

Major Depressive Disorder, Suicidal Ideation, and Suicide Attempt in Twins Discordant for Cannabis Dependence and Early-Onset Cannabis Use

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Background: Previous research has reported both a moderate degree of comorbidity between cannabis dependence and major depressive disorder (MDD) and that early-onset cannabis use is associated with increased risks for MDD.

Objective: To examine whether associations between both lifetime cannabis dependence and early cannabis use and measures of MDD, suicidal ideation, and suicide attempt persist after controlling for genetic and/or shared environmental influences.

Design: Cross-sectional survey of twin pairs discordant for lifetime cannabis dependence and those discordant for early cannabis use.

Setting: General population sample of twins (median age, 30 years).

Participants: Two hundred seventy-seven same-sex twin pairs discordant for cannabis dependence and 311 pairs discordant for early-onset cannabis use (before age 17 years).

Main Outcome Measures: Self-report measures of DSM-IV–defined lifetime MDD, suicidal ideation, and suicide attempt.

Results: Individuals who were cannabis dependent had odds of suicidal ideation and suicide attempt that were 2.5 to 2.9 times higher than those of their non-cannabis-dependent co-twin. Additionally, cannabis dependence was associated with elevated risks of MDD in dizygotic but not in monozygotic twins. Those who initiated cannabis use before age 17 years had elevated rates of subsequent suicide attempt (odds ratio, 3.5 [95% confidence interval, 1.4-8.6]) but not of MDD or suicidal ideation. Early MDD and suicidal ideation were significantly associated with subsequent risks of cannabis dependence in discordant dizygotic pairs but not in discordant monozygotic pairs.

Conclusions: Comorbidity between cannabis dependence and MDD likely arises through shared genetic and environmental vulnerabilities predisposing to both outcomes. In contrast, associations between cannabis dependence and suicidal behaviors cannot be entirely explained by common predisposing genetic and/or shared environmental predispositions. Previously reported associations between early-onset cannabis use and subsequent MDD likely reflect shared genetic and environmental vulnerabilities, although it remains possible that early-onset cannabis use may predispose to suicide attempt.

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GIVEN THE HIGH AND APPARENTLY increasing prevalence of cannabis use among youth,¹ there have been continuing concerns about whether the use of this drug may heighten risks of psychiatric illness and, in particular, depressive or suicidal behaviors.²⁻⁴ Clinical studies have reported that rates of depression are elevated among those seeking treatment for cannabis dependence⁵ and, conversely, that rates of cannabis use and abuse/dependence are elevated among those being treated for depression^{6,7} and among those making a serious suicide attempt.⁸ Although referral bi-

ases limit the generalizability of these results, the conclusion that cannabis abuse/dependence and depressive disorders co-occur at greater than expected rates has been confirmed by general population surveys.⁹⁻¹¹ In addition, a series of recent longitudinal studies has indicated that rates of subsequent depression are elevated in young people who use cannabis¹²⁻¹⁴ and in adults who meet criteria for cannabis abuse or dependence.^{15,16}

Further research has also considered the possibility that comorbidity between cannabis use/dependence and mental health problems may reflect processes whereby depression and other mental health prob-

lems heighten risks of substance use and abuse/dependence. Specifically, the self-medication hypothesis¹⁷ posits that substance use may develop in response to attempts to ameliorate aversive experiences associated with mental health problems. Although intuitively appealing, this hypothesis has remained controversial and has received only limited support in the empirical literature; recent longitudinal studies have found no significant associations between early depression and later risks of regular cannabis use or dependence.^{14,16}

Thus, while there appears to be little support for the hypothesis that early depressive or suicidal behaviors increase risks for the development of cannabis dependence, recent findings have implicated cannabis use as having a causal role in the development of depression.² However, pivotal to this conclusion is the assumption that cannabis users and nonusers are similar, if not identical, on a range of measures predisposing to both cannabis use and internalizing disorders. The previous studies have attempted to address this issue by including a range of measured covariates and controlling for these using regression or similar techniques. While Fergusson et al¹² used methods of fixed-effects regression analysis, which potentially control for non-observed sources of confounding (both genetic and environmental), no previous study has specifically assessed the influence of genetic factors on the association between early-onset cannabis use and subsequent risks of depression. Nonetheless, the existing evidence indicates that both cannabis use and dependence¹⁸⁻²⁰ and measures of depressive^{20,21} and suicidal behaviors^{22,23} are moderately heritable. Recent findings that the genetic factors associated with cannabis use and those associated with depression are moderately correlated²⁰ further support the hypothesis that some component of the apparent comorbidity between cannabis dependence and depressive and suicidal behaviors may be due to shared or correlated genetic vulnerabilities.

