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

Arpana Agrawal, Elliot C Nelson, Kathleen K Bucholz, Rebecca Tillman, Richard A Grucza, Dixie J Statham, Pamela AF Madden, Nicholas G Martin, Andrew C Heath, Michael T Lynskey

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.

Lancet Psychiatry 2017

Published Online
July 24, 2017
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

Department of Psychiatry, Washington University School of Medicine, St Louis, MO, USA (A Agrawal PhD, E C Nelson MD, K K Bucholz PhD, R Tillman MA, R A Grucza PhD, P A F Madden PhD, A C Heath DPhil); **QIMR Berghofer Medical Research Institute, Brisbane, QLD, Australia** (N G Martin PhD); **University of the Sunshine Coast, Sippy Downs, QLD, Australia** (D J Statham DPsych); **and National Addictions Centre, Institute of Psychiatry, Psychology, and Neuroscience, King's College London, London, UK** (M T Lynskey PhD)

Correspondence to:
Dr A Agrawal, Department of Psychiatry, Washington University School of Medicine, Saint Louis, MO 63110, USA
arpana@wustl.edu

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 behaviours[6] 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

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.

See Online for appendix

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 study[15] 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.

Procedures

Respondents in each of the three twin studies were questioned with versions of the Australian Semi-Structured Assessment for the Genetics of Alcoholism.[17,19] All three interviews included identical assessments of cannabis use and suicidal thoughts and behaviours, and similar measures of MDD and all covariates.

For cannabis use, respondents were asked whether they had ever used cannabis during their lifetime. Those who reported lifetime use were asked 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 cannabis use before the age of 18 years for twin sample 1 and before the age of 17 years for samples 2 and 3—approximately the bottom quartile of the population. Those who had used cannabis 100 times or more 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.

In samples 2 and 3, we used DSM-IV criteria to diagnose MDD.[20] We assessed DSM-IIIR criteria for sample 1 and we modified these to correspond to DSM-IV MDD. In samples 2 and 3, onset of MDD was conservatively assumed to occur when an individual reported experiencing recurring episodes of dysphoria (feeling depressed or down for most of the day for 2 weeks or longer) or anhedonia (loss of interest in most things for most of the day for 2 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 or anhedonic mood (or of the most severe episode, if sample 1) before onset of cannabis use (n=791). MDD diagnosis was set to missing in these individuals for analysis of MDD only.

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. Additionally, those who reported ideation were 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) before onset of cannabis use were set to missing for analyses related to these outcomes only.

To control for factors that potentially preceded or coincided with the onset of cannabis use and might have been associated with it, we assigned the following factors as covariates: early alcohol use (age <17 years in sample 1; age <15 years in samples 2 and 3); early tobacco smoking (age <17 years in sample 1; age <13 years in samples 2 and 3); conduct disorder; childhood sexual abuse (which was coded by use of a single common item on whether the respondent had been forced into sexual activity before age 18 years); and dysphoria or anhedonia before age 16 years for analyses of suicidal thoughts and behaviours. Different age cutoffs 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 (eg, cannabis*sex). A similar interaction term was used to test for differences in sample (1 *vs* 2 *vs* 3; cannabis*sample) as well as birth year (binned as 1941–54, 1955–64, 1965–71, 1972–79).

Statistical analysis

All primary analyses were done in SAS (version 9). We used logistic regression to examine the association between cannabis use and either MDD or 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).

We then examined the adjusted associations that were significant in the full sample within the pairs of monozygotic and dizygotic same-sex twins that were discordant for each cannabis use measure. We used conditional logistic regression for discordant twin (ie, within pair) analyses. Similar to the analyses in the full sample, we calculated an unadjusted OR for the discordant monozygotic and dizygotic pairs. For each unadjusted association that was significantly greater than 1·0 within the discordant monozygotic pairs, we calculated an adjusted OR by accounting for only those covariates that were associated with within-pair discordance for the respective cannabis measure. We re-analysed paired data using a conditional logistic regression bootstrapping approach in STATA, version 7. A comparison of the unadjusted OR from the discordant dizygotic and monozygotic pairs, in relation 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 OR of more than 1·0 in discordant monozygotic twin pairs.

For associations that were significant after covariate correction, we compared the prevalence of the corresponding MDD and suicidal thoughts and behaviours measure in discordant monozygotic pairs with its prevalence in monozygotic twin pairs that were concordant for cannabis use.

