Title: Directions of the relationship between substance use and depressive symptoms from adolescent to young adulthood

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Abstract
Purpose: Explore the longitudinal, potentially bidirectional, relationships between high-frequency substance use and depressive symptoms from adolescence into young adulthood.
Methods: Using data from the National Longitudinal Study of Adolescent to Adult Health we investigated longitudinal associations between substance use (alcohol, cigarettes, and marijuana) and depressive symptoms, stratified by gender, using linear mixed effects models.
Results: Increases in Wave I depressive symptoms are significantly associated with high frequency smoking for females. Conversely, high frequency smoking is significantly positively associated with depressive symptoms for both males and females.
Conclusions: These results indicate there is a bidirectional relationship between high frequency smoking and depressive symptoms for females. For males, there was only evidence for substance use being associated with later depressive symptoms and not for a self-medication pathway.

Substance use and depression are common in adolescence, frequently co-morbid, and have serious short- and long-term health implications.[1–3] Despite substantial research, the directionality between the two, and whether directionality varies by gender, remains unclear. The self-medication hypothesis asserts that risk taking is used to ameliorate depressive symptoms possibly through lowering impulse control or motivation. [3–5] Several studies support this pathway. Hooshmand and colleagues followed over 4,000 adolescents from grade 9 to grade 12 and found those reporting higher depressive symptoms in grade 9 reported faster increases in cigarette and marijuana use.[5] Burns et al. followed a small group of rural adolescents for two years and found baseline depression scores were associated with later tobacco use.[6] Gender complicates the self-medication hypothesis as adolescent females generally report more depression and less risk taking; the aforementioned studies did not examine gender differences.[1,3,7]

Alternatively, there is also support for the reverse pathway, that substance use leads to depression.[8,9] Hallfors et al., using data from Waves I and II of Add Health, found both sexual risk taking and substance use predicted an increased likelihood of future depression; the self-medication pathway was not supported in their analyses.[8] Similarly Goodman and Capitman, using Add Health data from Waves I and II, found no relationship between depression and later smoking but did find support for the reverse.[10] One explanation for risk taking leading to increases in depressive symptoms is the biological stress response, an endocrine reaction that increases inflammation and susceptibility to depression.[11–13] Risk taking may have implications for relationships with peers or family members and thereby interpersonal stress, to which females are particularly vulnerable.[14,15] Previous studies of the association between depression and substance use in adolescents are limited by cross-sectional design or, when longitudinal, by using non-representative samples or short time periods.[16,17] This paper prospectively examines directionality over a longer time period using the population-based Add Health sample.

Methods

Sample

Add Health includes a nationally representative sample of 20,745 adolescents who were in grades 7-12 in the 1994-95 school year (Wave I). The analysis sample is restricted to the 9,207 respondents subsequently interviewed at ages 18 to 26 (Waves III, 2001) and ages 24 to 32 (Wave IV, 2007-2009), and who had complete data on all variables of interest. We used the longitudinal multilevel weight component, which is only available for respondents interviewed at all four waves (including Wave II in 1996), thus restricting our sample. Details of the Add Health study and design are described elsewhere.[18]

Measures

Depression: We used nine questions from the Center for Epidemiologic Studies Depression scale (CES-D) that appear at each interview. Questions ask about frequency of symptoms in the past week, though 12-month re-test reliability is high.[19] Answers are scored from 0 to 3, indicating rarely to most of the time; the summed score ranges from zero to 27. The CES-D captures depressive symptoms but is not a diagnostic tool.[19]

