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# Major Depressive Disorder, Suicidal Thoughts and Behaviors, and Cannabis involvement in Discordant Twins: a Retrospective Cohort Study

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## Abstract

**Background—**Early-onset and frequent cannabis use are associated with an increased likelihood of major depressive disorder (MDD) as well as suicidal thoughts and behaviours. We identify associations between aspects of cannabis use and MDD as well as suicidal thoughts and behaviours and examine whether such associations persist after accounting for those predisposing factors, including genetic liability and early family environment, that are shared by identical twins who are discordant for cannabis exposure. Any residual association in such identical pairs might be indicative of individual – specific pathways that may be of a causal nature.

**Methods—**We did a logistic regression analysis of cannabis use from retrospective data on same-sex male and female twin pairs drawn from 3 studies that had recruited twins from the Australian Twin Registry, 1992–93 (sample 1), 1996–2000 (sample 2), and 2005–09 (sample 3). We studied associations between early use and frequent use of cannabis and MDD, suicidal ideation (ever and persistent), and suicide plan and attempt in the full sample as well as in pairs of monozygotic and dizygotic twins that were discordant for each measure of cannabis involvement at a single



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**Author contributions**

AA and MTL conceived the study; AA and RT conducted all analyses; AA was responsible for writing. ECN, KKB, MTL, RAG, DJS and ACH provided expertise on the analytic model, choice of outcomes and covariates; PAFM, DJS, NGM, ACH and MTL developed instruments, collected, processed, coded and harmonized all data.

**Declaration of interests**

Nothing to declare.

**Ethics committee approval**

Research outlined in this study was approved by the Institutional review Board at Washington University School of Medicine.

timepoint. Significant monozygotic associations were further adjusted for covariates, such as early alcohol or nicotine use, early dysphoric or anhedonic mood, conduct disorder, and childhood sexual abuse. Interactions between each cannabis measure and sex, sample or study effects, and birth year category were also examined as covariates.

**Findings—**In 13 986 twins (6181 monozygotic and 7805 dizygotic), cannabis use ranged from 1345 (30·4%) of 4432 people in sample 1 to 2275 (69·0%) of 3299 in sample 3. Mean age of first cannabis use ranged from 17·9 years (SD 3·3) in sample 3 to 21·1 years in sample 1, and frequent use (≥100 times) was reported by 214 (4·9%) people in sample 1 and 499 (15·2%) in sample 3. The prevalence of suicidal ideation ranged from 1102 (24·9%) in sample 1 to 1644 (26·3%) of 6255 people in sample 2 and 865 (26·2%) people in sample 3. Prevalence of MDD ranged from 901 (20·3%) people in sample 1 to 1773 (28·5%) people in sample 2. The monozygotic twin who used cannabis frequently was more likely to report MDD (odds ratio 1·98, 95% CI 1·11–3·53) and suicidal ideation (2·47, 1·19–5·10) compared with their identical twin who had used cannabis less frequently, even after adjustment for covariates. For early cannabis use, the monozygotic point estimate was not significant but could be equated to the significant dizygotic estimate, suggesting a possible association with suicidal ideation.

**Interpretation—**The increased likelihood of MDD and suicidal ideation in frequent cannabis users cannot be solely attributed to common predisposing factors.

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## INTRODUCTION

Cannabis use has been linked to both major depressive disorder (MDD) and suicidal thoughts and behaviours.[1] Daily cannabis use, especially during adolescence, was associated with a 6·8 odds of suicide attempt.[2] In a 30 – year longitudinal study, even weekly cannabis use was linked to onset of suicidal ideation, particularly in males, and the association largely persisted after controlling for the confounding effects of a variety of sociodemographic and mental health characteristics and familial risk factors.[3] MDD is partially correlated with suicidal thoughts and behaviors. However, associations between cannabis use and MDD are weaker than those noted for suicidal thoughts and behaviours[7] and often, have not survived covariate correction. [2]

One approach to understanding the nature of the relationship of cannabis use with MDD and suicidal thoughts and behaviours is to study monozygotic (MZ) twins reared together who are discordant for cannabis use. Cannabis use ($h^2$ = 50 – 60%), MDD ($h^2$ = 30 – 40%) and suicidal thoughts and behaviours ($h^2$ = 40 – 45%) are heritable.[9–13] MZ twins typically share all their segregating loci identical-by-descent and are also highly likely to share early familial influences. Therefore, if the twins who use cannabis show an increased likelihood of MDD or suicidal thoughts and behaviours, relative to their co-twins who do not use cannabis this residual association may be viewed as evidence supporting person – specific factors, and putatively, causal mechanisms. While cross-sectional discordant twin data cannot prove causality, the absence of an association in discordant twin pairs might be viewed as evidence against causal mechanisms. In one such study, we showed that relative to their co-twin, the cannabis dependent twin was at 3·4 conditional odds of reporting suicidal ideation and

attempts.[14] A similarly significant association was noted for suicide attempts when discordance for early cannabis use was examined.[14] Thus, some of the relationship between cannabis use and suicidal thoughts and behaviours is attributable to those predisposing factors that are shared by twin pairs; and even after accounting for those influences, cannabis dependence resulted in an increase in likelihood of suicidal thoughts and behaviours. In contrast, increased likelihood of MDD was noted in DZ but not MZ twin pairs that were discordant for cannabis dependence, suggesting that common genetic influences could alone be implicated in this association.[14]

In this study, we incorporate data from additional twin datasets (N=13,986 for current study, vs. 6,257 for prior study) resulting in substantially greater numbers of discordant MZ pairs and we examine additional aspects of cannabis use as well as suicidal thoughts and behaviours. The goals of the present study were to examine whether: (a) a lifetime history of cannabis use as well as early – onset use and frequent use was associated with MDD, suicidal ideation, persistent ideation, ideation with a plan and, suicide attempt; (b) any significant associations that were observed in the full sample of twins persisted when twin pairs discordant for each cannabis measure were examined; and (c) associations within pairs of twins persisted after accounting for additional covariates that might have contributed to discordance in cannabis use and subsequently, to MDD and suicidal thoughts and behaviours.

