



Cannabis and Intentional Self-injury: a Narrative Review

Alexander Denissoff^{1,2} · Jonna Levola^{3,4} · Solja Niemelä^{1,2} · Antti Mustonen^{5,6}

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Abstract

Purpose of Review Observational studies assessing the association of cannabis use with subsequent intentional self-injury have reported mixed findings. Longitudinal studies examining the association of cannabis use with subsequent suicide death are notably rare. Our objective was to review longitudinal studies examining cannabis use and subsequent self-harm, suicide attempt, or suicide death.

Recent Findings Few population-based studies have focused on self-harm with considerable variability across studies in how this outcome has been operationalized. Studies assessing the association between cannabis use and suicide attempt are equivocal in their conclusions and heterogenous in terms of samples utilized and assessment of confounding bias. The results of one meta-analysis were suggestive of dose dependency. For suicide death, the findings are inconsistent, and there is reason for concern of selection bias.

Summary The existing evidence base on these associations is not yet rigorous enough to allow drawing conclusions on causality. However, cannabis might be seen as an adverse prognostic marker for intentional self-injury.

Keywords Cannabis · Self-harm · Suicide attempt · Suicide death

Introduction

Cannabis use has been associated with adverse psychiatric sequelae such as psychosis [1, 2], depression, and anxiety disorders [3, 4, 5•]. Particularly, the association of cannabis use and psychotic disorders is supported by multiple lines of converging evidence [6–12]. However, the nature

of the association between cannabis use and different forms of intentional self-injury, such as suicide, suicide attempts, and non-suicidal self-injury is yet far from clear. Moreover, though the association between cannabis use and suicide attempts have been examined in a considerable number of studies with prospective data [5•, 13••], there is a paucity of knowledge regarding the association of cannabis exposure and other intentional self-injury-related outcomes such as self-harm and suicide [14•, 15]. In this review, intentional self-injury is used as an umbrella term for all self-injurious behaviors even encompassing suicide death. Suicide attempt is defined as an event of intentional self-injury with a preceding intent to die. Self-harm is used to denote self-inflicted injury regardless of preceding intent.

Suicide is among the leading causes of death among young people [16], and self-harm phenomena exert a particularly heavy burden on adolescents and young adults [17, 18]. Notably, self-harm requiring medical attention is of importance, as it has been estimated that one of the twenty-five people hospitalized due to intentional self-injury will die by suicide in the following 5 years [19, 20]. Thus, identifying potential environmental risk factors for intentional self-injury are an important public health priority.

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✉ Alexander Denissoff
aldeni@utu.fi

- ¹ Faculty of Medicine, Department of Psychiatry, University of Turku, Turku, Finland
- ² Addiction Psychiatry Unit, Department of Psychiatry, Turku University Hospital, Turku, Finland
- ³ Department of Psychiatry, University of Helsinki, Helsinki, Finland
- ⁴ Psychiatry Division, Hyvinkää Area, Hospital District of Helsinki and Uusimaa, Hyvinkää, Finland
- ⁵ Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland
- ⁶ Department of Psychiatry, Seinäjoki Central Hospital, Seinäjoki, Finland

Concerns regarding the possible effects of recent changes in legislation on cannabis use and its adverse sequelae are topical [21, 22]. Planning harm reduction measures is thus particularly timely, and knowledge of the mechanisms by which cannabis use is possibly associated with serious adverse outcomes such as intentional self-injury must be furthered to guide these efforts. While a mediating role of cannabis use in complex pathways between psychopathology and self-injury has been suggested, these theories are backed by only limited empirical evidence [23]. First cannabis use has been associated with psychiatric disorders such as psychosis and depression [1, 4, 5•, 24], both of which have been associated with self-harm, suicide attempt, and suicide death [25–27]. Moreover, cannabis withdrawal syndrome often presents with depressive mood or anxiety [28]. Thus, it is reasonable to believe that these affective symptoms related to cannabis withdrawal could elevate the risk of intentional self-injury. This theory is backed by findings indicating that risk of suicide attempt is elevated during the same day when cannabis is consumed [29], as withdrawal symptoms may emerge within 24 h of last exposure to cannabis [30]. Also, imaging studies with both experimental and observational designs point to the capacity of cannabis or tetrahydrocannabinol (THC) to induce changes in brain regions of relevance to impulse control [31], and poor impulse control has been associated with self-injurious behaviors [32]. Experimental research indicates that oral ingestion of THC, a partial cannabinoid receptor agonist, may cause suicidal ideation [33]. In the same vein, the cannabinoid receptor 1 antagonist rimonabant was associated with serious psychiatric side effects in a randomized controlled trial with more suicide deaths and suicide attempts observed in the group receiving active treatment than in the placebo group. [34]. Lastly, it has been postulated that human endocannabinoids may play a role in the pathophysiology of suicidal behaviors [35, 36]. Taken together, these data suggest that there might be a biological mechanism underlying the association between cannabis use and intentional self-injury.

Previous meta-analyses and systematic reviews have focused mutually exclusively on the association of cannabis use with either suicidal behaviors [5•, 13••, 15, 37] or non-suicidal self-injury [38•]. In this narrative review, we aim to present the existing evidence base on all forms of intentional self-injury, i.e., self-harm, suicide attempt, and suicide. Moreover, findings of the most recent studies are included [14•, 39•, 40•]. As studies with cross-sectional designs do not allow for accounting for reverse causality, we aim to focus primarily on studies with longitudinal data such as prospective cohort studies and high-quality register-linkage studies. Emphasis is placed on studies with population-based data as opposed to those utilizing at-risk cohorts, as the former are more likely void of selection bias and to yield generalizable results. Importantly, we also review the evidence

regarding a dose–response relationship between cannabis use and the subsequent intentional self-injury, as this is one of the key criteria when attempting to infer causality [41]. The findings of relevant meta-analyses are also described.

