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Original Contribution

Adolescent Cannabis Problems and Young Adult Depression: Male-Female Stratified Propensity Score Analyses

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Cannabis use and depression are two of the most prevalent conditions worldwide. Adolescent cannabis use is linked to depression in many studies, but the effects of adolescent cannabis involvement on young adult depression remain unclear and may differ for males versus females. In this cohort study of youth from a mid-Atlantic metropolitan area of the United States, repeated assessments from 1985 (at age 6 years) through 2002 (at age 21 years) were made for 1,494 individuals (55% female). Measured covariate differences between individuals with and without cannabis problems were controlled via propensity score techniques. The estimated risk of young adult depression for adolescents with cannabis problems was not significantly different from that for comparison adolescents for either females (odds ratio = 0.7, 95% confidence interval: 0.2, 2.3) or males (odds ratio = 1.7, 95% confidence interval: 0.8, 3.6). The evidence does not support a causal association linking adolescent-onset cannabis problems with young adult depression.

causal inference; comorbidity; mental disorders; sex factors; substance-related disorders

Abbreviations: CIDI, Composite International Diagnostic Interview; GBM, generalized boosted modeling; MLR, multivariable logistic regression.

In the United States and elsewhere, adolescent cannabis use and problems continue to be public health concerns (1, 2), and there is speculation that cannabis use or associated problems might be contributing to an increased prevalence of young adult depressive disorders (3, 4). Whether cannabis use is actually a cause of depressive disorders remains an open question (2, 5). Some prospective studies support the idea of a link from cannabis use or problems to later depression (6–10). Other studies fail to support a cause-effect relation (11–13). Hall and Degenhardt (14) argue that more prospective research with improved statistical analyses to better control for confounders is needed to test the potential causal relation linking cannabis and depression. The studies that have made the best attempts to control for confounders have been limited by their use of more traditional statistical methods, such as multivariable regression models (6, 9). In practice, these standard statistical approaches may be suboptimal and may lead to ill-founded causal inferences (15, 16). In contrast, this study makes use of statistical techniques specifically designed for causal inference, known as propensity score techniques (17, 18). We use propensity score techniques to estimate a suspected causal effect of adolescent-onset cannabis problems on later depression in young adulthood.

Based upon the most recent world literature on the age-of-onset distributions for cannabis problems, this study has a focus upon the developmentally important onsets during early-mid adolescence (i.e., before the age of 17 years). Epidemiologic evidence for the United States indicates that the greatest mass of these onsets will be found after the age of 17 years but that nearly 20 percent of the onsets occur before 17 years (19, 20). As such, in this study, the idea is that adolescent-onset cannabis problems might influence excess risk of depression in young adulthood. Also based

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upon the most recent world literature, the onset of depression and other mood disorders remains relatively uncommon until after the mid teens, with an age-related linear increase thereafter through late middle age. Epidemiologic evidence from the United States indicates that fewer than 25 percent of major depression onsets occur prior to age 19 years and that age 32 years is the median age of onset for major depression in the United States (19, 20). As such, this study's motivation might be characterized by evidence on the hypothesized possibility that adolescent-onset cannabis problems might account for an excess risk of depression during young adulthood.

The hypothesized causal effect of cannabis problems on depression is estimated through propensity score adjustment of data from a cohort study of youths followed from first grade into young adulthood, with stratification to shed light on possible male-female variation in the association, as suggested in prior research (21). The male-female stratification is motivated by prior epidemiologic studies in which there is a male excess in cannabis involvement but a female excess in occurrence of depression (22–27).

In this research, we estimate a suspected causal association linking cannabis problems with depression using propensity score techniques to achieve balanced distributions of measured covariates between those with adolescent-onset cannabis problems and comparison individuals. This ensures the comparison of individuals with and without cannabis problems who are as similar as possible on the other measured covariates. Propensity score techniques are growing in popularity, and a large variety of methods are available. This paper provides an introduction to a few of the methods and our criteria for how to select among the many methods available.