Role of the 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

	Sample 1 (n=4432)	Sample 2 (n=6255)	Sample 3 (n=3299)	Total (13 986)
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 of 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 1: **Characteristics of 13 986 male and female twins from three Australian samples**

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 (table 2, appendix pp 2–3). 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 than 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 between early cannabis use, MDD, and suicidal thoughts and behaviours, in analyses with and without never users, were significant within dizygotic twins (OR 2·23–6·50), but not monozygotic twins (OR 1·17–2·00; table 3). This pattern of results is consistent with shared genetic influences contributing to the association. In some instances (eg, suicidal ideation), the dizygotic and monozygotic OR had overlapping confidence intervals, indicating equality of effect sizes, with the association being non-significant in discordant monozygotic pairs, possibly because of marginally fewer discordant pairs.

Associations between frequent cannabis use and MDD, suicidal ideation, and persistent ideation were significant within both dizygotic and monozygotic 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 (appendix p 4). For instance, compared with their genetically identical twin who did not use cannabis as frequently, a monozygotic twin who reported using cannabis 100 times or more was more likely to meet criteria for MDD (OR 1·72), and report suicide ideation (OR 2·71) and persistent ideation (OR 3·14). A monozygotic OR of greater than one suggests that factors other than those shared by members of identical twin pairs contribute to the association. The magnitude of ORs within the dizygotic and monozygotic 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 (appendix p 5). However, even after accounting for conduct disorder, twins who frequently used cannabis were at 2·35–2·47 odds of reporting suicidal ideation when compared with their genetically identical twin who did not use cannabis so frequently or who had never used it at all (table 4; appendix pp 6–7). For MDD, the association in the subset of ever users was robust to covariate adjustment, with frequent users remaining at 1·98 odds of MDD when compared with their identical 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 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 twin (table 5). Importantly, although 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.

	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
Cannabis ever use		
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		
Full sample (n=13 986)		
Major depressive disorder	1·52 (1·36–1·69)	1·28 (1·13–1·45)
Suicidal ideation	2·03 (1·82–2·26)	1·57 (1·38–1·78)
Suicidal ideation >1 day	2·08 (1·78–2·43)	1·55 (1·29–1·87)
Suicide plan	2·39 (2·01–2·84)	1·77 (1·44–2·18)
Suicide attempt	3·63 (2·94–4·47)	2·04 (1·58–2·64)
Subsample of ever users (n=7361)		
Major depressive disorder	1·50 (1·33–1·70)	1·33 (1·16–1·53)
Suicidal ideation	2·03 (1·79–2·29)	1·68 (1·46–1·92)
Suicidal ideation >1 day	2·01 (1·68–2·40)	1·63 (1·33–2·00)
Suicide plan	2·44 (2·00–2·99)	2·04 (1·62–2·57)
Suicide attempt	3·52 (2·74–4·51)	2·38 (1·78–3·17)
Frequent cannabis use (≥100 times)		
Full sample (n=13 986)		
Major depressive disorder	1·74 (1·55–1·95)	1·53 (1·35–1·73)
Suicidal ideation	2·47 (2·20–2·76)	1·96 (1·73–2·23)
Suicidal ideation >1 day	2·27 (1·93–2·66)	1·69 (1·40–2·03)
Suicide plan	2·55 (2·13–3·05)	1·81 (1·47–2·22)
Suicide attempt	3·46 (2·78–4·30)	1·95 (1·51–2·51)
Subsample of ever users (n=7361)		
Major depressive disorder	1·74 (1·54–1·97)	1·60 (1·40–1·83)
Suicidal ideation	2·52 (2·22–2·86)	2·07 (1·81–2·38)
Suicidal ideation >1 day	2·19 (1·82–2·62)	1·68 (1·38–2·05)
Suicide plan	2·57 (2·10–3·16)	1·94 (1·55–2·42)
Suicide attempt	3·19 (2·49–4·10)	2·12 (1·61–2·80)

OR=odds ratio. *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), monozygotic twins, opposite sex dizygotic twins, conduct disorder, depressed mood or anhedonia ≤15 (not for major depressive disorder), and childhood sexual abuse.

