

# Examination of cumulative effects of early adolescent depression on cannabis and alcohol use disorder in late adolescence in a community-based cohort

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## ABSTRACT

**Background and Aims** Although they often co-occur, the longitudinal relationship between depression and substance use disorders during adolescence remains unclear. This study estimated the effects of cumulative depression during early adolescence (ages 13–15 years) on the likelihood of cannabis use disorder (CUD) and alcohol use disorder (AUD) at age 18. **Design** Prospective cohort study of youth assessed at least annually between 6th and 9th grades (~ age 12–15) and again at age 18. Marginal structural models based on a counterfactual framework that accounted for both potential fixed and time-varying confounders were used to estimate cumulative effects of depressive symptoms over early adolescence. **Setting** The sample originated from four public middle schools in Seattle, Washington, USA. **Participants** The sample consisted of 521 youth (48.4% female; 44.5% were non-Hispanic White). **Measurements** Structured in-person interviews with youth and their parents were conducted to assess diagnostic symptom counts of depression during early adolescence; diagnoses of CUD and AUD at age 18 was based the Voice-Diagnostic Interview Schedule for Children. Cumulative depression was defined as the sum of depression symptom counts from grades 7–9. **Findings** The past-year prevalence of cannabis and alcohol use disorder at the age 18 study wave was 20.9 and 19.8%, respectively. A 1 standard deviation increase in cumulative depression during early adolescence was associated with a 50% higher likelihood of CUD [prevalence ratio (PR) = 1.50; 95% confidence interval (CI) = 1.07, 2.10]. Although similar in direction, there was no statistically significant association between depression and AUD (PR = 1.41; 95% CI = 0.94, 2.11). Further, there were no differences in associations according to gender. **Conclusions** Youth with more chronic or severe forms of depression during early adolescence may be at elevated risk for developing cannabis use disorder compared with otherwise similar youth who experience fewer depressive symptoms during early adolescence.

**Keywords** Adolescence, alcohol, cannabis, depression, marginal structural model, substance use disorder.

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## INTRODUCTION

During the past decade, cannabis has surpassed tobacco with respect to prevalence of use among adolescents, joining alcohol as the two most commonly used substances among youth in the United States [1]. Also, prevalence of both cannabis use disorder (CUD) and alcohol use disorder (AUD) among young adults has increased according to one national study [2,3]. Cannabis and alcohol problems often co-occur with various forms of psychopathology, including depression [2–6]. Depression may lead to substance use as

a strategy for medicating distressing affect [7]. Indeed, many heavy cannabis and alcohol users report use as a coping strategy [8–10]. Despite this, longitudinal findings for this pathway are mixed for both cannabis and alcohol use [11,12]. For example, some studies document that depression is associated with elevated adolescent substance use and abuse [13–18]; others show no association [19–24]; others examining both alcohol and cannabis show associations for alcohol, but not cannabis [25]; and still others have found that despite cross-sectional positive associations between concurrent depression and substance

use, depressive symptoms in adolescence predicts slower increases in alcohol and substance use [26,27].

As pointed out in a recent systematic review by Pedrelli *et al.* [12], inconsistency in results may be due to the variety of measurement approaches for both substance use and depression. Throughout studies, substance use outcomes range from initiation to any use to quantity/frequency to disorder. Because cannabis and alcohol use become normative in late adolescence [1], depression may play a limited role in initiation of or occasional use relative to other social factors. If substance use was a coping strategy for depression, then associations between depression and heavier and disordered use may be more likely. How depression is characterized also varies. Most longitudinal studies have assessed adolescent depression at a single time-point without consideration for the longer longitudinal course [11]. Because depression often emerges over time and has an episodic presentation, a fuller history of depression, rather than a single assessment, could capture effects of chronic, or cumulative, experience of depression.

For estimation of effects of an exposure at a single time-point, it is common to use statistical adjustment to control for potential covariates that may confound the association between the exposure and the outcome. Accounting for confounding becomes more challenging when using repeated measures in order to characterize an exposure such as cumulative depression. With time-varying exposures, it is necessary to account for both time-fixed (e.g. gender, race) and time-varying confounders (e.g. prior depression, other mental health problems, substance use). The primary challenge is that time-varying covariates may act as confounders of the association between the outcome and depression assessed at one time, but also as intermediary variables when depression is assessed at another time [28]. Approaches that adjust for time-varying covariates by including them in a regression model (e.g. logistic regression) could, thus, be biased.

