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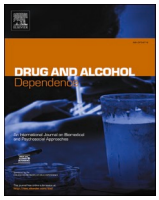

Review

The role of depression in the relationship between cannabis use and suicidal behaviours: A systematic review and meta-analysis

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ABSTRACT

Background: Depression has been cited as a possible confounder, moderator, and mediator of the relationship between cannabis use and suicidal behaviours. We aimed to assess the role of depression in the relationship between cannabis use and suicidal behaviours by systematically reviewing existing literature in the general population.
Methods: We systematically searched PubMed, Science Direct and PsycArticles from database inception to May 20th 2024, for quantitative observational studies investigating the role of depression in the association between cannabis use and suicidal behaviours. We conducted a meta-analysis to examine the confounding role of depression and search for qualitative arguments in favour of moderating and/or mediating roles of depression.
Results: We screened 1081 articles, selected 43 for full-text screening and finally included 25. Among adolescents, cannabis use was associated with suicidal ideation (OR = 1.46 [1.17, 1.83]) and suicide attempts (OR = 2.17 [1.56, 3.03]) in studies adjusting for depression. Among adults, cannabis use was associated with suicidal ideation (OR = 1.78 [1.28, 2.46]) in studies adjusting for depression. 12 out of 25 studies found no association between cannabis use and suicidality after adjustment for depression. Six studies investigated a potential moderating role of depression, with four reporting significant but conflicting results. No article investigated the mediating role of depression.
Discussion: There is a clear relationship between cannabis use and suicidal behaviours, which is partly confounded by depression. Studies investigating a moderating role of depression did not agree about the direction of moderation. Further research using methodologies that consider the chronology of events is needed.

1. Introduction

There is a growing body of evidence exploring the health consequences of cannabis use (Campeny et al., 2020; Memedovich et al., 2018; Solmi et al., 2023). Several factors have contributed to stimulate research on the health consequences of cannabis use, such as increased concentration of delta-9-tetrahydrocannabinol (THC) and changes in legal status in various countries (Solmi et al., 2023). Cannabis use has been found to be a risk factor of depression and anxiety (Solmi et al., 2023). This implies major public health implications, given that the populations vulnerable to poor mental health are also at risk for cannabis use (Solmi et al., 2023). Previous research has discussed the association between cannabis use and suicidality – defined as suicidal ideation, suicide attempt or suicide – with mixed findings (Borges et al., 2016; Campeny et al., 2020; Carvalho et al., 2022; Fresán et al., 2022; Gobbi et al., 2019). A review published in 2016 found consistent evidence that chronic cannabis use is associated with suicidality in adults (Borges et al., 2016). Another review, focusing on cohort studies, found no consensus in the scientific literature (Carvalho et al., 2022). A third review found evidence that cannabis use increased the risk of suicidality in young people aged 11–21 years, especially among those with early initiation (Fresán et al., 2022). These results are supported by another review focusing on young adult suicidality (Gobbi et al., 2019). The overall results seem to hint towards a positive association between

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cannabis use and suicidal behaviours, despite some inconsistencies. These inconsistencies could be explained by the variety of tools used to measure cannabis use and depression, as well as the heterogeneity of covariate adjustment.

Recent research suggests viewing mental health as a dynamic system of internal interactions rather than as separate, isolated disorders (Fried, 2022). This approach fits the study of suicidal behaviours, which are heterogeneous, interactionally complex and potentially transnosographic (Turecki and Brent, 2016). A widespread hypothesis is that cannabis use and suicidal behaviours could be linked through other mental conditions such as depression (Carvalho et al., 2022). Depression is consistently associated with both cannabis use and suicidality (K. Lönnqvist, 2000; Lev-Ran et al., 2014). Moreover, depression is often considered as a covariate in the association between cannabis use and suicidal behaviours, which might hide mediation or moderation (Carvalho et al., 2022). To our knowledge, only one review investigated this topic in the general population, restricting itself to the effects of cannabis use on depressed people (Tourjman et al., 2023). This review found three articles suggesting that cannabis use increases the risk of suicidal behaviours among depressed people (Tourjman et al., 2023).

There is a lack of exhaustive reviews on the role of depression in the relationship between cannabis and suicidality. Previous reviews have noted inconsistent adjustment for covariates such as depression, and meta-analyses often included adjusted and unadjusted results indiscriminately (Borges et al., 2016; Carvalho et al., 2022). Depression could partially or totally explain the relationship between cannabis use and suicidality, possibly increasing the risk of bias. Therefore, depression needs to be investigated as a confounder of the association between cannabis use and suicidality. Then again, depression could also play another role. First, it could mediate the relationship between cannabis use and suicidal behaviours, as cannabis use is linked to the onset of depression (Lev-Ran et al., 2014). Depression could also moderate the association between cannabis use and suicidal behaviours, increasing the risk of suicide among depressed people (Tourjman et al., 2023). Additionally, there is a need to study adolescents and adults separately but comparatively, as previous research either considered all populations indistinctively (Borges et al., 2016) or only focused on one of them (Fresán et al., 2022). Existing literature suggests that cannabis use may affect adults and adolescents differently, with adults being more vulnerable to adverse effects and adolescents more prone to developing addiction (Mokrysz et al., 2016).