Table 2: **Associations between aspects of cannabis use and suicidal thoughts and behaviours in male and female twins from the Australian Twin Registry**

	Dizygotic twins				Monozygotic twins			
	Number of pairs	OR (95% CI)	χ^2	p value	Number of pairs	OR (95% CI)	χ^2	p value
Discordant for early cannabis use (twin is never or later-onset user)								
Major depressive disorder	293	1·82* (1·22–2·70)	8·72	0·0031	260	1·34* (0·85–2·12)	1·60	0·2057
Suicidal ideation	271	2·23* (1·45–3·44)	13·38	0·0003	241	1·50* (0·91–2·46)	2·56	0·1093
Suicidal ideation lasting >1 day	271	4·00 (1·93–8·30)	13·84	0·0002	241	1·67 (0·82–3·41)	1·96	0·1618
Suicide plan	271	2·80 (1·36–5·76)	7·81	0·0052	241	1·17 (0·54–2·52)	0·15	0·6952
Suicide attempt	316	6·50 (2·27–18·62)	12·15	0·0005	278	1·90 (0·88–4·09)	2·70	0·1004
Discordant for early cannabis use in ever users (twin is later-onset user)								
Major depressive disorder	194	1·47 (0·92–2·33)	2·62	0·1058	194	1·55 (0·90–2·64)	2·53	0·1116
Suicidal ideation	176	2·24* (1·34–3·74)	9·42	0·0021	178	1·35* (0·76–2·41)	1·03	0·3090
Suicidal ideation lasting >1 day	176	4·00 (1·64–9·79)	9·22	0·0024	178	1·56 (0·67–3·59)	1·07	0·3011
Suicide plan	176	2·13 (0·92–4·92)	3·09	0·0787	178	1·44 (0·62–3·38)	0·72	0·3964
Suicide attempt	214	5·33* (1·55–18·30)	7·08	0·0078	209	2·00* (0·75–5·33)	1·92	0·1657
Discordant for frequent cannabis use (≥100 times; twin is never user or lighter user)								
Major depressive disorder	252	2·12* (1·33–3·37)	9·91	0·0016	199	1·72* (1·05–2·82)	4·65	0·0311
Suicidal ideation	241	2·63* (1·69–4·10)	18·29	<0·0001	190	2·71* (1·47–5·01)	10·20	0·0014
Suicidal ideation lasting >1 day	241	3·50* (1·60–7·68)	9·77	0·0018	190	3·14* (1·34–7·36)	6·96	0·0083
Suicide plan	241	1·64 (0·77–3·47)	1·66	0·1982	190	2·14 (0·87–5·26)	2·77	0·0959
Suicide attempt	276	4·40* (1·67–11·62)	8·94	0·0028	225	2·29* (0·94–5·56)	3·33	0·0681
Discordant for frequent cannabis use (≥100 times; twin is lighter user)								
Major depressive disorder	174	1·70* (1·01–2·84)	4·03	0·0446	156	1·95* (1·12–3·39)	5·58	0·0182
Suicidal ideation	165	2·84* (1·69–4·79)	15·33	<0·0001	147	2·91* (1·47–5·77)	9·33	0·0022
Suicidal ideation lasting >1 day	165	4·00* (1·50–10·66)	7·69	0·0056	147	3·60* (1·34–9·70)	6·42	0·0113
Suicide plan	165	1·00 (0·40–2·52)	0·00	1·0000	147	2·20 (0·76–6·33)	2·14	0·1438
Suicide attempt	192	6·50* (1·47–28·80)	6·07	0·0137	182	2·40* (0·85–6·81)	2·71	0·1000

*95% CI for these estimates overlap between groups, indicating equality of effect sizes, despite p values of less than 0·05. See appendix for bootstrapped CI. OR=odds ratio.

Table 3: **Unadjusted within-pair associations between aspects of cannabis use and suicidal thoughts and behaviours, in discordant monozygotic and dizygotic same-sex twin pairs, by dependent variable**

	Number of pairs	OR (95% CI)	χ^2	p value
Discordant for frequent cannabis use (≥100 times; twin never user or lighter user)				
Major depressive disorder	198	1·68 (1·01–2·80)	4·00	0·0455
Suicidal ideation	190	2·35 (1·24–4·48)	6·82	0·0090
Suicidal ideation lasting >1 day	190	2·24 (0·89–5·66)	2·89	0·0889
Discordant for frequent cannabis use in ever users (≥100 times; twin is lighter user)				
Major depressive disorder	156	1·98 (1·11–3·53)	5·30	0·0213
Suicidal ideation	147	2·47 (1·19–5·10)	5·94	0·0148
Suicidal ideation lasting >1 day	147	2·72 (0·94–7·85)	3·42	0·0643

Only associations of discordant monozygotic pairs from table 3 with significant unadjusted OR were reanalysed with covariates adjusted for conduct disorder (appendix). See appendix for bootstrapped CI. OR=odds ratio.