Method

The search strings described in the meta-analyses by Borges et al. and Escelsior et al. were used to conduct a PubMed search to identify longitudinal studies assessing the association of cannabis use and intentional self-injury [13••, 38]. The search string for suicide and suicide attempt was (“cannabis” OR “marijuana” OR “marihuana”) AND (“suicide” OR “suicide attempt” OR “suicide ideation” OR “suicidal” OR “suicidality”) [13••]. For self-injurious behaviors, the following search string was utilized (“non-suicidal self-injury” OR NSSI OR “self-injury” OR “self-injuries” OR “self-injurious” OR “self-harm” OR “self-inflicted violence” OR “self-abuse” OR “wrist-cutting” OR “self-mutilation” OR “enucleation” OR “skin cutting” OR “burning” OR “self-hitting” OR “hair pulling” OR “skin picking” OR “nail-biting” OR “skin scratching” OR “head banging” OR “bruising” OR “self-hitting” OR “biting” OR “wound-excoriation” OR “bone-breaking” OR “face slapping”) AND (“cannabi*” OR “delta-9-tetrahydrocannabinol” OR “tetrahydrocannabinol” OR “THC” OR “cannabidiol” OR “CBD” OR “marijuana” OR “hashish”) [38]. These searches were conducted from the dates until which the respective meta-analyses had concluded their searches and up to the beginning of May 2022. Also, relevant existing meta-analyses [5•, 13••, 38], systematic reviews [15, 37], and recently published important longitudinal studies [40•] assessing these associations were hand-searched to identify additional references to relevant studies with longitudinal designs.

Results

Self-harm

“Self-harm,” “deliberate-self harm,” and “self-injurious behaviors” have been used almost interchangeably to denote self-injurious behaviors irrespective of preceding objective, i.e., whether or not a preceding intent to die was tied to the event [14•, 17, 31, 34]. Hence, outcomes thus defined do not discern between non-suicidal self-injury and suicide attempt.

In the recent meta-analysis by Escelsior et al. with nine studies available for analysis, cannabis use was associated with subsequent self-injurious behaviors (OR = 2.57; 95% CI 2.03–3.26) [38•]. However, the studies pooled in this analysis were markedly heterogenous as it included two cross-sectional studies [43, 44], one Mendelian randomization

study [45], studies focusing on veterans [46], or individuals with psychiatric disorders [47]. Although the focus of this meta-analysis was on self-injurious behaviors regardless of preceding intent, one study pooled in the meta-analyses had an outcome operationalized as suicide attempt [48].

To our knowledge, there are four adolescent studies examining the association of cannabis use and subsequent self-harm [14•, 17, 40•, 49]. A summary of these studies is presented in the online supplement table of Denissoff et al. [14•]. Two of these are population-based studies [14•, 17], whereas one study focused on adolescents receiving treatment for mood disorders [40•] and another study utilized a cohort of socio-economically deprived adolescents [49]. Also, this association has been examined in one population-based adult cohort [50].

Moran et al. utilized a school-based cohort of 1809 adolescents with both self-harm and cannabis use during the past 6 months assessed at four time points [17]. Self-harm was defined broadly encompassing even risk-taking. Thus, the cumulative incidence of self-harm by end of adolescence was 8%. Cannabis use during the past 6 months was associated with subsequent self-harm independent of sex, depression or anxiety, cigarette use, high risk-alcohol use, antisocial behavior, and parental divorce (aHR = 1.8; 95% CI 1.0–3.1). However, adolescent cannabis use was not associated with incident self-harm in adulthood in this study.

Fontanella et al. published a large register-linkage study ($n = 204\,780$) focusing on the association of cannabis use disorder (CUD) and subsequent severe self-harm requiring medical attention in adolescents receiving treatment for mood disorders (mean age = 17.2) [40•]. The outcome variable was operationalized as ICD-10 diagnostic codes indicating severe intentional self-injury. With a follow-up of only 1 year, the cumulative incidence of the outcome thus defined was 1%. CUD was found to be associated with subsequent severe self-harm independently of comorbid substance use disorders (SUD), psychiatric comorbidities, age, sex, and ethnicity (aHR 3.28; 95% CI 2.55–4.22).

Denissoff et al. conducted the first population-based cohort study assessing the association of adolescent cannabis use and subsequent severe self-harm requiring medical attention [14•]. The adolescents participating in the Northern Finland 1986 Birth Cohort study were asked information about their substance use including cannabis at age 15/16 years after which they were followed for 18 years (i.e., until age 33 years) with nationwide healthcare registries for ICD-10 codes implying severe intentional self-injury requiring medical attention. Using this data, lifetime cannabis use by age 15/16 years was associated with subsequent severe self-harm independent of other illicit drug use, frequent alcohol intoxications, parental psychiatric disorders, and psychiatric disorders at baseline (HR 2.06; 95% CI 1.07–3.95).

An inclusive self-harm variable encompassing even “denying oneself a necessity” was utilized in a study by Moller et al. in their population-based study focusing on adults [50]. In this study, two cohorts of adults in their third and fifth decades of life were pooled to examine the antecedents of self-harm. Past year cannabis use was associated with self-harm even after extensive confounder control including use of ecstasy and amphetamines, problem alcohol use, smoking, and several sociodemographic variables (aOR 1.77; 95% CI 1.09–2.87).

In sum, five longitudinal studies on cannabis use and subsequent self-harm [14•, 17, 40•, 49, 50] have been published with four of them [14•, 17, 40•, 50] reporting a significant positive finding. The cannabis exposure variables of these studies vary greatly from lifetime use as a binary variable [14•] to cannabis use disorder [40•]. Even more importantly, outcome variables range from very inclusive definitions of self-harm [17, 50] to severe self-harm requiring medical attention [14•, 40•]. We are not aware of studies or meta-analyses focusing on heavy use or high-potency cannabis and subsequent self-harm.

Suicide Attempt

The association of cannabis use and subsequent suicide attempt has been assessed in two meta-analyses: The meta-analysis by Borges et al. (2016) included studies on both adolescent and adult populations with both longitudinal and case-control designs. There, pooled estimates were reported for the associations between cannabis use and suicide attempt (OR = 2.23; 95% CI 1.24–4.00) and heavy cannabis use and subsequent suicide attempt (OR = 3.20; 95% CI 1.72–5.94). In this meta-analysis, “heavy” cannabis use in the studies available for analysis ranged from monthly [51, 52] to daily [53] use. This was also assessed by Gobbi et al. (2019) in their meta-analysis pooling three longitudinal adolescent studies in which an association between adolescent cannabis use and subsequent suicide attempt was reported (OR = 3.46; 95% CI; 1.53–7.84) [5•]. A separate meta-analysis was not reported for heavy cannabis use.