Our first objective was to assess whether depression is a confounder of the association between cannabis use and suicidal behaviours. Second, we aimed to review existing evidence on the potential moderating or mediating role of depression in this relationship.

2. Methods

2.1. Search strategy and selection criteria

Our systematic review and meta-analysis followed PRISMA guidelines (Page et al., 2021). We searched three online databases (PubMed, PsycArticles, Science Direct) for full-text articles containing the following keywords: cannabis (OR marijuana) AND depression AND suicide, along with relevant synonyms (cannabi*, depressive disorder, depressivity – suicid*, suicidality, suicidal) and corresponding MeSH terms, from database inception to May 20th 2024. No language filters were applied. A quantitative studies filter was added in PsycArticles to reduce irrelevant results without excluding eligible studies. We initially searched Cochrane's CENTRAL but none of the reviews and trials identified fit for the subject. GMM conducted the database searches and extracted the titles and abstracts of resulting articles.

GMM and CS independently screened all references and assessed their eligibility using the software Rayyan (Ouzzani et al., 2016) with blinding enabled. Conflicts were resolved during an in-person reading session with insights from MM. We included studies with quantitative observational designs, either cross-sectional and longitudinal, which reported quantified associations between cannabis use as an exposure and suicidal behaviours as the outcome, adjusted for depression. Any measure of cannabis exposure (i.e cannabis use, frequent cannabis use, cannabis use disorder) was eligible for inclusion. We did not include studies which adjusted for depression using a broad-spectrum adjustment for psychiatric disorders (e.g "any psychiatric disorder" without separate effect estimates). We decided not to exclude cross-sectional studies because of their relevance to investigate confounding. Studies in which depression was considered as a potential mediator and/or moderator were also included. We excluded sub-group-specific research (e.g clinical samples, veterans, students) to ensure comparability with existing literature and avoid possible bias. We planned on excluding articles written in languages other than English, French, or Italian, but no eligible studies in other languages were identified during the search. We also excluded reviews, case reports and interventional studies. References from previous reviews (Borges et al., 2016; Carvalho et al., 2022; Fresán et al., 2022; Gobbi et al., 2019) were checked for additional eligible studies, leading to the inclusion of four more studies (Kahn and Wilcox, 2022; Silins et al., 2014; Swahn et al., 2012; Weeks and Colman, 2017).

2.2. Data analysis

GMM and CS independently extracted data from each study using a standardized table containing: author and publication year, country, sample size, sample age (adolescents/adults), exposure/outcome (definition, assessment and date of assessment if longitudinal), type of estimate, estimate, adjustment covariates, assessment of depression and type of inclusion of depression. After each reviewer completed data extraction, tables were cross-checked for inconsistencies which were resolved through discussion.

Risk of bias was independently assessed by GMM and CS using the Newcastle-Ottawa scale (NOS) (Stang, 2010) (appendix p.14). A modified version was used for cross-sectional studies (Moskalewicz and Oremus, 2020) (appendix p.16). Longitudinal studies were rated on a 9-point scale, while cross-sectional studies were rated on a 8-point scale. Disagreements over scores were resolved through discussion. Longitudinal studies scoring 4–6 were considered of medium quality while those scoring 7–9 points were considered of high quality. For cross-sectional studies, scores of 4–6 were considered medium quality and 7–8 were considered high quality.

A meta-analysis was implemented to assess the confounding effect of depression in the association between cannabis use and suicidal behaviours. Studies with adjusted odds-ratio (OR) which included depression among covariates were selected and grouped by exposure (any cannabis use, or frequent (at least weekly) cannabis use) and outcome (suicidal ideation/suicide attempts). We also separated estimates of studies of adolescents (from 11–21 years old at baseline) and adults. The age separation was based on previous literature to ensure comparability (Fresán et al., 2022). We conducted the meta-analysis across different sub-categories grouping at least 3 articles: any cannabis use/suicidal ideation among adolescents, any cannabis use/-suicide attempt among adolescents, any cannabis use/suicidal ideation among adults. There were not enough articles to study any cannabis use/suicide attempts among adults. Results focusing on frequent cannabis use ($>$ 1 per week) were put in supplementary materials (pp 3–4) to assess the influence of cannabis use exposure on effect estimates. We also conducted meta-regression analyses on pooled studies to test the effect of study type (longitudinal/cross-sectional), NOS quality rating (medium/high), other drugs use (control for at least tobacco and alcohol) and other mental health disorders.