Table 4: **Within-pair associations between cannabis use and suicidal thoughts and behaviours in discordant monozygotic twin pairs**

We did post-hoc analyses to identify whether frequent cannabis use was associated with MDD and suicidal thoughts and behaviours that occurred before the onset of cannabis use. When suicidal ideation occurred before the onset of cannabis use, frequent cannabis use was associated with 0·73 adjusted odds of ideation (appendix p 8), 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 (appendix p 9). We also defined discordant monozygotic pairs as twins who differed by at least ten 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 (appendix p 10) than their twin who used it less frequently.

Discussion

In this large retrospective study using data from three samples taken from the Australian Twin Registry, we found that early and frequent cannabis use were 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

	Concordant twins reporting frequent use		Discordant twins reporting frequent [less frequent] use		Concordant twins reporting less frequent or never use	
	Number of pairs	Prevalence (95% CI)	Number of pairs	Prevalence (95% CI)	Number of pairs	Prevalence (95% CI)
Twins from all monozygotic pairs						
Major depressive disorder	142	32·0% (26·6–37·5)	199	32·66% (26·1–39·2) [23·62% (17·7–29·5)*]	2200	19·7% (18·5–20·9)*
Suicidal ideation	130	40·0% (34·0–46·0)	190	32·11% (25·5–38·7) [19·47% (13·8–25·1)]	2101	17·2% (16·0–18·3)
Twins from monozygotic pairs reporting lifetime cannabis use						
Major depressive disorder	142	32·0% (26·6–37·5)	156	33·33% (25·9–40·7) [21·80% (15·3–28·3)*]	596	18·0% (15·9–20·2)*
Suicidal ideation	130	40·0% (34·0–46·0)	147	32·65% (25·1–40·2) [18·37% (12·1–24·6)]	523	16·7% (14·5–19·0)

*The estimate for less frequent or never users from discordant pairs falls outside the 95% CI for the estimate from concordant pairs.

Table 5: **Prevalence of major depressive disorder and suicidal ideation in monozygotic twins from pairs concordant for frequent cannabis use, pairs concordant for less frequent or never use, and discordant pairs where one twin reported frequent cannabis use and the other less frequent or never use**

and suicidal ideation, suggesting that factors beyond those shared by identical twins might contribute to the association.

The similarity in the ORs across dizygotic and monozygotic 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 previous studies with samples 2 and 3 suggested moderate genetic correlations.[21,22] The importance of the present study lies in our ability to disentangle predisposing factors that are related to genetic liability and early familial environment from environmental factors that are individual specific. Twins who report frequent cannabis use were more likely to report MDD and suicidal ideation than their identical twin who either did not use cannabis or used it less frequently. Unadjusted and adjusted ORs 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 made use of data from sample 2 and reported an association between early cannabis use and suicide attempt as well as between cannabis dependence and both suicidal ideation and attempt.[13] However, that study found no evidence for a residual association between MDD and early cannabis use or cannabis dependence in discordant monozygotic pairs. We see an identical null finding for early cannabis use but note that frequent use did increase liability to MDD in these twin pairs, perhaps because of the larger sample size seen in the study reported here.

Several mechanisms might explain these associations. Evidence from animal[23] and human studies[24] suggests that the endocannabinoid system might be crucial 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.[25,26] Frequent cannabis use might result in similar modifications in the endocannabinoid system and a corresponding increase in negative mood. The strong differences between pairs (ie, concordant frequent *vs* concordant monozygotic twins who were less frequent users or had never used cannabis) and within pairs (ie, monozygotic discordant pairs who either frequently used cannabis or who used cannabis less frequently or never used cannabis) 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 twin modified 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 (eg, increased trauma exposure)[27] or outcomes (eg, diminished life opportunities, other drug use)[4] that might also increase the likelihood of MDD and suicidal ideation. For MDD, the twins who used cannabis less frequently than their frequent-use twin were at an increased likelihood of reporting MDD than concordant unexposed twins, suggesting that the environment related to the twin's frequent cannabis use might modify liability to MDD. Accordingly, we cannot discount the possibility that an unmeasured individual-specific factor (eg, deviant peers, other traumas) is contributing to these associations in monozygotic 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.[28] On the basis of earlier examinations of the gateway theory, these results support the importance of temporal ordering of onsets, and hint at causal pathways.[29]

One strength of the current study is that suicidal ideation and suicide attempt were assessed in all individuals, regardless of their MDD status. Although suicidal thoughts and behaviours are noted to be a feature of MDD, they are also frequently viewed as distinct psychiatric entities that are related, in equal part, to the internalising aspects of mood disorders as well as to externalising behaviours (eg, subtypes of suicide attempt that relate to impulsive aggression).[30–32] Possibly, suicidal thoughts and behaviours are an early index of a broader liability to emotion dysregulation, with a subset of ideators who progress to MDD. Comparisons of MDD and suicidal ideation prevalence across less frequent or never users from concordant and discordant pairs also hint at potential differences (ie, no effect of co-twin status for suicidal ideation). Therefore, the associations between frequent cannabis use, MDD, and suicidal thoughts and behaviours might reflect partly distinct causative processes.