## METHODS

### Samples

Data on same – sex male and female twin pairs were drawn from 3 studies that recruited twins from the Australian Twin Registry.[15] **Sample 1 (n = 5,995)**: In 1992 – 1993, MZ and DZ twins aged 24 – 90 years (born between 1902 and 1964) who had participated in either a prior alcohol challenge study[16] or where at least one twin had participated in a survey conducted in 1989[17] were invited to participate in a short telephone interview, which included items on cannabis use, age of onset, frequency of use, suicidal thoughts and behaviours.[18] As the prevalence of cannabis use was extremely low in those born between 1902 and 1940 (n=1,414; Supplemental Table S1), these individuals were excluded from analyses. **Sample 2 (n = 6,257)**: Twins born between 1964 and 1971 who were initially recruited through the Australian school systems and mass media appeals were interviewed by telephone, from 1996–2000, when they were aged 24–36 years. This sample was used in the earlier discordant twin analysis.[19] **Sample 3 (n = 3,348)**: Twins born between 1972–1979 and aged 27 to 32 years when they were first interviewed in 2005–2009. [20] After exclusions for missing data, **13,986** twin individuals were available for analysis. MZ and same-sex DZ twin pairs were selected from this sample.

### Assessments

Respondents in each of the three twin studies were queried using versions of the Australian Semi-Structured Assessment for the Genetics of Alcoholism.[18, 21]. All three interviews included identical assessments of cannabis use and suicidal thoughts and behaviours, and highly comparable measures of all covariates.

### Cannabis use

Respondents were asked whether they had ever used cannabis during their lifetime. Those who reported lifetime use were further queried about the age at which they had used cannabis for the first time and how many times they had used cannabis during their lifetime. Early use was coded as onset prior to age 18 years for twin sample 1 and prior to age 17 years for samples 2 and 3 – approximately the bottom quartile. Those who had used cannabis ≥ 100 times across their lifetime were designated as frequent users. Early and frequent use were examined within the pool of individuals who reported a lifetime history of cannabis use as well as in the full sample.

### Major Depressive Disorder

In samples 2 and 3, DSM-IV criteria were used to diagnose MDD.[22] Sample 1 assessed DSM-IIIR criteria and these were modified to define DSM-IV MDD. In samples 2 and 3, onset was conservatively assumed to occur when an individual reported experiencing recurring episodes of dysphoria (feeling depressed or down for most of the day for two weeks or longer) or anhedonia (lot less interested in most things for most of the day for two weeks or longer). In sample 1, age at onset of the most severe depressive episode was used. Across the samples, a subset of participants meeting criteria for MDD reported onset of dysphoric/anhedonia mood (or of the most severe episode, if sample 1) prior to onset of cannabis use (n=791). MDD diagnosis was set to missing in these individuals for analysis of MDD only.

### Suicidal Thoughts and Behaviours

All participants were asked if they had ever thought about taking their own life (suicidal ideation) and whether they had ever tried to take their own life (suicide attempt), regardless of ideation. In addition, those who reported ideation were also asked if they had experienced ideation for longer than a day (persistent ideation) and whether they had made a plan to take their own life (suicide plan). Individuals reporting suicidal ideation (n=868) or suicide attempt (n=140) prior to onset of cannabis use were uninformative and, thus, set to missing for analyses related to these outcomes only.

### Covariates

To control for factors that potentially preceded or coincided with the onset of cannabis use and might have been associated with it, we co-varied for (a) early alcohol use (< 17 years in sample 1; < 15 years in samples 2 and 3); (b) early tobacco smoking (< 17 years in sample 1; < 13 years in samples 2 and 3); (c) conduct disorder; (d) childhood sexual abuse, which was coded using a single common item on whether the respondent had been forced into sexual activity prior to age 18; and (e) for suicidal thoughts and behaviours, dysphoria or anhedonia prior to age 16 years. Different age cut-offs were used for sample 1 to account for secular trends. Analysis of the full sample was also adjusted for age, sex, twin sample and zygosity. Within discordant twin analyses, an interaction term reflecting whether pairs were drawn from same-sex male or female pairs was included to test for sex effects (e.g., cannabis*sex). A similar interaction term was used to test for sample (1 *vs.* 2 *vs.* 3;

cannabis*sample) as well as birth year (binned as 1941 – 1954, 1955 – 1964, 1965 – 1971, 1972 – 1979) differences.

### Statistical analyses

All primary analyses were conducted within SAS (v9). Logistic regression was used to examine the association between cannabis use and MDD as well as suicidal thoughts and behaviours in the full sample. First, we examined whether each measure of cannabis use was associated with MDD and each index of suicidal thoughts and behaviours (unadjusted odds–ratio, OR). We re-examined these associations while accounting for covariates (adjusted OR).

Those adjusted associations that were significant in the full sample were then examined within pairs of MZ and DZ same – sex twins that were discordant for each cannabis use measure. Conditional logistic regression was used for discordant twin (i.e., within – pair) analyses. Similar to the analyses in the full sample, an unadjusted OR was computed for the discordant MZ and DZ pairs. For each unadjusted association that was significantly greater than 1.0 within the discordant MZ pairs, an adjusted OR was further computed by accounting for only those covariates that were associated with within-pair discordance for the respective cannabis measure. Paired data were also re-analyzed using a bootstrapping approach in STATA (v7). A comparison of the unadjusted OR from the discordant DZ and MZ pairs, relative to the full sample, provided an estimate of the extent to which genetic and environmental factors contributed to the association. Evidence for individual-specific factors that might be causal was derived from an adjusted MZ OR > 1.0.