Considering the high heterogeneity in study designs, assessment of cannabis use/depression/suicidal behaviours and covariates, we used random-effects pooled models. Resulting estimates were compared to previous literature to assess whether depression could be a confounder

of the relationship between cannabis use and suicidal behaviours (see Discussion). Articles included in the meta-analysis were checked for heterogeneity using I^2 (Ioannidis et al., 2007). Publication bias was checked using funnel plots screening and Egger's test. These analyses were implemented using packages meta (Schwarzer, 2024)/metasens (Schwarzer et al., 2023)/dmetar (Harrer et al., 2019) and forestplot (Gordon and Lumley, 2023) in R Statistical Software (R Core Team, 2021) version (v4.3.2).

Other articles were analysed qualitatively, focusing on findings about depression as a moderator and/or mediator of the relationship between cannabis use and suicidal behaviours. Both readers independently evaluated the articles and summarized the findings regarding moderation and mediation by depression before sharing their results. Both quantitative and qualitative analyses focused on suicidal ideation and suicide attempts, considering the low number of studies investigating suicides. Additionally, we checked for gender differences, dose-dependency and effects of other drugs. Finally, other marginal methodologies that could not be compared were analysed among articles that were already selected.

3. Results

A total of 1081 articles were screened, from which 43 were fully read and 25 were included in the systematic review (Fig. 1, complete list in appendix p18). A data summary of these articles can be found in appendix (pp6–13). Out of 17 cross-sectional studies, 6 were considered of intermediate quality and 11 of high quality. Among 8 longitudinal studies, 6 were of intermediate quality, while 2 were high quality.

3.1. Depression as a confounder

3.1.1. Pooled studies

12 articles met criteria to be included in the meta-analysis: 6 examining any cannabis use/suicidal ideation among adolescents (Hinckley et al., 2023; Lynskey et al., 2004; Rasic et al., 2013; Swahn et al., 2012; Weeks and Colman, 2017; Wong et al., 2013), 9 examining any cannabis use/suicide attempt among adolescents (du Roscoät et al., 2016; Hinckley et al., 2023; Lynskey et al., 2004; Oladunjoye et al., 2023; Rasic et al., 2013; Silins et al., 2014; Swahn et al., 2012; Weeks and Colman, 2017; Wong et al., 2013), and 5 examining any cannabis use/suicidal ideation among adults (Abdalla et al., 2019; Agrawal et al., 2017; Choi et al., 2016; Geda et al., 2022; Shalit et al., 2016). All articles adjusted for depression.

The pooled OR for suicidal ideation among adolescents cannabis users who use cannabis compared to adolescents who do not use cannabis was 1.46 [1.17, 1.83] (Fig. 1). Heterogeneity was high (I^2 = 94.6 % [91.6 %, 96.5 %]). The Egger's test (p = 0.088) and funnel plot showed slight asymmetry.

For suicide attempts among adolescent who use cannabis, the pooled OR was 1.85 [1.37, 2.5] (Fig. 2). Heterogeneity was high (I^2 = 95.1 % [93.1 %, 96.5 %]). The Egger's test (p = 0.013) and the funnel plot showed asymmetry, indicating probable publication bias.

Finally, for suicidal ideation among adults who use cannabis , the pooled OR was 1.78 [1.28, 2.46] (Fig. 3). Heterogeneity was high (I^2 = 85.8 % [72.8 %, 92.6 %]). Egger's test (p = 0.244) and the funnel plot

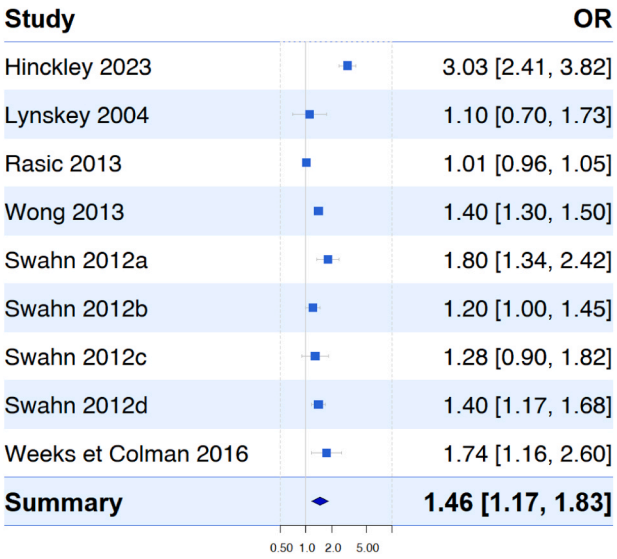

Fig. 2. Forest plot of the association between cannabis use and suicidal ideation among adolescents in articles with adjustment for depression.