Substance use: Substances include alcohol (binge drinking), cigarettes, and marijuana. In Add Health, substance use is assessed with either continuous or ordinal variables, and the time frame varies. For cigarette smoking, respondents are asked, at all waves, how many days they smoked

in the past thirty days. At Waves I and III, the question is very similar for marijuana use but captures instances of use in the past 30 days (e.g., 0 to >900). At Wave IV, the question changes to measure on how many days respondents used marijuana in the past thirty using a 0 to 6 ordinal scale for none to nearly every day or every day. Finally, binge drinking was assessed for the past year using the same ordinal variable. At Waves I and III, binge drinking was defined as "drinking five or more drinks in a row," but at Wave IV the measure was specified as four or more drinks for women and five or more drinks for men to match the definition of binge drinking from the Centers for Disease Control and Prevention.[18,20]

To make the measures of substance use frequency comparable in capturing number of days of use in a given time period, days of marijuana use and binge drinking per month were derived (see Table 1 for details). The derived measures were set at the midpoint of the frequencies and in this way the change from one value to another approximates the proportional increase in frequency, rather than a 1-unit increase. The range of values is higher for binge drinking because it was measured as frequency in the past year, rather than frequency in the past month like marijuana use and cigarette smoking.

Table 1
Measure transformations for binge drinking and marijuana

Binge Drinking		Marijuana Use	
Original Measure (# days in past year)	Derived Measure (# days in past year)	Original Measure (# times in past 30)	Derived Measure (# days in past 30)
0: none	0	0	0
1: 1-2 days/year	2	1	1
2: 1 day/month or less	10	2,3	2
3: 2-3 days/month	30	4,5	4
4: 1-2 days/week	84	6-10	8
5: 3-5 days/week	222	11-25	16
6: every day/almost every day	327	26-900[a]	30

[a] The midpoint was not used for this interval as the measure of marijuana use at Wave IV has a maximum of 30 and so we constrained this tail of the distribution at Waves I and III to 30, indicating daily use of marijuana in the past month

Controls: Respondent's self-identified race/ethnicity (Hispanic and non-Hispanic White, Black, Asian, Native American, and Other) from Wave I was included as a control as was mother's educational attainment (less than high school, high school graduate, some college, or college graduate or higher) as a proxy for socioeconomic status of the parental home. Respondent's educational attainment, reported at Waves III and IV, is also included, using the same categories as mother's educational attainment. Respondent's age at the wave at which the dependent variable was measured was also included as substance use can vary substantially by age and the age ranges are fairly wide within waves.

Analysis

Linear mixed effects models with lagged measures of the dependent variable were used to evaluate both the Self-Medication and reverse pathways. The CES-D score was scaled by 5 so the regression results display a substantively meaningful change. For the figures displaying predicted changes in substance use frequency or depressive symptoms for each gender, the race

was set to White, parental education was held at the modal value (college graduation or higher) as was respondent education (some college) and all other covariates were held at their means and we used the original CES-D scale to ease interpretability. All analyses were stratified by gender and used longitudinal weights to adjust for unequal probability selection into the sample and nonresponse over time. Additionally, we adjusted variance estimates for clustering at the primary sampling unit and stratification by region. We used Stata, version 13.0 (Stata Corp, College Station TX, 2013). We will test our assumptions of linearity in the ordinal substance use measures by treating the variables as ordinal and continuous in two different models and comparing the BIC between the two models. We will also test our assumption that the strengths of the association from Wave I to Wave III will be equivalent to the association between Wave III and Wave IV with an interaction term between a Wave IV indicator variable and the key predictors.

Results

Table 2 outlines the analysis sample's demographic characteristics. Approximately 40% identify as a racial/ethnic minority, and the majority report maternal education for some college or higher. Across all waves, the mean CES-D score is approximately one point higher for females than males. For both genders, CES-D scores peak at Wave I and substance use frequency often peaks in Wave III. Males consistently report more substance use than females.