For associations that further survived covariate correction, we compared the prevalence of the corresponding MDD and suicidal thoughts and behaviours measure in discordant MZ pairs with its prevalence in MZ twin pairs that were concordant for cannabis use (e.g., both frequent users or both infrequent/never users). For instance, the prevalence of MDD was contrasted across twins from MZ pairs where (a) both twins used cannabis frequently, (b) neither twin used cannabis frequently, (c) one twin used cannabis frequently while (d) the other did not (i.e., members of discordant pairs).

### Role of funding source

The research was funded by the National Institute on Drug Abuse (NIDA) with additional support for aspects of data collection and personnel support from the National Institutes of Health (NIH) and the Australian National Health and Medical Research Council (NHMRC). The funders had no role in study design, data collection, data analysis and interpretation, or writing of the study. AA and RT had full access to all data. AA submitted the study for publication.

## RESULTS

After exclusions for missing data in all three sample sets, 13 986 twin individuals (6181 monozygotic and 7805 dizygotic, including opposite-sex) from Australian datasets acquired between 1992 and 2009 were available for analysis for cannabis use and MDD or suicidal thoughts and behaviours. Monozygotic and same-sex dizygotic twin pairs were selected

from this sample. Cannabis use was higher in samples 2 (3741 [59·8%] of 6255) and 3 (2275 [69·0%] of 3299) than in sample 1 (1345 [30·4%] of 4432; table 1). Mean age at onset of cannabis use was higher in sample 1 (21·1 years) but similar in sample 2 (18·9 years) and sample 3 (17·9 years; appendix pp 11–12). Within cannabis users, early and frequent use were correlated ($r$=0·46; appendix p 13), with 44% of early users also reporting frequent use of cannabis and 49% of frequent users also reporting use from a young age. The prevalence of suicidal thoughts and behaviours (without temporal ordering) was lower in sample 1 (1102 [24·9%] of 4432) than in sample 2 (1644 [26·3%] of 6255) and sample 3 (865 [26.2%] of 3299); sample 1 had the lowest prevalence of MDD (901 [20·3%] of 4432) and sample 2 had the highest (1773 [28·3%] of 6255). Similar to cannabis, the age at onset of both suicidal ideation and suicide attempt was higher in sample 1 (24·5 years) than in samples 2 (20·2 years) and sample 3 (20·1 years). MDD and suicidal ideation ($r$=0·55) as well as suicide attempt ($r$=0·52) were moderately correlated. Nearly all individuals (541 [99·5%] of 544) who reported suicide attempt also reported ideation.

After temporal ordering, cannabis use was associated with MDD and suicidal thoughts and behaviours; however, these associations were no longer significant after accounting for covariates (Supplemental Table S2). Thus, we did not examine cannabis use in discordant twin models. On the other hand, both early and frequent cannabis use were robustly associated with MDD and all aspects of suicidal thoughts and behaviours (adjusted ORs ranging from 1·28 to 2·38), even after adjustment for covariates. These significant associations persisted even when lifetime never users of cannabis were excluded from the analysis; for instance, those who reported using cannabis ≥ 100 times were twice as likely to report suicidal ideation and suicide attempt, relative to those who reported lifetime cannabis use, but less frequently. Overall, these analyses suggest that early and frequent cannabis use are associated with MDD and suicidal thoughts and behaviours, even after accounting for key confounders.

Within – pair associations (Table 3) between early cannabis use, MDD and suicidal thoughts and behaviours, in analyses with and without never users, were significant within DZ (OR range from 2·23 to 6·50), but not MZ (OR 1·17 – 2·00), pairs. This pattern of results is consistent with the role of shared genetic influences contributing to the relationship. In some instances (e.g., ideation), the DZ and MZ OR had overlapping confidence intervals, indicating equality of effect sizes, with the association potentially being non-significant in discordant MZ pairs due to marginally fewer discordant pairs.

Associations between frequent cannabis use and MDD, suicidal ideation and persistent ideation were significant within both DZ and MZ pairs and with similar effect sizes. There was no association with suicide attempt (p=0.07) and more conservative bootstrapped confidence intervals suggest imprecision in the point estimates (Supplemental Table S3). For instance, relative to their genetically identical co-twin who did not use cannabis as frequently, a MZ twin who reported using cannabis ≥ 100 times was at 1·72, 2·71 and 3·14 odds of meeting criteria for MDD and reporting suicide ideation and persistent ideation respectively. An MZ OR > 1 suggests that factors other than those shared by members of identical twin pairs (including the effect of segregating loci and early familial environment) contribute to the association. A significant association within discordant MZ pairs, thus, is

suggestive of individual-specific factors that may be causal. Furthermore, the magnitude of ORs within the DZ and MZ pairs were similar to each other and to associations observed in the full sample (Table 2).

Interactions between the cannabis exposure variable and sex, sample or birth year category were not significant. Discordance on frequent cannabis use was associated with conduct disorder alone (Supplemental Table S4). However, even after accounting for conduct disorder, frequent cannabis-using twins were at 2·35 – 2·47 odds of reporting suicidal ideation when compared to their genetically identical (MZ) co-twins who did not use cannabis so frequently or never used it at all (Table 4; Supplemental Table S5 for bootstrapped confidence intervals; see Supplemental Table S6 for all adjusted OR for unadjusted OR from Table 3). For MDD, the association in the subset of ever users was also robust to covariate adjustment with frequent users remaining at 1·98 odds of MDD when compared to their identical co-twin who used cannabis less frequently. These results indicated that individual-specific factors other than these covariates contribute to the association between frequent cannabis use and MDD and suicidal ideation (but not persistent ideation).