MATERIALS AND METHODS

Study population

In the mid-1980s, the Prevention Research Center at The Johns Hopkins University enrolled 2,311 first-grade children in a randomized trial of two preventive interventions. The children came from 43 classrooms in 19 urban elementary schools in a Mid-Atlantic metropolitan area of the United States. All study protocols gained institutional review board approval. The resulting data are those of a longitudinal cohort study nested within the randomized prevention trial. Annual follow-up interviews were conducted from elementary school to late-middle school with subsequent follow-up in young adulthood of over 75 percent of the surviving participants. The young adult interviews contributed information for this research—a telephone interview and a subsequent in-person interview, with similar assessment protocols used in both of these two assessments (28).

Not all young adults were interviewed in both ways, but information from both young adult assessments was used in this research. Separate analyses conducted for data from the telephone and in-person assessments resulted in similar inferences and are not presented. After exclusion of individuals with missing data on adolescent cannabis involvement or young adult depression, 1,494 individuals remained in the analysis data set (826 females, 668 males). Other publications provide more detail on these young adult follow-up assessments (28–32), as well as sensitivity analyses about how missing data due to attrition may affect the results of studies that use these data (33).

Measures

Exposure. In this study, we are interested in the effect of an ''exposure'' variable—adolescent onset of cannabis problems. Specifically, this exposure is defined as the occurrence of cannabis problems during adolescence (before 17 years of age), where ''problems'' indicate either cannabis dependence or nondependent abuse. The exposure variable was dichotomized, indicating cannabis problems versus none, with onset ranging mainly between the ages of 12–16 years with four individuals with onset at age 11. The comparison group contained individuals who had never used cannabis and individuals who used cannabis but did not experience problems before age 17. The assessment was made on the basis of recall of age of first cannabis problems during the young adult interview, by using standardized items from the Composite International Diagnostic Interview (CIDI) (34) or a CIDI-like interview, depending on whether the young adult was interviewed over the telephone or in-person, respectively. The CIDI is a comprehensive, structured, diagnostic interview used by trained lay interviewers for the assessment of mental disorders as defined by the *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV* (35).

Outcome. The outcome was defined as a depressive episode occurring the year prior to the first available young adult interview date between the ages of 19 and 24 years. The telephone and in-person depression assessments followed the *DSM-IV* diagnostic criteria for major depression in that they asked a series of questions about depression and allied clinical features that occurred in the year prior to assessment.

Covariates. Potentially confounding covariates included in the analyses consisted of demographic, socioeconomic status, other drug use, childhood disturbances of psychological well-being, parental monitoring, and behavioral intervention status variables. All covariates were modeled as either categorical or binary factors. Race was categorized into Black, White, and other, which included Hispanic, Asian, and Native American groups. Family income was categorized as low (<$5,001), moderate ($5,001–$20,000), or high (>$20,000). Free or subsidized lunch eligibility was based on school records at the time of school entry. Parental supervision and monitoring (36) were assessed via a summary score divided into four categories: low, moderate, high, or higher. Concentration problems, behavior problems, and shyness were encoded as summary scores from the Teacher Observed Classroom Adjustment—Revised questionnaire. Depression and anxiety levels from a child self-reported ''How I Feel'' questionnaire were categorized into low, moderate, and high. The aforementioned covariates were all assessed before the age of 12 years. Tobacco involvement was indicated by onset of daily tobacco use, alcohol involvement was assessed by indications of alcohol abuse or dependence, and other drug use refers to

using any illegal drug besides cannabis. Tobacco, alcohol, and drug use covariates were assessed before the age of first cannabis problems for the cannabis problem users or before age 17 years for comparison individuals.

Missing data. A missing category was generated within each covariate when needed, and no individuals were removed from analyses if they had missing data on a covariate. In the male-female stratified analyses, the ''other'' race category was combined with the ''White'' category because of zero values in some cells. For females, the small sample size (66 female cannabis problem users) resulted in four other cells with zero female cannabis problem users. Because these covariate values would perfectly predict cannabis problem use, those cells were combined with either the null category (daily tobacco, other illegal drug use) or with a neighboring category (behavior problems, shyness).

