



# An analysis of within-subject and population level risk related to substance use and mental health outcomes among adolescents in the PATH study

Xiao Li, Jacob T. Borodovsky, Erin M. Kasson, Andrea Fentem, Patricia A. Cavazos-Rehg \*

Department of Psychiatry, Washington University School of Medicine, 660 South Euclid Avenue, Box 8134, St. Louis, MO, 63110, United States

## ARTICLE INFO

### Keywords:

Substance use  
Mental health  
Internalizing problems  
Externalizing problems  
PATH

## ABSTRACT

**Introduction:** The objective of this study was to understand how adolescent substance use patterns may lead to negative mental health outcomes.

**Methods:** Data from adolescents (12–17 years old at baseline, Wave 1) who participated in the first 3 waves of the Population Assessment of Health and Tobacco (PATH) study were used. Self-reported data on past 30-day substance use and internalizing/externalizing problems were used to conduct within-subject (fixed-effects model) and population-averaged (GEE model) analyses.

**Results:** In both within-subject and between-subject analyses, the use of other illicit drugs (e.g., opioids, cocaine, prescription drugs for non-medical use) was positively associated with internalizing problems (within-subject estimate, AOR: 1.65, 95 % CI = 1.36–2.01; between-subject estimate, AOR: 1.53, 95 % CI = 1.32–1.78) and alcohol use was positively associated with externalizing problems (within-subject estimate, AOR: 1.66, 95 % CI = 1.43–1.93; between-subject estimate, AOR: 1.67, 95 % CI = 1.48–1.89). Additionally, within-subject analysis suggested that alcohol, marijuana, and other illicit drugs were associated with increased odds of comorbid internalizing and externalizing problems (ranging from marijuana, AOR: 1.18, - alcohol, AOR: 1.58).

**Discussion:** Using within-subject and between-subject comparisons, this study demonstrated associations between adolescent substance use and internalizing and externalizing problems. Results suggest not only the need for individual level assessment and early intervention, but also the development and implementation of public health policy aimed at preventing or mitigating the negative effects of substance use in adolescence to promote improved mental health outcomes for this at-risk group.

## 1. Introduction

Substance use behaviors in adolescence can interfere with psychosocial development (Crews et al., 2007; Squeglia et al., 2009). While recent population-level trends indicate broad declines in adolescent use of several substances (e.g., combustible tobacco, alcohol, illicit drugs), newer substances (e.g., vaping) have become increasingly popular among adolescents (Hammond et al., 2019; Khan, 2019), with 11 % of middle school and 30 % of high school students using vaping products in 2018 alone (Johnston et al., 2019; Levy et al., 2019). Substance use and mental health problems among young people co-occur often, and accordingly, depression and anxiety have also risen among adolescents in the last decade (Ghandour et al., 2019). For example, the prevalence of major depression among a national sample of US adolescents rose from 8.7 % to, 11.3 % from 2005 to 2014 (Mojtabai et al., 2016). Prevalence changes in mental health concerns are potentially related to

shifts in substance use behaviors among adolescents and warrant further investigation in this topic area.

Existing research demonstrates a complex relationship between adolescent substance use behaviors and mental health symptoms. Numerous studies have investigated the use of substances among adolescents to cope with existing mental health problems (i.e., self-medication hypothesis), a relationship which has been demonstrated in national and convenience samples studies (Green et al., 2018; Harris and Edlund, 2005; Savage et al., 2016). For example, studies have shown that externalizing symptoms (e.g., conduct disorder, attention-deficit/hyperactivity disorder [ADHD], and oppositional defiant disorder) during early adolescence predict the onset and habitual use of tobacco (Mitchell et al., 2019; Wilens et al., 2011), and internalizing symptoms (e.g., depression, anxiety) have been shown to predict an increased likelihood of adolescent alcohol use (Marmorstein et al., 2010). However, studies reporting these associations are often

\* Corresponding author.

E-mail address: [pcavazos@wustl.edu](mailto:pcavazos@wustl.edu) (P.A. Cavazos-Rehg).

<https://doi.org/10.1016/j.drugalcdep.2020.108385>

Received 31 March 2020; Received in revised form 9 October 2020; Accepted 20 October 2020

Available online 27 October 2020

0376-8716/© 2020 Elsevier B.V. All rights reserved.

cross-sectional or report inconsistent findings in regards to evaluations of directionality (Esmaelzadeh et al., 2018; Gray and Squeglia, 2018).

There are contrasting and emerging findings that signal substance use occurs prior to the onset of mental health problems, and that this substance use can contribute to the development of these symptoms, possibly due to: 1) the impact of substance use on brain development, and 2) the impact of substance use on functional outcomes resulting in subsequent mental health symptom development. For instance, adolescent use of marijuana and alcohol have been linked to subsequent increases in depressive symptoms (Rowe et al., 2001; Stapinski et al., 2016) and this may be due to THC exposure and alcohol effects on the dopamine system (Subramaniam et al., 2018; Wright et al., 2016). In addition, several studies have similarly observed that adolescent cigarette use increases the risk of developing anxiety symptoms (Rowe et al., 2001; van Amsterdam et al., 2018). What is more, differing mental health outcomes have been found for those who use combustible versus non-combustible tobacco products, (i.e., externalizing symptoms are greater for those who use cigarettes while both internalizing and externalizing problems are increased among those who use e-cigarettes (Green et al., 2018; Riehm et al., 2019b)). As a whole, adolescent experimentation and initiation of single and polysubstance use has been associated with worsening mental health outcomes (Cohn et al., 2018; Moss et al., 2014; Taylor et al., 2020), suggesting the need for rigorous investigations of substance use impacts on mental health problems.

The present study uses a nationally representative longitudinal cohort from the PATH (Population Assessment of Tobacco and Health) study to examine whether substance use behaviors in adolescence are associated with an increase likelihood of experiencing internalizing and externalizing problems over time at both the subject- and population-level, respectively. Because of the complexity of the issue, we examined the potential effects of substance use on mental health problems in two ways. In the first analysis, each subject served as his/her own control. Stated differently, this a subject's substance use and mental health status at one point in time was examined in relation to his/her substance use and mental health status at another point in time. Conversely, the population-averaged model estimates the effect size for substance use by comparing the mental health status of those with substance use to those without substance use. This approach enables us to inform not only individual-level assessment and intervention strategies but also public health policy. The PATH study data additionally provides the advantage of within-person repeated measures data among adolescents and includes more mental health problem measures than other national cross-sectional studies, providing sufficient data to investigate our research question.

## 2. Methods

### 2.1. Study design and population

We used public-use data files from the Population Assessment of Tobacco and Health (PATH) study, a nationally representative, longitudinal cohort study of 45,971 U.S. respondents, aged 12 and above at baseline (United States Department of Health and Human Services (USDHHS, 2019). Baseline (i.e., Wave 1) interviews were conducted in 2013–2014. Wave 2 and Wave 3 follow-up interviews were conducted in 2014–2015 and 2015–2016, respectively. Our analyses only include adolescents aged 12–17 at baseline who provided complete data on primary independent (substance use) and outcomes (mental health symptoms) variables for all three waves. Of those 13,651 participants at baseline, we excluded 2778 respondents due to attrition or incomplete responses, thus only complete cases were included in the following analysis. By Wave 2, 1661 adolescents had aged into the adult group (i.e., participants who were age 17 in Wave 1 but were age 18 by Wave 2) and another 1689 subject aged into the adult group by Wave 3. These participants responded to the adult questionnaire rather than the youth version but were still included in our analyses. The total sample size was

10,873 participants.