Our study has some limitations. First, our sample is restricted to Australians, and sample 1 was older and is likely to represent secular differences. To address this possibility, we excluded the earliest-born members of sample 1 (born in 1902–40). To show the generalisability 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 of other indices of cannabis use. Similarly, we were unable to look in a more nuanced way at subgroups of individuals with suicidal ideation and suicide attempt (eg, severity). Third, even though we only studied early-onset behaviours as covariates, some covariates might have occurred subsequent to the onset of cannabis use. In such cases, our covariate correction might 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, to create discordant pairs, we selected thresholds to represent early and frequent use. Although our choice of age and frequency cutoffs might have influenced our estimates, results were consistent with post-hoc analyses of continuous discordance in frequency of use. Finally, even though our discordant monozygotic twin design is powerful in excluding possible causal explanations, it cannot be used to prove causation.

On the basis of 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. Although we cannot identify the nature of this increased susceptibility, 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.

Contributors

AA and MTL conceived the study. AA and RT analysed all data. AA was responsible for writing the first draft of the manuscript. ECN, KKB, RAG, DJS, ACH, and MTL provided expertise on the analytical model, choice of outcomes, and covariates. PAFM, DJS, NGM, ACH, and MTL developed instruments, and collected, processed, and coded all data.

Declaration of interests

AA and RAG have received NIH funding and compensation for grant reviews for NIH outside the submitted work. All other authors declare no competing interests.

Acknowledgments

The analyses outlined in this study are supported by funds from the National Institute on Drug Abuse (NIDA) grants R01DA040411 and K02DA032573. Additional support for data collection was via National Institutes of Health grants: AA07728, AA10248, AA13321, AA09022, AA10249, AA11998 (ACH), and DA18267 (MTL). Data collection was also supported by the National Health and Medical Research Council via 628911, 951023, and 981351. ACH acknowledges AA017688; NGM acknowledges support from the Australian NHMRC Centre for Research Excellence on Suicide Prevention (CRESP). Funding sources were not involved in any aspect of the current research.

References

1 Volkow ND, Compton WM, Weiss SR. Adverse health effects of marijuana use. *N Engl J Med* 2014; **371:** 879.

2 Price C, Hemmingsson T, Lewis G, Zammit S, Allebeck P. Cannabis and suicide: longitudinal study. *Br J Psychiatry* 2009; **195:** 492–97.

3 Borges G, Bagge CL, Orozco R. A literature review and meta-analyses of cannabis use and suicidality. *J Affect Disord* 2016; **195:** 63–74.

4 Silins E, Horwood J, Patton GC, et al. Young adult sequelae of adolescent cannabis use: an integrative analysis. *Lancet Psychiatry* 2014; **1:** 286–93.

5 van Ours JC, Williams J, Fergusson D, Horwood LJ. Cannabis use and suicidal ideation. *J Health Econ* 2013; **32:** 524–37.

6 Horwood LJ, Fergusson DM, Coffey C, et al. Cannabis and depression: an integrative data analysis of four Australasian cohorts. *Drug Alcohol Depend* 2012; **126:** 369–78.

7 Verweij KJ, Zietsch BP, Lynskey MT, et al. Genetic and environmental influences on cannabis use initiation and problematic use: a meta-analysis of twin studies. *Addiction* 2010; **105:** 417–30.

8 Maciejewski DF, Creemers HE, Lynskey MT, et al. Overlapping genetic and environmental influences on nonsuicidal self-injury and suicidal ideation: different outcomes, same etiology? *JAMA Psychiatry* 2014; **71:** 699–705.

9 Statham DJ, Heath AC, Madden PA, et al. Suicidal behaviour: an epidemiological and genetic study. *Psychol Med* 1998; **28:** 839–55.