To our knowledge, there are 16 prospective longitudinal studies assessing the association between specifically adolescent cannabis use and subsequent suicide attempt [48, 51–65], of which eight [48, 53, 55–57, 60, 63, 64] reported a statistically significant association. While there is a lack of consistency in the findings, the studies are also very heterogeneous in terms of measurement of suicidal behaviors, sample sizes and characteristics, lengths of follow-up, and covariates controlled for (for a summary, please see online supplement table in Denissoff et al.) [14•]. Notably, four studies focused on special populations such as individuals with suicidal ideation [57], individuals with suicidal ideation or a history of non-suicidal self-harm [48], individuals

with a substantial genetic disposition to alcohol use disorders [54], and a sample consisting of participants of African American origin [59]. Furthermore, of the eight studies reporting a significant positive finding, four [48, 55, 56, 60] did not adjust for any other substance use in adolescence.

Most of the few longitudinal studies examining this association in adults have utilized selective samples: A Danish register-linkage study examined the association of cannabis use disorder with suicide attempt in individuals diagnosed with psychiatric disorders and found this association only in patients diagnosed with schizophrenia [66]. A study focusing on people who inject drugs reported a negative finding on an association of cannabis use and suicide attempt. [67]. A cohort study with a sample comprising of African Americans found an association between cannabis and suicide attempt in the male subsample only [68]. Population-based studies are scarce. One large population-based prospective study with a 3-year follow-up using data from the National Epidemiological Survey on Alcoholism and Related Conditions (NESARC) examined the association between cannabis use and “suicidality” with ideation and attempt compressed into a single outcome variable [69]. The analyses were stratified by sex, and a significant positive association was reported for men (aOR = 4.28; 95% CI 1.32–13.28) but not for women (aOR = 0.75 (95% CI 0.28–2.05). When suicide attempt was studied as a separate outcome, the analyses yielded statistically nonsignificant findings for both sexes.

To conclude, longitudinal studies examining adolescent cannabis use and subsequent suicide attempt are inconsistent in their findings and markedly heterogenous in accounting for confounding bias introduced by other substance use. The few longitudinal observational studies assessing this association using adult cohorts have mostly utilized samples from high-risk populations limiting the generalizability of the results. There is some meta-analytic evidence implying a dose–response relationship between cannabis use and suicide attempt [13••].

Suicide

In the meta-analysis by Borges et al. pooling case–control and longitudinal studies, cannabis use was associated with subsequent suicide death (OR 2.55; 95% CI 1.25–5.27). Dose response was not assessed in these analyses. The nine longitudinal studies assessing this association are summarized in Table 1 [14•, 39•, 40•, 66, 70••, 71–74]. Again, these studies are markedly heterogenous in terms of sample characteristics and cannabis exposure variables. To date, only three studies have utilized population-based data. Price et al. and Denissoff et al. utilized population-based cohorts with prospective data and cannabis use history-type exposure variables [14•, 70••], and Crump et al. conducted a

register-linkage study including all adults living in Sweden with CUD as the exposure variable [39•].

Six studies have focused on special populations such as adolescents receiving treatment for mood disorders or individuals diagnosed with psychiatric disorders [40•, 66], veterans [74], and patients treated for CUD [71] or other substance use disorders [73]. Lastly one study utilized a cohort of individuals reported by authorities of cannabis possession [72]. The findings have been mixed with five studies reporting a significant positive finding [39•, 66, 71, 72, 74]. Only one study with a suicide death outcome assessed frequency of cannabis use with a multiclass exposure variable [70••]. The sample of this study comprised of males only thus limiting the generalizability of the findings.

Crump et al. conducted a register base study on all 6,947,191 adults in Sweden [39•]. Those diagnosed with SUD, including CUD, were identified from national registries on ICD-10 diagnoses made in clinical practice. After adjusting for age, sex, marital status, education, employment, income, psychiatric, and SUD comorbidities, CUD was associated with subsequent suicide death as compared to the general population (aHR = 3.10, 95% CI 2.42–3.97). In an analysis stratified by sex, the effect sizes for men and women did not differ with statistical significance. While statistical significance was retained for all SUDs including CUD in all fully adjusted multivariable models, opioid and sedative/hypnotic use disorders were associated with the greatest risk of suicide death.

Price et al. conducted the largest population-based prospective cohort study assessing this association [70••]. The sample included all Swedish males aged 18–20 who were conscripted during the year 1969–1970 ($n = 50,087$). IQ tests were conducted by a psychologist and detailed information on alcohol and drug use gathered at the time of conscription. If a psychiatric disorder was reported by the conscript or suspected by the psychologist, the conscript was referred to a psychiatrist for diagnostic evaluation according to the ICD-8. Lifetime cannabis use at baseline was coded as never, 1–10 times, 11–50 times, and more than 50 times. Lifetime use was studied both as binary variable (yes/no) and as a four-class variable with the aforementioned categories. Lifetime cannabis use at baseline was reported by 10.7% of the participants. During 33 years of follow-up, the cumulative incidences of definite suicides and undetermined deaths were 0.9% and 0.3%, respectively. A crude association was reported for lifetime cannabis use (OR 1.63; 95% CI 1.28–2.07). With the multiclass cannabis variable, an association was seen for those reporting lifetime use of at least 50 times even in crude analysis (OR 3.45; 95% CI 2.21–5.39). The association of both binary and multiclass cannabis use variables and suicide death attenuated to nonsignificant after extensive confounder control including variables such as smoking more than > 20 cigarettes/day, alcohol

Table 1 Studies with longitudinal data examining association of cannabis exposure with suicide death