### 2.2. Measures

#### 2.2.1. Substance use (Independent Variables, all 3 waves)

Substance use was assessed at each wave of the study. We examined past 30-day use (yes/no) across four categories of substances: (1) marijuana (including blunts), (2) alcohol (counting small tastes or sips), (3) tobacco, and (4) other illicit drugs (including prescription-drugs for non-medical use and other substances such as cocaine, crack, stimulants, heroin, inhalants, solvents, hallucinogens, and non-medical use of prescription stimulants, opioids, sedatives, or tranquilizers). In questionnaires, participants were asked: “have you ever smoked/used/had [substances] in the past 30 days” at each wave.

Tobacco use was assessed by asking adolescents if they had ever used any of the following tobacco products: cigarettes, electronic nicotine delivery systems (ENDS, including e-cigarettes), traditional cigars, cigarillos, filtered cigars, pipe, hookah, smokeless tobacco (i.e., loose snus, moist snuff, dip, spit, or chewing tobacco), snus pouches, dissolvable tobacco, bidis, and kreteks. Due to the low prevalence of bidis and kreteks use among adolescents, these products were not queried in the adult questionnaire. To be consistent with the adult questionnaire, analysis of bidis and kreteks use was excluded from this study. Tobacco products were grouped as combustible and non-combustible tobacco products (FDA, 2019). Previous studies have demonstrated positive associations between the use of tobacco products (i.e., e-cigarette, combustible cigarette) and mental health problems (e.g., depression) and suggest differences in effect size estimates and mental health outcomes relative to the use of combustible (e.g., cigarettes) and non-combustible tobacco products (e.g., e-cigarettes) (Johnson et al., 2000; Obisesan et al., 2019; Riehm et al., 2019b). Taking advantage of the comprehensive assessment of various tobacco products in the PATH study, we classified tobacco products as either combustible (including cigarettes, traditional cigars, cigarillos, filtered cigars, pipes, and hookah) or non-combustible tobacco product (including e-cigarettes, smokeless tobacco, snus, and dissolvable tobacco) and compared them in the following analysis. We chose to group tobacco products in this way as previous studies have suggested bidirectional associations between mental health and tobacco use, as well as differing mental health outcomes for those who use combustible versus non-combustible products (Green et al., 2018; King et al., 2018; Riehm et al., 2019b).

#### 2.2.2. Mental health problems (Dependent Variables, all 3 waves)

Participants' mental health problems were examined at each wave through self-reports of internalizing and externalizing problems within the past 30-days via the short version of the Global Appraisal of Individual Needs (GAIN-SS), a screening measure that has been validated in adolescents and adults (Conway et al., 2017; Dennis et al., 2006). Internalizing and externalizing problem subscales have been analyzed as an outcome variable in many PATH studies (Conway et al., 2017; Riehm et al., 2019a). Four items assessed how recently a participant had experienced various internalizing problems, while five items assessed how recently a participant had experienced various externalizing problems. Due to the strong relationship between hyperactivity and externalizing symptoms (Conway et al., 2017), we included two additional hyperactivity items as part of the total externalizing score (Green et al., 2018). Each symptom item was recoded as a binary variable to indicate whether the participant had experienced the mental health problem within the past 30 days. We summed each of these binary items to create an internalizing score (ranging from 0–4) and an externalizing score (ranging from 0 to 7) for each participant. To remain consistent with previous research (Conway et al., 2017), each score was categorized into two groups: 0–3 internalizing problems (no/low/moderate) vs. 4 internalizing problems (severe), and 0–3 externalizing problems (no/low/moderate) vs.  $\geq 4$  externalizing problems (severe). We also created a third outcome variable for participants with both severe

internalizing (> 4 problems) and severe externalizing problems ( $\geq 4$  symptoms) in the same wave to allow for additional comparisons with this high-risk group, as consistent with previous literature (Conway et al., 2017; Riehm et al., 2019a).

### 2.2.3. Covariates

Sociodemographic information was collected at baseline and updated at each wave, including age range (12–14 years old vs. 15–17 years old vs. 18 years old and above (Wave 2 and Wave 3)), gender (female vs. male), race (white alone vs. black alone vs. others) and ethnicities (Hispanic vs. not Hispanic).

### 2.3. Statistical analyses

Distributions of sociodemographic information (age range, gender, race, and ethnicities), substance use (tobacco, drug, marijuana, and alcohol), and mental health problems (severe internalizing problems, severe externalizing problems, both severe internalizing and externalizing problems) were examined at each wave.

Fixed effect models (conditional logistic regression) were used to estimate the within-person association between substance use and mental health problems over the measurement periods. The fixed-effect model describes the within-person variation on the response variable and thus each person serves as his or her own control (Allison, 2009). The relationship between each substance and each mental health outcome was analyzed in a separate unadjusted conditional logistic regression model. We then fit models to calculate the adjusted odds ratio (AOR) and 95 % confidence interval (CI) while controlling for changes in patterns of use of all other types of substances analyzed in the study. The fixed effects models required that we exclude participants who did not change on mental health outcomes during the 3 waves of assessments.

Fixed effects models ignore between-group variance and respondents whose outcome status does not change. This results in a loss of potentially important information. Thus, we performed Generalized Estimating Equation (GEE) to obtain between-subject population-averaged estimates and examine differences across time-invariant demographic variables (e.g., gender). In secondary analyses, population-averaged differences in the odds of mental health outcomes between adolescents who do and do not use substances were estimated via GEE methods (Liang and Zeger, 1986). Unadjusted and weighted multivariable-adjusted logistic regressions were conducted to examine each combination of substance use and mental health problems. Given the dichotomous outcomes and repeated measure study design, GENMOD procedures for clustered longitudinal data were used to account for repeated measures and to calculate the AOR and 95 % CI. Additional analyses were performed to examine the effects of tobacco type on mental health problems (i.e., no tobacco users vs. combustible tobacco users vs. non-combustible tobacco users) while controlling for substance use.

Since polysubstance use is a possible substance use pattern, in both fixed effect and GEE models, we included all six possible co-use patterns (including alcohol\*marijuana; alcohol\*tobacco; alcohol\*drug; marijuana\*tobacco; marijuana\*drug; tobacco\*drug) as the interaction and examined them separately.

All analyses were performed using SAS Version 9.4 (SAS Institute, Cary, North Carolina, USA). Frequencies and estimates (in GEE approaches) were weighted by using all-waves weights (United States Department of Health and Human Services (USDHHS, 2019), balanced repeated replication (BRR) method with Fay's adjustment were applied to get national representative estimates (Edwards et al., 2020). All the statistical analyses were two-sided, and P values < 0.05 were considered statistically significant.

