic and non-clinic subjects. *Journal of Child Psychology and Psychiatry*, 47(9), 927-934.

Caspi, A., Houts, R. M., Belsky, D. W., Goldman-Mellor, S. J., Harrington, H., Israel, S., ... & Moffitt, T. E. (2014). The p factor: one general psychopathology factor in the structure of psychiatric disorders?. *Clinical psychological science*, *2*(2), 119-137.

Colder, C. R., Lee, Y. H., Frndak, S., Read, J. P., & Wieczorek, W. F. (2019). Internalizing symptoms and cannabis and alcohol use: Between-and within-person risk pathways with coping motives. *Journal of consulting and clinical psychology*, 87(7), 629.

Crum, R. M., & Pratt, L. A. (2001). Risk of heavy drinking and alcohol use disorders in social phobia: a prospective analysis. *American Journal of Psychiatry*, *158*(10), 1693-1700.

Fox, C. L., Towe, S. L., Stephens, R. S., Walker, D. D., & Roffman, R. A. (2011). Motives for

cannabis use in high-risk adolescent users. *Psychology of addictive behaviors*, *25*(3), 492.

Gil, A. G., Wagner, E. F., & Tubman, J. G. (2004). Associations between early-adolescent substance use and subsequent young-adult substance use disorders and psychiatric disorders among a multiethnic male sample in South Florida. *American journal of public health*, *94*(9), 1603-1609.

Gobbi, G., Atkin, T., Zytynski, T., Wang, S., Askari, S., Boruff, J., ... & Mayo, N. (2019). Association of cannabis use in adolescence and risk of depression, anxiety, and suicidality in young adulthood: a systematic review and meta-analysis. *JAMA psychiatry*, *76*(4), 426-434.

Greene, J. W., Walker, L. S., Hickson, G., & Thompson, J. (1985). Stressful life events and somatic complaints in adolescents. *Pediatrics*, *75*(1), 19-22.

Hall, D. H., & Queener, J. E. (2007). Self-medication hypothesis of substance use: testing Khantzian's updated theory. *Journal of Psychoactive Drugs*, *39*(2), 151-158.

Hankin, B. L., Snyder, H. R., Gulley, L. D., Schweizer, T. H., Bijttebier, P., Nelis, S., ... & Vasey, M. W. (2016). Understanding comorbidity among internalizing problems: Integrating latent structural models of psychopathology and risk mechanisms. *Development and Psychopathology*, 28(4pt1), 987-1012.

Hasin, D. S., Shmulewitz, D., & Sarvet, A. L. (2019). Time trends in US cannabis use and cannabis use disorders overall and by sociodemographic subgroups: a narrative review and new findings. *The American journal of drug and alcohol abuse*, *45*(6), 623-643.

Hingson, R. W., Heeren, T., & Winter, M. R. (2006). Age at drinking onset and alcohol dependence: age at onset, duration, and severity. *Archives of pediatrics & adolescent medicine*, *160*(7), 739-746.

Hirschfeld, R. M. (2001). The comorbidity of major depression and anxiety disorders: recognition and management in primary care. *Primary care companion to the Journal of clinical psychiatry*, *3*(6), 244.

Jones, S, Claster, S (2001) Cross-cultural study of people's perceptions of marijuana users. Sociological Viewpoints 19: 37–46.

Kelly, A. B., Chan, G. C., Mason, W. A., & Williams, J. W. (2015). The relationship between psychological distress and adolescent polydrug use. *Psychology of Addictive Behaviors*, *29*(3), 787.

Khantzian, E. J. (1997). The self-medication hypothesis of substance use disorders: A reconsideration and recent applications. *Harvard review of psychiatry*, *4*(5), 231-244.

King, K. M., Meehan, B. T., Trim, R. S., & Chassin, L. (2006). Marker or mediator? The effects of adolescent substance use on young adult educational attainment. *Addiction*, *101*(12), 1730-1740.

Kline, R. B. (2005). Principles and practice of structural equation modeling 2nd ed. New York: Guilford, 3.

Leadbeater, B. J., Ames, M. E., & Linden-Carmichael, A. N. (2019). Age-varying effects of cannabis use frequency and disorder on symptoms of psychosis, depression and anxiety in adolescents and adults. *Addiction*, *114*(2), 278-293.

Leshner, A. I. (1999). Science-based views of drug addiction and its treatment. Jama, 282(14), 1314-1316.

Levine, A., Clemenza, K., Rynn, M., & Lieberman, J. (2017). Evidence for the risks and consequences of adolescent cannabis exposure. *Journal of the American Academy of Child & Adolescent Psychiatry*, *56*(3), 214-225.

March, J. S., Parker, J. D., Sullivan, K., Stallings, P., & Conners, C. K. (1997). The Multidimensional Anxiety Scale for Children (MASC): factor structure, reliability, and validity. *Journal of the American academy of child & adolescent psychiatry*, *36*(4), 554-565.

McCarty, C. A., Stoep, A. V., & McCauley, E. (2007). Cognitive features associated with depressive symptoms in adolescence: Directionality and specificity. *Journal of Clinical Child and Adolescent Psychology*, *36*(2), 147-158.

McCarty, C. A., Wymbs, B. T., Mason, W. A., King, K. M., McCauley, E., Baer, J., & Vander Stoep, A. (2013). Early adolescent growth in depression and conduct problem symptoms as predictors of later substance use impairment. *Journal of abnormal child psychology*, *41*(7), 1041-1051.

