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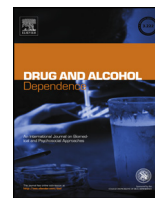
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The relationship between cannabis involvement and suicidal thoughts and behaviors[☆]



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ABSTRACT

Background: In the present study, we examined the relationship between cannabis involvement and suicidal ideation (SI), plan and attempt, differentiating the latter into planned and unplanned attempt, taking into account other substance involvement and psychopathology.

Methods: We used two community-based twin samples from the Australian Twin Registry, including 9583 individuals (58.5% female, aged between 27 and 40). The Semi-Structured Assessment of the Genetics of Alcoholism (SSAGA) was used to assess cannabis involvement which was categorized into: (0) no cannabis use (reference category); (1) cannabis use only; (2) 1–2 cannabis use disorder symptoms; (3) 3 or more symptoms. Separate multinomial logistic regression analyses were conducted for SI and suicide attempt with or without a plan. Twin analyses examined the genetic overlap between cannabis involvement and SI.

Results: All levels of cannabis involvement were related to SI, regardless of duration (odds ratios [ORs] = 1.28–2.00, $p < 0.01$). Cannabis use and endorsing ≥ 3 symptoms were associated with unplanned (SANP; ORs = 1.95 and 2.51 respectively, $p < 0.05$), but not planned suicide attempts ($p > 0.10$). Associations persisted even after controlling for other psychiatric disorders and substance involvement. Overlapping genetic ($rG = 0.45$) and environmental ($rE = 0.21$) factors were responsible for the covariance between cannabis involvement and SI.

Conclusions: Cannabis involvement is associated, albeit modestly, with SI and unplanned suicide attempts. Such attempts are difficult to prevent and their association with cannabis use and cannabis use disorder symptoms requires further study, including in different samples and with additional attention to confounders.

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1. Introduction

Worldwide, the lifetime prevalence of suicidal ideation (SI), suicide planning, and attempt is estimated between 3.1 and 56.0%,

between 0.9 and 19.5%, and between 0.4 and 5.1%, respectively, in adult populations (Nock et al., 2008a). Among adults reporting SI and a plan, 56% are estimated to have made an attempt, while 15.4% have made an attempt without a plan (Nock et al., 2008b). Suicide attempts are amongst the most powerful predictors of completed suicide (World Health Organization, 2014). Regardless of completion, suicide attempts exact a considerable economic burden via medical care accrued and lost productivity (American Foundation for Suicide Prevention, 2012). Alarming, between 2011 and 2012, suicide attempts rose by 2.4% and remain the 10th leading cause of mortality in the U.S. (Xu et al., 2014).

[☆] Supplementary material can be found by accessing the online version of this paper. See Appendix A for more details.

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Suicidal thoughts and behaviors (STB; ideation, planning, attempt) are strongly related to substance use behaviors, including cannabis involvement (Byrne et al., 2004; Calabria et al., 2010; Johns, 2001; Moore et al., 2007; Pompili et al., 2012), especially early (Byrne et al., 2004; Lynskey et al., 2004) and heavy cannabis use or cannabis use disorders (CUD; Fergusson et al., 2002; Johns, 2001; Lynskey et al., 2004; Pedersen, 2008; Pompili et al., 2012; Van Ours et al., 2013). For instance, Silins et al. (2014) recently reported that suicide attempts were substantially increased (adjusted odds-ratio >6) in young daily cannabis users.

Other studies suggest that the relationship between cannabis involvement and STB may be explained by shared risk and protective influences (Harris and Barraclough, 1997). For instance, in a longitudinal study of Swedish conscripts, the association between cannabis use and completed suicide was entirely explained by confounders, including other substance use and psychological adjustment (Price et al., 2009). Likewise, Wilcox et al. (2010) found that the relation between CUD and SI in college students disappeared when accounting for confounding factors such as depressive symptoms and maternal depression.