Statistical analyses

This study focuses on estimating the causal effect of adolescent-onset cannabis problems on the odds of young adult depression by using propensity score techniques, with stratification to capture possible male-female variation in the link between cannabis problems and depression. Results from more traditional epidemiologic analyses (multivariable logistic regressions) are also presented. Two parametric models and one nonparametric model were used to estimate the propensity score. We then applied the estimated propensity score to the final outcome logistic regression using three different application models. Details of these propensity score estimation and application techniques are included in the *Models and software* section below.

Decision criteria. Although this study builds and tests nine combinations of estimation and application techniques for the propensity score-adjusted models, the reported results are limited to estimates from the better performing propensity score techniques, as determined through decision criteria based on the assessment of covariate effect sizes (37). The propensity score techniques that perform well may vary for other data sets and research questions. These decision criteria can help researchers select which method is better for their particular study. The ''effect size'' for a particular covariate is the difference in average covariate values between the exposed and comparison groups divided by the standard error in the exposed group. In brief, the decision criteria identify the techniques that yield the smallest effect size across the majority of the covariates and across a few theoretically critical confounding covariates, while minimizing the extreme values of effect size for all covariates. Of importance, the propensity score techniques that meet the decision criteria are chosen prior to running the final outcome regressions, thus preventing bias through the selection of a method that yields a desired result.

Average causal effect. This article presents the estimated average causal effects of the ''treatment on the treated.'' In the causal inference methodology literature, the exposure variable is referred to as a ''treatment,'' but in this article we retain the epidemiologic terminology of exposure. The ''treatment on the treated'' is an estimate of the average causal effect that would be seen if everyone in the exposed group had been exposed versus no one in the exposed group being exposed. The other commonly reported average causal effect is referred to simply as the ''average treatment effect'' and is described elsewhere (38). In this article, we present the ''treatment on the treated'' estimate.

Models and software. Multivariable logistic regression (MLR), MLR with critically chosen interaction terms (39, 40), and generalized boosted modeling (GBM), a nonparametric regression tree technique (41), were used to estimate the propensity score. Each of these techniques models cannabis problem use as a function of the measured covariates. The propensity scores are the resulting predicted probabilities of cannabis problems for each individual. One to one (1:1) matching (18), full matching (42, 43), and weighting by the odds (44) were used to apply the propensity score to the final regression. Prior to running the final logistic regressions predicting young adult depression, we compared the resulting covariate effect sizes from each of the nine combinations of estimation and application techniques utilizing the aforementioned decision criteria. For females, the two propensity score techniques that performed well were MLR paired with full matching and MLR paired with weighting by the odds. For males, GBM paired with weighting by the odds and MLR paired with weighting by the odds both performed well. For the combined sample, GBM paired with weighting by the odds performed well with regard to the decision criteria.

All statistical analyses were conducted in the R language (45). Two propensity score packages written for the R environment were used: MatchIt (46) and Twang (47). The two parametric propensity score estimation techniques used MatchIt, while the nonparametric estimation technique used Twang, which utilized the GBM package in R (48). The final logistic regression models were adjusted for the preexposure covariates used in the propensity score models to account for residual confounding. The results presented below are the propensity score-adjusted odds ratios from these logistic regressions, run for males and females separately, as well as for the combined sample.

RESULTS

Preexposure differences

Cannabis problem users (the ''exposed'' group) are different from comparison individuals on many measured preexposure covariates. Across males, females, and the combined sample, the cannabis problem users and comparison individuals do not appear to have markedly different preexposure depression or anxiety levels. However, a higher percentage of the cannabis problem users were daily tobacco users, had problem alcohol use, or had slightly higher concentration and behavior problems than the comparison individuals (tables 1 and 2). The application of the propensity score corrected for these imbalances, as evidenced by the decrease in all measured covariate effect sizes below 0.25 and by nonsignificant chi-squared test statistics for all covariates after propensity score adjustment (table 2).