10 Glowinski AL, Bucholz KK, Nelson EC, et al. Suicide attempts in an adolescent female twin sample. *J Am Acad Child Adolesc Psychiatry* 2001; **40:** 1300–07.

11 Flint J, Kendler KS. The genetics of major depression. *Neuron* 2014; **81:** 484–503.

12 Kendler KS, Neale MC, MacLean CJ, Heath AC, Eaves LJ, Kessler RC. Smoking and major depression: a causal analysis. *Arch Gen Psychiatry* 1993; **50:** 36–43.

13 Lynskey MT, Glowinski AL, Todorov AA, et al. Major depressive disorder, suicidal ideation, and suicide attempt in twins discordant for cannabis dependence and early-onset cannabis use. *Arch Gen Psychiatry* 2004; **61:** 1026–32.

14 Hansell NK, Agrawal A, Whitfield JB, et al. Long-term stability and heritability of telephone interview measures of alcohol consumption and dependence. *Twin Res Hum Genet* 2008; **11:** 287–305.

15 Martin NG, Perl J, Oakeshott JG, Gibson JB, Starmer GA, Wilks AV. A twin study of ethanol metabolism. *Behav Genet* 1985; **15:** 93–109.

16 Heath AC, Martin NG. Genetic influences on alcohol consumption patterns and problem drinking: results from the Australian NH & MRC twin panel follow-up survey. *Ann NY Acad Sci* 1994; **708:** 72–85.

17 Heath AC, Bucholz KK, Madden PA, et al. Genetic and environmental contributions to alcohol dependence risk in a national twin sample: consistency of findings in women and men. *Psychol Med* 1997; **27:** 1381–96.

18 Lynskey MT, Agrawal A, Henders A, Nelson EC, Madden PA, Martin NG. An Australian twin study of cannabis and other illicit drug use and misuse, and other psychopathology. *Twin Res Hum Genet* 2012; **15:** 631–41.

19 Bucholz KK, Cadoret RJ, Cloninger RC, et al. A new, semi-structured psychiatric interview for use in genetic linkage studies. *J Stud Alcohol* 1994; **55:** 149–58.

20 American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th edn. Washington, DC: American Psychiatric Association, 1994.

21 Delforterie MJ, Lynskey MT, Huizink AC, et al. The relationship between cannabis involvement and suicidal thoughts and behaviors. *Drug Alcohol Depend* 2015; **150:** 98–104.

22 Fu Q, Heath AC, Bucholz KK, et al. Shared genetic risk of major depression, alcohol dependence, and marijuana dependence: contribution of antisocial personality disorder in men. *Arch Gen Psychiatry* 2002; **59:** 1125–32.

23 Hill MN, Gorzalka BB. Impairments in endocannabinoid signaling and depressive illness. *JAMA* 2009; **301:** 1165–66.

24 Agrawal A, Nelson EC, Littlefield AK, et al. Cannabinoid receptor genotype moderation of the effects of childhood physical abuse on anhedonia and depression. *Arch Gen Psychiatry* 2012; **69:** 732–40.

25 Sam AH, Salem V, Ghatei MA. Rimonabant: from RIO to ban. *J Obes* 2011; **2011:** 432607.

26 Topol EJ, Bousser MG, Fox KA, et al. Rimonabant for prevention of cardiovascular events (CRESCENDO): a randomised, multicentre, placebo-controlled trial. *Lancet* 2010; **376:** 517–23.

27 Werner KB, McCutcheon VV, Agrawal A, et al. The association of specific traumatic experiences with cannabis initiation and transition to problem use: differences between African-American and European-American women. *Drug Alcohol Depend* 2016; **162:** 162–69.

28 Agrawal A, Tillman R, Grucza RA, et al. Reciprocal relationships between substance use and disorders and suicidal ideation and suicide attempts in the Collaborative Study of the Genetics of Alcoholism. *J Affect Disord* 2017; **213:** 96–104.

29 Kandel DB. Does marijuana use cause the use of other drugs? *JAMA* 2003; **289:** 482–83.

30 Klonsky ED, Qiu T, Saffer BY. Recent advances in differentiating suicide attempters from suicide ideators. *Curr Opin Psychiatry* 2017; **30:** 15–20.

31 Turecki G. Dissecting the suicide phenotype: the role of impulsive-aggressive behaviours. *J Psychiatry Neurosci* 2005; **30:** 398–408.

32 Nock MK, Borges G, Bromet EJ, Cha CB, Kessler RC, Lee S. Suicide and suicidal behavior. *Epidemiol Rev* 2008; **30:** 133–54.