Meier, M. H., Caspi, A., Ambler, A., Harrington, H., Houts, R., Keefe, R. S., ... & Moffitt, T. E. (2012). Persistent cannabis users show neuropsychological decline from childhood to midlife. *Proceedings of the National Academy of Sciences*, *109*(40), E2657-E2664.

Muthén, L.K.; Muthén, B.O. *Mplus User's Guide*, 8th ed.; Muthén & Muthén: Los Angeles, CA, USA, 2017.

Patrick, M. E., Schulenberg, J. E., O'malley, P. M., Johnston, L. D., & Bachman, J. G. (2011). Adolescents' reported reasons for alcohol and marijuana use as predictors of substance use and problems in adulthood. *Journal of studies on alcohol and drugs*, *72*(1), 106-116.

Patrick, M. E., & Schulenberg, J. E. (2014). Prevalence and predictors of adolescent alcohol use and binge drinking in the United States. *Alcohol research: current reviews*, *35*(2), 193.

Prince, D. M., Adrian, M. C., Storer, H. L., Namkung, N., Thompson, K., McCauley, E., & Vander Stoep, A. (2015). Contextualizing change points in alcohol use from early adolescence through young adulthood. *Social Work Research*, *39*(2), 94-106.

Rehm, J., Mathers, C., Popova, S., Thavorncharoensap, M., Teerawattananon, Y., & Patra, J. (2009). Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. *The lancet*, *373*(9682), 2223-2233.

Rhew, I. C., Fleming, C. B., Vander Stoep, A., Nicodimos, S., Zheng, C., & McCauley, E. (2017). Examination of cumulative effects of early adolescent depression on cannabis and alcohol use disorder in late adolescence in a community-based cohort. *Addiction*, *112*(11), 1952-1960.

Rynn, M. A., Barber, J. P., Khalid-Khan, S., Siqueland, L., Dembiski, M., McCarthy, K. S., & Gallop, R. (2006). The psychometric properties of the MASC in a pediatric psychiatric sample. *Journal of anxiety disorders*, *20*(2), 139-157.

SAMHSA. (2020). *Results from the 2019 National Survey on Drug Use and Health: Detailed Tables.* Substance Abuse and Mental Health Services Administration.

Schulenberg, J., Wadsworth, K. N., O'Malley, P. M., Bachman, J. G., & Johnston, L. D. (1997). Adolescent risk factors for binge drinking during the transition to young adulthood: variable-and pattern-centered approaches to change.

Schulte, Marya and Hser, Yih-Ing. (2014). Substance Use and Associated Health Conditions throughout the Lifespan. *Physiology & Behavior*, *176*(3), 139–148.

Staff, J., Schulenberg, J. E., Maslowsky, J., Bachman, J. G., O'Malley, P. M., Maggs, J. L., & Johnston, L. D. (2010). Substance use changes and social role transitions: Proximal developmental effects on ongoing trajectories from late adolescence through early adulthood. *Development and psychopathology*, *22*(4), 917-932.

Sund, A. M., Larsson, B., & Wichstrøm, L. (2001). Depressive symptoms among young Norwegian adolescents as measured by the Mood and Feelings Questionnaire (MFQ). *European child & adolescent psychiatry*, *10*(4), 222-229.

Snyder, H. R., Young, J. F., & Hankin, B. L. (2017). Strong homotypic continuity in common psychopathology-, internalizing-, and externalizing-specific factors over time in adolescents. *Clinical Psychological Science*, *5*(1), 98-110.

Vander Stoep, A., Mccauley, E., Thompson, K. A., Herting, J. R., Kuo, E. S., Stewart, D. G., ... & Kushner, S. (2005). Universal emotional health screening at the middle school transition. *Journal of Emotional and Behavioral Disorders*, *13*(4), 213-223.

Vander Stoep, A., Adrian, M., Mc Cauley, E., Crowell, S. E., Stone, A., & Flynn, C. (2011). Risk for suicidal ideation and suicide attempts associated with co-occurring depression and conduct problems in early adolescence. *Suicide and Life-Threatening Behavior*, *41*(3), 316-329.

Wasserman, G. A., McReynolds, L. S., Lucas, C. P., Fisher, P., & Santos, L. (2002). The Voice DISC-IV with Incarcerated Male Youths: Prevalence of Disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, *41*(3), 314–321. https://doi.org/10.1097/00004583-200203000-00011

Weinberger, A. H., Pacek, L. R., Sheffer, C. E., Budney, A. J., Lee, J., & Goodwin, R. D. (2019). Serious psychological distress and daily cannabis use, 2008 to 2016: Potential implications for mental health?. *Drug and alcohol dependence*, *197*, 134-140.

Zahn–Waxler, C., Klimes–Dougan, B., & Slattery, M. J. (2000). Internalizing problems of childhood and adolescence: Prospects, pitfalls, and progress in understanding the development of anxiety and depression. *Development and Psychopathology*, *12*(3), 443–466.

Zeigler, D. W., Wang, C. C., Yoast, R. A., Dickinson, B. D., McCaffree, M. A., Robinowitz, C. B., & Sterling, M. L. (2005). The neurocognitive effects of alcohol on adolescents and

college students. *Preventive medicine, 40*(1), 23-32.

Zimmermann, P., Wittchen, H. U., Höfler, M., Pfister, H., Kessler, R. C., & Lieb, R. (2003). Primary anxiety disorders and the development of subsequent alcohol use disorders: a 4-year community study of adolescents and young adults. *Psychological medicine, 33*(7), 1211-1222.