Methods based on a counterfactual framework, such as marginal structural models (MSMs), have been developed to reduce bias associated with time-varying confounding [29]. MSMs use inverse probability weights (IPWs), where weights are the inverse of the predicted probability, akin to a propensity score, of one's observed exposure according to time-varying and time-fixed covariates. The IPWs are used to re-weight the study sample in order to create a 'pseudo-population' with the goal, similar to that of randomization in a randomized trial, of making exposure groups comparable in distribution of putative confounders. In the weighted sample, those with a lower model-predicted propensity for their observed level of exposure are given greater weight, while those with a higher likelihood are given lower weight. This results in balanced distribution of confounders across levels of the exposure. Using the weighted sample, one can estimate the unconfounded effect of the exposure

without inclusion of time-varying confounders in the final statistical model. This approach has been increasingly used to estimate causal effects of exposures in epidemiology and within the field of substance use research [30,31]. Additional introductions of MSMs are provided in greater detail elsewhere [32–34].

The role of gender in the relationship between depression and substance misuse is another important consideration. During adolescence, females show higher prevalence of depression and males show greater substance use and misuse [35,36]. This suggests that the relationship between depression and substance use disorder may differ by gender. For example, one study observed that increases in depression were associated with marijuana use frequency for males, but not females [37].

To understand more clearly the relationship between depression and substance use disorders during an important developmental period when prevalence of both are increasing, this study used marginal structural modeling to estimate effects of cumulative depression during early adolescence (grades 7–9; ages 13–15) on CUD and AUD in late adolescence (age 18). Additional analyses tested if the associations between cumulative depression and substance use disorders differed by gender.

## METHOD

### Design and sample

Data for this study were from the Developmental Pathways Project (DPP), a community-based prospective cohort study designed to examine the antecedents, phenomenology and outcomes of adolescent depression and conduct problems. Participants were recruited from four Seattle public schools located in areas that together are representative of the racial/ethnic composition of the school district student population. The sampling procedures oversampled for students with depressive and/or conduct problems. Universal screening was performed with validated measures of depression symptoms, the Mood and Feelings Questionnaire (MFQ) [38], and conduct problems, the Youth Self Report (YSR) externalizing scale [39]. Screening was conducted with 2187 (74.9%) of 2920 eligible sixth-grade students throughout four consecutive years (2001–04). At each of these 4 years those screened were stratified, using a cut-off of 0.5 standard deviations (SD) above the screening sample mean on the MFQ and YSR, to one of four groups: high depression and conduct problem score (comorbid; CM), high depression and low conduct problem score (DP), low depression and high conduct problem score (CD) and low depression and low conduct problem score (NE). From these groups, 807 students were identified randomly according to the ratio of 1 CM : 1 DP : 1 CP : 2 NE. Of those selected, 521 (64.6%) students and their parents/guardians provided consent [40]. To account for

oversampling of those with elevated depression and/or conduct problems as well as to account for differences in demographic characteristics (e.g. race, educational program) between the study sample and the general student population, two-component weights were created and utilized in analyses.

At baseline, the average age of the sample was 12.0 years (SD = 0.4) and 48.4% were female. With regard to race/ethnicity, 44.5% were non-Hispanic white, 27.5% non-Hispanic black, 16.9% non-Hispanic Asian, 1.0% Native American and 10.2% Hispanic of any race. The median educational attainment for caregivers of study participants was having completed some college after high school, and the median combined household income was ~\$50 000.

### Procedures

The DPP was approved by the University of Washington Institutional Review Board. Consent was obtained from both students and parents/guardians. In-home interviews were conducted face-to-face with adolescents and parents/guardians by two trained research interviewers blind to the psychopathology risk group status of participants. Baseline interviews were conducted within 3 months of screening. Follow-up interviews were conducted at 6, 12, 18, 24, 36 and 72 months. In the current study, we used data from the baseline and 12- (grade 7, ~ age 13), 24- (grade 8, ~ age 14), 36- (grade 9, ~ age 15) and 72-month (age 18) follow-up interviews. Completion rates at the early adolescent follow-up waves ranged from 79 to 85%, and 471 (90.4%) participants completed their 72-month follow-up interviews.