Another challenge is that items querying STB are frequently embedded in diagnostic interview sections assessing major depressive or bipolar disorder, such that only individuals reporting mood-related symptoms or episodes are presented with these questions. In addition, a majority of studies have disregarded intensity and duration of ideation (Joiner and Rudd, 2000) and the distinction between planned and unplanned attempts, even though their etiology may differ. In particular, planned attempts are more common in samples that require presence of dysphoric or anhedonic mood in the assessment of suicide (Simon et al., 2002) and their relationship with substance use may also vary. For example, Borges et al. (2000) showed that using one or more substances was related to suicide attempts without planning (SANP), but not to suicide attempts that were planned (SAP). The authors attributed this difference to the disinhibition hypothesis, which proposes that, when using drugs, inhibitions to make an impulsive attempt are reduced, therefore increasing the risk of suicide attempts (Mayfield and Montgomery, 1972; Rossow and Wichström, 1994), although whether attempts were in the context of substance use was not assessed. The finding is also consistent with the notion, as stated by Conner et al. (2007) in their study on alcohol dependent men and women, that SANP are related to impulsivity, while SAP are more related to depression, and are also more likely to result in completion (Harris et al., 2005).

Cannabis involvement and SI are both influenced by genetic factors to a similar degree ($h^2 = 40\text{--}60\%$; Maciejewski et al., 2014; Verweij et al., 2010) with evidence for non-additive genetic influences on SI. However, little is known of the extent to which shared genetic factors contribute to their comorbidity. One study (Lynskey et al., 2004) found that CUD was associated with SI and suicide attempts, even in identical twin pairs who shared 100% of their genetic background. The twin with cannabis dependence was at 2.9 and 2.5 greater odds of SI and suicide attempt relative to their genetically-related nondependent co-twin, suggesting that individual-specific environmental factors that are correlated across cannabis involvement and STB but are not shared by members of a twin pair were important. However, the extent of the genetic and environmental overlap between cannabis involvement and STB was not examined.

The present study expands upon this prior research by (a) studying varying levels of cannabis involvement, including use and use disorders; (b) examining both SI and suicide attempt separately; (c) expanding the definition of suicide attempts to include planning and (d) estimating the magnitude of genetic overlap between cannabis involvement and STB. We hypothesized that cannabis

involvement would be associated with SI and suicidal attempts in a dose-response fashion, however, associations with the latter would only be restricted to those reporting SANP. Furthermore, we expected moderate genetic and individual-specific environmental correlations to contribute to the association between cannabis involvement and SI.

2. Method

2.1. Sample and respondents

Data were derived from two community-based samples from the Australian Twin Registry (ATR). Sample 1 included 6257 individuals (55.2% female) aged 24–36 (mean age 29.9, SD = 2.5) who were interviewed between 1996 and 2000 (Lynskey et al., 2002). Sample 2 included 3326 twins (64.8% female), aged 27–40 (mean age 31.9, SD = 2.5), who were interviewed between 2005 and 2009 (Lynskey et al., 2012). Additionally, 476 nontwin siblings were interviewed. However, as the age range was broad (21–46 years) and some of them may not have been past the age of risk for CUD symptoms (Wagner and Anthony, 2002), we excluded the nontwin siblings from analyses. Despite different birth years and different years at interview, the twins from both samples were approximately (within two years) the same age at the time of the interview. The total sample consisted of 9583 individuals (58.5% female), with a mean age of 30.6 (SD = 2.6). There were 2472 female identical (monozygotic; MZ) twins, 1630 male MZ twins, 1877 female non-identical (dizygotic; DZ) twins, 1314 male DZ twins, and 2290 opposite-sex DZ twins.

2.2. Procedure

In both ATR samples, assessments were administered using a computer-based telephone or face-to-face interview of the Semi-Structured Assessment of the Genetics of Alcoholism (Australian version SSAGA-OZ; Bucholz et al., 1994; Kramer et al., 2009). Assessments included lifetime history of substance use as well as DSM-IV diagnostic criteria for abuse, dependence as well as other diagnoses, such as conduct disorder (CD), major depressive disorder (MDD), and anxiety disorders, including social anxiety and panic disorders. All participants provided informed consent prior to the interview, as approved by the institutional review boards of Washington University School of Medicine, St. Louis, MO, United States and the Queensland Institute of Medical Research, Brisbane, Queensland, Australia.