We compared the prevalence of MDD and suicidal ideation across twins drawn from pairs where both had used cannabis frequently (concordant exposed), neither had used it frequently (concordant unexposed) and twins from discordant pairs. The prevalence of MDD and suicidal ideation in concordant exposed twins was greater than in concordant unexposed twins (Table 5), suggesting a strong, main effect of frequent cannabis use on suicidal ideation. Consistent with the discordant twin analyses, the exposed twin from discordant pairs was more likely to report suicidal ideation and MDD than their identical but unexposed co-twin (Table 5). Importantly, while there was minimal effect of the co-twin's exposure status on an individual twin's report of suicidal ideation, the rate of MDD was slightly higher in unexposed twins from discordant than concordant pairs (Table 5).

We conducted post-hoc analyses to examine whether frequent cannabis use was associated with MDD and suicidal thoughts and behaviours that occurred prior to the onset of cannabis use. Despite large sample sizes (Supplemental Table S7), associations between frequent (as well as early and ever) cannabis use and MDD as well as suicidal thoughts and behaviours were inconsistent. For instance, when suicidal ideation occurred prior to the onset of cannabis use, frequent cannabis use was associated with 0.73 adjusted odds of ideation (Supplemental Table S7), whereas the corresponding OR for MDD was 1.40. Second, we tested whether our definition of "frequent" cannabis use as a dichotomous measure had influenced our primary findings. Both continuous and categorical measures of cannabis frequency were associated with MDD and suicidal thoughts and behaviours (Supplemental Table S8). We also defined discordant MZ pairs as twins who differed by at least 10 units in their frequency of use. Even within these discordant pairs, the twin who used cannabis more frequently was more likely to report suicidal ideation and MDD (Supplemental Table S9) than their co-twin who used it less often.

## DISCUSSION

In this study, frequent cannabis use was associated with MDD and suicidal thoughts and behaviours, even after controlling for confounders. When these associations were examined within identical twin pairs, frequent use remained associated with MDD and suicidal ideation, suggesting that factors beyond those shared by identical twins might contribute to the association. Analyses conducted in the smaller subset of cannabis users did not significantly differ, suggesting that risk for MDD and suicidal ideation in never and lighter users may be comparably low.

The similarity in the ORs across DZ and MZ twin pairs indicates that genetic factors play only a modest role in the association between cannabis involvement and MDD and suicidal thoughts and behaviours, even though prior studies with samples 2 and 3 suggested moderate genetic correlations.[5, 24] The importance of the present study lies in our ability to disentangle predisposing factors, related to genetic liability and early familial environment, from environmental factors that are individual - specific and might be causal. Twins reporting frequent cannabis use were more likely to report MDD and suicidal ideation when compared to their identical co – twin who either did not use cannabis or used it less frequently. Unadjusted and adjusted OR from the discordant pair analyses were similar to the full population, suggesting that the associations might be due to individual-specific factors, possibly, of a causal nature. These results are broadly consistent with, but more conservative than, our previous discordant twin study that used data from sample 2 and reported an association between early cannabis use and suicide attempt as well as between cannabis dependence and both ideation and attempt.[14] However, that study found no evidence for a residual association between MDD and early cannabis use or cannabis dependence in discordant MZ pairs. We see an identical null finding for early cannabis use but note that frequent use did increase liability to MDD in these pairs, perhaps due to the larger sample size.

Several mechanisms might explain the associations. Evidence from animal[8] and human studies[25] suggests that the endocannabinoid system may be critical in modulation of mood, especially in the context of stress. MDD and suicidal ideation were among the adverse side effects in clinical trials of the endocannabinoid receptor (CB1) inverse agonist.[26, 27] Frequent cannabis use may result in similar modifications in the endocannabinoid system and a corresponding increase in negative mood. The strong between (i.e., concordant frequent *vs.* concordant less frequent/never user MZ twins) and within – pair (i.e., frequent *vs.* less frequent/never user members of MZ discordant pairs) differences in rates of suicidal ideation as a function of frequent cannabis use imply that such a direct effect is plausible. For ideation, there was little evidence that the presence of an unexposed co-twin modified the likelihood of an individual’s liability to suicidal ideation, hinting at a potential direct biological effect of cannabis exposure. Alternatively, frequent cannabis use might lead to increased exposure to environmental factors (e.g., increased trauma exposure)[28] or outcomes (e.g., diminished life opportunities, other drug use)[2] that might also increase the likelihood of MDD and suicidal ideation. For MDD, the non-frequently using co – twins of frequent use twins were at a somewhat increased likelihood of reporting MDD than concordant never - use twins, suggesting that the environment related to the co-twin’s frequent cannabis use

might modify liability to MDD. Relatedly, we cannot discount the possibility that an unmeasured individual – specific factor (e.g., deviant peers, other traumas), is responsible for these associations in MZ pairs.