### Measures

The DPP utilized psychosocial measures that have shown evidence of validity in adolescent samples (citations to validation studies for measures used in the current study provided below).

#### *Depression disorder symptoms*

The Diagnostic Interview Schedule for Children (DISC-IV) depression module was administered to each adolescent and a parent/guardian during the baseline, 12-, 24- and 36-month interviews [41]. The C-DISC was developed for large-scale epidemiological studies and can be administered by trained lay interviewers [8,9]. Algorithms applied to responses yield diagnoses based on DSM-IV criteria. Depression symptoms endorsed as occurring within the past year were summed to form symptom counts.

#### *Substance use disorders*

At the 72-month interview, two modules from the Voice-Diagnostic Interview Schedule for Children (V-DISC) were

administered that yield DSM-IV diagnoses of past year cannabis and alcohol abuse and dependence. CUD and AUD were defined as a diagnosis of cannabis abuse or dependence, or alcohol use or dependence, respectively. The V-DISC allows the adolescent to answer sensitive questions without interviewer involvement and has comparable reliability with other versions of the DISC [42,43].

#### *Covariates*

Time-fixed measures at baseline included socio-demographic measures, including adolescent-reported race, ethnicity, sex and age, and the parent-reported educational attainment of parents in the household, number of children in the household and household income. Time-varying covariates included student-report measures of substance use and other psychosocial measures. The 12-item Perceived Social Support Scale (PSS) was administered at each interview to assess the amount of support the adolescent feels the adolescent receives from friends, family and significant others [44]. The six-item scholastic competence domain score from the 36-item Self-Perception Profile for Adolescents, known commonly as 'What I am Like' (WIAL) [45] and a self-report version of the Life Events Checklist were administered to parents at baseline to identify stressful life events that had occurred during the past 6 months [46]. Participants completed the Customary Drinking and Drug Use Record (CDDR) at the baseline, 12- and 24-month evaluations [47]. Because prevalence was rather low during early adolescence, binary measures for alcohol, tobacco or cannabis were created to indicate whether adolescents reported any use within the past 6 months. Conduct disorder symptoms were ascertained during the same C-DISC interview used to obtain the depression disorder symptoms [41]. Total anxiety symptom scores were assessed using the 39-item Multidimensional Anxiety Scale for Children (MASC) [48]. Additional dimensional measures of internalizing and externalizing scale scores from Achenbach's Child Behavioral Checklist (CBCL) [49].

#### *Data analysis*

We used marginal structural modeling as the primary analytical approach. MSMs require multiple steps. The first step in the analyses was to create the IPWs for depression at each of the early adolescent assessments (grades 7, 8 and 9). For this study, we utilized a stabilized form of the IPW to increase precision [50]. The stabilized IPW is a ratio of the predicted probability of the observed level of depression according to selected time-fixed covariates (the numerator) to the predicted probability of observed level of depression according to both time-varying and time-fixed covariates (denominator).

Predicted probabilities of one's own level of depression at the 12-, 24- and 36-month visits were calculated. We collapsed symptom counts into nine categories (0–8) at each time-point. We then modeled this as an ordinal outcome using an ordinal logistic (also known as cumulative probability) regression model. This categorical binning approach has been shown to be less biased than other methods [51]. For calculation of the denominator of the IPWs, covariates in the ordinal logistic model included time-varying covariates (described in the Measures section) assessed at prior visits (i.e. for depression at time  $t$ , covariates in the model were assessed at  $t-1$  or earlier) as well as time-fixed covariates. These covariates were selected a priori for inclusion because they were believed to be related to both depression and substance use disorder. For the numerator of the stabilized weights, ordinal logistic regression models were used to calculate predicted probability of one's depression level but only according to time-fixed covariates.