2.3. Measures

2.3.1. STBs. All participants, regardless of prior history of depression or psychopathology, were queried about suicidal behaviors (Statham et al., 1998). The question “Have you ever thought about taking your own life?” was used to define SI. Subsequently, participants were asked whether these thoughts lasted for more than a day. Participants were then divided into one of three groups: (1) no SI ($N = 7074$); (2) SI for less than a day ($N = 1602$); and (3) SI for more than a day ($N = 907$). Those who reported SI were queried about whether they had ever made a plan. Regardless of ideation or planning, all participants were asked about whether they had ever tried to take their own life (i.e., suicidal attempt). Those individuals who reported a suicidal attempt and a history of suicidal planning, regardless of whether the plan pertained to the attempt, comprised the group of *suicide attempt with planning* (SAP), while those reporting to have attempted suicide in the absence of a lifetime history of suicide planning comprised the group of *suicide attempt without planning* (SANP). Participants were divided into one of four groups: (1) no suicide plan or attempt, regardless of ideation ($N = 8748$); (2) suicide plan without attempt ($N = 427$); (3) SAP ($N = 246$); and (4) SANP ($N = 162$).

2.3.2. Cannabis involvement. Lifetime cannabis use was assessed with the question “Have you ever used (ever experimented even once with) marijuana or hashish?” During data collection for sample 1, to reduce respondent burden, only 6 CUD symptoms, including two abuse symptoms (use in hazardous situations; interference with major role obligations) and four dependence (needing larger amounts to get an effect [tolerance]; using more frequently or in larger amounts than intended; continued use despite emotional or psychological problems due to use; recurrent desire to cut down) symptoms were queried. These criteria showed good sensitivity and specificity, and a high level of agreement compared to two other national surveys (Lynskey et al., 2002), indicating that this is a valid measure of CUD. While the full set of DSM-IV criteria were available for sample 2 (i.e., 4 abuse and 6 dependence criteria, and withdrawal), we only selected the subset of 6 items that were consistently available across both samples. For cannabis involvement, participants were divided into one of four mutually exclusive groups: (0) no cannabis use ($N = 3566$); (1) cannabis use only (having used at least once, without endorsement of CUD symptoms; $N = 4084$); (2) endorsement of 1–2 CUD symptoms ($N = 939$); and (3) endorsement of 3 or more CUD symptoms ($N = 994$). No cannabis use served as the reference category. However, to satisfy the assumption of multivariate normality, groups 1 and 2 were combined to create a three-level measure for the twin analyses.

Table 1
Prevalences of suicidal ideation (SI) and suicide plan/attempt, and prevalences of the covariates in these subgroups.

	Suicidal ideation (SI)			Suicidal plan/attempt			
	No SI	SI, less than a day	SI, more than a day	No suicide plan or attempt	Suicide plan without attempt	Suicide attempt with planning	Suicide attempt without planning
<i>N</i> (%)	7074 (73.8%)	1602 (16.7%)	907 (9.5%)	8748 (91.3%)	427 (4.5%)	246 (2.6%)	162 (1.7%)
Men (%)	2941 (74.0%)	692 (17.4%)	340 (8.6%)	3659 (92.1%)	185 (4.7%)	80 (2.0%)	49 (1.2%)
Women (%) [#]	4133 (73.7%)	910 (16.2%)	567 (10.1%)	5088 (90.7%)	242 (4.3%)	166 (3.0%)	113 (2.0%)
Mean age (SD)	30.56 (2.63)	30.77 (2.63)	30.63 (2.63)	30.59 (2.63)	30.62 (2.71)	30.78 (2.51)	30.66 (2.68)
<i>Nicotine</i>							
No symptoms	4054 (57.3%)	781 (48.8%)	377 (41.6%)	4904 (56.1%)	188 (44.0%)	78 (31.7%)	42 (25.9%)
1–2 symptoms	844 (11.9%)	125 (7.8%)	72 (7.9%)	983 (11.2%)	26 (6.1%)	19 (7.7%)	13 (8.0%)
3+ symptoms	2176 (30.8%)	696 (43.4%)	458 (50.5%)	2861 (32.7%)	213 (49.9%)	149 (60.6%)	107 (66.0%)
<i>Alcohol</i>							
No symptoms	2078 (29.4%)	375 (23.4%)	196 (21.6%)	2489 (28.5%)	81 (19.0%)	45 (18.3%)	34 (21.0%)
1–2 symptoms	2836 (40.1%)	551 (34.4%)	267 (29.4%)	3421 (39.1%)	133 (31.1%)	59 (24.0%)	41 (25.3%)
3+ symptoms	2160 (30.5%)	676 (42.2%)	444 (49.0%)	2838 (32.4%)	213 (49.9%)	142 (57.7%)	87 (53.7%)
Use of other illicit drugs	2107 (29.8%)	784 (48.9%)	511 (56.3%)	2891 (33.0%)	230 (53.9%)	174 (70.7%)	107 (66.0%)
Conduct disorder	594 (8.9%)	285 (17.8%)	221 (24.4%)	864 (9.9%)	96 (22.5%)	94 (38.2%)	46 (28.4%)
Major depressive disorder	1235 (17.6%)	670 (41.8%)	683 (75.3%)	2017 (23.2%)	277 (64.9%)	190 (77.2%)	104 (64.2%)
Anxiety disorder	592 (8.4%)	316 (19.7%)	305 (33.7%)	934 (10.7%)	136 (31.9%)	100 (40.7%)	43 (26.7%)
Childhood sexual abuse	417 (5.9%)	236 (14.7%)	237 (26.1%)	641 (7.3%)	86 (20.1%)	111 (45.1%)	52 (32.1%)