Causal inferences regarding the effects of frequent cannabis use on the subsequent onset of MDD and suicidal thoughts and behaviours cannot be drawn from these cross-sectional data. Even though we only included individuals with onset of MDD and suicidal thoughts and behaviours subsequent to onset of cannabis use, we might not have adequately accounted for confounders. However, post-hoc analyses found inconsistent associations when this temporal ordering was reversed. We have previously noted that cannabis use is negatively correlated with MDD and suicidal thoughts and behaviours that precede it.[30] Based on earlier examinations of the gateway theory, these results further support the importance of temporal ordering of onsets, and hint at causal pathways.[29]

A strength of the current study is that suicidal ideation and suicide attempt were assessed in all individuals, regardless of their MDD status. While suicidal thoughts and behaviours are a feature of MDD, they are also frequently viewed as distinct psychiatric entities that are related, in equal part, to the internalizing aspects of mood disorders as well as to externalizing behaviours (e.g., subtypes of suicide attempt that relate to impulsive aggression).[31–33] Possibly, suicidal thoughts and behaviours are an early index of a broader liability to emotion dysregulation with a subset of ideators progressing to MDD. Comparisons of MDD and suicidal ideation prevalence across less frequent/never users from concordant and discordant pairs also hint at potential differences (i.e., no effect of co-twin status for suicidal ideation). Therefore, the associations between frequent cannabis use, MDD and, suicidal thoughts and behaviours might reflect partially distinct etiological processes.

Our study has some limitations. First, our sample is restricted to Australians, and sample 1 was older and likely represents secular differences. To address this possibility, we excluded the earliest-born members of sample 1 (1902 – 1940; Supplemental Table S1). To demonstrate the generalizability of the discordant pair analyses, future studies should attempt to validate the model in independent datasets. Second, we were limited by the available cannabis – related variables in the data and could not test for discordance on other indices of cannabis use. Similarly, we were unable to look in a more nuanced fashion at sub – groups of individuals with suicidal ideation and suicide attempt (e.g., severity). Third, even though we only studied early-onset behaviours as covariates, some covariates may have occurred subsequent to the onset of cannabis use. In such cases, our covariate correction may be viewed as overly conservative. Fourth, it is possible that interactions between early and frequent use are more strongly related to MDD and suicidal thoughts and behaviours than either measure is alone. Studies of larger samples might be able to model such interaction effects within a discordant twin framework. Fifth, in order to create discordant pairs, we selected thresholds to represent “early” and “frequent” use. While our choice of age and frequency cut-offs might have influenced our estimates, results were consistent with post-hoc analyses of continuous discordance in frequency of use (Supplemental Table S9). Finally, even though our discordant MZ twin design is powerful in excluding possible causal explanations, it cannot be used to prove causation.

Based on these results, we are unable to exclude the possibility that frequent cannabis use might increase risks for MDD and suicidal ideation, independent of shared predisposing influences. While we cannot identify the nature of this increased vulnerability, such a persisting increase in likelihood of MDD and suicidal ideation in frequent cannabis users is important to consider, especially against the backdrop of evidence supporting a role of the endocannabinoid system in mood regulation. However, interventions aiming to curb cannabis use should form only one part of the broader strategies to reduce its mental health correlates. Risk and protective influences that encourage cannabis use in one individual but not their sibling can also exacerbate their liability to MDD or suicidal thoughts and behaviours, and the identification of such factors that generate discordance in cannabis use within twin pairs is of considerable importance.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Research in Context

### Evidence before this study

We searched PubMed (Jan 1 1990 – Feb 15 2017) using the search terms “cannabis”, “marijuana”, “depression”, “suicide”, “twin” with no language restrictions. While associations between early and heavy/frequent cannabis use and suicidal thoughts and behaviours are robust to adjustment for confounders, associations with Major Depressive Disorder (MDD) are neither as strong nor as independent. Rodent models also support the role of the endocannabinoid system in mood regulation. Cannabis involvement, MDD and suicidal thoughts and behaviours are heritable. One prior study found that cannabis dependent individuals were more likely to report suicidal thoughts and behaviours relative to their monozygotic (MZ) and dizygotic (DZ) co-twins who were not dependent on cannabis, while associations with MDD were only significant in DZ pairs. An association was also noted between suicide attempt and DZ as well as MZ twin discordance for early cannabis use. These results suggested that early and problem cannabis use may be related to MDD via genetic pathways alone while associations with suicidal thoughts and behaviours may be attributable to non-genetic, individual-specific environmental factors, which could be of a causal nature.

### Added value of this study

To our knowledge, this is the largest twin study of cannabis, MDD and suicidal thoughts and behaviours. Using a substantially larger cohort of twins (n=13,986), we found that even within MZ pairs, twins who used cannabis ≥ 100 times were significantly more likely to meet criteria for MDD and to report suicidal ideation, when compared to their genetically identical co-twin who either never used cannabis or used it less frequently, even after accounting for covariates. We also show that ever using cannabis is not as robustly associated with MDD and suicidal thoughts and behaviours as early or frequent use.

### Implications of all available evidence

Given the well-documented role of endocannabinoid signaling in mood regulation, and the present results, a causal role of frequent cannabis use on MDD and suicidal ideation cannot be discounted. Preventing escalation in cannabis use may ameliorate a portion of the morbidity associated with these serious mental illnesses.