Additional details about methods to create the IPWs (e.g. specification of time-fixed and time-varying covariates in the model) are found in the Supporting Information (Appendix S1). Further, Appendix S1 provides additional details about MSM assumptions including exchangeability (no unmeasured confounders) and positivity (a non-zero likelihood for any given level of exposure across all levels of covariates included in the model to calculate IPWs).

The predicted probabilities for the denominator and numerator were saved and used to create stabilized IPWs at each time-point. The product of the three IPWs for depression at 12, 24 and 36 months was then calculated to create a single IPW reflecting the inverse probability of one's observed depression history throughout grades 7–9. Because of the over-sampling of participants based on their mental health status, as well as under-representation of certain demographic groups, we multiplied the IPW by the two-component sampling weight to generalize findings to the greater Seattle public school district population. Finally, to improve precision of the weights, we truncated the IPWs such that extreme values at the tail ends of the distribution were recoded to the value at the 1st and 99th percentiles [50].

These IPWs were then applied to regression models to estimate the effect of cumulative depression on cannabis and alcohol use disorder at age 18. Cumulative depression was defined as the sum of the nine-category ordinal depression variable from 7th, 8th and 9th grades (range = 0–24). For ease of interpretation, the cumulative depression score was then standardized with a mean of 0 and standard deviation of 1. We used Poisson regression with robust standard errors to estimate prevalence ratios (PRs) [52]. Time-fixed covariates were also included to further increase precision. Dummy variables for the school from which one was sampled were

included to account for the potential for school-level clustering.

Secondary analyses were performed. To assess differences in the effects of cumulative depression, additional models included an interaction between cumulative depression and sex. To understand the influence of the time-varying covariates, we ran models that were only weighted according to the sampling weights rather than the full IPWs and adjusted only for time-fixed covariates. Finally, as a comparison to effects of cumulative experience of depression, *post-hoc* analyses were run that separately estimated grade-specific (grades 7, 8 and 9) effects of early adolescent depression on substance use disorders at age 18. Here, the corresponding grade-specific IPWs were used for weighting rather than the product of the three grade-specific IPWs.

#### Missing data

While completion rates for assessments at follow-up waves were high (from 78% at grade 9 to 90% at age 18), listwise deletion would have resulted in a substantial loss in sample size and power. To include information from cases with partially missing data, we used multiple imputation via the multiple imputation by chained equations (MICE) approach. MICE runs a series of regression models for each missing variable conditional upon other specified variables [53]. In addition to all covariates included in the models to generate the IPWs and the final marginal structural models, other variables included the CBCL internalizing and externalizing subscales. Twenty imputed data sets were created, and IPWs were calculated for each imputed data set. The final MSMs were run in each data set, and pooled parameter estimates and their standard errors were calculated according to Rubin's rules to account for the between- and within-imputation variance [54]. All analyses were performed using Stata version 14.0 (StataCorp, College Station, TX, USA).

## RESULTS

Table 1 shows the prevalence of cannabis and alcohol use and the mean number of depression diagnosis symptoms from 6th grade to age 18. After categorizing the symptoms into bins, the mean cumulative depression bin count from grades 7 to 9 was 12.2 (SD = 6.6; range = 0–24). The prevalence of past-year cannabis and alcohol use disorder at 12th grade was 20.9 and 19.8%, respectively.

Table 2 shows PRs from the MSMs for CUD and AUD associated with cumulative depression as well as baseline covariates. MSM findings indicated that cumulative depression during adolescence had a statistically significant effect on CUD at 12th grade. A 1-SD increase in

**Table 1** Descriptive statistics for depression symptoms and cannabis and alcohol use at 7th, 8th and 9th grades and age 18.

	6th grade n = 521	7th grade n = 445	8th grade n = 448	9th grade n = 408	Age 18 n = 470
Past-year depression symptom count, mean (SD)	7.32 (4.86)	5.40 (4.46)	5.00 (4.36)	5.43 (4.30)	5.80 (3.66)
Any past 6-month cannabis use, %	1.73	2.70	6.89	18.53	44.89 <sup>a</sup>
Any past 6-month alcohol use, %	4.23	6.31	11.86	23.40	54.09

<sup>a</sup>Based on past 12 months rather than past 6 months. SD = standard deviation.