[#] Chi square difference across men and women for SI is 7.93, $p < 0.05$; for suicidal plan/attempt 17.60, $p < 0.01$.

2.3.3. Covariates.

2.3.3.1. *Demographics.* We included gender, age, zygosity (identical or not), same or opposite sex pair, and belonging to sample 1 or 2.

2.3.3.2. *Other substance use and use disorders.* Nicotine dependence and alcohol abuse/dependence were both categorized into (0) no symptoms; (1) 1–2 symptoms; and (2) 3 or more symptoms. Other illicit use of any of the following drugs was considered: (a) sedatives, (b) cocaine, (c) amphetamines and other stimulants, (d) opioids, (e) hallucinogens, (f) dissociatives (phencyclidine, ketamine), (g) solvents, and (h) inhalants.

2.3.3.3. *Psychopathology.* We included DSM-IV diagnoses of (a) conduct disorder (CD), (b) major depressive disorder (MDD), and (c) anxiety disorders (social anxiety or panic disorder).

2.3.3.4. *Early adversity.* Based on analyses by Van Ours et al. (2013) and Nelson et al. (2002), a measure reflecting childhood sexual abuse (CSA), which was based on a single common item across both assessments that queried whether the respondent had been forced into sexual intercourse or another form of sexual activity prior to age 18, was also included.

2.4. Statistical analyses

2.4.1. *Association analysis.* Descriptive statistics were calculated using the Statistical Package of Social Sciences version 21.0 for Windows (SPSS Inc., Chicago, IL). All associations were examined using Mplus v6.0 (Muthén and Muthén, 1998–2012), which allows for clustering of data due to familial relatedness via estimation of robust standard errors. Separate multinomial logistic regression analyses, with and without covariates, were used to examine the relationship between cannabis involvement and SI, and suicide plan/attempt. To examine whether the strength of the association (i.e., ORs) across levels of cannabis involvement (e.g., cannabis use vs. 1–2 CUD symptoms vs. ≥ 3 symptoms) was significantly different (i.e., a dose response relationship), the magnitude of the association (i.e., OR) between STB and each level of cannabis involvement was equated to all other levels of cannabis involvement (e.g., $OR_{\text{cannabis use}} = OR_{1-2 \text{ CUD symptoms}}$; Satorra, 2000).

2.4.2. *Twin analysis.* Variance in and covariance between cannabis involvement and those aspects of STB that remained associated with it, after adjustment for confounding, was decomposed into additive genetic (A), shared environmental (C) or non-additive genetic (D) and individual-specific environmental (E) factors (Neale and Cardon, 1992). As there is evidence for an ACE model for cannabis involvement and an ADE model for SI, both were tested and compared using their $-2 \log$ likelihood fit.

3. Results

3.1. Descriptive statistics

In the present study, 1602 participants (16.7%) reported *SI less than a day*, and 907 (9.5%) reported *SI more than a day*. Of those reporting any ideation, 17.02% (427 participants, or 4.5% of the total sample) reported suicide plan without an attempt. Regardless of ideation, 246 attempters (2.6% of the total sample) reported a prior history of suicide planning (SAP) and 162 attempters (1.7% of the total sample) did not report ever making a plan (SANP). In general, rates of psychopathology, substance use, and CSA were higher in those reporting any STB (Table 1).

The lifetime prevalence of cannabis use was 62.8% ($n = 6017$). In total, 20.2% ($n = 1933$) reported at least one CUD symptom (32.1% of ever-users). STB increased with increasing number of CUD symptoms (Table 2). For instance, SI, regardless of duration, was more common in those reporting 3–6 CUD symptoms (21–28%) relative to never users (6–12%), those with no symptoms (9–17%) and those with 1–2 CUD symptoms (13–21%). Correlations between cannabis involvement and all covariates are available in Supplemental Table S1.