TABLE 1. Baseline characteristics of 1,494 adolescent-onset cannabis problem users and comparison individuals from the original 2,311 individuals in the Prevention Research Center cohort, United States, 1985–2001

	Cannabis problem users		Comparison individuals		Chi square*	*p* value, two sided
	No.	%	No.	%		
Sex					63.54	<0.005
Male	151	70	517	40		
Female	66	30	760	60		
Race					19.05	<0.005
Black	132	61	948	74		
White	84	39	315	25		
Other†	1	0	14	1		
Family income					1.90	0.59
Low	19	9	115	9		
Middle	54	25	373	29		
High	71	33	381	30		
Missing	73	34	408	32		
Free lunch					1.68	0.43
No	62	29	314	25		
Yes	149	69	931	73		
Missing	6	3	32	3		
Daily tobacco smoker					336.08	<0.005
No	69	32	1,089	85		
Yes	146	67	163	13		
Missing	2	1	25	2		
Alcohol abuse or dependence					376.62	<0.005
No	113	52	1,210	95		
Yes	93	43	39	3		
Missing	11	5	28	2		
Other illegal drug use					21.06	<0.005
No	206	95	1,262	99		
Yes	7	3	5	0		
Missing	4	2	10	1		
Parental monitoring					0.91	0.92
Low	39	18	220	17		
Moderate	42	19	238	19		
High	38	18	232	18		
Higher	43	20	285	22		
Missing	55	25	302	24		
Concentration problems‡					22.11	0.001
Lowest	15	7	157	12		
Lower	28	13	235	18		
Low	39	18	262	21		
Moderate	47	22	256	20		
High	30	14	99	8		
Higher	7	3	17	1		
Missing	51	24	251	20		
Behavior problems‡					41.98	<0.005
Lower	32	15	397	31		
Low	69	32	377	30		
Moderate	30	14	171	13		
High	25	12	60	5		
Higher	10	5	21	2		
Missing	51	24	251	20		
Shyness‡					3.24	0.70
Lower	7	3	65	5		
Low	49	23	310	24		
Moderate	76	35	457	36		
High	31	14	171	13		
Higher	3	1	23	2		
Missing	51	24	251	20		
Depression symptoms§					4.40	0.22
Low	29	13	182	14		
Moderate	117	54	764	60		
High	14	6	64	5		
Missing	57	26	267	21		
Anxiety symptoms§					5.47	0.14
Low	45	21	235	18		
Moderate	94	43	657	51		
High	21	10	118	9		
Missing	57	26	267	21		
Intervention status (classroom)					0.31	0.86
Standard setting	129	59	736	58		
Good behavior game	42	19	266	21		
Mastery learning	46	21	275	22		
Intervention status (school)					0.04	0.98
Standard setting	60	28	347	27		
Good behavior game	75	35	439	34		
Mastery learning	82	38	491	38		

* First category in each covariate is the reference. Fisher's exact tests used when cells have less than five individuals.

† Other race includes Hispanics, Asians, and Native Americans.

‡ Based on the standardized Teacher Observed Classroom Adjustment-Revised teacher's rating summary score.

§ Based on a child's self-reported mood questionnaire summary score.

Propensity score adjustment

The final estimated odds ratios from the propensity score-adjusted regression models that met the decision criteria are presented in table 3. Female cannabis problem users experienced a modestly lower prevalence of major depression, while male problem users experienced a modestly higher prevalence of major depression, but the variation was not

TABLE 2. Balance of baseline characteristics by males and females separately, before and after propensity score adjustment of 1,494 adolescent-onset cannabis problem users and comparison individuals from the original 2,311 individuals in the Prevention Research Center cohort, United States, 1985–2001