**Table 1**

Characteristics of 13,986 male and female twins from 3 Australian samples

| | Sample 1 (n=4432) | Sample 2 (n=6255) | Sample 3 (n=3299) | Total (n=13986) |
|---|---|---|---|---|
| Birth years | 1941–64 * | 1964–71 | 1972–79 | 1941–79 |
| Year interviewed | 1992–93 | 1996–2000 | 2005–09 | 1992–2009 |
| Sex | | | | |
| Male | 1615 (36·4%) | 2801 (44·8%) | 1157 (35·1%) | 5573 (39·8%) |
| Female | 2817 (63·5%) | 3454 (55·2%) | 2142 (64·9%) | 8413 (60·2%) |
| Mean age | 38·4 (6·2) | 29·9 (2·5) | 31·8 (2·5) | 33·1 (5·5) |
| Monozygotic twins | 2089 (47·1%) | 2636 (42·1%) | 1456 (44·1%) | 6181 (44·2%) |
| Opposite sex twins | 1067 (24·1%) | 1543 (24·7%) | 741 (22·5%) | 3351 (24·0%) |
| Cannabis use | | | | |
| Ever used cannabis | 1345 (30·4%, 29·0–31·7) | 3741 (59·8%, 58·6–61·0) | 2275 (69·0%, 67·4–70·5) | 7361 (52·6%, 51·8–53·5) |
| Early use #& | 286 (21·3%, (19·1–23·5) | 863 (23·1%, (21·7–24·4) | 857 (37·7%, 35·7–39·7) | 2006 (27·3%, 26·2–28·3) |
| Frequent use (≥100 times) & | 214 (15·9%, 14·0–17·9) | 1045 (27·9%, 26·5–29·4) | 499 (21·9%, 20·3–23·6) | 1758 (24·1%, 23·1–25·1) |
| Mean age at onset | 21·1 (5·2) | 18·9 (3·3) | 17·9 (3·3) | 19·0 (3·9) |
| Mean lifetime frequency of use | 92·4 (239·5) | 185·3 (341·3) | 138·3 (300·3) | 154·2 (314·7) |
| Major depressive disorder | | | | |
| Major depressive disorder prevalence | 901 (20·3%, 19·1–21·5) | 1773 (28·3%, 27·1–29·5) | 814 (24·7%, 23·2–26·1) | 3488 (24·9%, 24·3–25·7) |
| Mean age at onset $ | 31·0 (7·8) | 22·3 (5·5) | 22·8 (5·9) | 24·8 (7·4) |
| Suicidal thoughts and behaviours | | | | |
| Suicidal ideation | 1102 (24·9%, 23·6–26·1) | 1644 (26·3%, 25·2–27·4) | 865 (26·2%, 24·7–27·7) | 3611 (25·8%, 25·1–26·5) |
| Mean age at onset | 24·5 (8·8) | 20·2 (5·6) | 20·1 (6·0) | 21·5 (7·1) |
| Suicidal ideation (>1 day) | 402 (9·1%, 8·2–9·9) | 577 (9·2%, 8·5–9·9) | 331 (10·0%, 9·0–11·1) | 1310 (9·4%, 8·9–9·9) |
| Suicidal ideation with plan | 293 (6·6%, 5·9–7·3) | 451 (7·2%, 6·6–7·8) | 222 (6·7%, 5·9–7·6) | 966 (6·9%, 6·5–7·3) |
| Suicide attempt | 136 (3·1%, 2·6–3·6) | 260 (4·2%, 3·7–4·7) | 148 (4·5%, 3·8–5·2) | 544 (3·9%, 3·6–4·2) |
| Mean age at onset | 24·5 (9·2) | 19·4 (5·1) | 19·8 (5·9) | 20·8 (6·9) |

Data are n (%), mean (SD), or n (%, 95% CI).

* Participants born 1902–40 (n=1414) were excluded from analyses because the prevalence of cannabis use was <2% (appendix p 1).

[#]Early use was defined as first use before the age of 18 years in sample 1 and before the age of 17 years in samples 2 and 3.

[&]Percentages are given out of number of people who have ever used cannabis.

[$]Age of onset defined as age at which first experienced dysphoric or anhedonic mood in samples 2 and 3, and most severe episode in sample 1. Prevalence of major depressive disorder and suicidal thoughts and behaviours is presented without accounting for temporal orderings (ie, cannabis before outcomes or outcomes before cannabis). For the analyses of major depressive disorder, suicidal ideation, and suicide attempt, we excluded people who had onset of outcomes before onset of cannabis use (791 for major depressive disorder, 868 for suicidal ideation, and 140 for suicide attempt).

**Table 2**

Odds ratios (with 95% confidence intervals) representing association between aspects of cannabis use and suicidal thoughts and behaviours in full sample of 13,986 male and female twins from the Australian Twin Registry.

| | ***Cannabis ever use*** | | | |
|---|---|---|---|---|
| | **Unadjusted OR** | **Adjusted OR** | | |
| Major Depressive Disorder | 1·15 (1·06, 1·25) | 1·02 (0·93, 1·12) | | |
| Suicidal ideation | 1·26 (1·16, 1·37) | 1·08 (0·98, 1·19) | | |
| Suicidal ideation >1 day | 1·35 (1·19, 1·54) | 1·19 (1·02, 1·38) | | |
| Suicide plan | 1·34 (1·15, 1·56) | 1·11 (0·93, 1·33) | | |
| Suicide attempt | 1·76 (1·43, 2·16) | 1·13 (0·88, 1·44) | | |
| | ***Early Cannabis Use*** | | | |
| | In the full sample | | In the subsample of ever users (N = 7361) | |
| | Unadjusted OR | Adjusted OR | Unadjusted OR | Adjusted OR |
| Major Depressive Disorder | 1·52 (1·36, 1·69) | 1·28 (1·13, 1·45) | 1·50 (1·33, 1·70) | 1·33 (1·16, 1·53) |
| Suicidal ideation | 2·03 (1·82, 2·26) | 1·57 (1·38, 1·78) | 2·03 (1·79, 2·29) | 1·68 (1·46, 1·92) |
| Suicidal ideation >1 day | 2·08 (1·78, 2·43) | 1·55 (1·29, 1·87) | 2·01 (1·68, 2·40) | 1·63 (1·33, 2·00) |
| Suicide plan | 2·39 (2·01, 2·84) | 1·77 (1·44, 2·18) | 2·44 (2·00, 2·99) | 2·04 (1·62, 2·57) |
| Suicide attempt | 3·63 (2·94, 4·47) | 2·04 (1·58, 2·64) | 3·52 (2·74, 4·51) | 2·38 (1·78, 3·17) |
| | ***Frequent Cannabis Use (≥ 100 times)*** | | | |
| | In the full sample | | In the subsample of ever users (N = 7361) | |
| | Unadjusted OR | Adjusted OR | Unadjusted OR | Adjusted OR |
| Major Depressive Disorder | 1·74 (1·55, 1·95) | 1·53 (1·35, 1·73) | 1·74 (1·54, 1·97) | 1·60 (1·40, 1·83) |
| Suicidal ideation | 2·47 (2·20, 2·76) | 1·96 (1·73, 2·23) | 2·52 (2·22, 2·86) | 2·07 (1·81, 2·38) |
| Suicidal ideation >1 day | 2·27 (1·93, 2·66) | 1·69 (1·40, 2·03) | 2·19 (1·82, 2·62) | 1·68 (1·38, 2·05) |
| Suicide plan | 2·55 (2·13, 3·05) | 1·81 (1·47, 2·22) | 2·57 (2·10, 3·16) | 1·94 (1·55, 2·42) |
| Suicide attempt | 3·46 (2·78, 4·30) | 1·95 (1·51, 2·51) | 3·19 (2·49, 4·10) | 2·12 (1·61, 2·80) |