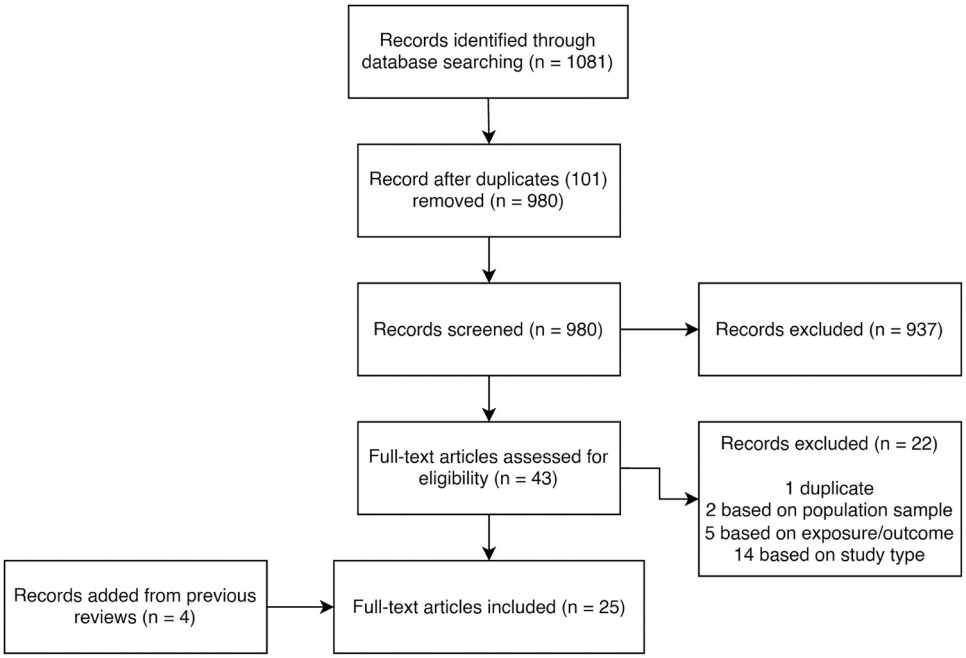

Fig. 1. PRISMA flow chart.

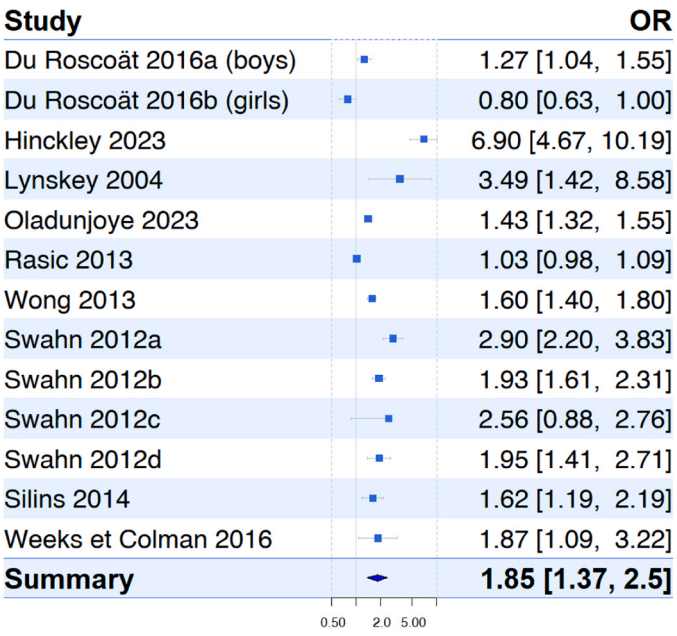

Fig. 3. Forest plot of the association between cannabis use and suicide attempt among adolescents in articles with adjustment for depression.

showed no apparent problem. All funnel plots are available in appendix (pp3–5). An additional model assessing the relationship between frequent cannabis use (weekly or more) and suicide attempts among adolescents is also available in the appendix (pp3–4).

In all cases, cannabis use was associated with suicidal behaviours while adjusting for depression with medium to high effect sizes. This indicates that cannabis use and suicidality might be associated independently of depression.

Results of meta-regression analyses are presented in Table 1. Longitudinal studies had lower estimates (i.e strength of association between cannabis use and suicidal behaviours) than cross-sectional ones for every outcome and in all populations, but with low significance. Medium-quality rated studies also yielded lower estimates than high-quality rated ones but the differences were not significant either. After controlling for tobacco and alcohol use, the association between cannabis use and suicidality yielded lower estimates (β = −0.4182 [-0.8808, 0.0445] for adolescents' suicidal ideation, β = −0.6422 [-1.4059, 0.1216] for adolescents' suicide attempts, β = −0.5405 [-1.0716, −0.0094] for adults' suicidal ideation). Controlling for other mental health disorders did not alter the estimates among adults, and there were not enough studies to evaluate difference among adolescents.