	Males							Females†						
	Cannabis problem users		Comparison individuals			Chi square, unadjusted‡	Chi square, propensity score adjusted‡	Cannabis problem users		Comparison individuals			Chi square, unadjusted‡	Chi square, propensity score adjusted‡
	No.	% unadjusted	No.	% unadjusted	% propensity score adjusted			No.	% unadjusted	No.	% unadjusted	% propensity score adjusted		
Race						2.42	0.11						19.54*	0.32
Black	99	66	372	72	67			33	50	576	76	52		
Other§	52	34	145	28	33			33	50	184	24	48		
Family income						0.97	0.56						2.36	5.61
Low	17	11	48	9	12			2	3	67	9	0		
Middle	38	25	137	26	23			16	24	236	31	24		
High	49	32	157	30	33			22	33	224	29	34		
Missing	47	31	175	34	33			26	39	233	31	41		
Free lunch						0.58	2.78						4.40	2.26
No	39	26	135	26	33			23	35	179	24	39		
Yes	110	73	370	72	67			39	59	561	74	58		
Missing	2	1	12	2	0			4	6	20	3	3		
Daily tobacco smoker						145.60**	6.62						165.73**	2.95
No	51	34	428	83	44			18	27	675	89	33		
Yes	98	65	78	15	56			48	73	85	11	67		
Missing	2	1	11	2	0									
Alcohol abuse or dependence						202.00**	8.59						81.27**	9.47
No	67	44	481	93	55			46	70	729	96	72		
Yes	77	51	24	5	39			16	24	15	2	17		
Missing	7	5	12	2	7			4	6	16	2	10		
Other illegal drug use						6.61	0.52						25.59	3.71
No	145	96	512	99	96			61	92	757	100	95		
Yes	2	1	2	0	2			5	8	3	0	5		
Missing	4	3	3	1	2									
Parental monitoring						4.06	8.42						9.4	8.73
Low	29	19	82	16	16			10	15	138	18	21		
Moderate	33	22	101	20	18			9	14	137	18	14		
High	29	19	82	16	16			9	14	150	20	10		
Higher	31	21	123	24	25			12	18	162	21	14		
Missing	29	19	129	25	25			26	39	173	23	41		
Concentration problems						6.49	6.98						9.43	13.12
Lowest	4	3	36	7	2			11	17	121	16	12		
Lower	19	13	82	16	16			9	14	153	20	20		

Low	30	20	93	18	20			9	14	169	22	12			
Moderate	36	24	117	23	25			11	17	139	18	17			
High	24	16	64	12	11			6	9	35	5	7			
Higher	6	4	14	3	2			1	2	3	0	0			
Missing	32	21	111	21	23			19	29	140	18	32			
Behavior problems						20.92*	3.36						5.11	5.72	
Lower	13	9	104	20	10			19	29	293	39	33			
Low	50	33	158	31	36			19	29	219	29	24			
Moderate	24	16	92	18	12			6	9	79	10	7			
High	22	15	37	7	12			3	5	29	4	3			
Higher	10	7	15	3	7										
Missing	32	21	111	21	24			19	29	140	18	33			
Shyness						3.39	7.5						5.27	8.97	
Lower	2	1	20	4	2			5	8	45	6	7			
Low	36	24	102	20	19			13	20	208	27	25			
Moderate	55	36	197	38	40			21	32	260	34	27			
High	23	15	78	15	14			8	12	107	14	8			
Higher	3	2	9	2	0										
Missing	32	21	111	21	24			19	29	140	18	32			
Depression symptoms						3.09	2.06						5.65	17.48	
Low	22	15	81	16	16			7	11	101	13	19			
Moderate	83	55	300	58	54			34	52	464	61	45			
High	10	7	18	3	5			4	6	46	6	2			
Missing	36	24	118	23	25			21	32	149	20	34			
Anxiety symptoms						1.30	3.87						10.48	12.56	
Low	36	24	104	20	20			9	14	131	17	10			
Moderate	70	46	261	50	45			24	36	396	52	44			
High	9	6	34	7	9			12	18	84	11	12			
Missing	36	24	118	23	25			21	32	149	20	34			
Intervention status (classroom)						2.88	0.06						4.38	0.03	
Standard setting	89	59	305	59	59			40	61	431	57	60			
Good behavior game	24	16	108	21	16			18	27	158	21	28			
Mastery learning	38	25	104	20	25			8	12	171	23	12			
Intervention status (school)						0.83	6.38						3.05	0.03	
Standard setting	37	25	144	28	28			23	35	203	27	34			
Good behavior game	51	34	175	34	26			24	36	264	35	36			
Mastery learning	63	42	198	38	47			19	29	293	39	29			

* $p < 0.01$; ** $p < 0.005$, two sided.
† Cells with zero individuals are combined with the reference group if binary or combined with the nearest neighbor if categorical.
‡ First category in each covariate is the reference. Fisher's exact tests are used when cells have less than five individuals.
§ Other race includes Whites and other non-Blacks.