3.2. Associations between cannabis involvement and STBs

Even after accounting for covariates, all levels of cannabis involvement remained significantly associated with SI, both less than a day (odds-ratios [ORs] between 1.28 and 2.00, $p < 0.05$), and more than a day (ORs between 1.35 and 1.98, $p < 0.01$) compared to no SI (Table 3). A dose response relationship was observed such that those endorsing 3–6 CUD symptoms (OR 1.98–2.00) were most likely to report SI relative to those with fewer (OR 1.50–1.53) or no symptoms (OR 1.28–1.35).

Likewise, after adjustment for other substance involvement and psychopathology, using cannabis and endorsing ≥ 3 CUD symptoms (but not 1–2 symptoms) remained significantly related to SANP (OR = 1.95, $p < 0.05$, and OR = 2.51, $p < 0.05$, respectively). Despite a pattern of odds-ratios that indicated a dose-response relationship (Table 4), the odds-ratios for these associations could be statistically equated across all levels of cannabis involvement (combined ORs = 1.90, $p < 0.05$; $\Delta \chi^2 = 5.39$, $df = 2$, $p > 0.05$). Only

Table 2
Frequency (proportion) of each subgroup of suicidal ideation (SI) and plan/attempt across levels of cannabis involvement.

	Suicidal ideation (SI)			Suicidal plan/attempt				Total N
	No SI	SI, less than a day	SI, more than a day	No suicide plan or attempt	Suicide plan without attempt	Suicide attempt with planning	Suicide attempt without planning	
No use	2912 (81.7%)	437 (12.3%)	217 (6.1%)	3386 (95.0%)	103 (2.9%)	55 (1.5%)	22 (0.6%)	3566 (100.0%)
Use, no CUD symptoms	3039 (74.4%)	687 (16.8%)	358 (8.8%)	3754 (92.0%)	173 (4.2%)	84 (2.0%)	73 (1.8%)	4084 (100.0%)
1–2 CUD symptoms	614 (65.4%)	201 (21.4%)	124 (13.2%)	825 (87.9%)	55 (5.9%)	41 (4.4%)	18 (1.8%)	939 (100.0%)
3–6 CUD symptoms	509 (51.2%)	277 (27.9%)	208 (20.9%)	783 (78.8%)	96 (10.9%)	66 (6.6%)	49 (4.9%)	994 (100.0%)
Total N	7074 (73.8%)	1602 (16.7%)	907 (9.5%)	8748 (91.3%)	427 (4.5%)	246 (2.6%)	162 (1.7%)	9583 (100.0%)

Table 3
Multinomial logistic regression of cannabis involvement with suicidal ideation (SI), adjusted for psychopathology.

	Suicidal ideation (SI)			
	SI, less than a day ^a		SI, more than a day	
	OR	95% CI	OR	95% CI
Cannabis use ^b	1.28 a [*]	1.02–1.60	1.35 b ^{**}	1.16–1.57
1–2 CUD symptoms ^b	1.50 a [*]	1.09–2.08	1.53 b ^{**}	1.22–1.92
3–6 CUD symptoms ^b	2.00 ^{**}	1.44–2.79	1.98 ^{**}	1.57–2.50
Age	0.90	0.76–1.06	0.83 ^{**}	0.74–0.94
Gender (Male = 0)	0.90	0.75–1.08	0.92	0.81–1.05
Dizygotic	1.05	0.86–1.27	1.06	0.92–1.21
Dizygotic opposite sex	1.18	0.96–1.46	1.01	0.87–1.18
Cohort	1.02	0.85–1.23	0.84 ^{**}	0.74–0.96
Nicotine 1–2 symptoms ^c	0.77	0.58–1.03	0.61 ^{**}	0.49–0.75
Nicotine 3+ symptoms ^c	0.94	0.78–1.15	0.92	0.81–1.06
Alcohol 1–2 symptoms ^d	0.81	0.65–1.01	0.90	0.77–1.06
Alcohol 3+ symptoms ^d	1.06	0.84–1.35	1.01	0.85–1.21
Other drug use	1.60 ^{**}	1.31–1.95	1.56 ^{**}	1.36–1.79
Conduct disorder	1.77 ^{**}	1.42–2.21	1.47 ^{**}	1.23–1.75
Major depressive disorder	10.40 ^{**}	8.73–12.40	2.74 ^{**}	2.41–3.12
Anxiety disorder	2.74 ^{**}	2.26–3.32	1.93 ^{**}	1.64–2.28
Childhood sexual abuse	3.04 ^{**}	2.44–3.80	1.95 ^{**}	1.61–2.35

Odds-ratios with the same letters (a and b) are statistically equal to each other; constraining them does not produce a significant chi-square difference at $p < 0.05$.