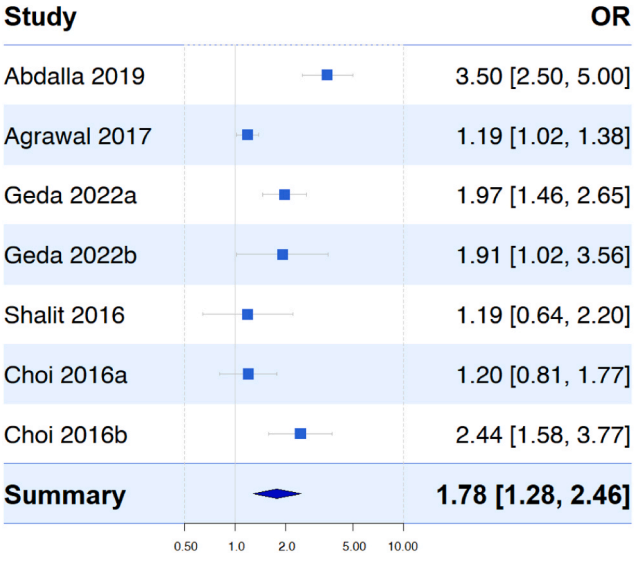

Fig. 4. Forest plot of the association between cannabis use and suicidal ideation among adults in articles with adjustment for depression.

Table 1
Meta-regression analysis.

Moderators	Population		
	Adolescents		Adults
	Suicidal ideation	Suicide attempt	Suicidal ideation
Study type (longitudinal vs. cross-sectional)	−0.1870 [−0.7349, 0.3609] (p = 0.36)	−0.3378 [−1.0536, 0.3779] (p = 0.35)	−0.4502 [−1.5044, 0.6029] (p = 0.40)
NOS quality rating (medium vs. high)	−0.2567 [−0.6955, 0.1822] (p = 0.18)	−0.1501 [−0.8326, 0.5324] (p = 0.67)	−0.5655 [−1.1673, 0.0363] (p = 0.07)
Control for other drugs use* (yes vs. no)	−0.4182 [−0.8808, 0.0445] (p = 0.076)	−0.6422 [−1.4059, 0.1216] (p = 0.099)	**−0.5405 [−1.0716, −0.0094] (p = 0.046)**
Control for other mental health disorders** (yes vs. no)	/	/	−0.0902 [−0.8149, 0.6345] (p = 0.81)

* Control for at least tobacco and alcohol consumption.
** Mental health disorders were only controlled for in one article focusing on adolescents.

3.1.2. All studies

3.1.2.1. Suicide ideation among adolescents. In total, 15 studies investigated the association between cannabis use and suicidality among adolescents while adjusting for depression. Among them, 14 investigated the association between cannabis use and suicidal ideation while adjusting for depression (Bolanis et al., 2020; H. Chabrol et al., 2008; Henri Chabrol et al., 2008; Fergusson et al., 1996; Hinckley et al., 2023; Kahn and Wilcox, 2022; Lynskey et al., 2004; Rasic et al., 2013; Rubio et al., 2020; Swahn et al., 2012; Weeks and Colman, 2017; Wilcox and Anthony, 2004; Wong et al., 2013). Half of them (7 studies) found a higher risk of suicidal ideation among people who use cannabis compared to people who do not use cannabis (H. Chabrol et al., 2008; Henri Chabrol et al., 2008; Hinckley et al., 2023; Kahn and Wilcox, 2022; Swahn et al., 2012; Weeks and Colman, 2017; Wong et al., 2013). Two others reported results that did not reach statistical significance (Fergusson et al., 1996; Rubio et al., 2020). One found a significant association in girls but not in boys (Wilcox and Anthony, 2004).

3.1.2.2. Suicide attempts among adolescents. The relationship between cannabis use and suicide attempts was investigated in 11 studies (du Roscoät et al., 2016; Fergusson et al., 1996; Hinckley et al., 2023; Kahn and Wilcox, 2022; Lynskey et al., 2004; Rasic et al., 2013; Silins et al., 2014; Swahn et al., 2012; Weeks and Colman, 2017; Wilcox and Anthony, 2004; Wong et al., 2013). Among those, eight found a higher risk of suicide attempts among people who use cannabis compared to people who do not use cannabis (Hinckley et al., 2023; Kahn and Wilcox, 2022; Lynskey et al., 2004; Silins et al., 2014; Swahn et al., 2012; Weeks and Colman, 2017; Wilcox and Anthony, 2004; Wong et al., 2013), and one found the same results in girls but not boys (du Roscoät E et al., 2016). Those findings suggest an association between cannabis use and suicidality among adolescents while controlling for depression status, which is consistent with the pooled analysis, but the number of studies reporting non-significant results remains high.

3.1.2.3. Suicide ideation among adults. Only five studies explored a relationship between cannabis use and suicidal behaviours among adults while controlling for depression (Abdalla et al., 2019; Agrawal et al., 2017; Choi et al., 2016; Geda et al., 2022; Shalit et al., 2016). All of them investigated suicidal ideation, three reporting a higher risk among people who use cannabis (Abdalla et al., 2019; Agrawal et al., 2017; Geda et al., 2022), and one finding the same result in men only (Shalit et al., 2016). Three analysed the link between cannabis use and suicide attempts: two found a higher risk of suicide attempts among people who use cannabis (Abdalla et al., 2019; Agrawal et al., 2017), and one of them found the same result among men only (Shalit et al., 2016). The lack of research prevents clear conclusions, although almost all studies consistently found statistically significant results.