One approach to addressing the issue of preexisting differences between those who are cannabis dependent and those who are not involves the use of a co-twin control design in which rates of depressive and suicidal behaviors are compared within twin pairs where 1 twin is cannabis dependent and the co-twin is not. In the case of dizygotic (DZ) twins raised together, these methods provide optimal control for shared environmental influences, while for monozygotic (MZ) twins, they provide control for both genetic and shared environmental factors.

Against this background, we report on a series of co-twin control analyses comparing rates of lifetime *DSM-IV* major depressive disorder (MDD) and suicidal thoughts and behaviors in same-sex twin pairs discordant for (1) lifetime cannabis dependence and (2) the early initiation of cannabis use (prior to age 17 years). Additionally, we conducted a series of co-twin control analyses comparing rates of cannabis dependence in twin pairs discordant for MDD and suicidal ideation before age 17 years.

METHODS

Interviewees were members of the young adult cohort of the Australian Twin Register, a volunteer twin panel, born 1964 through 1971.^{18,24} Nearly all were first registered with the panel between

1980 and 1982 by their parents in response to approaches either through Australian school systems or via mass media appeals. The data presented in this report are derived from responses to a single telephone interview during the period 1996 through 2000 when the median age of the sample was 30 years (range, 24-36 years). Informed consent was obtained from participants prior to administering the interviews, as approved by the institutional review boards of Washington University School of Medicine, St Louis, Mo, and the Queensland Institute of Medical Research, Brisbane, Queensland, Australia.

Of 4010 pairs that could be traced, interviews were completed with both members of 2765 pairs (69% pairwise response rate) and 1 member of another 735 (78% individual response rate). The analyses in this article are based on 4 subsets of the sample:

1. Same-sex twin pairs discordant for cannabis dependence: Individuals reporting using cannabis at least monthly were questioned, using items from the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA),²⁵ about whether they had experienced symptoms of cannabis dependence (using more frequently/for longer periods than intended; needing larger amounts to achieve an effect [tolerance]; continued use despite use causing emotional problems; recurrent desire to cut down on use). Those reporting 2 or more of these criteria were classified as meeting lifetime criteria for cannabis dependence. While this measure did not provide formal *DSM-IV*²⁶ criteria, previous analyses exploring the validity of these modified criteria indicated that they had both excellent sensitivity (96.7%) and specificity (94.6%) when compared with *DSM-IV* criteria.¹⁸ Eleven percent of the sample (418 men [15.1%] and 269 women [7.8%]) met these criteria for lifetime cannabis dependence, and 277 (40.2%) of these were from same-sex pairs discordant for cannabis dependence. This subset of 277 twin pairs (70 female MZ pairs, 67 male MZ pairs, 55 female DZ pairs, and 85 male DZ pairs) was used in the current analyses.

2. Same-sex twin pairs discordant for early cannabis use: 863 (13.8%) members of the sample reported initiating cannabis use before age 17 years.²⁷ Three hundred eleven (36.1%) of these were from same-sex twin pairs in which their co-twin had not used cannabis by age 17 years. This subset of the sample (74 female and 62 male MZ pairs; 84 female and 91 male DZ pairs) was used in a second set of analyses.

3. Same-sex twin pairs discordant for early MDD: The SSAGA,²⁵ modified for telephone administration, was used to collect information on full *DSM-IV* criteria for MDD, including age of onset. Two hundred seventy-four members of the sample (4.4%) reported onset of MDD before age 17 years. One hundred fifty-six (56.9%) of these were from same-sex twin pairs in which their co-twin did not meet criteria for MDD before age 17 years. This subset of the sample included 63 female and 38 male MZ pairs and 24 female and 31 male DZ pairs.

4. Same-sex twin pairs discordant for early suicidal ideation: Four hundred seventy-seven members of the sample (7.6%) reported suicidal ideation before age 17 years. Two hundred fifty-seven (53.9%) of these were from same-sex twin pairs in which their co-twin did not report experiencing suicidal ideation before age 17 years. This subset of the sample included 80 female and 54 male MZ pairs and 68 female and 55 male DZ pairs.