^a Reference category is no SI.

^b Reference category is no cannabis use.

^c Reference category is no nicotine dependence symptoms.

^d Reference category is no alcohol use symptoms.

^{*} $p < 0.05$.

^{**} $p < 0.01$.

endorsing 3–6 CUD symptoms was related to planning without attempt (OR = 1.65, $p < 0.05$). In contrast, there was no significant association between any level of cannabis involvement and SAP (p values > 0.08).

Regression diagnostics were used to identify 4 and 36 putatively extreme observations for SI and SANP respectively. Re-running the models after the exclusion of these values did not alter the findings. For instance, the odds-ratio between SANP and 3–6 CUD symptoms was 3.18, which was well within the confidence limits of the estimate presented in Table 4.

3.3. Twin analyses

The best fitting model decomposed variance in cannabis involvement into additive genetic (74%) and individual-specific environmental factors across men and women (Table 5; Supplemental Table S2¹). As the association between cannabis involvement and ideation did not vary by duration, SI was modeled as a binary measure with additive (9%), non-additive (33–47%) and individual-specific environmental contributions (Table 5; Supplemental Table S2). To compute covariance, A and D were combined to estimate broad heritability ($G = 47%$; Table 5) for SI

as has been previously recommended (Maciejewski et al., 2014). The phenotypic correlation between cannabis involvement and SI was primarily attributable to shared genetic factors ($r_G = 0.47$) with overlapping individual-specific environmental factors also playing a role ($r_E = 0.21$).

4. Discussion

Our results confirm previous studies, which have shown support for an association between cannabis involvement and STB (e.g., Fergusson et al., 2002; Moore et al., 2007; Pedersen, 2008). In addition, unlike some other studies, associations in our sample were not explained by confounding measures (Price et al., 2009; Wilcox et al., 2010). Differences between our study and others may be related to sample characteristics, measurement of ideation/attempt, or the possible inclusion or exclusion of certain covariates. To identify potential contributions of differences in measurement we differentiated SI by duration (> 1 day) but associations with cannabis involvement did not vary. In contrast, we did show a difference between suicide attempts with and without a plan: cannabis involvement was related to SANP only, confirming previous studies on number of substances used (Borges et al., 2000) and alcohol dependence (Conner et al., 2007). Even though SANPs are found to be less likely to result in completed suicide (Harriss et al., 2005), suicidal attempts, in and of themselves are amongst the leading contributors to economic burden (Palmer et al., 1995)

¹ Supplementary material can be found by accessing the online version of this paper. See Appendix A for more details.

Table 4
Multinomial logistic regressions of cannabis involvement with suicidal plan/attempt, adjusted for psychopathology.