3.2. Depression as a moderator of the association between cannabis use and suicidal behaviours

A total of six studies investigated the role of depression and symptoms of depression as possible moderators of the relationship between cannabis use and suicidality (Choi et al., 2016; Han et al., 2021; Oladunjoye et al., 2023; Onaemo et al., 2022; Rubio et al., 2020; Weeks and Colman, 2017). Among these, three focused on adolescents (Oladunjoye et al., 2023; Rubio et al., 2020; Weeks and Colman, 2017). One study found that adolescents experiencing cannabis use disorder (CUD) and depression had higher odds of attempting suicide that those with CUD but no depression (Oladunjoye et al., 2023). However, estimates of associations between respectively concomitant CUD and depression, and depression without CUD and suicidal behaviours, were similar. Another study found that the association between cannabis use and suicidal behaviours was only significant among adolescents with no history of depression (Weeks and Colman, 2017). The last study found no evidence of an interaction between cannabis use and depression (Rubio et al., 2020). Therefore, among adolescents, the results are inconsistent, and there is no consensus on the direction of moderation.

Three other articles studied adult populations (Choi et al., 2016; Han et al., 2021; Onaemo et al., 2022). One study found that the frequency of cannabis use was associated with suicidal ideation only among adults with major depressive disorder (MDE) (Choi et al., 2016). Another study found that simultaneous CUD and MDE were more strongly associated with suicidal ideation than CUD only or MDE only (Onaemo et al., 2022). The last study found no statistically significant differences in the association between cannabis use and suicidality in people with MDE compared to people without (Han et al., 2021). The results are slightly more consistent among adults, but there is still no consensus on the presence of moderation. However, the first two articles suggest that the association between cannabis use and suicidality is stronger among depressed adults.

3.3. Depression as a mediator of the association between cannabis use and suicidal behaviours

To our knowledge, no observational quantitative study investigated the mediating role of depression in the relationship between cannabis use and suicidal behaviours. Bolanis et al. (2020) used a cross-lagged panel model involving cannabis use, depression and suicidal ideation, which could be considered as a specific form of mediation analysis, but found no statistically significant results. Other articles with a longitudinal design did not use more than two time points, with no place for proper mediation analysis.

3.4. Other methodologies

Some articles using other methodologies contributed to explore the role of depression but were too marginal to be efficiently compared. Two articles (Bovasso, 2001; Diep et al., 2022) studied suicidal ideation as a symptom of depression, comparing its association with cannabis to other depressive symptoms. Bovasso et al. (Bovasso, 2001) found that suicidal ideation and anhedonia were the only symptoms significantly associated with cannabis use among people with no symptoms at baseline. Diep et al. (2022) compared the association between cannabis use and suicidal ideation to the association between cannabis use and PHQ-9 assessed depression, finding similar effect sizes in both cases. Furthermore, two articles explored the hypothesis that cannabis could be associated with suicide attempts requiring medical attention (Kahn and Wilcox, 2022; Wong et al., 2013). Both found a stronger association when studying severe suicide attempts rather than other suicidal behaviours. Finally, one article (Choi et al., 2016) found that a dose-dependent association between cannabis use and suicidal ideation was significant among people with major depressive episode (MDE), but not among those without.

4. Discussion

Our systematic review yielded three main results. First, we observed a statistically significant association between cannabis use and suicidality even after controlling for depression. Simultaneously, almost half of the articles we reviewed found no statistically significant association after adjusting for depression. It is then likely that depression does not entirely explain the effect of cannabis use on suicidality. Second, the scientific literature hints at a moderating role of depression, but inconsistencies refrain from identifying a direction. Finally, there is a lack of studies investigating a potential mediation of the association between cannabis use and suicidality via depression. Overall, these results imply that while cannabis use is associated with the risk of depression, depression may contribute to an increased risk of suicidality among some people who use cannabis but does not entirely explain this association.