TABLE 3. Estimated association by males and females separately, linking young adult depression with adolescent-onset cannabis problems, with covariate adjustment and use of propensity score techniques for 1,494 individuals from the Prevention Research Center cohort, United States, 1985–2001

Propensity score adjustment models	No. of adolescent cannabis problem users	Odds ratio	95% confidence interval	*p* value, two sided
Males				
GBM* and weighting by the odds	151	1.72	0.77, 3.86	0.19
MLR* and weighting by the odds		1.67	0.77, 3.60	0.19
Females				
MLR and full matching	66	0.63	0.25, 1.58	0.32
MLR and weighting by the odds		0.68	0.20, 2.34	0.54
Combined sample				
GBM and weighting by the odds	217	1.33	0.76, 2.33	0.32

* GBM, generalized boosted modeling propensity score estimation technique; MLR, multivariable logistic regression propensity score estimation technique.

statistically significant by conventional frequentist standards ($p > 0.05$). The other propensity score-adjusted ''treatment on the treated'' models mentioned above (those not selected by the decision criteria) produce similar odds ratio estimates (male odds ratio range = 1.6–2.1; female odds ratio range = 0.6–1.1), with only one odds ratio of 18 with $p < 0.05$. The final odds ratios from the propensity score-adjusted models for the combined sample are all slightly above the null (odds ratio range = 1.1–1.8) with two of the nine with $p < 0.05$.

Traditional adjustment

The more traditional epidemiologic regression model for these data, multivariable logistic regression, produces results that are similar in the combined sample but slightly different in the male-female stratified subgroups. For males, the traditional odds ratio estimate comparing young adult depression among adolescents with and without cannabis problem use is over 2 and is statistically significant (odds ratio = 2.6; $p < 0.01$). For females, the result is essentially null (odds ratio = 0.9; $p = 0.72$). The cannabis-depression estimate for the combined sample is positive but not significant (odds ratio = 1.5; $p = 0.11$). The propensity score-adjusted analyses are generally preferred because they ensure the similarity of covariates between the exposed and comparison groups.

DISCUSSION

Studying a sample of youth followed from childhood through adolescence and into adulthood, we found essentially null associations linking adolescent-onset cannabis problems with later young adult depression. Propensity score techniques were used to estimate the causal effects in the combined sample as well as separately for males and females. Results were confirmed through sensitivity analyses by using traditional multivariable logistic regressions. The magnitude of the association was found to be lower for females than males, but with little evidence of statistically robust associations for either males or females. Previous research examining similar questions suggested that female cannabis users might be slightly more likely than males to experience depression in adulthood (8, 13, 49). Our relatively small sample size of female cannabis problem users ($n = 66$) may be responsible for the qualitatively different results between males and females. There is a clear need for study replication with larger sample sizes.

Our study does not support the hypothesis that adolescent-onset cannabis problem use causes young adult depression. Two other causal hypotheses remain: 1) Depression causes individuals to manage their symptoms through self-medication by use of cannabis, and 2) a common genetic or environmental influence causes both depression and cannabis use. Although there is consistent evidence that depression does not cause cannabis use (50), there is evidence in support of the common cause hypothesis through the use of co-twin methodology to control for genetic influences (51). Our findings do not rule out the common cause hypothesis and, in fact, may add support to it by virtue of ruling out the hypothesis that adolescent cannabis problem use might be functioning as a causal factor for young adult depression.