Table 2

Characteristics of the analysis sample

Characteristic	Males (n=4166) n (weighted %)	Females (n=5041) n (weighted %)
Race/Ethnicity[a]		
Hispanic	659 (17.8)	745 (19.1)
Black	760 (15.2)	1131 (16.9)
Asian	308 (5.6)	293 (4.6)
Native American	85 (2.0)	90 (1.5)
Other	36 (1.1)	35 (1.0)
White	2318 (58.3)	2747 (57.0)
Maternal Education		
Less than high school	459 (12.2)	650 (14.9)
High school graduate	976 (22.9)	1302 (24.0)
Some college	1237 (30.2)	1417 (27.6)
College graduate or higher	1494 (34.8)	1672 (33.5)
Respondent Education (Wave IV)		
Less than high school	355 (9.0)	304 (6.3)
High school graduate	761 (19.2)	646 (12.8)
Some college	1780 (42.1)	2200 (44.9)
College graduate or higher	1270 (30.0)	1891 (36.0)
Age (mean (SE[b]))		
Wave I	15.4 (0.11)	15.2 (0.11)
Wave III	21.7 (0.11)	21.5 (0.11)
Wave IV	28.2 (0.11)	28.0 (0.11)
CES-D (mean (SE))		
Wave I	5.1 (0.11)	6.5 (0.13)
Wave III	4.2 (0.11)	5.0 (0.10)
Wave IV	4.8 (0.10)	5.6 (0.10)
Binge Drinking (mean (SE))		
Wave I	14.3 (1.32)	7.8 (0.80)

Wave III	33.6 (1.86)	12.1 (0.99)
Wave IV	28.8 (1.84)	13.6 (1.16)
Cigarettes (mean (SE))		
Wave I	4.0 (0.30)	4.1 (0.40)
Wave III	8.6 (0.41)	7.5 (0.48)
Wave IV	8.9 (0.33)	6.7 (0.41)
Marijuana Use (mean (SE))		
Wave I	1.6 (0.19)	0.9 (0.13)
Wave III	3.9 (0.24)	2.0 (0.15)
Wave IV	3.4 (0.23)	1.5 (0.13)

[a] All other race/ethnicities are non-Hispanic
[b] SE: Standard error

Table 3 shows the results of the three linear mixed effects models with substance use frequency of each substance rotating as the dependent variable to test the self-medication pathway. CES-D is the independent variable and the other substances are included as controls in addition to race, age, and respondent and maternal education. Each dependent variable is lagged by one wave so that the model estimates the relationship between earlier depressive symptoms and later substance use frequencies (e.g., examining the relationship between Wave I depressive symptoms and Wave III substance use frequency). The intercept of this model was allowed to vary randomly by respondent ID. The results indicate that for males, increases in depressive symptoms at earlier waves are not associated with increases in substance use frequency at a later wave. Also, the standard deviation of the intercept of marijuana frequency when depressive symptoms and all other covariates are at zero is 2.19, indicating meaningful variation in the intercept by respondent ID.

Table 3
Linear mixed effects models of the relationship between depressive symptoms at an earlier wave and substance use frequencies at a later wave, Males

Coefficients	M1: Binge drinking	M2: Cigarettes	M3: Marijuana
CES-D	-0.50	0.34	0.27
Binge drinking		0.03***	0.01***
Cigarettes	0.87***		0.16***
Marijuana	0.99***	0.40***	
Age	1.79***	0.77***	0.18***
Race			
Hispanic	-2.54	-2.47***	1.14
Black	-5.38*	-3.95***	0.62*
Asian	-12.81***	-1.18*	-0.40
Native American	-6.17	0.42	1.07
Other	12.16	-2.98*	1.19
White	(referent)	(referent)	(referent)
Maternal Education			
Less than high school	2.33	-1.70*	-0.38
High school graduate	0.87	0.44	-0.89*
Some college	-3.32	-0.17	-0.44
College graduate	(referent)	(referent)	(referent)
Respondent Education			
Less than high school	-6.57	7.14***	0.68
High school graduate	-11.63**	5.09***	0.64
Some college	-11.51***	4.37***	0.48
College graduate	(referent)	(referent)	(referent)

Constant	-16.98*	-17.29***	-3.95***
Variance Estimates (SD)[a]			
Respondent ID	131.08 (11.45)	26.59 (5.16)	4.80 (2.19)
Residual	2892.60 (53.78)	81.99 (9.05)	37.53 (5.13)

*p<0.05; **p<0.01; ***p<0.001

[a] When the slope was allowed to randomly vary by age, there was not meaningful variation and so the final models only allow for random intercepts.