A direct association between cannabis use and suicidality could be explained by several mechanisms. People could smoke cannabis to self-medicate in case of mental health issues, actually worsening their health in the long-term (Dekker et al., 2009). Cannabis use could also lower the effectiveness of antidepressants, therefore increasing the risk of suicide among depressed people (Hen-Shoval et al., 2022). Previous research also found that heavy cannabis use was associated with increased impulsivity (McKowen et al., 2022), possibly leading to a higher risk of suicide. All these hypotheses are consistent with a direct link between cannabis use and suicidality, rather than mediation via depression. One of the possible solutions to rule out these hypotheses is to separate depressive symptoms (e.g grouping by positive emotions, negative emotions, psychosomatic symptoms and interpersonal issues) when studying their link with cannabis use. On that matter, one article showed that suicidal ideation was one of two symptoms of depression associated with cannabis use (Bovasso, 2001), but another similar study contradicted those results (Diep et al., 2022). Therefore, our suggestion for future research is to explore the link between cannabis use and each symptom of depression separately. This could solve the issue of suicidal ideation being included in depression psychometric scales, increasing the risk of over-adjustment. This could also improve our understanding of underlying mechanisms and limit confounding. Another approach is to compare the association between cannabis use and depression with its association to other mental health disorders potentially linked to suicidality (e.g anxiety). This could help disentangle the relationships between cannabis use, mental health outcomes, and suicidality. Additionally, our review found that there were not enough studies investigating suicide attempts among adults, and further research in this area should be conducted.

While depression may confound the association between cannabis use and suicidality, it could also act as a mediator or moderator. Focusing on adjustment rather than moderation might yield incomplete results and lead to bias (Yzerbyt et al., 2004). That is why we assessed the moderating role of depression in the relationship between cannabis use and suicidal behaviors. Our results were inconclusive, with no

consensus on the presence or direction of the moderation. Most of the studies assessing moderation used a cross-sectional setting, while only one used a longitudinal design, decreasing robustness (Weeks and Colman, 2017). Our results contribute to a rather inconsistent research context. While epidemiological research links cannabis use with adverse psychiatric outcomes (e.g. psychosis, affective disorders and anxiety) (Campeny et al., 2020), recent research about therapeutical cannabis suggest it could reduce the severity of depressive symptoms (Mangoo et al., 2022; Specka et al., 2024). It is therefore crucial to improve our understanding of the causal pathways linking cannabis use to depression and suicidality. Distinguishing between confounding, mediation, and moderation would help identify populations at higher risk of suicidal behaviors. A direct association between cannabis use and suicidality, or a worsening of depressive symptoms due to cannabis use, would support targeted interventions aimed at reducing substance use among individuals with depression. In contrast, evidence of mediation alone would suggest the need for broader, population-level strategies to reduce substance use more generally. Moreover, cannabis is also linked to social factors such as unemployment and low social support (Henkel, 2011; Li and Rhubart, 2024), in turn associated with poor mental health (Assari, 2017; Ridley et al., 2020). This further complexifies the study of the pathways between cannabis use, depression and suicidality. Interactions between the social environment and mental health are complex to measure and track, making epidemiological studies in this area hard to conduct.

The differential study of confounding, mediation and moderation implies the consideration of the chronology of events – an aspect that has been notably lacking in the existing literature. Most studies included in our analyses were cross-sectional – which highlights a significant lack of longitudinal studies in the literature. On the other hand, most of the longitudinal studies only included two time points. Implied that it is difficult to discern confounding and mediation – as both would lower the strength of the initial association. The bidirectionality of the relationship between cannabis use and depression complicates the understanding of the link between cannabis use and suicidality. Depression moderating the association between cannabis use and suicidality, as well as dose-dependency (Choi et al., 2016) and the severity of suicide attempts linked to cannabis use (Kahn and Wilcox, 2022; Wong et al., 2013), suggest an association with the deterioration of depression rather than its onset. However, one study found no association between cannabis use and suicidality among adolescents with a history of depression (Weeks and Colman, 2017). Once again, this encourages conducting longitudinal studies with consideration of chronology to test this hypothesis. These studies should come with adequate statistical methods to take temporality into account. One example that is relevant to suicidology is survival analysis (Bohnert et al., 2017; Denissoff et al., 2022). Additionally, the delay between time points in longitudinal studies is heterogeneous, lowering comparability.

Another issue is the lack of consideration for comorbid mental health conditions. Psychiatric conditions other than depression could also confound, mediate or moderate the association between cannabis use and suicidality. Among adults, controlling for these conditions did not significantly alter the association between cannabis use and suicidality. The same meta-regression analysis could not be implemented among adolescents because of the small sample size. Cannabis use is systematically associated with a higher prevalence of bipolar (Maggu et al., 2023), borderline (Gillespie et al., 2018; Trull et al., 2018) and psychotic disorders (Moore et al., 2007), which are all correlated both with depression and suicidality (Association, 2013; Gonda et al., 2012; Gournellis et al., 2018; Pompili et al., 2005). Further research is needed to identify whether mental disorders other than depression could also confound the association between cannabis use and suicidality. Hence comorbid mental health disorders should be adjusted for whenever. Mental health disorders other than depression could also moderate the association between cannabis use and suicidality. A few inpatient studies investigated the relationship between cannabis and suicidal behaviors among people hospitalized for mental health disorders, with mixed findings (Kvitland et al., 2014; Serafini et al., 2012; Shoval et al., 2006; Waterreus et al., 2018). Uncovering the mechanisms linking mental disorders, cannabis use and suicidality could help resolve controversies surrounding diagnoses of depression and substance use disorders, which are often considered to have similar symptomatology despite possibly different causes (Nunes and Rounsaville, 2006). Moreover, adjustment for use of other drugs lowered the strength of the association between cannabis use and suicidality. This supports the need to compare the effect of cannabis alone and the joint use of multiple substances. Additionally, most studies opted for binary cannabis use variables, often overlooking the diversity of cannabis consumption habits and a potentially dose-dependent association. This forced us to use a year-long "ever-use" exposure, therefore including experimentation rather than steady use only.