## 3. Results

Of participants who responded to all three waves of substance use

and mental health items, 48.8 % were female (Table 1). In general, the number of respondents who reported using substances within the past 30 days increased at each wave. For example, the proportion of the study population who reported non-combustible tobacco (Wave 1: 1.7 % (0.1); Wave 3: 4.9 % (0.2)) use or alcohol (Wave 1: 7.4 % (0.3); Wave 3: 20.5 % (0.6)) use increased nearly three-fold by Wave 3 compared to baseline use. Increases were mainly driven by those participants who turned 18 years old during the follow-up period. This effect was especially pronounced for marijuana, alcohol, and combustible tobacco. Across all three waves, the number of participants endorsing internalizing problems within the past 30 days remained steady across our analyzed timeframe. A similar trend was observed in concurrent severe internalizing and externalizing problems. Across all three waves, the prevalence of externalizing problems slightly decreased.

Results from the fixed effects models indicate that the change in substance use status (i.e., Wave 1 no use; Wave 2 use; Wave 3 use) for alcohol or other illicit drugs was associated with an increased odds of experiencing severe internalizing and externalizing problems, or both (in Table 2). For example, those who used alcohol were nearly 1.5 times as likely as those who did not use alcohol to experience severe internalizing problems (AOR: 1.47, 95 % CI: 1.25–1.72). After adjusting for other substance use, marijuana use was no longer statistically significant but the odds remained elevated (AOR: 1.10, 95 % CI: 0.91–1.34). In addition, we did not observe notable changes with stratifying tobacco products into combustible and non-combustible. Interactions among polysubstance use were examined, but these were not found to be statistically significant.

Results from the population-averaged GEE models controlling for all substance use variables together, suggested using any type of substance – as opposed to not using that particular substance – is associated with an increased odds of endorsing all mental health outcomes (Table 3). The exception was tobacco use which was not associated with severe externalizing problems. Additionally, for analyses of internalizing problems, we adjusted for externalizing problems, and conversely for analyses of externalizing problems, we adjusted for internalizing problems. After adjusting for demographic variables and applying survey-weights, those who were P30D users of other illicit drugs (AOR: 1.53, 95 % CI: 1.32–1.78), alcohol (AOR: 1.36, 95 % CI: 1.20–1.55), tobacco (AOR: 1.27, 95 % CI: 1.10–1.46), marijuana (AOR: 1.22, 95 % CI: 1.05–1.43) had higher odds of endorsing internalizing problems, compared with those who were not P30D users of these substances. Similarly, those who were P30D users of other illicit drugs (AOR: 1.89, 95 % CI: 1.61–2.21), alcohol (AOR: 1.75, 95 % CI: 1.52–2.02), marijuana (AOR: 1.46, 95 % CI: 1.21–1.75), tobacco (AOR: 1.30, 95 % CI: 1.10–1.55) had higher odds of endorsing comorbid internalizing and externalizing problems compared with those who were not users of these substances. Those who were P30D users of alcohol (AOR: 1.67, 95 % CI: 1.48–1.89), other illicit drugs (AOR: 1.56, 95 % CI: 1.38–1.76), marijuana (AOR: 1.43, 95 % CI: 1.27–1.61), had higher odds of endorsing externalizing problems, compared with those who were not users of these substances. One exception was that tobacco use was no longer a statistically significant predictor of externalizing problems (AOR: 1.10, 95 % CI: 0.96–1.26). See Fig. 1 for a detailed overview of results from both the fixed effects approach and GEE approach by substance use and mental health problems.

In order to see if there were any differences between combustible and non-combustible tobacco products, we performed unadjusted and weighted multivariable-adjusted GEE subgroup analyses (Table 4). In the survey-weighted multivariable regression, the results demonstrated that combustible tobacco product users had higher odds of endorsing severe internalizing problems relative to non-combustible tobacco product users after controlling for demographics and externalizing problems (AOR: 1.33, 95 % CI: 1.15–1.54). Conversely, non-combustible tobacco product users had higher odds than combustible tobacco product users of endorsing severe externalizing problems after controlling for demographics and internalizing problems (AOR: 1.29, 95 % CI:

**Table 1**  
Frequencies and weighted percentage of participants overall 3 waves (PATH, 2013 - 2016).

	Wave 1(2013–2014)		Wave 2 (2014–2015)		Wave 3(2015–2016)	
	Frequency	Weighted %, (SE)	Frequency	Weighted %, (SE)	Frequency	Weighted %, (SE)
Age Range						
12–14 y	5675	50.8 (0.1)	3816	34.0 (0.1)	1937	17.6 (0.2)
15–17 y	5198	49.2 (0.1)	5396	49.2 (0.2)	5586	50.0 (0.3)
≥ 18 y			1661	16.8 (0.2)	3350	32.5 (0.2)
Gender						
Female	5324	48.8 (0.1)				
Race						
White	7514	70.8 (0.3)				
Black	1664	15.1 (0.1)				
Other	1695	14.2 (0.3)				
Ethnicities						
Non-Hispanics	7742	77.9 (0.0)				
Hispanics	3131	22.1 (0.0)				
Substance Use <sup>d</sup>						
Marijuana	519	5.0 (0.2)	1086	10.6 (0.4)	1186	11.6 (0.4)
Alcohol	743	7.4 (0.3)	1581	15.7 (0.5)	2091	20.5 (0.6)
Any tobacco <sup>a</sup>	841	8.2 (0.3)	1398	13.7 (0.4)	1896	18.3 (0.5)
Combustible tobacco <sup>b</sup>	670	6.4 (0.3)	1108	10.8 (0.4)	1385	13.4 (0.4)
Non-combustible tobacco <sup>c</sup>	171	1.7 (0.1)	290	2.9 (0.2)	511	4.9 (0.2)
Other illicit drugs	482	4.5 (0.2)	604	5.4 (0.2)	778	7.2 (0.3)
Mental Health Problems <sup>d</sup>						
Severe internalizing problem	1159	10.7 (0.4)	1302	11.9 (0.3)	1418	12.7 (0.4)
Severe externalizing problem	1626	15.0 (0.4)	1568	14.2 (0.4)	1425	13.2 (0.4)
Severe internalizing & externalizing problems	520	4.7 (0.2)	605	5.5 (0.3)	629	5.7 (0.3)

<sup>†</sup> Gender, race, and ethnicity are time-invariant variables of this study, which indicates the estimates will keep constant at follow-up.

<sup>\*</sup> Study population was assessed baseline youth (12–17 y at Wave 1, 2013–2014). During follow-up, some respondents aged up to 18 years old and answered the adult version of the questionnaire rather than the youth version, but were their data is still included in the study.

<sup>a</sup> Tobacco product included: cigarettes, traditional cigars, cigarillos, filtered cigars, pipes, hookah, e-cigarettes, smokeless tobacco, snus, and dissolvable tobacco.

<sup>b</sup> Combustible tobacco product include: cigarettes, traditional cigars, cigarillos, filtered cigars, pipes, and hookah.