Table 4 displays results of parallel linear mixed effects models for testing the self-medication pathway for females. Results indicate that for females, a 5-point increase in depressive symptoms is associated ($p<0.05$) with a 0.44 (or nearly a half day) later increase in 30 day cigarette smoking frequency. Also, the standard deviation of the intercept of smoking frequency when depressive symptoms and all other covariates are at zero is 4.17 indicating meaningful variation in the intercept by respondent ID.

Table 4

Linear mixed effects models of the relationship between depressive symptoms at an earlier wave and substance use frequencies at a later wave, Females

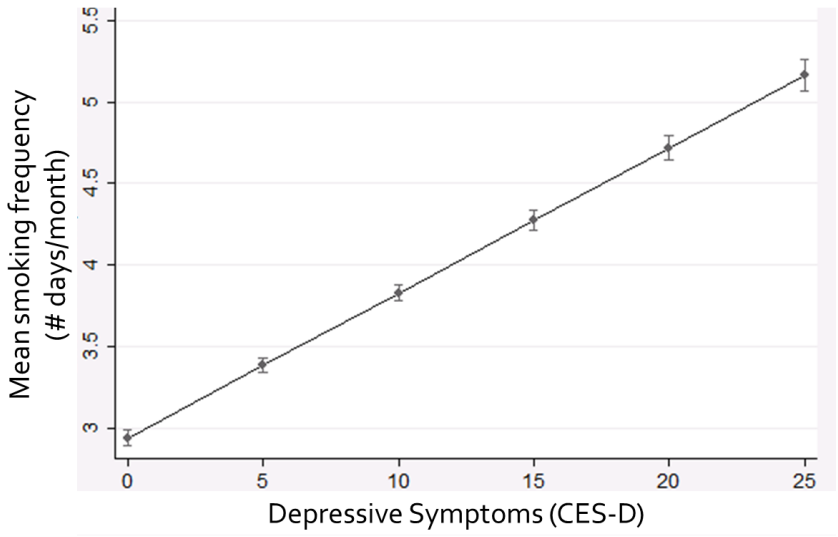
Coefficients	M1: Binge drinking	M2: Cigarettes	M3: Marijuana
CES-D	0.14	0.44*	0.06
Binge drinking		0.05***	0.02***
Cigarettes	0.59***		0.11***
Marijuana	1.27***	0.51***	
Age	0.27*	0.71***	0.06***
Race			
Hispanic	0.32	-3.02***	0.20
Black	-1.08	-5.25***	0.21
Asian	-1.46	-2.48***	0.00
Native American	-1.44	0.60	-0.13
Other	-8.31***	1.22	-0.20
White	(referent)	(referent)	(referent)
Maternal Education			
Less than high school	-3.55*	0.85	-0.69**
High school graduate	-2.91*	2.02***	-0.68***
Some college	1.13	0.78*	-0.29
College graduate	(referent)	(referent)	(referent)
Respondent Education			
Less than high school	1.05	7.71***	0.51
High school graduate	-2.79*	4.23***	0.41
Some college	-2.94*	3.83***	0.23
College graduate	(referent)	(referent)	(referent)
Constant	1.39	-15.81***	-1.20**
Variance Estimates (SD)[a]			
Respondent ID	11.55 (3.40)	24.71 (4.97)	1.84 (1.36)
Residual	1108.88 (33.30)	70.58 (8.40)	16.78 (4.10)

*p<0.05; **p<0.01; ***p<0.001

[a] When the slope was allowed to randomly vary by age, there was not meaningful variation and so the final models only allow for random intercepts.