Study	Study type	Sample	Sample size	Exposure variable	Length of follow-up (years)	Effect size (95% CI)	Covariates
Arendt et al. (2013) [71]	Register-linkage	Patients treated for CUD, Denmark in years 1996–2006	6445	CUD (ICD-10) Standardized mortality ratios utilized	4.1 (mean)	SMR All: 5.3 (3.3–7.9) Excluding those with use of other illicit 4.8 (2.4–8.9)	None
Bohnert et al. (2017) [74]	Register-linkage	All VHA users in 2005 alive in beginning of 2006, USA	4,863,086	CUD (ICD-10)	6	HR Males: 1.16 (1.02–1.33) Females: 1.01 (0.45–2.26)	Age, Charlson Comorbidity Index, and psychiatric diagnoses
Crump et al. (2021) [39]	Register-linkage	All persons aged ≥ 18 years living in Sweden at least 2 years	6,947,191	CUD (ICD-10)	13	HR 3.10 (2.42–3.97)	Age, sex, marital status, education, employment, and income, psychiatric, SUD, and somatic comorbidities
Denissoff et al. (2021) [14]	Prospective cohort	Northern Finland 1986 Birth Cohort	6582	Lifetime use at age 15/16 (yes/no)	18	HR 2.60 (0.77–8.78)	None
Fontanella (2021)	Register-linkage	Adolescents receiving treatment for mood disorders	204,780	CUD (ICD-10)	1	HR 1.22 (0.44–3.43)	Age, sex, race, insurance status, urbanicity, psychiatric and SUD comorbidities, and prior psychiatric history (including self-harm)
Hesse (2020)	Register-linkage	People treated for drug use disorders in Denmark 2000–2010 and matched controls	DUD-patients 27,942	Cannabis use (yes/no)	10 at most	Lower risk for cannabis users! HR 0.69 (0.50–0.96)	None
Pavardi (2011)	Register-linkage	Heroin users, reported to authorities for cannabis possession and in treatment for DUD, Bologna, Italy	191	DUD patient reported for cannabis possession to authorities Standardized mortality ratios utilized	14 at most	SMR 25.32 (8.17–78.50)	None
Price (2009)	Prospective cohort	Conscripted males in 1969–1970, Sweden	50,087	Lifetime use Never, 1–10 times, 1–50 times, over 50 times	33 years	Negative finding for both lifetime use and with multiclass variable	Daily smoking, hazardous drinking, other illicit drug use, psychiatric disorder at baseline, low IQ, demographics

Table 1 (continued)

Study	Study type	Sample	Sample size	Exposure variable	Length of follow-up (years)	Effect size (95% CI)	Covariates
Ostergaard (2017)	Register-linkage	People born in Denmark diagnosed with psychiatric disorders	Schizophrenia 35,625 Bipolar disorder 9279 Depression 72,530 Personality disorder 63,958	CUD ICD-10	Lengths of follow-up reported for each diagnosis group in person years	Only for bipolar disorder significant positive finding HR = 1.86 (1.15–2.99)	Sex, calendar year and age at first diagnosis of the mental illness in question

Statistically significant findings in bold. CUD cannabis use disorder, DUD drug use disorder, SMR standardized mortality rate, HR hazard ratio, CI confidence interval

consumption of more than 250 g/week, other illicit drug use, and psychiatric disorder at baseline.

The study by Denissoff et al. is described in detail in the section on self-harm [14•]. In this birth cohort study with a follow-up of 18 years, the cumulative incidence of suicide was 0.3%. Cannabis use was not associated with suicide even in crude analysis. In univariable screening, the prevalence of lifetime cannabis use did not differ significantly among those who died by suicide and other study participants (13.6% vs 5.7%, $p = 0.128$).

In conclusion, most observational studies with prospective data examining cannabis use and suicide have focused on at-risk populations (for a summary of these studies, please see Table 1). Of the three population-based studies published thus far [14•, 39•, 70••], only one reported a statistically significant positive association [39•]. Lastly, while it would be important to learn more about the association of frequency of cannabis use and suicide death, most studies examining this association have operationalized the exposure as CUD. This methodological choice precludes dose–response analysis.

Discussion

Key considerations when studying causality include plausibility of the association and complementary lines of evidence, consistency of findings, evidence of dose response, temporality of the association, and issues pertaining to confounding bias [41]. As described in the introduction, theories have been presented regarding putative mechanisms by which cannabis use could be linked to subsequent self-injurious behaviors [23]. There is limited complementary evidence from experimental studies indicating that orally ingested THC has the capacity to induce suicidal ideation [33], and Mendelian randomization studies on these associations have also been published recently [45, 75, 76]. However, as described in the previous sections, the findings from longitudinal observational studies examining the association of cannabis use and all forms of intentional self-injury are markedly inconsistent. Furthermore, the variation across studies in the way in which self-harm has been operationalized limits the comparability of the results.

There seems to be limited evidence of a dose–response effect for cannabis use and subsequent suicide attempt [13••] and insufficient such evidence for self-harm or suicide. Notably, the majority of studies examining suicide have examined this association with CUD as a predictor limiting the analyses for dose response [39•, 40•, 71]. When assessing dose response, it should be noted that the potency of cannabis has increased steadily during the last three decades [77], and thus the risks of cannabis consumption today may be higher than, e.g., in 1969–1970, when data on cannabis

consumption was gathered in the Swedish conscript cohort study [70••]. Importantly, we are not aware of studies in which the persistence of cannabis use and its effects on subsequent risk of intentional self-injury would have been studied by assessing cannabis use at multiple time points. Neither have complementary sources of information on cannabis exposure, such as urine screens or hair samples, been utilized in the longitudinal observational studies assessing these associations. Lastly, while the association of high-potency cannabis with other adverse outcomes such as psychotic and affective disorders has been examined in previous literature [78], this exposure has not been studied with respect to subsequent intentional self-injury.