<sup>c</sup> Non-combustible tobacco products include e-cigarettes, smokeless tobacco, snus, and dissolvable tobacco.

<sup>d</sup> The measurement period of substance use and mental health problems are within the past 30 days.

1.03–1.60). After adjusting for demographic covariates, combustible tobacco product use was positively associated with both internalizing and externalizing problems (AOR: 1.37, 95 % CI: 1.12–1.67).

#### 4. Discussion

The present study examined associations between adolescent mental health problems and substance use behaviors over time using longitudinal data from the PATH study. Findings demonstrate that as adolescents get older, the prevalence of substance use and mental health concerns increase. Additionally, results indicate that adolescents that use substances have increased odds of experiencing all mental health problems, at both the individual and population level, a finding in line with previous literature (Kessler et al., 2007; Schulte and Hser, 2013). The current study is especially timely and relevant given a vastly different marijuana and tobacco policy and marketing landscape from previous years; furthermore, our results can provide vital information about substance use and the later development of mental health symptoms, and may aid in early detection and intervention efforts for this population.

Similar results were found in within- and between-subject analyses for internalizing and externalizing problems when examined separately. In both models, the use of other illicit drugs was associated with an increased odds of endorsing internalizing problems, while the use of alcohol was associated with an increased odds of endorsing externalizing problems. Regarding comorbid internalizing and externalizing problems, results suggest that alcohol and other illicit drugs were associated with increased odds of experiencing mental health outcomes in the individual level fixed effect analysis. Within population level analysis, GEE models yielded a stronger association between all substance use status changes and comorbid internalizing and externalizing problems. Overall, adolescents that use illicit drugs were found to have increased odds of experiencing mental health problems. Adolescents

that are more likely to use illicit substances may also engage in other risk-taking behaviors, such as physical fights or carrying a weapon, unsafe sex, or reckless driving, as shown in previous literature (Borodovsky et al., 2019, 2020; Luk et al., 2016; Rew et al., 2011; Schulte and Hser, 2013) and engaging in this substance use may additionally impact future decision-making skills. Additionally, results reflect that while not statistically significant in adjusted fixed effects models, associations between marijuana and mental health problems continued to be elevated, which follows previous research demonstrating significant associations between early marijuana use and the development of depression and anxiety (Fergusson and Boden, 2008; Patton et al., 2002; Volkow et al., 2014). Of note, results reported in the current study regarding mental health symptom increases after the use of marijuana, alcohol, and combustible tobacco were found to be driven by those participants who turned age 18 at follow up. These findings suggest that adolescents within this older age group are particularly at risk for not only increases in substance use, but also for the development of subsequent mental health concerns related to this substance use, perhaps due to social and environmental transitions (e.g., college, work force) and shifts in support and autonomy (e.g., moving away from home, parents) during this timeframe (Shepardson and Hustad, 2015; Suerken et al., 2014).

Results from the fixed effect and GEE models also differed in several ways. Specifically, tobacco use was found to be significantly associated with increased odds of endorsing, internalizing problems along and comorbid internalizing and externalizing problems at the population level. Tobacco use, however, was not found to be associated with internalizing, externalizing, or both problems at any time points in the fixed model. Increased cigarette use has been associated with ADHD (Blase et al., 2009; Tong et al., 2016), depression (Roberts et al., 2010) and anxiety-related symptoms (Cranford et al., 2009). These findings support the results of the current study, demonstrating that combustible tobacco users had higher odds of endorsing severe internalizing and

**Table 2**  
Conditional logistic regression (fixed effects models) for past 30-day severe internalizing/externalizing problems and substance use.

	Severe Internalizing Problem (past 30-day, Ref: no/mild/moderate problem)		Severe Externalizing Problem (past 30-day, Ref: no/mild/moderate problem)		Severe Internalizing & Externalizing Problem (simultaneously) (past 30-day, Ref: no/mild/moderate problem)	
	OR <sup>a</sup> , 95% CI	AOR <sup>b</sup> , 95% CI	OR <sup>a</sup> , 95% CI	AOR <sup>b</sup> , 95% CI	OR <sup>a</sup> , 95% CI	AOR <sup>b</sup> , 95% CI
Marijuana (Ref: No Marijuana use)	1.23 (1.02, 1.49)*	1.10 (0.91, 1.34)	1.34 (1.13, 1.59)*	1.18 (0.99, 1.42)	1.35 (1.06, 1.71)*	1.18 (0.91, 1.51)
Alcohol (Ref: No Alcohol Use)	1.52 (1.31, 1.77)*	1.47 (1.25, 1.72)*	1.72 (1.49, 1.99)*	1.66 (1.43, 1.93)*	1.66 (1.36, 2.02)*	1.58 (1.28, 1.94)*
Tobacco (Ref: No Tobacco use)	1.04 (0.87, 1.25)	1.10 (0.93, 1.30)	1.10 (0.93, 1.30)	0.87 (0.71, 1.07)	1.09 (0.86, 1.38)	1.04 (0.78, 1.37)
Combustible	1.08 (0.88, 1.32)	0.96 (0.77, 1.19)	1.04 (0.85, 1.26)	0.87 (0.71, 1.07)	1.19 (0.91, 1.55)	1.04 (0.78, 1.37)
Non-combustible	0.96 (0.71, 1.28)	0.89 (0.67, 1.20)	1.25 (0.96, 1.61)	1.17 (0.90, 1.52)	0.88 (0.60, 1.29)	0.81 (0.55, 1.19)
Other Illicit Drugs (Ref: No Other Illicit Drug Use)	1.72 (1.41, 2.10)*	1.65 (1.36, 2.01)*	1.47 (1.23, 1.75)*	1.40 (1.17, 1.67)*	1.47 (1.16, 1.87)*	1.39 (1.09, 1.77)*

Abbreviations: OR, odds ratio, AOR, (multi-variable) adjusted odds ratio, CI, confident interval. \* Statistically significant at P-value ≤ .05.

<sup>a</sup> Each substance was analyzed separately.

<sup>b</sup> Controlling for all substances (tobacco products separated as: combustible and non-combustible).

externalizing problems. Tobacco use may not have the same marked or immediate effects on neurobiological mechanisms in adolescents relative to other drugs, resulting in no association between internalizing and externalizing problems at the individual level in this study (Medina et al., 2007; Squeglia et al., 2009).

The present investigation has several strengths, including the use of two analyses at different levels; within-person and population level. We leveraged the longitudinal design of PATH study to examine within-subject change using fixed effect models. To compensate for the potential loss of information required in conditional logistic models, we conducted between-subject level analyses using the same exposure and outcome variables. The PATH study survey also asked adolescents to endorse items related to substance use in the past 30 days, allowing for an analysis of recent changes in adolescent substance use behavior.

In addition to the strengths of this study, there were also several limitations that should be considered. First, fixed effect models assume no feedback effects, assuming that substance use leads to changes in mental health and not the other way around. We acknowledge that the causality of substance use and mental health outcomes could be bidirectional and that reciprocal feedback effects could also exist in which the use of substances exacerbates mental health symptoms and perpetuates the continued use of substances to attenuate these symptoms (Fergusson et al., 2011). Secondly, all measures were self-reported which may be subject to bias (Solbergdottir et al., 2004).