The predicted mean smoking frequency for increases in depressive symptoms for females from Table 4 is displayed in Figure 1. An increase from the minimum to the maximum score on the CES-D is predicted to increase female mean smoking frequency in the past 30 days from approximately 3 days to over 5 days.

Figure 1
Predicted mean frequency of cigarette use in days in the past 30 days by CES-D score, Females[a]



[a] The figure shows results from the same model as outlined in Table 4, but the horizontal axis was changed to the unscaled measure of depressive symptoms to maximize interpretability.

Table 5 shows the results of the linear mixed effects models testing the relationship between earlier substance use frequency and later depressive symptoms for males and females. In these models the dependent variable is depressive symptoms, lagged by one wave, and the independent variables are substance use frequency of all three substances. The intercept of this model was allowed to vary randomly by respondent ID. The results indicate that an increase in smoking frequency of one day per month is associated with a 0.003 ($p<0.01$) increase for males and a 0.01 ($p<0.001$) increase for females in later depressive symptoms. There also appears to be non-trivial variation in the intercept across respondent IDs, as the standard deviation of the intercept was 0.40 for males and 0.45 for females. All of the linear mixed effects models presented in this study were also tested without controls for use of other substances and the results were largely unchanged, except for a significant relationship between earlier depressive symptoms and later marijuana use for males. Further, the linearity assumption for the ordinal substance use measures was supported as the BIC estimates from both models were nearly identical. The assumption that the strengths of associations between the waves would be equivalent was also supported as the interaction between the Wave IV indicator variable and the substance use predictors were not statistically significant.

Table 5
Linear mixed effects models of the relationship between substance use frequency at an earlier wave and depressive symptoms at a later wave, Males and Females

Coefficients	Males	Females
Binge drinking	0.00	0.00
Cigarettes	0.003**	0.01***
Marijuana	0.00	0.00
Age	-0.02***	-0.02***
Race		
Hispanic	0.14**	0.14**
Black	0.17***	0.17***

Asian	0.29***	0.29***
Native American	0.13	0.08
Other	0.19	-0.09
White	(referent)	(referent)
Maternal Education		
Less than high school	0.23***	0.21***
High school graduate	0.07	0.11**
Some college	0.02	0.12**
College graduate	(referent)	(referent)
Respondent Education		
Less than high school	0.1436**	0.41***
High school graduate	0.06	0.26***
Some college	-0.04	0.09**
College graduate	(referent)	(referent)
Constant	1.21***	1.29***
Variance Estimates (SD)[a]		
AID	0.16 (0.40)	0.20 (0.45)
Residual	0.34 (0.58)	0.50 (0.71)

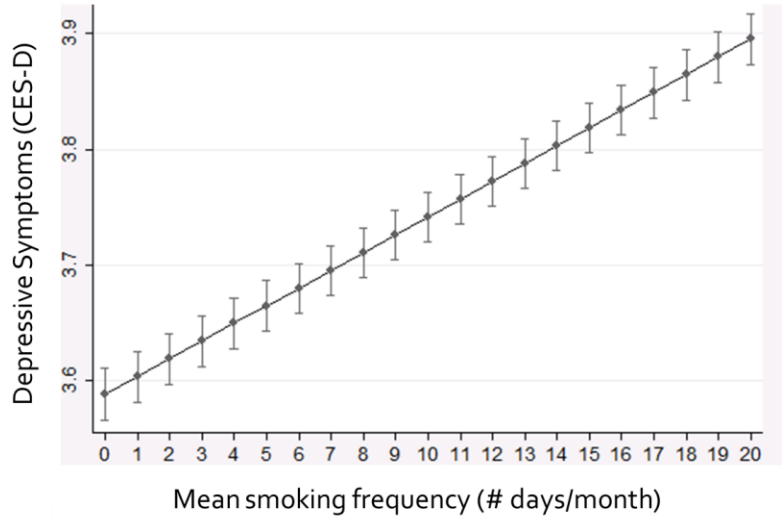
*p<0.05; **p<0.01; ***p<0.001

[a] When the slope was allowed to randomly vary by age, there was not meaningful variation and so the final models only allow for random intercepts.