Residual confounding is always a concern in observational studies. Particularly, addressing confounding bias introduced by other substance use is of significance, as polysubstance use is common [79], other illicit drug use and heavy drinking have been found to be associated with suicide attempt [80, 81], and opioid and sedative use disorders may predict subsequent suicide more strongly than CUD [39•]. As discussed in the respective section on suicide attempt, a significant proportion of adolescent studies reporting a positive outcome regarding this association failed to adjust any concomitant use of substances other than cannabis [48, 55, 56, 60]. Assessing the confounding effect of psychiatric disorders preceding cannabis use is also crucial, as psychiatric disorders are established risk factors for intentional self-injury [82–84], and conversely early psychopathology has been also associated with initiation of cannabis use [85]. Most adolescent studies assessing outcomes related to intentional self-injury have taken to account this source of confounding (see online supplement in Denissoff et al.) [14•]. It may also be that the mechanism by which cannabis use confers risk to subsequent intentional self-injury involves contribution to the onset of psychiatric disorders. Thus, as Carvalho et al. point out, psychiatric disorders emerging after onset of cannabis use may be regarded as mediators rather than confounders of these associations [15]. Lastly, though temporality is not an issue when examining incidental behavior such as intentional self-injury with longitudinal data, previous self-injurious behavior is known to be a particularly strong predictor of future intentional self-injury [19, 20]. It is imperative that this source of confounding be addressed by some means in longitudinal observational studies, e.g., by excluding those with previous intentional self-injury from the analyses [14•].

The lack of evidence for a positive association between cannabis use and suicide may be due to the fact that suicide is such a rare outcome, and the pathway leading to death by suicide is notoriously complex and involves a confluence developmental and acquired risk factors as well as acute stressors [86]. A positive finding regarding an association between CUD and subsequent suicide has been reported in

only one population-based register-linkage study [39•]. Most importantly the large Swedish conscript cohort study with detailed information on heavy lifetime cannabis exposure and a long follow-up of 33 years reported a negative finding [70••]. Notably, using the same data and a similar multivariable model, a positive association was found between cannabis use and schizophrenia, another rare outcome [87]. Thus, Price et al. concluded that the lack of an association between cannabis use and suicide death was not explained by power issues only and that cannabis use might not in fact be associated with suicide death.

Conclusions

The association of cannabis use and intentional self-injury has frequently been reported in existing literature. However, the existing evidence base is not rigorous enough to draw definite conclusions. Even if cannabis use might not prove to be independently associated with intentional self-injury, it may yet have clinical importance as an adverse prognostic marker for such outcomes. Adequately powered longitudinal population-based studies, with preferably multiple time points of cannabis use assessment are needed to shed further light on these associations. To elucidate a possible dose–response relationship between cannabis use and different forms of subsequent self-harm, studies focusing on high potency cannabis and subsequent self-injury would be an important increment to the existing evidence base. In the same vein, knowledge of THC content of cannabis consumed and even utilization of standard unit doses for THC would serve this purpose as well [88, 89]. There is also a need to gain consensus on the definition of self-harm to improve the comparability of the results of future studies. Lastly, studies with within-person analyses may be needed to account for unmeasured confounding and mitigate concerns for type II error [90].