Further, several aspects of the PATH study dataset should be considered in the context of our results. First, the PATH study survey structure did not allow us to evaluate the dosage of each substance individually used, therefore we could not conduct analyses on this construct. Individuals could have been using multiple substances at once

**Table 3**  
GEE approach for past 30-day severe internalizing/externalizing problem and substance use.

	Severe Internalizing Problem (past 30-day, Ref: no/mild/moderate problem)		Severe Externalizing Problem (past 30-day, Ref: no/mild/moderate problem)		Severe Internalizing & Externalizing Problem (simultaneously) (past 30-day, Ref: no/mild/moderate problem)	
	Model 1 <sup>a</sup>	Model 2 <sup>b</sup>	Model 1 <sup>a</sup>	Model 2 <sup>b</sup>	Model 1 <sup>a</sup>	Model 2 <sup>b</sup>
Marijuana users (Ref: no marijuana users)	AOR, 95 % CI	AOR, 95 % CI	AOR, 95 % CI	AOR, 95 % CI	AOR, 95 % CI	AOR, 95 % CI
Marijuana users	1.22 (1.07, 1.39)*	1.22 (1.05, 1.43)*	1.29 (1.14, 1.46)*	1.43 (1.27, 1.61)*	1.32 (1.09, 1.59)*	1.46 (1.21, 1.75)*
Alcohol users (Ref: no alcohol users)	1.59 (1.43, 1.76)*	1.36 (1.20, 1.55)*	1.67 (1.52, 1.84)*	1.67 (1.48, 1.89)*	1.73 (2.01)*	1.75 (2.02)*
Tobacco users (Ref: no tobacco product users)	1.13 (1.01, 1.27)*	1.27 (1.10, 1.46)*	1.07 (0.96, 1.19)	1.10 (0.96, 1.26)	1.16 (0.98, 1.36)	1.30 (1.10, 1.55)*
Other illicit drugs users (Ref: no other illicit drug users)	1.90 (1.69, 2.14)*	1.53 (1.32, 1.78)*	1.78 (1.59, 2.00)*	1.56 (1.38, 1.76)*	2.04 (1.73, 2.41)*	1.89 (1.61, 2.21)*
Age range (Ref: 12–14 y)	Ref	Ref	Ref	Ref	Ref	Ref
15–17 y	1.18 (1.08, 1.29)*	0.90 (0.82, 0.98)*	1.05 (0.92, 1.19)	0.92 (0.82, 0.98)*	1.05 (0.92, 1.19)	1.05 (0.92, 1.19)
≥ 18 y	0.72 (0.62, 0.84)*	0.47 (0.39, 0.56)*	0.47 (0.39, 0.56)*	0.47 (0.39, 0.56)*	0.47 (0.39, 0.56)*	0.47 (0.39, 0.56)*
Gender (Ref: Female)	Ref	Ref	Ref	Ref	Ref	Ref
Male	0.38 (0.34, 0.42)*	1.19 (1.09, 1.30)*	0.49 (0.42, 0.56)*	0.49 (0.42, 0.56)*	0.49 (0.42, 0.56)*	0.49 (0.42, 0.56)*
Ethnicity (Ref: non-Hispanics)	Ref	Ref	Ref	Ref	Ref	Ref
Hispanics	1.01 (0.90, 1.13)	0.88 (0.80, 0.97)*	1.00 (0.86, 1.16)	1.00 (0.86, 1.16)	1.00 (0.86, 1.16)	1.00 (0.86, 1.16)
Race (Ref: White)	Ref	Ref	Ref	Ref	Ref	Ref
Black	0.72 (0.61, 0.86)*	1.11 (0.96, 1.29)	0.85 (0.69, 1.04)	0.85 (0.69, 1.04)	0.85 (0.69, 1.04)	0.85 (0.69, 1.04)
Other	0.99 (0.88, 1.18)	1.00 (0.89, 1.12)	1.00 (0.85, 1.19)	1.00 (0.85, 1.19)	1.00 (0.85, 1.19)	1.00 (0.85, 1.19)
Severe internalizing problem (Ref: No/mild/moderate problem)		5.68 (5.15, 6.26)*		5.68 (5.15, 6.26)*		5.68 (5.15, 6.26)*
Severe externalizing problem (Ref: No/mild/moderate problem)		5.59 (5.05, 6.19)*		5.59 (5.05, 6.19)*		5.59 (5.05, 6.19)*

Abbreviations: OR, odds ratio, AOR, (multi-variable) adjusted odds ratio, CI, confident interval. \* Statistically significant at P-value ≤ .05.

<sup>a</sup> Controlling for all substances together (marijuana, alcohol, drug, and combined tobacco products).

<sup>b</sup> Weighted multivariable-adjusted model, adjusted by: gender (female vs. male), ethnicities (Hispanic vs. Non-Hispanic), race (Black alone vs. White alone vs. Others), age range (12–14 y vs. 15–17 y vs. 18 y and above). For internalizing problems additionally adjusted externalizing problems and for externalizing problem additionally adjusted by internalizing problem.

or in varying amounts, which could impact both their overall substance use patterns and their mental health problem severity. Further, the reference groups used were specific to each substance; therefore, the magnitude of AORs could not be compared across substances. Additionally, while the GAIN-SS measure utilized does have limitations in regards to the assessment of mental health outcomes, this scale has been used in previous literature to examining expressions of mental health problems among youth (Dennis et al., 2006; Leslie et al., 2016; Stucky et al., 2014). In addition, several types of illicit drugs were collapsed into one variable in our analysis, which may have led to underreporting. Also, the definition of ENDS was expanded at Wave 2 to include other electronic nicotine products (i.e., e-hookah, e-pipe) which may have impacted the assessment of tobacco use in our analyses. Further, more fine-grained approaches to illicit drug categorization could have provided additional details on which type of illicit drug affected internalizing and externalizing problems. Despite limitations of the PATH study dataset outlined in regards to the depth of exposure and outcome measurements, the advantages of individual- and national-level repeated measures longitudinal data and the inclusion of a greater number of mental health measures than other national cross-sectional studies made this a strong data source for use in the current investigation.

Overall, the findings of this study extend the literature by identifying the relationship between substance use behavior in adolescents and the development of internalizing and externalizing mental health problems, demonstrating associations at both the individual and population level to inform clinicians as well as public health professionals. Future studies with this population should incorporate evaluations of the multi-

directionality of these relationships, time-dynamic analyses, and parametric analysis of substance frequency. Results reported in this study signal the need to prioritize the identification of and interventions for adolescent substance use to mitigate the development of mental health problems, especially for those older adolescents transitioning away from home, possibly by integrating assessment and prevention strategies within in pediatric care and school settings. Implementation of drug education, early screening, and effective interventions that address both substance use and mental health concerns are critical toward promoting improvements in overall health and mental health outcomes among adolescents.

**Contributors**

All authors have contributed significantly to the development of the manuscript and have approved the final manuscript for submission.