Results from a recent large national survey in the United States suggest that the relation between cannabis use and depression may be explained by associations between cannabis use and bipolar disorders, which are also associated with other drug use disorders (5). In our study, preexposure reports of other drug problem use (tobacco, alcohol, or illegal drugs) were controlled. This additional statistical control might explain why this report is not entirely consistent with what has been observed by others, such as Stinson et al. (5). Together with these findings and the findings from other studies also reporting null associations between cannabis use and depression (11–13), it appears that there is mounting evidence against the hypothesized causal association. Even if this study lacked power to detect a causal association, there may be a small association for males and for the

combined sample, but it is unlikely that there is a direct causal pathway linking adolescent-onset cannabis problems to young adult depression.

Continued efforts to resolve the debate over the nature of the association between cannabis and depression are warranted, given recent reports of the link between cannabis and psychosis. Schizophrenia (psychosis) has been linked with cannabis problems in longitudinal studies (52–55). Four recent reviews (56–59) agree, and one review disagrees (60) with the claim of causality. It should be noted that none of the aforementioned studies applied propensity scores or other causal inference statistical techniques. Regardless, there is a general overall consensus that cannabis use may be a contributory cause of psychosis among individuals with susceptibility to psychosis (61). This situation of uncertainty motivates a more complete examination of the evidence about whether cannabis problems cause other mental health disorders, such as depression.

The findings of this study must be interpreted in light of potential methodological limitations. For example, in this study, the age at the occurrence of first cannabis problems was assessed retrospectively during the young adult interview, concurrently with the assessment of the age at first depressive episode. As such, the link from cannabis problems to depression is not strictly longitudinal, although we used ancillary information about age at onset to be sure that the cannabis problems had occurred before the age of 17 years, and depression was assessed afterwards. Fortunately, there is some evidence that recalled age of cannabis involvement can be measured reliably (62, 63). Another limitation of the study is that we could not balance unobserved (unmeasured) covariates. Researchers may be hesitant to apply propensity score techniques because of the major limitation that they do not control for unmeasured covariates. However, this concern over potential unmeasured confounders is common to both propensity score techniques and traditional multivariable regression applied to observational data. Therefore, because the same limitation applies, it is not a special concern for this study in particular. Given some findings that males experience onset of depression at a later age than females do (64), it is possible that our limited range and relatively young age for assessing depression have resulted in a downwardly biased estimate for the occurrence of male depression and a resulting effect estimate biased toward the null. This question can be addressed in the ongoing follow-up of this cohort in the future. Another limitation of this study is the length of time between surveys. Our ability to define the exposure during adolescence and the outcome in young adulthood leaves a gap of as little as 3 years to as large as 11 years between an individual's age at first cannabis problems and that individual's age at the young adult interview. Future research applying longitudinal propensity score techniques (65) to questions of causation linking cannabis and depression may be possible if an appropriate data set is identified with repeated measures of cannabis use and depression across the developmental period from adolescence into adulthood.

One of the strengths of this study involves its capacity to control for many potential confounding variables measured over a long span of time (i.e., over 15 years). As such, the nature of these data has allowed us to control for numerous critical preexposure confounding covariates (other drug use, childhood psychological distress, and socioeconomic factors). In addition, the use of structured diagnostic interviews allowed for the assessment of clinically relevant definitions of both cannabis problems and depression. A final strength of the present study involves the use of propensity scores, a fairly recent causal inference statistical method. The process of first estimating the propensity score and then later applying the propensity score allows for the evaluation of several propensity score estimation techniques based on the balance of the preexposure covariates prior to running the final propensity score-adjusted outcome model.

In conclusion, the evidence from propensity score adjusted analyses does not support the hypothesized causal link between adolescent-onset cannabis problem use and young adult depression. If adolescent cannabis problem use is causing some cases of young adult depression, the causal link is modest at best and may be limited to males. On the basis of this study's evidence, cannabis problems do not appear to contribute to depression among young adult females. If we are able to prevent adolescents from developing problem cannabis use, we may see very little reduction in the occurrence or prevalence of depressive episodes. If there is any cause-effect relation, it might be more readily found among males compared with females.

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