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References

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

1. Moore TH, Zammit S, Lingford-Hughes A, Barnes TR, Jones PB, Burke M, Lewis G. Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. *Lancet*. 2007;370:319–28.
2. Mustonen A, Niemelä S, Nordström T, Murray GK, Mäki P, Jääskeläinen E, Miettunen J. Adolescent cannabis use, baseline prodromal symptoms and the risk of psychosis. *Br J Psychiatry*. 2018;212:227–33.
3. Mustonen A, Hielscher E, Miettunen J, Denissoff A, Alakokkare A-E, Scott JG, Niemelä S. Adolescent cannabis use, depression and anxiety disorders in the Northern Finland Birth Cohort 1986. *BJPsych Open*. 2021;7:e137.
4. Lev-Ran S, Roerecke M, Le Foll B, George TP, McKenzie K, Rehm J. The association between cannabis use and depression: a systematic review and meta-analysis of longitudinal studies. *Psychol Med*. 2014;44:797–810.
5. ● Gobbi G, Atkin T, Zytynski T, et al. Association of cannabis use in adolescence and risk of depression, anxiety, and suicidality in young adulthood: a systematic review and meta-analysis. *JAMA Psychiat*. 2019;76:426–34. **Only meta-analysis focusing on adolescent cannabis use and suicide attempt**
6. Marconi A, Di Forti M, Lewis CM, Murray RM, Vassos E. Meta-analysis of the association between the level of cannabis use and risk of psychosis. *Schizophr Bull*. 2016;42:1262–9.
7. Di Forti M, Quattrone D, Freeman TP, et al. The contribution of cannabis use to variation in the incidence of psychotic disorder across Europe (EU-GEI): a multicentre case-control study. *The Lancet Psychiatry*. 2019;6:427–36.
8. Hindley G, Beck K, Borgan F, Ginstet CE, McCutcheon R, Kleinloog D, Ganesh S, Radhakrishnan R, D'Souza DC, Howes OD. Psychiatric symptoms caused by cannabis constituents: a systematic review and meta-analysis. *The Lancet Psychiatry*. 2020;7:344–53.
9. Vaucher J, Keating BJ, Lasserre AM, et al. Cannabis use and risk of schizophrenia: a Mendelian randomization study. *Mol Psychiatry*. 2018;23:1287–92.
10. Hjorthøj C, Posselt CM, Nordentoft M. Development over time of the population-attributable risk fraction for cannabis use disorder in schizophrenia in Denmark. *JAMA Psychiat*. 2021;78:1013–9.
11. Robinson T, Ali MU, Easterbrook B, Hall W, Jutras-Aswad D, Fischer B. Risk-thresholds for the association between frequency of cannabis use and the development of psychosis: a systematic review and meta-analysis. *Psychol Med*. 2022;24:1–11.
12. D'Souza DC, DiForti M, Ganesh S, et al. Consensus paper of the WFSBP task force on cannabis, cannabinoids and psychosis. *World J Biol Psychiatry*. 2022. p. 1–24.
13. ●● Borges G, Bagge CL, Orozco R. A literature review and meta-analyses of cannabis use and suicidality. *J Affect Disord*. 2016;195:63–74. **Important meta-analysis focusing on cannabis use, suicide attempt and suicide death, with a separate meta-analysis on specifically heavy cannabis use and suicide attempt**
14. ● Denissoff A, Niemelä S, Scott JG, Salom CL, Hielscher E, Miettunen J, Alakokkare AE, Mustonen A. Does cannabis use in adolescence predict self-harm or suicide? Results from a Finnish Birth Cohort Study. *Acta Psychiatr Scand*. 2021;145(3):234–43. **First population-based study on early cannabis use and severe self-harm requiring medical attention**
15. Carvalho JV, Souza LS, Moreira EC. Association between cannabis use and suicidal behavior: a systematic review of cohort studies. *Psychiatry Res*. 2022;312:114555.
16. WHO. Suicide in the world: global health estimates. Geneva. 2019. <https://www.who.int/publications/i/item/9789240026643>. Accessed 01 Nov 2022.
17. Moran P, Coffey C, Romaniuk H, Olsson C, Borschmann R, Carlin JB, Patton GC. The natural history of self-harm from adolescence to young adulthood: a population-based cohort study. *Lancet*. 2012;379:236–43.
18. Swannell SV, Martin GE, Page A, Hasking P, St John NJ. Prevalence of nonsuicidal self-injury in nonclinical samples: systematic review, meta-analysis and meta-regression. *Suicide Life-Threatening Behav*. 2014;44:273–303.
19. Bostwick JM, Pabbati C, Geske JR, McKean AJ. Suicide attempt as a risk factor for completed suicide: even more lethal than we knew. *Am J Psychiatry*. 2016;173:1094–100.
20. Carroll R, Metcalfe C, Gunnell D. Hospital presenting self-harm and risk of fatal and non-fatal repetition: systematic review and meta-analysis. *PLoS ONE*. 2014;9(2):e89944.
21. Hinckley J, Bhatia D, Ellingson J, Molinero K, Hopfer C (2022) The impact of recreational cannabis legalization on youth: the Colorado experience. *Eur Child Adolesc Psychiatry*.
22. Cerdá M, Mauro C, Hamilton A, Levy NS, Santaella-Tenorio J, Hasin D, Wall MM, Keyes KM, Martins SS. Association between recreational marijuana legalization in the United States and changes in marijuana use and cannabis use disorder from 2008 to 2016. *JAMA Psychiat*. 2020;77:165–71.
23. Bartoli F, Lev-Ran S, Crocamo C, Carrà G. The interplay between cannabis use and suicidal behaviours: epidemiological overview, psychopathological and clinical models. *J Psychopathol*. 2018;2018:180–6.
24. Kiburi SK, Molebatsi K, Ntlantsana V, Lynskey MT. Cannabis use in adolescence and risk of psychosis: are there factors that moderate this relationship? A systematic review and meta-analysis. *Subst Abus*. 2021;42(4):527–42.
25. Lim KX, Rijdsdijk F, Hagenaars SP, Socrates A, Choi SW, Coleman JRI, Glanville KP, Lewis CM, Pingault JB. Studying individual risk factors for self-harm in the UK Biobank: a polygenic scoring and Mendelian randomisation study. *PLoS Med*. 2020;17(6):e1003137.
26. Huang X, Fox KR, Ribeiro JD, Franklin JC. Psychosis as a risk factor for suicidal thoughts and behaviors: a meta-analysis of longitudinal studies. *Psychol Med*. 2018;48:765–76.
27. Ribeiro JD, Huang X, Fox KR, Franklin JC. Depression and hopelessness as risk factors for suicide ideation, attempts and death: meta-analysis of longitudinal studies. *Br J Psychiatry*. 2018;212:279–86.
28. Bahji A, Stephenson C, Tyo R, Hawken ER, Seitz DP. Prevalence of cannabis withdrawal symptoms among people with regular or dependent use of cannabinoids: a systematic review and meta-analysis. *JAMA Netw open*. 2020;3(4):e202370.
29. Sellers CM, Diaz-Valdes Iriarte A, Wyman Battalen A, O'Brien KHMM. Alcohol and marijuana use as daily predictors of suicide ideation and attempts among adolescents prior to psychiatric hospitalization. *Psychiatry Res*. 2019;273:672–7.