ASSESSMENTS

A structured diagnostic interview designed for genetic studies on alcoholism, the SSAGA,²⁵ was adapted for telephone use with an Australian sample and updated for *DSM-IV* diagnostic criteria.²⁶ The interview also included assessments of sociodemo-

Table 1. Major Depressive Disorder, Suicidal Ideation, and Attempted Suicide in 277 Twin Pairs Discordant for Cannabis Dependence*

	Lifetime Prevalence		Unadjusted Conditional OR (95% CI)	Conditional OR Adjusted for Covariates†	
	Cannabis-Dependent Users	Co-twins		OR (95% CI)	Significant Covariates
Major depressive disorder					
Monozygotic twins	39.4 (54)	35.8 (49)	1.25 (0.69-2.25)	1.16 (0.64-2.17)	1
Dizygotic twins	49.3 (69)	23.6 (33)	3.40 (1.91-6.05)	3.40 (1.91-6.05)	...
Suicidal ideation	50.5 (140)	30.3 (84)	3.43 (2.16-5.46)	2.89 (1.76-4.76)	1,2
Attempted suicide	13.0 (36)	5.1 (14)	3.44 (1.64-7.23)	2.53 (1.12-5.67)	1

Abbreviations: CI, confidence interval; OR, odds ratio.

*Values are presented as percentage (number) of cases unless otherwise indicated.

†1, Alcohol dependence; 2, childhood sexual abuse. Other covariates examined were conduct disorder and nicotine dependence, but neither were significant predictors.

graphic factors, childhood family environment, and experiencing childhood sexual abuse.²⁴ These measures are described next.

Measures of DSM-IV MDD, Suicidal Ideation, and Attempted Suicide

The modified SSAGA collected information on full DSM-IV criteria for MDD as well as separate information on whether subjects had ever contemplated or attempted suicide. Information on age at onset of these conditions was also collected.

Family, Social, and Individual Factors

A number of control variables were included in the analyses.

1. Psychiatric disorders: DSM-IV²⁶ conduct disorder, alcohol dependence, and nicotine dependence were assessed using the modified SSAGA, and diagnoses were assigned by computer algorithm.

2. Early tobacco use: Subjects who reported smoking at least 1 day a week for a period of 3 weeks or more before age 17 years were classified as early tobacco users.

3. Early regular alcohol use: Subjects who reported that they started drinking alcohol at least once a month for a period of 6 months or more before age 17 years were classified as early regular alcohol drinkers.

4. Childhood sexual abuse: Respondents were also asked a series of questions concerning their exposure to unwanted sexual contact, sexual molestation, or rape. A composite measure was constructed, which classified respondents who reported any such experiences before the age of 18 years as having a history of childhood sexual abuse.²⁴

STATISTICAL ANALYSES

All statistical analyses were conducted using Stata.²⁸ Conditional logistic regression models were fitted to test for excess risk of MDD, suicidal ideation, and suicide attempt in (1) individuals meeting criteria for cannabis dependence and (2) individuals who commenced cannabis use before age 17 years. Further models tested for excess of cannabis dependence in (1) individuals meeting DSM-IV criteria for MDD before age 17 years and (2) individuals reporting suicidal ideation before age 17 years. The significance of the interactions between exposure (cannabis dependence, early measures of early cannabis use, early MDD, and early suicidal ideation) and both twin pair zygosity and sex was tested and, when non-significant, data were pooled across zygosity and across sex. Analy-

ses were repeated including the control variables described earlier. For analyses of early-onset cannabis use, information on onset and duration were included so that only those reporting experiencing an episode of MDD or contemplating/attempting suicide after age 17 years were classified as positive for those outcomes. Additionally, in these analyses, corresponding measures of MDD and contemplated/attempted suicide before age 17 years were included as potential covariates in the conditional logistic regression analyses. Stepwise regression with backward selection was conducted with the measure of either cannabis dependence or early cannabis use forced into the model. Hence, for models in which there were no significant covariates, the unadjusted and adjusted odds ratios are identical.

Finally, a series of bivariate genetic Cholesky models were fitted to the data on both onset of cannabis use and lifetime cannabis dependence and risks of MDD to assess the extent of correlation between genetic influences associated with cannabis use and those associated with MDD. These models were fitted to the data using the program Mx,²⁹ using the method of maximum likelihood estimation.