**Table 2** Prevalence ratios (PR) and 95% confidence intervals (CI) for cannabis and alcohol use disorder at 12th grade according to early adolescent cumulative depression<sup>a</sup> from marginal structural models.

	Cannabis use disorder		Alcohol use disorder	
	PR	95% CI	PR	95% CI
Cumulative depression <sup>a</sup>	1.50	1.07, 2.10	1.41	0.94, 2.11
Female sex	0.63	0.36, 1.11	0.58	0.33, 1.02
Race/ethnicity				
White (ref.)	–	–	–	–
Black	0.38	0.16, .89	0.41	0.18, .96
Asian	0.25	0.08, .77	0.39	0.14, 1.11
Hispanic	1.00	0.54, 1.86	0.91	0.49, 1.71
Baseline annual income <sup>b</sup>	1.17	0.89, 1.55	1.21	0.92, 1.60
Baseline age <sup>b</sup>	0.83	0.63, 1.09	0.86	0.66, 1.11
Parental education completed <sup>b</sup>	0.81	0.62, 1.07	1.07	0.76, 1.51

<sup>a</sup>Standardized with a mean of 0 and standard deviation of 1. <sup>b</sup>Characterized as ordinal categorical variables.

cumulative depression symptom bin count was associated with a 50% higher prevalence of CUD [PR = 1.50; 95% confidence interval (CI) = 1.07, 2.10;  $P = 0.017$ ]. Although the effect estimate was in the same direction, the association between cumulative depression and AUD was not statistically significant at  $P < 0.05$  (PR = 1.41; 95% CI = 0.94, 2.11;  $P = 0.096$ ). Additional MSMs with sex  $\times$  cumulative depression interaction terms did not show any evidence for differential effects of cumulative depression  $\times$  sex (interaction- $P$  for CUD = 0.55; interaction- $P$  for AUD = 0.79).

When compared to MSMs, estimated effects from non-weighted models of cumulated depression were smaller than estimates from the MSMs. In the models without IPW weighting, the PR for the effect of cumulative depression on cannabis use disorder was 1.20 (95% CI = 0.98, 1.46), and the PR for the effect of cumulative depression on alcohol use disorder was 1.13 (95% CI = 0.94, 1.37).

Finally, *post-hoc* weighted analyses estimated effects of depression at each grade separately (Table 3). Although the grade-specific effects were generally in the same direction as the cumulative depression effect, none were statistically significant.

**Table 3** Prevalence ratios (PR) and 95% confidence intervals (CI) for cannabis and alcohol use disorder at 12th grade according to depression<sup>a</sup> at specific grades from separate marginal structural models.

	Cannabis use disorder		Alcohol use disorder	
	PR	95% CI	PR	95% CI
Depression, grade 7 <sup>b</sup>	1.13	0.87, 1.47	1.22	0.93, 1.59
Depression, grade 8 <sup>b</sup>	1.08	0.82, 1.44	0.87	0.66, 1.15
Depression, grade 9 <sup>b</sup>	1.35	0.96, 1.89	1.06	0.73, 1.54

<sup>a</sup>Adjusted for other time-fixed covariates in weighted models including sex, race/ethnicity, baseline household income, baseline age, parental educational attainment and school. <sup>b</sup>Standardized with a mean of 0 and standard deviation of 1.

## DISCUSSION

Using an MSM approach to improve causal inference, we found that cumulative depression during early adolescence was associated with an increased likelihood of CUD in later adolescence. This suggests that individuals with a longer history and/or more severe episodes of depression during adolescence are at elevated risk of later cannabis use

disorders. Although some prior studies have found that reports of using substances to cope with depression are associated with greater use [8,9], evidence supporting a directional effect of depression on the likelihood of later CUD has been mixed.

The association between depression and later AUD was positive, but not statistically significant. This may be related to limited statistical power. It is possible that the slightly weaker and non-significant effects on AUD compared to CUD may be related to other factors. For example, because depression tends to be related to social withdrawal [55] and adolescents tend to use alcohol, more so than cannabis, when socializing with peers, the effect of depression on CUD compared to AUD may be more prominent.