Adjusted for sex, age, cohort, alcohol use ≤16 (cohort 1) or ≤14 (cohorts 2, 3), nicotine use ≤16 (cohort 1) or ≤12 (cohorts 2, 3), MZ, opposite sex DZ, conduct, depressed mood or anhedonia ≤15 (not for MDD), childhood sexual abuse

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**Table 3**

Unadjusted odds ratios and 95% confidence intervals reflecting unadjusted within-pair associations between aspects of cannabis use and suicidal thoughts and behaviours, separately, in discordant monozygotic and dizygotic same-sex twin pairs.

| | **Discordant for Early Cannabis Use (Co – twin is never or later – onset user)** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **DZ** | | | | | **MZ** | | | | |
| **Dependent Variable** | **OR** | **95% CI** | **$\chi^2$** | **p** | **N pairs** | **OR** | **95% CI** | **$\chi^2$** | **p** | **N pairs** |
| Major Depressive Disorder | 1·816# | (1·22, 2·70) | 8·72 | 0·0031 | 293 | 1·344# | (0·85, 2·12) | 1·60 | 0·2057 | 260 |
| Suicidal ideation | 2·233# | (1·45, 3·44) | 13·38 | 0·0003 | 271 | 1·500# | (0·91, 2·46) | 2·56 | 0·1093 | 241 |
| Suicidal ideation lasting >1 day | 4·000 | (1·93, 8·30) | 13·84 | 0·0002 | 271 | 1·667 | (0·82, 3·41) | 1·96 | 0·1618 | 241 |
| Suicide plan | 2·800 | (1·36, 5·76) | 7·81 | 0·0052 | 271 | 1·167 | (0·54, 2·52) | 0·15 | 0·6952 | 241 |
| Suicide attempt | 6·500 | (2·27, 18·62) | 12·15 | 0·0005 | 316 | 1·900 | (0·88, 4·09) | 2·70 | 0·1004 | 278 |
| | **Discordant for Early Cannabis Use (co-twin is later – onset user)** | | | | | | | | | |
| | DZ | | | | | MZ | | | | |
| **Dependent Variable** | **OR** | **95% CI** | **$\chi^2$** | **p** | **N pairs** | **OR** | **95% CI** | **$\chi^2$** | **p** | **N pairs** |
| Major Depressive Disorder | 1·467 | (0·92, 2·33) | 2·62 | 0·1058 | 194 | 1·545 | (0·90, 2·64) | 2·53 | 0·1116 | 194 |
| Suicidal ideation | 2·238# | (1·34, 3·74) | 9·42 | 0·0021 | 176 | 1·350# | (0·76, 2·41) | 1·03 | 0·3090 | 178 |
| Suicidal ideation lasting >1 day | 4·000 | (1·64, 9·79) | 9·22 | 0·0024 | 176 | 1·556 | (0·67, 3·59) | 1·07 | 0·3011 | 178 |
| Suicide plan | 2·125 | (0·92, 4·92) | 3·09 | 0·0787 | 176 | 1·444 | (0·62, 3·38) | 0·72 | 0·3964 | 178 |
| Suicide attempt | 5·333# | (1·55, 18·30) | 7·08 | 0·0078 | 214 | 2·000# | (0·75, 5·33) | 1·92 | 0·1657 | 209 |
| | **Discordant for Frequent (≥ 100 times; co – twin never user or lighter user)** | | | | | | | | | |
| | DZ | | | | | MZ | | | | |
| **Dependent Variable** | **OR** | **95% CI** | **$\chi^2$** | **p** | **N pairs** | **OR** | **95% CI** | **$\chi^2$** | **p** | **N pairs** |
| Major Depressive Disorder | 2·115# | (1·33, 3·37) | 9·91 | 0·0016 | 252 | 1·720# | (1·05, 2·82) | 4·65 | 0·0311 | 199 |
| Suicidal ideation | 2·630# | (1·69, 4·10) | 18·29 | <0·0001 | 241 | 2·714# | (1·47, 5·01) | 10·20 | 0·0014 | 190 |
| Suicidal ideation lasting >1 day | 3·500# | (1·60, 7·68) | 9·77 | 0·0018 | 241 | 3·143# | (1·34, 7·36) | 6·96 | 0·0083 | 190 |
| Suicide plan | 1·636 | (0·77, 3·47) | 1·66 | 0·1982 | 241 | 2·143 | (0·87, 5·26) | 2·77 | 0·0959 | 190 |
| Suicide attempt | 4·400# | (1·67, 11·62) | 8·94 | 0·0028 | 276 | 2·286# | (0·94, 5·56) | 3·33 | 0·0681 | 225 |
| | **Discordant for Frequent (≥ 100 times; co – twin is lighter user)** | | | | | | | | | |