Ms. Li participated in the acquisition of the data, analyses, interpretation of results and manuscript writing.

Dr. Borodovsky participated in the analysis of the data, interpretation of results, and manuscript writing.

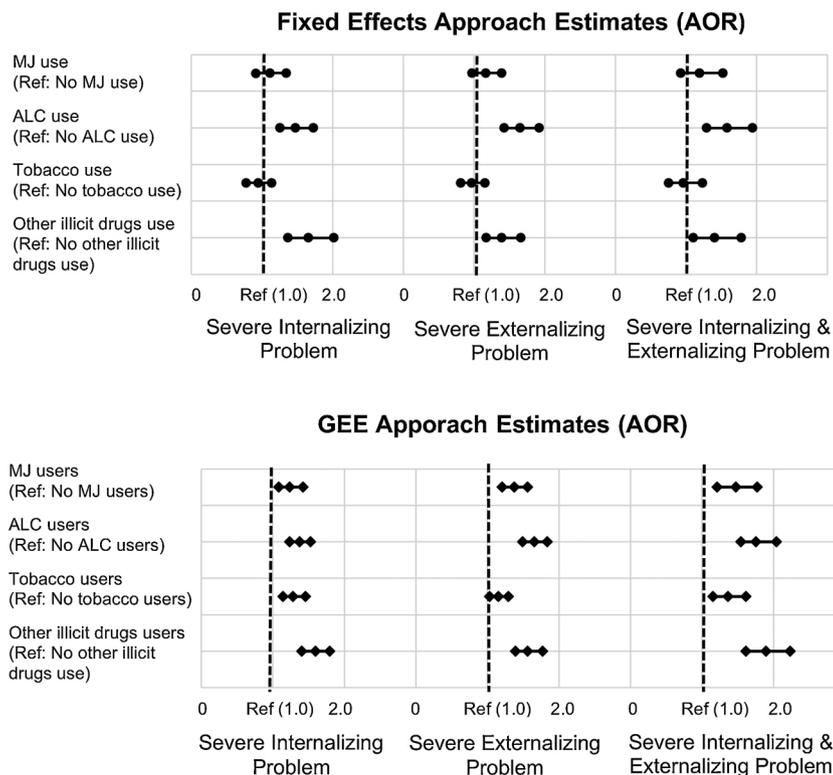
Ms. Kasson participated in drafting and revising the manuscript.

Ms. Fentem participated in drafting and revising the manuscript.

Dr. Cavazos-Rehg provided mentoring on all aspects of the project, including the study design, acquisition of the data, analyses, interpretation of results, and revisions to the manuscript.

**Funding**

Financial support for this study was provided by the National Institutes of Health (NIH K02 DA043657) (PI: Patricia A. Cavazos-Rehg) and the National Institute on Alcohol Abuse and Alcoholism (NIAAA F32AA027941), (PI: Jacob T. Borodovsky). The content of this paper is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the National Institute on Alcohol Abuse and Alcoholism.



**Fig. 1.** Estimates for past 30-day severe internalizing/externalizing disorder and substance use by using two approaches (fixed effects approach vs. GEE approach). MJ, marijuana; ALC, alcohol; AOR, (multivariable) adjusted odds ratio; GEE, generalizing estimating equation.  
<sup>a</sup> All measurement periods were within the past 30-day.  
<sup>†</sup> Fixed effect approach estimates were calculated by controlling all substances use together. GEE approach estimates were calculated by controlling all substances use and demographic variables (age range, gender, race and Ethnicities). For internalizing disorders additionally adjusted externalizing disorders and for externalizing disorders additionally adjusted by internalizing disorders.

**Table 4**  
Subgroup analyses for tobacco product users (GEE approach).

Tobacco	Severe Internalizing Problem (past 30-day, Ref: no/mild/moderate problem)		Severe Externalizing Problem (past 30-day, Ref: no/mild/moderate problem)		Severe Internalizing & Externalizing Problem (past 30-day, Ref: no/mild/moderate problem)	
	Model 1 <sup>a</sup>	Model 2 <sup>b</sup>	Model 1 <sup>a</sup>	Model 2 <sup>b</sup>	Model 1 <sup>a</sup>	Model 2 <sup>b</sup>
	AOR, 95 % CI	AOR, 95 % CI	AOR, 95 % CI	AOR, 95 % CI	AOR, 95 % CI	AOR, 95 % CI
No tobacco product users (Ref)	Ref	Ref	Ref	Ref	Ref	Ref
Combustible tobacco users	1.15 (1.01, 1.31)*	1.33 (1.15, 1.54)*	0.99 (0.88, 1.12)	1.09 (0.95, 1.24)	1.17 (0.98, 1.40)	1.37 (1.12, 1.67)*
Non-combustible tobacco users	1.09 (0.91, 1.31)	1.18 (0.95, 1.47)	1.30 (1.10, 1.53)*	1.29 (1.03, 1.60)*	1.13 (0.86, 1.47)	1.15 (0.89, 1.49)

Abbreviations: OR, odds ratio, AOR, (multi-variable) adjusted odds ratio, CI, confident interval. \* Statistically significant at P-value  $\leq .05$ .

<sup>a</sup> Controlling for all substances (marijuana, alcohol, drug, tobacco products separated as: combustible and non-combustible).

<sup>b</sup> Weighted multivariable-adjusted model, adjusted by: drug use (yes vs. no), alcohol use (yes vs. no), marijuana use (yes vs. no), gender (female vs. male), ethnicity (Hispanic vs. Non-Hispanic), race (Black alone vs. White alone vs. Others), age range (12–14 y vs. 15–17 y vs.  $\geq 18$  y). For internalizing problems additionally adjusted externalizing problems and for externalizing problems additionally adjusted by internalizing problems.

## Role of funding source

Financial support for this study was provided by the National Institutes of Health (NIH), Grant K02 DA043657 (PI: Patricia Cavazos-Rehg) and the National Institute on Alcohol Abuse and Alcoholism (NIAAA), Grant F32AA027941 (PI: Jacob Borodovsky). No funding sources had any role in the study design, collection, analysis or interpretation of the data, writing the manuscript, or the decision to submit the paper for publication.

## Data sharing statement

Data will be made available upon request.

## Declaration of Competing Interest

JTB is a member of the board of directors and treasurer of MySafeRx Inc., a non-profit scientific research organization. He receives no financial compensation from this organization. No other conflicts declared.