This study took advantage of a longitudinal design with repeated measures of depression symptoms assessed via a structured diagnostic interview. Depressive symptoms often emerge across early adolescence and are episodic in presentation. Research that utilized only one time-point to assess depression may have missed cases that occurred within relatively short windows before or after the assessment. Further, ascertaining depression over multiple waves allowed us to observe effects of the cumulative experience of depression. *Post-hoc* analyses used the wave-specific IPWs to examine the relationships between late adolescent substance use disorder and depression symptoms at each of the early adolescent study waves separately. Findings indicated no statistically significant associations with late adolescent CUD or AUD and depression at any specific wave. This highlights that the experience of elevated depression symptoms at any one period may not be as meaningful a risk factor as the cumulative experience during the course of adolescence.

The use of MSMs was an important feature of this study. The MSM allowed us to examine effects of cumulative depression by accounting for multiple time-varying as well as time-fixed confounders. Time-varying covariates included prior levels of depression, conduct disorder problems, cannabis and alcohol use and other psychosocial problems. Because the MSM uses IPWs to weight the sample to generate a 'pseudo-population' balanced in distribution of putative confounders across levels of depression rather than condition on these covariates, the threat of confounding as well as bias associated with adjusting for a causal intermediate was reduced. The importance of the weighting was notable. The estimates from MSMs were stronger compared to traditional non-weighted models that did not account for time-varying covariates. Rather than attenuate the observed effects of unadjusted findings, the combined influence of the time-varying covariates revealed stronger associations.

Counterfactual-based approaches, such as MSM, can be used to articulate potential effects of hypothetical interventions that prevent or reduce the exposure on the likelihood

of the outcome [33]. Our findings suggest an intervention that could reduce chronic levels of depression symptoms during early adolescence would yield reduction in prevalence of CUD. This study adds to a body of evidence showing adolescent depression portends functional impairment across multiple life domains [56] and the importance of intervention during early adolescence. Some promising interventions that target and attempt to prevent the emergence of depression and related transdiagnostic features during this time-period have been developed [57–59].

Another notable aspect of this study was the high prevalence of CUD in the sample. This may be due, in part, to the over-reporting of substance use related problems in the self-administered V-DISC instrument. This may also be related to where and when the data were gathered. Age 18 substance use disorder assessments occurred in 2007–10. Washington State legalized medical cannabis in 1998, and its medical cannabis market expanded greatly after 2009 when the federal justice department issued its Ogden Memo [60]. Further, in 2003 the city of Seattle made cannabis offences the lowest enforcement priority for police and the city attorney [61]. Thus, the local policy context may have contributed to the high prevalence of CUD found in this study, despite the fact that prevalence of marijuana use among adolescents in Washington at this time was only slightly about the national average [62].

This study had limitations worth noting. Although measures of substance use were available, early study waves did not have measures of CUD or AUD. However, the prevalence of marijuana and alcohol use was low during this developmental period, and it is unlikely there would be a substantial number of individuals with a CUD or AUD. This study relied upon self-report measures to ascertain important covariates such as substance use. Although it is possible this could lead to residual confounding, the 'exposure' and outcome variables were assessed via structured diagnostic interview, which is often considered the gold standard for psychiatric research. The sample originated from one urban area in Washington State and may not be representative of the broader population of youth in the United States. However, given the shifting socio-political context for recreational cannabis use, understanding the etiology of CUD in this legal environment may be informative. Finally, it cannot be determined definitively whether important assumptions of MSMs including positivity and exchangeability are violated. However, descriptive statistics suggest that the positivity assumption was probably not violated, and we assessed a number of important confounders including other psychopathology and substance use.

Our findings suggest that greater cumulative experience of depression during early adolescence may place individuals at elevated risk for cannabis misuse in later adolescence. This highlights the importance of

identification and implementation of effective intervention strategies that can prevent and/or treat chronic depression among youth during this critical development period.

#### Declaration of interests

None.

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### **Supporting Information**

Additional Supporting Information may be found online in the supporting information tab for this article.

**Appendix S1** Calculation of the inverse probability weights.