Power was estimated using the conditional logistic model, using parameters derived from our sample. Our results indicated that power would be 80% or better for an odds ratio (OR) higher than approximately 1.9 for the analyses of cannabis dependence and depression, ORs higher than approximately 2.4 for cannabis dependence and suicidal ideation, and ORs higher than approximately 2.8 for cannabis dependence and attempted suicide. When early cannabis use was used as the exposure variable, power was 80% or better for ORs of approximately 1.3 or higher with depression, ORs of approximately 1.6 or higher with suicidal ideation, and ORs of 2.8 or better with suicide attempt. Power was more than 80% for ORs higher than approximately 2.2 for the analyses of early suicidal ideation and for ORs higher than approximately 2.4 for the analyses of early depression.

RESULTS

ASSOCIATIONS BETWEEN CANNABIS DEPENDENCE AND DSM-IV MDD, SUICIDAL IDEATION, AND ATTEMPTED SUICIDE

Table 1 presents estimates of the lifetime prevalence (percentage) of MDD, suicidal ideation, and attempted suicide for those meeting lifetime criteria for cannabis dependence and for their co-twins who did not meet these

Table 2. Major Depressive Disorder, Suicidal Ideation, and Attempted Suicide in 311 Twin Pairs Discordant for Cannabis Use Before Age 17 Years*

	Lifetime Prevalence		Unadjusted Conditional OR (95% CI)	Conditional OR Adjusted for Covariates†	
	Early Cannabis Users (%)	Co-twins (%)		OR (95% CI)	Significant Covariates
Major depressive disorder					
Monozygotic twins	30.9 (42)	33.8 (46)	0.86 (0.50-1.48)	0.86 (0.50-1.48)	...
Dizygotic twins	39.4 (69)	28.0 (49)	1.69 (1.07-2.67)	1.14 (0.66-1.97)	1,3,5
Suicidal ideation	41.8 (117)	31.2 (87)	1.73 (1.18-2.54)	1.10 (0.70-1.73)	2,3,6
Attempted suicide	8.4 (31)	3.9 (12)	3.38 (1.53-7.43)	3.49 (1.42-8.58)	1

Abbreviations: CI, confidence interval; OR, odds ratio.

*Values are expressed as percentage (number) of cases unless otherwise indicated.

†1, conduct disorder; 2, childhood sexual abuse; 3, early regular tobacco use; 4, early regular alcohol use; 5, major depression (<17 y); suicidal ideation (<17 y).

criteria. The strength of the association between cannabis dependence and these outcomes was assessed using the conditional OR, both before and after control, for a range of measured covariates. For MDD, these estimates are shown separately for MZ and DZ twin pairs, because there was evidence of a significant ($P < .05$) interaction between zygosity and cannabis dependence. However, for the remaining 2 measures, these interactions were nonsignificant ($P > .20$) and data were therefore pooled across zygosity. The results in Table 1 show:

1. Relative to their nondependent co-twins, those who met criteria for cannabis dependence had elevated lifetime rates of MDD, suicidal ideation, and attempted suicide. The unadjusted conditional ORs indicated that, in individuals who were cannabis dependent, the odds of MDD, suicidal ideation, and attempted suicide were 1.3 to 3.4 times higher than in their co-twins who were not cannabis dependent. Importantly, there was evidence that cannabis dependence was associated with increased risks of MDD in DZ twin pairs discordant for cannabis dependence but not in MZ twins.

2. After further controlling for known risk factors associated with increased risk of MDD, suicidal ideation, and attempted suicide, rates of these outcomes were still significantly elevated in individuals meeting criteria for cannabis dependence.

ASSOCIATIONS BETWEEN EARLY CANNABIS USE AND SUBSEQUENT MDD, SUICIDAL IDEATION, AND ATTEMPTED SUICIDE

The results of analyses comparing rates of MDD, suicidal ideation, and attempted suicide (all required to have onset after age 16 years) in twin pairs discordant for initiation of cannabis use before age 17 years are summarized in **Table 2**. Again, there was a significant interaction between early cannabis use and zygosity for risk of MDD (but not for risks of either suicidal ideation or attempt), and therefore, data are presented separately by zygosity for this outcome. The results in Table 2 show:

1. Relative to their co-twins who had not used cannabis by age 17 years, those who had used cannabis by this age had significantly elevated rates of both suicidal ideation and suicide attempt. However, in the case of MDD, this association was significant only for discordant DZ pairs.