## References

- Allison, P.D., 2009. *Fixed Effects Regression Models*, 160. SAGE publications.
- Blase, S.L., Gilbert, A.N., Anastopoulos, A.D., Costello, E.J., Hoyle, R.H., Swartzwelder, H.S., Rabiner, D.L., 2009. Self-reported ADHD and adjustment in college: cross-sectional and longitudinal findings. *J. Atten. Disord.* 13 (3), 297–309.
- Borodovsky, J.T., Krueger, R.F., Agrawal, A., Grucza, R.A., 2019. A decline in propensity toward risk behaviors among U.S. Adolescents. *J. Adolesc. Health* 65 (6), 745–751. <https://doi.org/10.1016/j.jadohealth.2019.07.001>.
- Borodovsky, J., Krueger, R.F., Agrawal, A., Elbanna, B., de Looze, M., Grucza, R., 2020. US Trends in Adolescent Substance Use and Conduct Problems and Their Relation to Trends in Unstructured In-Person Socializing With Peers. Available at SSRN 3643972.
- Cohn, A.M., Johnson, A.L., Rose, S.W., Pearson, J.L., Villanti, A.C., Stanton, C., 2018. Population-level patterns and mental health and substance use correlates of alcohol, marijuana, and tobacco use and co-use in US young adults and adults: results from

- the population assessment for tobacco and health. *Am. J. Addict.* 27 (6), 491–500. <https://doi.org/10.1111/ajad.12766>.
- Conway, K.P., Green, V.R., Kasza, K.A., Silveira, M.L., Borek, N., Kimmel, H.L., et al., 2017. Co-occurrence of tobacco product use, substance use, and mental health problems among adults: findings from Wave 1 (2013–2014) of the population assessment of tobacco and health (PATH) Study. *Drug Alcohol Depend.* 177, 104–111. <https://doi.org/10.1016/j.drugalcdep.2017.03.032>.
- Cranford, J.A., Eisenberg, D., Serras, A.M., 2009. Substance use behaviors, mental health problems, and use of mental health services in a probability sample of college students. *Addict. Behav.* 34 (2), 134–145.
- Crews, F., He, J., Hodge, C., 2007. Adolescent cortical development: a critical period of vulnerability for addiction. *Pharmacol. Biochem. Behav.* 86 (2), 189–199.
- Dennis, M.L., Chan, Y.F., Funk, R.R., 2006. Development and validation of the GAIN Short Screener (GSS) for internalizing, externalizing and substance use disorders and crime/violence problems among adolescents and adults. *Am. J. Addict.* 15 (Suppl 1), 80–91. <https://doi.org/10.1080/10550490601006055>.
- Edwards, K.C., Kasza, K.A., Tang, Z., et al., 2020. Correlates of tobacco product reuptake and relapse among youth and adults in the USA: findings from the PATH Study waves 1–3 (2013–2016). *Tob. Control* 29 (Suppl 3), s216–s226.
- Esmaelzadeh, S., Moraros, J., Thorpe, L., Bird, Y., 2018. Examining the association and directionality between mental health disorders and substance use among adolescents and young adults in the US and Canada—a systematic review and meta-analysis. *J. Clin. Med.* 7 (12), 543.
- FDA, 2019. Tobacco Products: Products, Guidance and Regulations. Retrieved on July 24, 2019 from. <https://www.fda.gov/tobacco-products/products-guidance-regulations>.
- Fergusson, D.M., Boden, J.M., 2008. Cannabis use and later life outcomes. *Addiction* 103 (6), 969–976.
- Fergusson, D.M., Boden, J.M., Horwood, L.J., 2011. Structural models of the comorbidity of internalizing disorders and substance use disorders in a longitudinal birth cohort. *Soc. Psychiatry Psychiatr. Epidemiol.* 46 (10), 933–942. <https://doi.org/10.1007/s00127-010-0268-1>.
- Ghandour, R.M., Sherman, L.J., Vladutiu, C.J., Ali, M.M., Lynch, S.E., Bitsko, R.H., Blumberg, S.J., 2019. Prevalence and treatment of depression, anxiety, and conduct problems in US children. *J. Pediatr.* 206, 256–267. <https://doi.org/10.1016/j.jpeds.2018.09.021> e253.
- Gray, K.M., Squeglia, L.M., 2018. Research Review: What have we learned about adolescent substance use? *J. Child Psychol. Psychiatry* 59 (6), 618–627. <https://doi.org/10.1111/jcpp.12783>.
- Green, V.R., Conway, K.P., Silveira, M.L., Kasza, K.A., Cohn, A., Cummings, K.M., et al., 2018. Mental health problems and onset of tobacco use among 12- to 24-Year-Olds in the PATH study. *J. Am. Acad. Child Adolesc. Psychiatry* 57 (12), 944–954. <https://doi.org/10.1016/j.jaac.2018.06.029> e944.
- Hammond, D., Reid, J.L., Rynard, V.L., Fong, G.T., Cummings, K.M., McNeill, A., et al., 2019. Prevalence of vaping and smoking among adolescents in Canada, England, and the United States: repeat national cross sectional surveys. *Bmj* 365.
- Harris, K.M., Edlund, M.J., 2005. Self-medication of mental health problems: new evidence from a national survey. *Health Serv. Res.* 40 (1), 117–134. <https://doi.org/10.1111/j.1475-6773.2005.00345.x>.
- Johnson, J.G., Cohen, P., Pine, D.S., Klein, D.F., Kasen, S., Brook, J.S., 2000. Association between cigarette smoking and anxiety disorders during adolescence and early adulthood. *Jama* 284 (18), 2348–2351. <https://doi.org/10.1001/jama.284.18.2348>.
- Johnston, L.D., Miech, R.A., O'Malley, P.M., Bachman, J.G., Schulenberg, J.E., Patrick, M.E., 2019. Monitoring the future national survey results on drug use, 1975–2018: overview. Key Findings on Adolescent Drug Use. Institute for Social Research.
- Kessler, R.C., Angermeyer, M., Anthony, J., C, De Graaf, R., Demyttenaere, K., Gasquet, I., et al., 2007. Lifetime prevalence and age-of-onset distributions of mental disorders in the World Health Organization's World Mental Health Survey Initiative. *World Psychiatry* 6 (3), 168.
- Khan, L., 2019. Substance use in adolescents: latest trends. *Pediatr. Ann.* 48 (11), e418–e422. <https://doi.org/10.3928/19382359-20191018-02>.
- King, J.L., Reboussin, B.A., Spangler, J., Ross, J.C., Sutfin, E.L., 2018. Tobacco product use and mental health status among young adults. *Addict. Behav.* 77, 67–72.
- Leslie, K., Manning, S.J., Maser, C., Snelgrove, D., Thornton, T., Wills, A., Brands, B., 2016. Long-term health and psychosocial status of youth who received substance abuse treatment in adolescence. *Int. J. Ment. Health Addict.* 14 (2), 111–119.
- Levy, D.T., Warner, K.E., Cummings, K.M., Hammond, D., Kuo, C., Fong, G.T., et al., 2019. Examining the relationship of vaping to smoking initiation among US youth and young adults: a reality check. *Tob. Control* 28 (6), 629–635.
- Liang, K.-Y., Zeger, S.L., 1986. Longitudinal data analysis using generalized linear models. *Biometrika* 73 (1), 13–22.
- Luk, J.W., Worley, M.J., Winiger, E., Trim, R.S., Hopper, C.J., Hewitt, J.K., et al., 2016. Risky driving and sexual behaviors as developmental outcomes of co-occurring substance use and antisocial behavior. *Drug Alcohol Depend.* 169, 19–25. <https://doi.org/10.1016/j.drugalcdep.2016.10.006>.
- Medina, K.L., Hanson, K.L., Schweinsburg, A.D., Cohen-Zion, M., Nagel, B.J., Tapert, S.F., 2007. Neuropsychological functioning in adolescent marijuana users: subtle deficits detectable after a month of abstinence. *J. Int. Neuropsychol. Soc.* 13 (5), 807–820.
- Mojtabai, R., Olfson, M., Han, B., 2016. National trends in the prevalence and treatment of depression in adolescents and young adults. *Pediatrics* 138 (6), e20161878.
- Moss, H.B., Chen, C.M., Yi, H.-y., 2014. Early adolescent patterns of alcohol, cigarettes, and marijuana polysubstance use and young adult substance use outcomes in a nationally representative sample. *Drug Alcohol Depend.* 136, 51–62. <https://doi.org/10.1016/j.drugalcdep.2013.12.011>.
- Obisesan, O.H., Mirbolouk, M., Osei, A.D., Orimoloye, O.A., Uddin, S.M.I., Dzaye, O., et al., 2019. Association Between e-Cigarette Use and Depression in the Behavioral