	Suicidal plan/attempt					
	Suicide plan without attempt ^a		Suicide attempt with planning		Suicide attempt without planning	
	OR	95% CI	OR	95% CI	OR	95% CI
Cannabis use ^b	1.25	0.94–1.66	0.68	0.45–1.05	1.95 ^c	1.12–3.37
1–2 CUD symptoms ^b	1.26	0.84–1.89	0.81	0.47–1.39	1.29 ^c	0.59–2.81
3–6 CUD symptoms ^b	1.65 [*]	1.10–2.46	0.74	0.42–1.31	2.51 ^{c**}	1.27–4.96
Age	0.85	0.69–1.05	0.84	0.63–1.13	0.90	0.65–1.25
Gender (Male = 0)	0.87	0.69–1.09	1.11	0.79–1.56	1.58 [*]	1.09–2.29
Dizygotic	1.10	0.86–1.40	0.89	0.65–1.24	0.98	0.68–1.41
Dizygotic opposite sex	1.06 ^{**}	0.82–1.38	1.14	0.80–1.62	0.67	0.43–1.06
Cohort	0.69 [*]	0.54–0.88	1.18	0.87–1.60	0.78	0.54–1.14
Nicotine 1–2 symptoms ^c	0.61	0.40–0.92	1.10	0.65–1.91	1.21	0.63–2.32
Nicotine 3+ symptoms ^c	0.95	0.75–1.20	1.37	0.95–1.98	1.92 ^{**}	1.26–2.93
Alcohol 1–2 symptoms ^d	1.01	0.76–1.35	0.78	0.51–1.20	0.60 [*]	0.37–0.96
Alcohol 3+ symptoms ^d	1.32	0.96–1.83	1.28	0.84–1.96	0.92	0.58–1.46
Other drug use	1.41 ^{**}	1.10–1.81	2.45 ^{**}	1.69–3.56	2.00 ^{**}	1.34–2.98
Conduct disorder	1.41 [*]	1.07–1.87	2.72 ^{**}	1.95–3.79	1.67 ^{**}	1.12–2.49
Major Depressive Disorder	4.41 ^{**}	3.53–5.50	6.26 ^{**}	4.50–8.71	3.54 ^{**}	2.48–5.05
Anxiety disorder	2.38 ^{**}	1.86–3.04	2.31 ^{**}	1.70–3.15	1.52 [*]	1.03–2.24
Childhood sexual abuse	1.89 ^{**}	1.42–2.51	5.04 ^{**}	3.70–6.85	2.88 ^{**}	1.98–4.20

Odds-ratios with the same letter (c) are statistically equal to each other; constraining them does not produce a significant chi-square difference at $p < 0.05$.

^a Reference category is no suicide plan or attempt.

^b Reference category is no cannabis use.

^c Reference category is no nicotine dependence symptoms.

^d Reference category is no alcohol use symptoms.

^{*} $p < 0.05$.

^{**} $p < 0.01$.

and are powerful predictors of later completed suicide (Harris and Barraclough, 1997; Suominen et al., 2004), emphasizing the need for effective prevention strategies.

The relationship between cannabis involvement and STB could be explained in multiple ways. For example, the self-medication hypothesis states that individuals use psychoactive substances to reduce negative affective states, such as STB (Khantzian, 1985, 1997). However, longitudinal studies have found little support for this hypothesis (Harris and Barraclough, 1997; Van Ours et al., 2013). Alternatively, the impaired functioning theory hypothesizes that cannabis involvement causes STB (Newcomb et al., 1999). Physical, psychological, or emotional functioning is impaired by the repeated and, often, early onset, use of cannabis, resulting in a higher risk of suicidal behaviors. Some longitudinal studies indeed showed a significant relationship between early cannabis use and later risk of suicidal behaviors (e.g., Lynskey et al., 2004; Van Ours et al., 2013; Wilcox and Anthony, 2004). In the present study, while we did not have data on age at first CUD symptom, median age at first cannabis use coincided with the median age at first SI (18 years) in cannabis users and only preceded first suicide attempt by a year. Hence, cannabis involvement likely occurred contemporaneously. Finally, as stated by the disinhibition theory, cannabis intoxication prior to an attempt could also directly lead to an increased risk of suicide attempt. Related studies (Borges et al., 2000; Conner et al., 2007) allude to the possible role of facets of disinhibited behavior as mediators. While we did not assess substance-induced disinhibition or trait level aggression in our study, the inclusion of conduct disorder (which encompasses both facets to some degree)

did not attenuate the association. In addition, only 56 individuals (13.7% of attempters) indicated that their suicide attempt was related to co-occurring drug use. A more likely alternative is that both cannabis involvement and STBs are influenced by and related to a common set of risk and protective influences and that any observed association is due to these confounding effects (Price et al., 2009).

We also found that the link between cannabis involvement and SI was strongly influenced by shared genetic influences. This is consistent with pre-clinical evidence regarding the role of the endocannabinoid system in both the behavioral effects of cannabis and the regulation of depressive and anhedonic mood states (Gorzalka and Hill, 2011). One prior study of 277 discordant twins (Lynskey et al., 2004; utilizing data from sample 1) found that CUD was associated with a 2.5–2.9 increased OR of SI and attempt. In other words, even when individuals were matched for their segregating genes and early family environment, a history of CUD significantly increased the likelihood of STB, suggesting the possibility of causal/individual-specific factors in this association. We found support for such individual-specific factors influencing both cannabis involvement and SI in male and female twins ($rE = 0.21$). Furthermore, due to the smaller sample size, twin models with SANP could not be fit to the data.