Figure 2 shows the predicted mean CES-D score as smoking frequency increases for males. To create a plausible range of smoking frequency, measured as number of days on which a respondent smoked in the past 30, we selected the minimum of zero days and extended up to roughly two standard deviations above the mean or up to 20 days. The figure shows a predicted 0.3 point increase in the mean CES-D score for a 20 day increase in smoking frequency in the past 30 days.

Figure 2

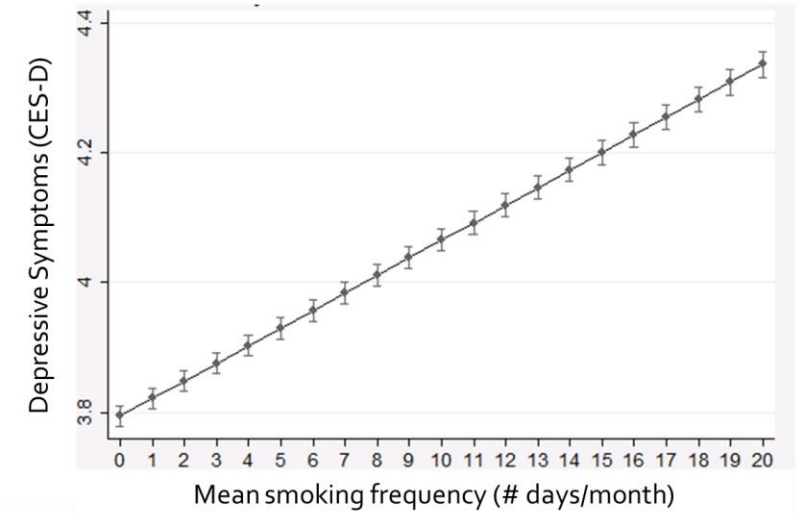
Predicted change in depressive symptoms as smoking frequency increases, Males[a]



[a] The figure shows results from the same model as outlined in Table 5, but the vertical axis was changed to the unscaled measure of depressive symptoms to maximize interpretability.

Figure 3 shows the predicted mean CES-D score as smoking frequency increases from Table 5 for females. The figure shows a predicted 0.6 point increase in the CES-D score for a 20 day increase in smoking frequency in the past 30 days, both the intercept and slope are higher than estimates for males.

Figure 3
Predicted change in depressive symptoms as smoking frequency increases, Females[a]



[a] The figure shows results from the same model as outlined in Table 5, but the vertical axis was changed to the unscaled measure of depressive symptoms to maximize interpretability.

Discussion

We assessed the relationship between depressive symptoms and high frequency substance use from adolescence into young adulthood using a nationally representative sample. Overall, we found only modest support for each pathway. Increases in depressive symptoms are associated with significant increases in later smoking frequency for females. This finding is consistent with the self-medication hypothesis.[4] However, there is also a significant relationship between smoking frequency and later increases in depressive symptoms for both males and females, a finding consistent with the idea that substance use can elevate depressive symptoms. Contrary to expectations, associations between depressive symptoms and binge drinking or marijuana use were not statistically significant for males or females in adjusted models.

The evidence for females self-medicating their depression with cigarettes is consistent with some existing literature.[5,6] Interestingly, Needham et al., using Waves I through III of the Add Health data, found partial support for the self-medication hypothesis but then found those with high depressive symptoms and substance use were less vulnerable to subsequent increases in substance use, especially for females and smoking.[21] By comparison, we found increases in depression are associated with later increases in smoking frequency, controlling for prior substance use. However, Needham et al. did not use time varying depression measures and used Wave II data.[21]