- Risk Factor Surveillance System, 2016-2017. *JAMA Network Open* 2 (12), e1916800. <https://doi.org/10.1001/jamanetworkopen.2019.16800>.
- Patton, G.C., Coffey, C., Carlin, J.B., Degenhardt, L., Lynskey, M., Hall, W., 2002. Cannabis use and mental health in young people: cohort study. *Bmj* 325 (7374), 1195-1198. <https://doi.org/10.1136/bmj.325.7374.1195>.
- Rew, L., Horner, S.D., Brown, A., 2011. Health-risk behaviors in early adolescence. *Issues Compr. Pediatr. Nurs.* 34 (2), 79-96. <https://doi.org/10.3109/01460862.2011.574452>.
- Riehm, K.E., Feder, K.A., Tormohlen, K.N., Crum, R.M., Young, A.S., Green, K.M., et al., 2019a. Associations Between Time Spent Using Social Media and Internalizing and Externalizing Problems Among US Youth. h, pp. 1-9. <https://doi.org/10.1001/jamapsychiatry.2019.2325>.
- Riehm, K.E., Young, A.S., Feder, K.A., Krawczyk, N., Tormohlen, K.N., Pacey, L.R., et al., 2019b. Mental health problems and initiation of e-cigarette and combustible cigarette use. *Pediatrics* 144 (1).
- Roberts, S.J., Glod, C.A., Kim, R., Houchell, J., 2010. Relationships between aggression, depression, and alcohol, tobacco: implications for healthcare providers in student health. *J. Am. Acad. Nurse Pract.* 22 (7), 369-375.
- Rowe, C.L., Liddle, H.A., Dakof, G.A., 2001. Classifying clinically referred adolescent substance abusers by level of externalizing and internalizing symptoms. *J. Child Adolesc. Subst. Abuse* 11 (2), 41-65.
- Savage, J.E., Kaprio, J., Korhonen, T., Pulkkinen, L., Rose, R.J., Verhulst, B., Dick, D.M., 2016. The effects of social anxiety on alcohol and cigarette use across adolescence: results from a longitudinal twin study in Finland. *Psychol. Addict. Behav.* 30 (4), 462.
- Schulte, M.T., Hser, Y.-I., 2013. Substance use and associated health conditions throughout the lifespan. *Public Health Rev.* 35 (2), 3.
- Shepardson, R.L., Hustad, J.T.P., 2015. Hookah tobacco smoking during the transition to college: prevalence of other substance use and predictors of initiation. *Nicotine Tob. Res.* 18 (5), 763-769. <https://doi.org/10.1093/ntr/ntv170>.
- Solbergstodt, E., Bjornsson, G., Gudmundsson, L.S., Tyrffingsson, T., Kristinnsson, J., 2004. Validity of self-reports and drug use among young people seeking treatment for substance abuse or dependence. *J. Addict. Dis.* 23 (1), 29-38. [https://doi.org/10.1300/J069v23n01\\_03](https://doi.org/10.1300/J069v23n01_03).
- Squeglia, L.M., Jacobus, J., Tapert, S.F., 2009. The influence of substance use on adolescent brain development. *Clin. EEG Neurosci.* 40 (1), 31-38.
- Stapinski, L.A., Montgomery, A.A., Araya, R., 2016. Anxiety, depression and risk of cannabis use: examining the internalising pathway to use among Chilean adolescents. *Drug Alcohol Depend.* 166, 109-115.
- Stucky, B.D., Edelen, M.O., Ramchand, R., 2014. A psychometric assessment of the GAIN Individual Severity Scale (GAIN-GISS) and Short Screeners (GAIN-SS) among adolescents in outpatient treatment programs. *J. Subst. Abuse Treat.* 46 (2), 165-173.
- Subramaniam, P., Rogowska, J., DiMuzio, J., Lopez-Larson, M., McGlade, E., Yurgelun-Todd, D., 2018. Orbitofrontal connectivity is associated with depression and anxiety in marijuana-using adolescents. *J. Affect. Disord.* 239, 234-241.
- Suerken, C.K., Reboussin, B.A., Sutfin, E.L., Wagoner, K.G., Spangler, J., Wolfson, M., 2014. Prevalence of marijuana use at college entry and risk factors for initiation during freshman year. *Addict. Behav.* 39 (1), 302-307. <https://doi.org/10.1016/j.addbeh.2013.10.018>.
- Taylor, K.A., Sharma, E., Edwards, K.C., Halenar, M.J., Kissin, W., Kasza, K.A., et al., 2020. Longitudinal pathways of exclusive and polytobacco cigarette use among youth, young adults and adults in the USA: findings from the PATH Study waves 1-3 (2013-2016). *Tob. Control* 29 (Suppl 3), s139. <https://doi.org/10.1136/tobaccocontrol-2020-055630>.
- Tong, L., Shi, H.-J., Zhang, Z., Yuan, Y., Xia, Z.-J., Jiang, X.-X., Xiong, X., 2016. Mediating effect of anxiety and depression on the relationship between attention-deficit/hyperactivity disorder symptoms and smoking/drinking. *Sci. Rep.* 6, 21609.
- United States Department of Health and Human Services (USDHHS), 2019. Population Assessment of Tobacco and Health (PATH) Study [United States] Public-Use Files. Inter-university Consortium for Political and Social Research [distributor]. <https://doi.org/10.3886/ICPSR36498.v10>, 11-21.
- van Amsterdam, J., van der Velde, B., Schulte, M., van den Brink, W., 2018. Causal factors of increased smoking in ADHD: a systematic review. *Subst. Use Misuse* 53 (3), 432-445.
- Volkow, N.D., Baler, R.D., Compton, W.M., Weiss, S.R.B., 2014. Adverse health effects of marijuana use. *N. Engl. J. Med.* 370 (23), 2219-2227. <https://doi.org/10.1056/NEJMr1402309>.
- Wright, N.E., Scerpella, D., Lisdahl, K.M., 2016. Marijuana use is associated with behavioral approach and depressive symptoms in adolescents and emerging adults. *PLoS One* 11 (11), e0166005.