Finally, due to the relatively small number of individuals reporting SAP and SANP, we did not further probe whether intent to die, an aspect of self injury that is associated with risk influences similar to suicide completion, including a greater than 2-fold increase in drug use disorders, modified these associations (Nock

Table 5
Estimates [95% confidence intervals] from twin analyses examining the association between cannabis use disorders and SI.

	Cannabis use	Suicidal ideation	Correlation
Males and females			
Broad heritability (A + D) [*]	0.74 (0.69–0.78)	0.47 (0.41–0.54)	0.45 (0.37–0.54)
Individual-specific environment	0.26 (0.22–0.31)	0.53 (0.46–0.59)	0.21 (0.09–0.32)

Note: A = additive genetic influences, E = nonshared environmental influences. All parameters could be equated for women and men when examining broad heritability.

^{*} When A and D were estimated separately, genetic effects on cannabis use could be equated across men and women, but there was greater non-additive genetic influence on suicidal ideation among women than men: A = 0.09 (0.06–0.36), D = 0.47 (0.36–0.51) for women; A = 0.09 (0.06–0.36), D = 0.33 (0.02–0.44) for men.

and Kessler, 2006). Of those reporting SAP and SANP, 60% and 40% reported intent respectively. Stratifying by intent alone (no attempt, attempt without intent and attempt with intent) did not yield significant associations with any level of cannabis involvement (OR=0.78–1.17, $p>0.05$). Similarly, associations with SAP remained non-significant when stratified by intent. For SANP, while the point estimates were no longer statistically significant, the magnitude of the ORs suggested that while intent may enhance the association, SANP without intent was also associated with cannabis involvement. For instance, the OR for SANP with intent was 2.89 [95% C.I. 0.94–8.88] relative to an OR of 1.98 [95% C.I. 0.88–4.47] for SANP without intent.

The present study has some limitations. First, as age of onset of CUD symptoms was not queried and age of onset of STBs was limited to SI and attempt, it is not possible to make causal inferences. Second, with self-report data, participants could be unwilling to report or unable to recall cannabis use and CUD symptoms or STB. Third, the most severely affected (i.e., those completing suicide) are not represented. Fourth, an abbreviated version of the CUD assessment was used. When analyses were conducted with the full CUD assessment in sample 2 and the abbreviated assessment in sample 1, results remained largely unchanged (available upon request). Fifth, we utilized a sample of twins for epidemiological analyses. However, it is important to note that twins, after statistical accommodation of the clustered nature of their data (as done in this study), are representative of the general population (Kendler et al., 1995; Pulkkinen et al., 2003). Finally, despite the statistically significant association with suicide ideation as well as SANP, cannabis involvement was not the strongest correlate of STBs. In addition to cannabis involvement, substance use and misuse, as a whole, different psychopathologies such as MDD and conduct disorder, and childhood sexual abuse should be considered in the etiology of STBs. Relatedly, despite the inclusion of several important confounders, the possibility that an unmeasured covariate was responsible for this association cannot be excluded.

As SI was reported by 26.2% in the present study and SANP are particularly difficult to prevent (Conner, 2004), research on possible correlated factors is important. In the present study, cannabis involvement was related to SI regardless of duration and to SANP, even when controlling for possible confounders. However, the odds ratio was modest and results from some previous studies differed from ours, emphasizing the need for further replication. If cannabis use and endorsing CUD symptoms exacerbate the likelihood of these behaviors, then more well-designed studies are required to unpack the etiological mechanisms underpinning this association. Such research is particularly important in light of current developments regarding the legalization of cannabis use in the U.S. in the states of Washington and Colorado and also in other countries. As 3.9% of first-time cannabis users have been found to develop cannabis dependence within 24 months (Chen et al., 2005), with risk increasing with chronic use, the study of potential harmful correlates and consequences of cannabis use and escalating cannabis involvement should be made a priority.

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Contributors

Hypotheses were conceived by MD, MTL, AH and AA. MD and AA conducted all analyses; JDG conducted twin analyses with HC, JDG and LF providing support with phenotype coding and statistical methods. KKB, AG, TJT, PAFM and DS facilitated coding of phenotypes. AH, ACH and NGM provided support with alternate analytic models and methods. Data were collected by ACH, KKB, PAFM, MTL, DS and NGM. MD and AA wrote the first version of the study and all revisions. All authors reviewed the submission and approved the final version.

Conflict of interest

No conflict declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.drugalcdep.2015.02.019>.

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