Although a review of emotion regulation strategies found that men are more likely to cope by using alcohol, we find no support for self-medication among males.[22] This is consistent with earlier Add health analyses following respondents only into emerging adulthood.[8] As binge drinking was the most common substance use pattern in this sample it is possible there is a self-medication pattern within the data for the small proportion of men with depression but it is occluded by the high proportion of men in the sample engaging in binge drinking as a social and normative—rather than self-medication—activity.[5,21] Although prior studies have found evidence for male self-medication with marijuana during adolescence, we find no support for this hypothesis over the time period of adolescence into young adulthood.[23–25]

Regarding the reverse pathway, we do find that cigarette smoking frequency at an earlier wave is significantly associated with later increases in depressive symptoms in emerging and young adulthood among both males and females. Earlier analyses using Add Health data that were limited to the adolescent period also found smoking to be predictive of later depressive symptoms.[8,24] Using data from Waves I and II of Add Health, Goodman and Capitman found that smoking at Wave I produced a 3.90 odds ratio of being depressed at Wave II, supporting our results in this paper.[10] These results match a k-means cluster analysis of Add Health data from the same waves that found adolescents who reported regular smoking and having vaginal sex had odds ratios of 3.05, for males, and 2.72, for females, of being depressed at Wave II.[8]

Taken together, these findings suggest a bidirectional relationship between depressive symptoms and cigarette smoking for females. This could be interpreted as evidence that self-medication of depressive symptoms with nicotine does not ameliorate the symptoms. Further, as females increase their cigarette smoking frequency, they are engaging in a non-normative activity that could increase interpersonal stress, thereby increasing depressive symptoms.[14,15] For males, we only find support for one direction, an association between smoking and later depressive symptoms. Past studies examining the association between smoking and a dichotomous measure of depression (versus depressive symptoms) using Add Health data[8,10] and a sample of Canadian adolescents[5] did not find significant bidirectional associations. However, the other Add Health analyses used a different measure of smoking[8,10] and a more limited time line.[8,10]
Finally, the Goodman and Capitman paper did produce a significant relationship between depression and later smoking, but found covariates could explain away the association, likely because they used covariates specifically for smoking behavior in adolescents like irritability and peer smoking patterns.[10] Future research could examine this bidirectional relationship between depressive symptoms and smoking frequency for females and whether covariates unique to smoking behavior help explain it.

Our findings should be considered in the context of this study's strengths and limitations. The strengths of this study include the longitudinal and nationally representative sample as well as use of robust methods that allowed for assessing both fixed and random effects in the data while testing a temporal hypothesis. The limitations include the use of self-reported measures of substance use and depressive symptoms; however the use of audio computer-assisted self-interviewing method likely decreased under-reporting. Additionally, although we assumed linearity in the measures of use frequency for both marijuana and binge drinking, we tested this assumption with sensitivity analyses and it was supported. Finally, our analytical methods assumed the strength of the association between high frequency substance use and depressive

symptoms are equivalent from Wave I to Wave III and from Wave III to Wave IV but this assumption was also tested and supported.

We find support for a bidirectional relationship between high levels of smoking and depressive symptoms, but only for females. For males only support for smoking being linked to later depressive symptoms was found. We anticipated that, regardless of direction, we would find more numerous associations; we speculate that finding fewer associations may be linked to the longer time line we examine in this study. Where most previous research is focused on adolescence, we examined the developmental trajectory from adolescence to emerging adulthood and into young adulthood. The results of this study indicate the self-medication hypothesis is an explanation for the co-morbidity of depressive symptoms and substance use among youth, but it is not the only explanation. This paper, using models allowing for both fixed and random effects, provides evidence for high frequency smoking being associated with later increases in depressive symptoms. Future research is needed to understand potential mediators of this pathway, such as the body's inflammatory stress response, feelings of shame, strained peer or parental relationships, etc. In the meantime, the results of this study can inform depression treatment programs for adolescents as it appears providers should also screen for substance use. These findings are timely given the recent recommendation from the United States Preventive Services Task Force that adolescents should be screened for depression.[26]

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