| | Discordant for Early Cannabis Use (Co – twin is never or later – onset user) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | DZ | | | | | MZ | | | | |
| **Dependent Variable** | **OR** | **95% CI** | **$\chi^2$** | **p** | **N pairs** | **OR** | **95% CI** | **$\chi^2$** | **p** | **N pairs** |
| | DZ | | | | | MZ | | | | |
| **Dependent Variable** | **OR** | **95% CI** | **$\chi^2$** | **p** | **N pairs** | **OR** | **95% CI** | **$\chi^2$** | **p** | **N pairs** |
| Major Depressive Disorder | 1·696# | (1·01, 2·84) | 4·03 | 0·0446 | 174 | 1·947# | (1·12, 3·39) | 5·58 | 0·0182 | 156 |
| Suicidal ideation | 2·842# | (1·69, 4·79) | 15·33 | <0·0001 | 165 | 2·909# | (1·47, 5·77) | 9·33 | 0·0022 | 147 |
| Suicidal ideation lasting >1 day | 4·000# | (1·50, 10·66) | 7·69 | 0·0056 | 165 | 3·600# | (1·34, 9·70) | 6·42 | 0·0113 | 147 |
| Suicide plan | 1·000 | (0·40, 2·52) | 0·00 | 1·0000 | 165 | 2·200 | (0·76, 6·33) | 2·14 | 0·1438 | 147 |
| Suicide attempt | 6·500# | (1·47, 28·80) | 6·07 | 0·0137 | 192 | 2·400# | (0·85, 6·81) | 2·71 | 0·1000 | 182 |

#The 95% Confidence Intervals for these estimates overlap indicating equality of effect sizes, despite p-values. Table S3 for bootstrapped CI.

**Table 4**

Adjusted odds ratios and 95% C.I. reflecting within-pair associations between cannabis use and suicidal thoughts and behaviours in MZ pairs. Only associations of discordant MZ pairs (Table 3) with significant unadjusted OR were reanalyzed with covariates*.

| | Discordant for Frequent (≥ 100 times; co – twin never user or lighter user) | | | | |
|---|---|---|---|---|---|
| **Dependent Variable** | **OR** | **95% CI** | **$\chi^2$** | **p** | **N pairs** |
| Major Depressive Disorder | 1·681 | (1·01, 2·80) | 4·00 | 0·0455 | 198 |
| Suicidal ideation | 2·354 | (1·24, 4·48) | 6·82 | 0·0090 | 190 |
| Suicidal ideation lasting >1 day | 2·238 | (0·89, 5·66) | 2·89 | 0·0889 | 190 |
| | **Discordant for Frequent (≥ 100 times; co – twin is lighter user)** | | | | |
| **Dependent Variable** | **OR** | **95% CI** | **$\chi^2$** | **p** | **N pairs** |
| Major Depressive Disorder | 1·976 | (1·11, 3·53) | 5·30 | 0·0213 | 156 |
| Suicidal ideation | 2·466 | (1·19, 5·10) | 5·94 | 0·0148 | 147 |
| Suicidal ideation lasting >1 day | 2·719 | (0·94, 7·85) | 3·42 | 0·0643 | 147 |

*Adjusted for conduct disorder (Table S4). Bootstrapped CI in Table S5.

**Table 5**

Prevalence (95% CI) of major depressive disorder (MDD) and suicidal ideation (SI) in monozygotic twins from pairs concordant for frequent cannabis use and less frequent/never use, as well as in the frequent user and never/less frequent using member of discordant pairs.

| **Twins from all MZ pairs** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Concordant** | | | **Discordant** | | | | | **Concordant** | | |
| | **Frequent** | | | **Frequent** | | **Less Frequent/Never** | | **N pairs** | **Less Frequent/Never** | | |
| | **%** | **95% CI** | **N pairs** | **%** | **95% CI** | **%** | **95% CI** | | **%** | **95% CI** | **N pairs** |
| Major Depressive Disorder | 32·042 | (26·6, 37·5) | 142 | 32·663 | (26·1, 39·2) | 23·618 | (17·7, 29·5)[a] | 199 | 19·682 | (18·5, 20·9)[a] | 2200 |
| Suicidal ideation | 40·000 | (34·0, 46·0) | 130 | 32·105 | (25·5, 38·7) | 19·474 | (13·8, 25·1) | 190 | 17·182 | (16·0, 18·3) | 2101 |
| Twins from MZ pairs reporting lifetime cannabis use | | | | | | | | | | | |
| | **Concordant** | | | **Discordant** | | | | | **Concordant** | | |
| | Frequent | | | Frequent | | Less Frequent | | N pairs | Less Frequent | | |
| | % | 95% CI | N pairs | % | 95% CI | % | 95% CI | | % | 95% CI | N pairs |
| Major Depressive Disorder | 32·042 | (26·6, 37·5) | 142 | 33·333 | (25·9, 40·7) | 21·795 | (15·3, 28·3)[a] | 156 | 18·037 | (15·9, 20·2)[a] | 596 |
| Suicidal ideation | 40·000 | (34·0, 46·0) | 130 | 32·653 | (25·1, 40·2) | 18·367 | (12·1, 24·6) | 147 | 16·730 | (14·5, 19·0) | 523 |

[a]The estimate for less frequent/never users from discordant pairs falls outside the 95% CI for the estimate from concordant pairs.