30. Vandrey RG, Budney AJ, Hughes JR, Liguori A. A within-subject comparison of withdrawal symptoms during abstinence from cannabis, tobacco, and both substances. *Drug Alcohol Depend.* 2008;92:48–54.
31. Wrege J, Schmidt A, Walter A, Smieskova R, Bendfeldt K, Radue E-W, Lang U, Borgwardt S. Effects of cannabis on impulsivity: a systematic review of neuroimaging findings. *Curr Pharm Des.* 2014;20:2126–37.
32. Klonsky ED, May A. Rethinking impulsivity in suicide. *Suicide Life-Threatening Behav.* 2010;40:612–9.
33. Koppel BS, Brust JCM, Fife T, Bronstein J, Youssof S, Gronseth G, Gloss D. Systematic review: efficacy and safety of medical marijuana in selected neurologic disorders: report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology.* 2014;82:1556–63.
34. 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.
35. Mannekote Thippaiah S, Iyengar SS, Vinod KY. Exo- and endocannabinoids in depressive and suicidal behaviors. *Front psychiatry.* 2021;12:636228.
36. Herranz-Herrer J, Gil-Benito E, Ponte-López T, Ortega-Gutiérrez S, Macicior J, Rosado-García S, Sánchez-López AJ, Blasco-Fontecilla H. Serum endocannabinoid levels in suicide attempters: a pilot study. *Eur Neuropsychopharmacol.* 2020;40:52–60.
37. Schmidt K, Tseng I, Phan A, Fong T, Tsuang J. A systematic review: adolescent cannabis use and suicide. *Addict Disord Treat.* 2020;19:146–51.
38. Escelsior A, Belvederi Murri M, Pietro CG, et al. Cannabinoid use and self-injurious behaviours: a systematic review and meta-analysis. *J Affect Disord.* 2021;278:85–98 (Only meta-analysis focusing on cannabis use and self-harm).
39. Crump C, Sundquist J, Kendler KS, Edwards AC, Sundquist K. Comparative risk of suicide by specific substance use disorders: a national cohort study. *J Psychiatr Res.* 2021;144:247–54. **Exceptionally large register-linkage study focusing on SUDs (including CUD) and suicide death**
40. Fontanella CA, Steelesmith DL, Brock G, Bridge JA, Campo JV, Fristad MA. Association of cannabis use with self-harm and mortality risk among youths with mood disorders. *JAMA Pediatr.* 2021;175:377. **Large register-linkage study focusing on adolescent CUD, severe self-harm requiring medical attention and suicide death**
41. Van Reekum R, Streiner DL, Conn DK. Applying Bradford Hill's criteria for causation to neuropsychiatry: challenges and opportunities. *J Neuropsychiatry Clin Neurosci.* 2001;13:318–25.
42. Samari E, Shahwan S, Abdin E, Zhang Y, Sambasivam R, Teh WL, Ong SH, Chong SA, Subramaniam M. An exploration of differences between deliberate self-harm with and without suicidal intent amongst a clinical sample of young people in Singapore: a cross-sectional study. *Int J Environ Res Public Health.* 2020;17(4):1429.
43. Few LR, Grant JD, Nelson EC, et al. Cannabis involvement and nonsuicidal self-injury: a discordant twin approach. *J Stud Alcohol Drugs.* 2016;77:873.
44. Harford TC, Chen CM, Grant BF. Other- and self-directed forms of violence and their relationship with number of substance use disorder criteria among youth ages 12–17: results from the National Survey on Drug Use and Health. *J Stud Alcohol Drugs.* 2016;77:277–86.
45. Hodgson K, Coleman JRI, Hagenaaers SP, Purves KL, Glanville K, Choi SW, O'Reilly P, Breen G, Lewis CM. Cannabis use, depression and self-harm: phenotypic and genetic relationships. *Addiction.* 2020;115:482–92.
46. Kimbrel NA, Meyer EC, DeBeer BB, Gulliver SB, Morissette SB. The impact of cannabis use disorder on suicidal and nonsuicidal self-injury in Iraq/Afghanistan-Era Veterans with and without mental health disorders. *Suicide Life-Threatening Behav.* 2018;48:140–8.
47. Carabellese F, Candelli C, Martinelli D, La Tegola D, Catanese R. Cannabis use and violent behaviour: a psychiatric patients cohort study in Southern Italy. *Riv Psichiatri.* 2013;48:43–50.
48. Mars B, Heron J, Klonsky ED, Moran P, O'Connor RC, Tilling K, Wilkinson P, Gunnell D. Predictors of future suicide attempt among adolescents with suicidal thoughts or non-suicidal self-harm: a population-based birth cohort study. *The Lancet Psychiatry.* 2019;6:327–37.
49. Spears M, Montgomery AA, Gunnell D, Araya R. Factors associated with the development of self-harm amongst a socio-economically deprived cohort of adolescents in Santiago, Chile. *Soc Psychiatry Psychiatr Epidemiol.* 2014;49:629–37.
50. Moller CI, Tait RJ, Byrne DG. Self-harm, substance use and psychological distress in the Australian general population. *Addiction.* 2013;108:211–20.
51. Pedersen W. Does cannabis use lead to depression and suicidal behaviours? A population-based longitudinal study. *Acta Psychiatr Scand.* 2008;118:395–403.
52. Rasic D, Weerasinghe S, Asbridge M, Langille DB. Longitudinal associations of cannabis and illicit drug use with depression, suicidal ideation and suicidal attempts among Nova Scotia high school students. *Drug Alcohol Depend.* 2013;129:49–53.
53. Silins E, Horwood LJ, Patton GC, et al. Young adult sequelae of adolescent cannabis use: an integrative analysis. *The Lancet Psychiatry.* 2014;1:286–93.
54. 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.
55. Borowsky IW, Ireland M, Resnick MD. Adolescent suicide attempts: risks and protectors. *Pediatrics.* 2001;107:485–93.
56. Borges G, Benjet C, Orozco R, Medina-Mora ME, Menendez D. Alcohol, cannabis and other drugs and subsequent suicide ideation and attempt among young Mexicans. *J Psychiatr Res.* 2017;91:74–82.
57. Clarke MC, Coughlan H, Harley M, Connor D, Power E, Lynch F, Fitzpatrick C, Cannon M. The impact of adolescent cannabis use, mood disorder and lack of education on attempted suicide in young adulthood. *World Psychiatry.* 2014;13:322–3.
58. Hengartner MP, Angst J, Ajdacic-Gross V, Rössler W. Cannabis use during adolescence and the occurrence of depression, suicidality and anxiety disorder across adulthood: findings from a longitudinal cohort study over 30 years. *J Affect Disord.* 2020;272:98–103.
59. Juon HS, Ensminger ME. Childhood, adolescent, and young adult predictors of suicidal behaviors: a prospective study of African Americans. *J Child Psychol Psychiatry Allied Discip.* 1997;38:553–63.
60. Roberts RE, Roberts CR, Xing Y. One-year incidence of suicide attempts and associated risk and protective factors among adolescents. *Arch Suicide Res.* 2010;14:66–78.
61. Thompson MP, Light LS. Examining gender differences in risk factors for suicide attempts made 1 and 7 years later in a nationally representative sample. *J Adolesc Heal.* 2011;48:391–7.
62. Weeks M, Colman I. Predictors of suicidal behaviors in Canadian adolescents with no recent history of depression. *Arch Suicide Res.* 2017;21:354–64.
63. Wilcox HC, Anthony JC. The development of suicide ideation and attempts: an epidemiologic study of first graders followed into young adulthood. *Drug Alcohol Depend.* 2004;76:S53–S67.
64. Fergusson DM, Horwood LJ, Swain-Campbell N. Cannabis use and psychosocial adjustment in adolescence and young adulthood. *Addiction.* 2002;97:1123–35.