2. Controlling for known risk factors substantially reduced these associations. After such control, there was no significant association between early cannabis use and either MDD or suicidal ideation. However, compared with nonearly users, those who initiated cannabis use before age 17 years had 3.5 times the odds of reporting a subsequent suicide attempt.

BIVARIATE GENETIC MODEL FITTING

Application of techniques of genetic model fitting confirmed the key findings of these analyses; there were significant correlations with risks of MDD with genetic liability for age of onset of cannabis use (men, $r = 0.23$ [95% confidence interval (CI), 0.05-0.43]; women, $r = 0.35$ [95% CI, 0.18-0.57]) and lifetime cannabis dependence (men, $r = 0.44$ [95% CI, 0.17-1.00]; women, $r = 0.69$ [95% CI, 0.30-1.00]), confirming that a significant component of the comorbidity between cannabis use and MDD arose from the influence of shared or correlated genetic liabilities.

ASSOCIATIONS BETWEEN EARLY MDD, SUICIDAL IDEATION, AND SUBSEQUENT CANNABIS DEPENDENCE

Table 3 compares rates of lifetime cannabis dependence between members of twin pairs discordant for early MDD or for early suicidal ideation. Comparisons are shown separately for MZ and DZ twin pairs because the interaction between zygosity and early internalizing for risk of cannabis dependence was significant for MDD ($P < .05$) and marginally significant for suicidal ideation ($P < .10$).

Relative to their co-twins who did not report MDD or suicidal ideation before age 17 years, rates of cannabis dependence were significantly elevated in (1) DZ twins who met *DSM-IV* criteria for MDD before age 17 years (OR, 9.5 [95% CI, 2.21-40.78]) and (2) DZ twins who reported suicidal ideation before age 17 years (OR, 5.5 [95% CI, 1.90-15.96]). In contrast, there were no significant differences in rates of cannabis dependence in MZ twins discordant for either early MDD or early suicidal ideation.

Analyses including statistical control for observed covariates are not reported herein, because once the ef-

Table 3. Cannabis Dependence in Twin Pairs Discordant for Major Depressive Disorder (n = 156 Pairs) and Suicidal Ideation (n = 257 Pairs) Before Age 17 Years*

	No. of Pairs	% (No.) of Cannabis-Dependent Cases		Unadjusted Conditional OR (95% CI)
		Exposed	Not Exposed	
Major depressive disorder				
Monozygotic twins	87	19.5 (17)	16.1 (14)	1.38 (0.55-3.42)
Dizygotic twins	69	31.9 (22)	7.2 (5)	9.50 (2.21-40.78)
Suicidal ideation				
Monozygotic twins	134	18.7 (25)	13.4 (18)	1.78 (0.79-4.02)
Dizygotic twins	123	21.1 (26)	6.5 (8)	5.50 (1.90-15.96)

Abbreviations: CI, confidence interval; OR, odds ratio.

*Once early-onset depression and suicidal ideation were controlled for, no significant covariate effects were observed.

fects of internalizing problems were taken into account, there were no statistically significant associations between these measures and later risks of cannabis dependence. Therefore, the addition of these covariates did not materially influence our conclusions.

COMMENT

Results of our co-twin control analyses indicated a moderate degree of comorbidity between cannabis dependence and measures of mental health: individuals who met lifetime criteria for cannabis dependence had odds of MDD, suicidal ideation, and attempted suicide that were 1.3 to 3.4 times higher than their non-cannabis-dependent co-twins. These results are consistent with previous findings that rates of depressive and suicidal behaviors are elevated in those who meet criteria for cannabis dependence.⁹⁻¹¹ Importantly, however, there was evidence that a substantial component of the association between cannabis dependence and MDD could be attributed to shared genetic vulnerabilities. Specifically, the finding of a significant interaction between zygosity and cannabis dependence on risks of MDD, with cannabis dependence being associated with significantly elevated risks of MDD (relative to their non-cannabis-dependent co-twin) in DZ but not in MZ twins, implies that shared or correlated genetic vulnerabilities make substantial contributions to the comorbidity between cannabis dependence and MDD. In contrast, the finding of no significant interaction between zygosity and either early-onset cannabis use or lifetime cannabis use on risks of suicidal behaviors implies that genetic influences are relatively less important in explaining the observed associations between these sets of behaviors.

