

Major depressive disorder, suicidal thoughts and behaviours, and cannabis involvement in discordant twins: a retrospective cohort study



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Summary

Background Early 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, MDD, and 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 might 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 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 (5.2) in sample 1, and frequent use (≥ 100 times) was reported by 214 (15.9%) of 1345 users in sample 1 and 499 (21.9%) of 2275 in sample 3. The prevalence of suicidal ideation ranged from 1102 (24.9%) of 4432 people in sample 1 to 1644 (26.3%) of 6255 people in sample 2 and 865 (26.2%) of 3299 people in sample 3. Prevalence of MDD ranged from 901 (20.3%) people in sample 1 to 1773 (28.3%) 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.

Funding National Institute on Drug Abuse, National Institutes of Health, Australian National Health and Medical Research Council.

Introduction

Cannabis use has been linked to both major depressive disorder (MDD) and suicidal thoughts and behaviours.^{1,2,3} Daily cannabis use, especially during adolescence, has been associated with a 6.8 odds of suicide attempt.⁴ In a 30-year longitudinal study, even weekly cannabis use has been linked to onset of suicidal ideation, particularly in men, and the association largely persisted after controlling for the confounding effects of various sociodemographic and mental health characteristics and familial risk factors.⁵ MDD is partly correlated with suicidal thoughts and behaviours. However, associations between cannabis use and MDD are weaker than those

noted for suicidal thoughts and behaviours⁶ and often dissipate after covariate correction.⁴

One approach to understanding the nature of the association between cannabis use and MDD and suicidal thoughts and behaviours is to study monozygotic twins reared together who are discordant for cannabis use. Some studies have shown the high heritability of cannabis use ($h^2=50-60\%$), MDD ($h^2=30-40\%$), and suicidal thoughts and behaviours ($h^2=40-45\%$).⁷⁻¹¹ Monozygotic twins typically share all their segregating loci and are also highly likely to share early familial influences. Therefore, if a twin who uses cannabis shows an increased likelihood of MDD or

Lancet Psychiatry 2017

Published Online

July 24, 2017

[http://dx.doi.org/10.1016/S2215-0366\(17\)30280-8](http://dx.doi.org/10.1016/S2215-0366(17)30280-8)

[http://dx.doi.org/10.1016/S2215-0366\(17\)30280-8](http://dx.doi.org/10.1016/S2215-0366(17)30280-8)

See Online/Comment

[http://dx.doi.org/10.1016/S2215-0366\(17\)30311-5](http://dx.doi.org/10.1016/S2215-0366(17)30311-5)

[http://dx.doi.org/10.1016/S2215-0366\(17\)30311-5](http://dx.doi.org/10.1016/S2215-0366(17)30311-5)

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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”, and “twin” with no language restrictions. Although associations between early and heavy or frequent cannabis use and suicidal thoughts and behaviours are robust when adjusted for confounders, associations with major depressive disorder (MDD) are neither as strong nor as independent. Rodent models support the role of the endocannabinoid system in mood regulation. Cannabis involvement, MDD, and suicidal thoughts and behaviours are heritable. One previous study found that cannabis-dependent individuals were more likely to report suicidal thoughts and behaviours than their monozygotic and dizygotic twins who were not dependent on cannabis, although associations with MDD were significant only in dizygotic pairs. An association was also noted between suicide attempt and discordance in early cannabis use in dizygotic as well as monozygotic twins. These results suggested that early and heavy or frequent cannabis use, or use resulting in abuse and dependence, might be related to MDD via genetic pathways alone whereas associations with suicidal thoughts and behaviours might be attributable to non-genetic,

individual-specific environmental factors, which could be of a causal nature.

Added value of this study

In this large retrospective study of cannabis, MDD, and suicidal thoughts and behaviours in twins (n=13 986), we found that even within monozygotic pairs, twins who used cannabis 100 times or more were significantly more likely to meet criteria for MDD and to report suicidal ideation than their genetically identical twin who had either never used cannabis or had used it less frequently, even after accounting for covariates. We have also shown 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 signalling in mood regulation and the results from our study, a causal role of frequent cannabis use in MDD and suicidal ideation cannot be discounted. Preventing escalation in cannabis use might ameliorate a portion of the morbidity associated with these serious mental illnesses.

suicidal thoughts and behaviours compared with their twin who does not use cannabis, this residual association might be viewed as evidence supporting person-specific factors and causal mechanisms.¹² Although 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,¹³ we have shown that, relative to their twin, the cannabis-dependent twin was 3·4 times more likely to report suicidal ideation and attempts. A similarly significant association was noted for suicide attempts when discordance for early cannabis use was examined.¹³ By contrast, increased likelihood of MDD was noted in the cannabis-dependent twin in dizygotic but not monozygotic twin pairs that were discordant for cannabis dependence, suggesting that common genetic influences could alone be implicated in this association.¹³

In this study, we incorporated data from additional twin datasets (n=13 986 for current study, vs 6257 for the previous study) and we examine additional aspects of cannabis use with suicidal thoughts and behaviours. The goals of the study were to examine whether: a lifetime history of cannabis use as well as early-onset use and frequent use were associated with MDD, suicidal ideation, persistent ideation, ideation with a plan, and suicide attempt; any significant associations that were observed in the full sample of twins persisted when twin pairs discordant for each cannabis measure were examined; and 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**Study design and participants**

Data on same-sex male and female twin pairs were drawn from 3 studies that had recruited twins from the Australian Twin Registry.¹⁴ Three groups of samples formed the population for the retrospective analysis reported in this study. Sample 1 (n=5846) included monozygotic and dizygotic twins aged 24–90 years (born between 1902 and 1964) who had either participated in a previous alcohol challenge study¹⁵ or at least one twin had participated in a survey done in 1989.¹⁶ They were invited to participate in a short telephone interview in 1992–93, which asked questions on cannabis use, age of onset, frequency of cannabis use, MDD, and suicidal thoughts and behaviours.¹⁷ As the prevalence of cannabis use was low (ie, secular difference) in those born between 1902 and 1940 (n=1414; appendix p 1), these individuals were excluded from the analyses in this study. Sample 2 (n=6255) recruited twins aged 24–36 years (born between 1964 and 1971) who were initially included through the Australian school systems and mass media appeals and were interviewed by telephone from 1996 to 2000. This sample was used in an earlier discordant twin analysis.¹³ Sample 3 (n=3299) included twins aged 27–32 years (born 1972–79) when they were first interviewed in 2005–09.¹⁸ Research outlined in this study was approved by the Institutional Review Board at Washington University School of Medicine.

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