65. Newcomb MD, Scheier LM, Bentler PM. Effects of adolescent drug use on adult mental health: a prospective study of a community sample. *Exp Clin Psychopharmacol*. 1993;1:215–41.
66. Østergaard MLD, Nordentoft M, Hjorthøj. Associations between substance use disorders and suicide or suicide attempts in people with mental illness: a Danish nation-wide, prospective, register-based study of patients diagnosed with schizophrenia, bipolar disorder, unipolar depression or personality disorder. *Addiction*. 2017;112(7):1250–9.
67. Artenie AA, Bruneau J, Zang G, Lespérance F, Renaud J, Tremblay J, Jutras-Aswad D. Associations of substance use patterns with attempted suicide among persons who inject drugs: can distinct use patterns play a role? *Drug Alcohol Depend*. 2015;147:208–14.
68. Friedman AS, Terras A, Zhu W, McCallum J. Depression, negative self-image, and suicidal attempts as effects of substance use and substance dependence. *J Addict Dis*. 2008;23(4):55–71.
69. Shalit N, Shoval G, Shlosberg D, Feingold D, Lev-Ran S. The association between cannabis use and suicidality among men and women: a population-based longitudinal study. *J Affect Disord*. 2016;205:216–24.
70. ●● Price C, Hemmingsson T, Lewis G, Zammit S, Allebeck P. Cannabis and suicide: longitudinal study. *Br J Psychiatry*. 2009;195:492–7. **Large nationally representative cohort study on cannabis use and suicide death with extensive confounder control**
71. Arendt M, Munk-Jørgensen P, Sher L, Jensen SOW. Mortality following treatment for cannabis use disorders: predictors and causes. *J Subst Abuse Treat*. 2013;44:400–6.
72. Pavarin RM, Berardi D. Mortality risk in a cohort of subjects reported by authorities for cannabis possession for personal use. Results of a longitudinal study - PubMed. *Epidemiol prev*. 2011;35:89–93.
73. Hesse M, Thylstrup B, Seid AK, Skogen JC. Suicide among people treated for drug use disorders: a Danish national record-linkage study. *BMC Public Health*. 2020;20(1):146.
74. Bohnert KM, Ilgen MA, Louzon S, McCarthy JF, Katz IR. Substance use disorders and the risk of suicide mortality among men and women in the US Veterans Health Administration. *Addiction*. 2017;112:1193–201.
75. Orri M, Séguin JR, Castellanos-Ryan N, Tremblay RE, Côté SM, Turecki G, Geoffroy MC. A genetically informed study on the association of cannabis, alcohol, and tobacco smoking with suicide attempt. *Mol Psychiatry*. 2021;26(9):5061–70.
76. Lim KX, Rijdsdijk F, Hagenaars SP, Socrates A, Choi SW, Coleman JRI, Glanville KP, Lewis CM, Pingault JB. Studying individual risk factors for self-harm in the UK Biobank: a polygenic scoring and Mendelian randomisation study. *PLoS Med*. 2020;17(6):e1003137.
77. Freeman TP, Craft S, Wilson J, Stylianou S, ElSohly M, Di Forti M, Lynskey MT. Changes in delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) concentrations in cannabis over time: systematic review and meta-analysis. *Addiction*. 2021;116:1000–10.
78. Hines LA, Freeman TP, Gage SH, Zammit S, Hickman M, Cannon M, Munafo M, MacLeod J, Heron J. Association of high-potency cannabis use with mental health and substance use in adolescence. *JAMA Psychiat*. 2020;77:1044.
79. Halladay J, Woock R, El-Khechen H, et al. Patterns of substance use among adolescents: a systematic review. *Drug Alcohol Depend*. 2020;216:108222.
80. Wong SS, Zhou B, Goebert D, Hishinuma ES. The risk of adolescent suicide across patterns of drug use: a nationally representative study of high school students in the United States from 1999 to 2009. *Soc Psychiatry Psychiatr Epidemiol*. 2013;48:1611–20.
81. Aseltine RH, Schilling EA, James A, Glanovsky JL, Jacobs D. Age variability in the association between heavy episodic drinking and adolescent suicide attempts: findings from a large-scale, school-based screening program. *J Am Acad Child Adolesc Psychiatry*. 2009;48:262–70.
82. Olfson M, Stroup TS, Huang C, Wall MM, Crystal S, Gerhard T. Suicide risk in Medicare patients with schizophrenia across the life span. *JAMA Psychiat*. 2021;78:876–85.
83. Nordentoft M, Wahlbeck K, Hällgren J, Westman J, Ösby U, Alinaghizadeh H, Gissler M, Laursen TM. Excess mortality, causes of death and life expectancy in 270,770 patients with recent onset of mental disorders in Denmark, Finland and Sweden *PLoS One*. 2013;8: e55176.
84. Novick DM, Swartz HA, Frank E. Suicide attempts in bipolar I and bipolar II disorder: a review and meta-analysis of the evidence. *Bipolar Disord*. 2010;12:1–9.
85. Miettunen J, Murray GK, Jones PB, et al. Longitudinal associations between childhood and adulthood externalizing and internalizing psychopathology and adolescent substance use. *Psychol Med*. 2014;44:1727–38.
86. Turecki G, Brent DA. Suicide and suicidal behaviour. *Lancet*. 2016;387:1227–39.
87. Zammit S, Allebeck P, Andreasson S, Lundberg I, Lewis G. Self reported cannabis use as a risk factor for schizophrenia in Swedish conscripts of 1969: historical cohort study. *BMJ*. 2002;325:1199–201.
88. Volkow ND, Weiss SRB. Importance of a standard unit dose for cannabis research. *Addiction*. 2020;115:1219–21.
89. Freeman TP, Lorenzetti V. Moving forwards with the standard THC unit. *Addiction*. 2020;115:1222–3.
90. Van Os J, Pries LK, Ten Have M, De Graaf R, Van Dorsselaer S, Bak M, Wittchen HU, Ruten BPF, Guloksuz S. Schizophrenia and the Environment: within-person analyses may be required to yield evidence of unconfounded and causal association—the example of cannabis and psychosis. *Schizophr Bull*. 2021;47:594–603.

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