Several results indicate a high risk of general bias and publication bias, including the low overall rating of studies, significant Egger's tests and funnel plots asymmetry. The poor-quality rating is mostly due to self-reported variables, but some studies were also penalized because of a low sample size, high attrition or limited adjustment. We chose to remove rating points for the lack of adjustment for other drugs or mental health disorders other than depression, as both were shown to be linked to cannabis use and poor mental health (Hasin and Walsh, 2020; Hindley et al., 2020; National Academies of Sciences et al., 2017). We recommend that further research includes the most important covariates, such as drug use and mental health disorders other than depression, in addition to the most common ones (age, sex, socio-economic status). Additionally, our findings show the likely presence of publication bias. It appeared that adjustment variables were highly heterogeneous, which could explain the lack of consistency in effect sizes. This made the meta-analysis more difficult to conduct, as we chose to only include studies with sufficient comparability. However, this does not explain the asymmetry between statistically significant and non-significant results. While publication bias is common in a large number of reviews (Thornton and Lee, 2000), its consequences are harmful to the state of research (Joober et al., 2012; Thornton and Lee, 2000). It is particularly the case in this context, due to the sensitivity and importance of the subject (Decorte et al., 2020; Skliamis et al., 2022). Therefore, it is crucial to guarantee the integrity of research by ensuring that non-significant results are published.

Our review should be interpreted with consideration of its limitations. The high risk of bias of some studies tempers the overall results, and potential publication bias weakens the robustness of the results of the meta-analysis. Moreover, the comparability criteria used to select pooled articles possibly induced bias, as the only type of statistical model included was logistic regression. This put aside less commonly used methods which were equally valid but suffered from impossible statistical comparability. We chose to conduct both qualitative and quantitative analyses to reduce this impact of these limitations and provide an exhaustive review of the scientific literature. By doing so, we made sure that the meta-analysis was not the only way our findings were reported, and we highlighted original methods that yielded interesting results. Another limitation is the low number of studies, particularly in the meta-analysis, added to the low number of longitudinal studies – preventing the investigation of mediation. The scarcity of research particularly affected adult populations, which limited findings in this population. However, the heterogeneity tests we conducted show that the number of studies included in our study was sufficient to conduct the statistical analyses we present. Finally, the variety of tools used to assess cannabis use and depression in the included articles (see Appendix) could potentially introduce bias into the comparisons and meta-analyses. The analyses restricted to frequent cannabis use (see Appendix) did not reveal any major difference in findings due to the low number of studies. Small sample sizes in the studies assessing the effect of cannabis use frequency (Agrawal et al., 2017; Choi et al., 2016; Hinckley et al., 2023; Rasic et al., 2013; Shalit et al., 2016; Silins et al.,

2014) did not allow us to draw any conclusions about a possible dose-effect relationship.

In light of all evidence, depression might confound the association between cannabis use and suicidality, yet cannabis use remains linked to a higher risk of suicidal behaviors even after adjusting for depression. Additionally, the scientific literature is inconsistent regarding a moderating role, and the evidence is insufficient to study a potential mediation. Our results have major public health implications, especially in a context of debate about the legalization of cannabis in many countries. Depression only partially confounding the association between cannabis use and suicidality suggest that cannabis use should not only be seen as a possible risk factor of mental health disorders, but also as an independent risk factor of suicidal behaviors. This is an important finding, as cannabis self-medication is common in some countries and could therefore have unanticipated consequences. Moreover, further investigating moderation could help to target interventions to specific populations. As previously discussed, the potential for cannabis use to worsen depressive symptoms could support viewing it as a catalyst for depression rather than merely a risk factor. This has major implications as depression criteria exclude conditions induced by substance use (American Psychiatric Association, 2013), which could lead to the neglect of potential major depressive episodes. Also, the studies investigating cannabis use as a treatment for depression should be careful about the possible long-term outcomes.

Registration and protocol

The research protocol was registered on PROSPERO (CRD42024542948) on May 13th, 2024.

CRediT authorship contribution statement

Gustave Maffre Maviel: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Camille Davisse-Paturet:** Writing – review & editing, Validation, Supervision. **Camilla Somma:** Writing – review & editing, Investigation, Formal analysis, Data curation, Conceptualization. **Maria Melchior:** Writing – review & editing, Validation, Supervision. **Guillaume Airagnes:** Writing – review & editing, Validation, Supervision.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.drugalcdep.2025.112714.

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