Further analyses indicated that individuals who initiated cannabis use before age 17 years were at increased risk of subsequently attempting suicide, but there was no association between early cannabis use and subsequent measures of either MDD or suicidal ideation. These results provide only limited support for the hypothesis that early cannabis use is a risk factor for the subsequent development of MDD and suicidal behaviors, as has been reported by a number of previous studies.¹²⁻¹⁶ The apparent discrepancy between our results and previous results may be partially due to the fact that, by

using co-twin control methods, we were able to provide more effective control for background predisposing factors (both genetic and shared environmental) than had previously been attained. Indeed, the finding of a significant interaction between early cannabis use and later risks of MDD again suggests that a substantial component of this association may be due to shared genetic vulnerabilities. While our results are consistent with the hypothesis that early cannabis use increases risks for subsequent suicide attempt, we cannot exclude the possibility that both these outcomes result from aspects of the nonshared environment that were not controlled in our analyses. In addition to the pharmacological effects of cannabis, there are a number of other potential mechanisms that may underlie any association between cannabis use and risks of suicidal behaviors. In particular, the social context within which cannabis is used and obtained may also promote access to other drugs²⁷ and a range of life events and circumstances, including risks of legal sanctions against possession and use of cannabis,³⁰ that may predispose cannabis users to suicidal behaviors.

Finally, we found that early-onset MDD and early-onset suicidal ideation were both associated with increased risks for the development of cannabis dependence in DZ twins but not in MZ twins from discordant pairs. These results qualify recent reports that early internalizing behaviors are not associated with increased risks for cannabis dependence^{2,14,16} by indicating that there may indeed be an association, albeit one that is largely explained by common genetic, as opposed to environmental, factors predisposing to both outcomes. Again, this result is consistent with recent evidence of a moderate overlap in the heritable factors associated with cannabis dependence and those associated with MDD.²⁰

These analyses also identified a range of other risk factors, including childhood conduct disorder, exposure to childhood sexual abuse, and early substance use, that were associated with increased risks for the development of MDD and suicidal behaviors. These findings are consistent with an accumulating literature demonstrating the effect of these factors on risks for psychopathology^{31,32} and highlighting that end points such as suicide attempt or MDD are often the outcomes of a life path characterized by multiple disadvantages and dysfunction in

which a range of adverse exposures, which by themselves increase risks only slightly, accumulate to increase risks substantially.³³⁻³⁶

By quantifying the extent to which associations between both early-onset cannabis use/dependence and measures of MDD, suicidal ideation, and suicide attempt can largely be explained by common genetic and/or environmental risk factors, our analyses highlight that the development of these behaviors is intertwined. It therefore appears likely that risk-factor based interventions may have benefits in reducing risks of a range of outcomes.^{32,37} However, while our results indicate that comorbidity between these disorders largely arises from the influence of multiple risk factors on both sets of outcomes, it remains possible that continued cannabis use may exacerbate the prognosis for those with existing depression and other conditions. Although this issue has received relatively little attention, there is a parallel literature indicating that continuing cannabis use may exacerbate the clinical course of those diagnosed with psychosis.^{38,39}

In interpreting these results, a number of potential limitations should be considered. First, the sample was based on a volunteer sample of twins, and the nature of this sample may potentially have introduced some selection biases into the sample. Nonetheless, based both on relatively high recruitment and retention rates and on previous comparisons with characteristics of the Australian population, we are confident that any biases introduced by the volunteer nature of the sample would be slight. Second, we have relied on the use of cross-sectional data and retrospective reports of lifetime behaviors, including age of onset for different behaviors. Finally, our measure of early-onset use did not take into account the frequency of early use, and it is possible that increased risks for the development of MDD and other problems may occur only in those who use cannabis frequently at young ages. Indeed, there is some evidence to support this conjecture to the extent that previous research has demonstrated a dose-response relationship between the frequency of early cannabis use and risks for mental health problems.¹² While we have not been able to address this issue fully, the current analyses do address a pivotal issue in public policy: the extent to which early-onset cannabis use is associated with increased risks and, concomitant with this, the extent to which delaying the onset of cannabis use may decrease subsequent risks. While acknowledging these potential limitations, our results highlight that early cannabis use—or lifetime cannabis dependence—constitutes only one of many potential risk factors predisposing to MDD and suicidal behaviors.

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