Cannabis use and risk of Suicidal behavior related outcomes: A Systematic Review and Meta-analysis

Sohrab Amiri[1], Alexander Kieu[2], Nailah Mahmood [2], Moien AB Khan*[3,]

[1]Medicine, Quran and Hadith Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran

[2] Division of Health Research, Lancaster University, Lancaster, United Kingdom

[3]Health and wellness research group, Department of Family Medicine, College of Medicine and Health Sciences, United Arab Emirates University, Al-Ain, United Arab Emirates

Correspondence

Dr Moien AB Khan

Health and wellness research group

Department of Family Medicine

College of Medicine and Health Sciences

United Arab Emirates University

Al-Ain

United Arab Emirates

moien.khan@uaeu.ac.ae

Abstract

Aim

Cannabis is a commonly used recreational substance that can have diverse effects on both the physical and mental well-being of individuals. We examined the relationship between cannabis use and suicidal-related behavioral outcomes,

Methods

A systematic review and meta-analysis were conducted using three databases (PubMed, Web of Science, and Scopus) and manual searches of Google Scholar and ResearchGate.

Results

The results showed that cannabis use was significantly associated with an increased likelihood of suicidal ideation and suicide attempts, as well as suicide plans, mortality, and self-injury. The odds ratios and 95% confidence intervals for each relationship were calculated, and a random-effects method was used for the meta-analysis. Specifically, the odds ratio for suicidal ideation was 1.63 (95% confidence interval=1.44-1.85; P<0.001), and the odds ratio for suicide attempts was 1.93 (95% confidence interval=1.56-2.37; P<0.001). Furthermore, women who used cannabis were more likely to experience suicidal ideation, while men and women who used cannabis were more likely to experience suicidality.

Conclusion

Results suggest individuals who use cannabis are more likely to experience suicidal-related outcomes than those who do not use cannabis.

Keywords: Cannabis use, meta-analysis, self-injury, suicidal behaviors, systematic review, risky behaviors

Introduction

The World Health Organization (WHO) estimates that approximately 700,000 deaths occur every year worldwide as a result of suicide and self-harm (WHO, 2021; Yip et al., 2022). Globally, suicide deaths have increased by 20,000 between 1990 and 2019 (Yip et al., 2022). Suicide has attracted a lot of attention worldwide in recent years and many countries have developed suicide prevention strategies. World Suicide Prevention Day's theme from 2021-2023, "Creating hope through action," aims to inspire empowerment and optimism by promoting hope and positivity. A study conducted by WHO has shown that the lifetime prevalence of suicidal ideation and suicide attempts is 9.2% and 2.7%, respectively (Nock et al., 2008; WHO, 2021). In children, the estimated prevalence of other types of suicidal behavior, such as suicidal ideation, suicide attempts, suicide plans, self-harm, and non-suicidal self-injury are 7.5%, 1.3%, 2.2%, 1.4%, and 21.9%, respectively (Geoffroy et al., 2022). Gender differences in suicidal behavior have been shown; the rate of suicidal ideation and attempts is higher in women, and suicide mortality rate is higher in men (Borges et al., 2010; Nock et al., 2008). Suicide is a variable based on, and affected by, different factors (Amiri & Behnezhad, 2018, 2020a, 2020b; Turecki & Brent, 2016). One of the factors that can play a role in understanding suicide-related outcomes is cannabis use.

Cannabis is the most commonly used illicit substance, with around 3.5% of the global population reporting its use (Gowing et al., 2015). Cannabis use has been

linked to an increase in health problems including risk of cancers (Ghasemiesfe et al., 2019), heart failures (Kalla et al., 2018), risk of cardiovascular hospitalizations (Auger et al., 2020), psychotic outcomes (Moore et al., 2007), development of depressive disorders (Lev-Ran et al., 2014a), and anxiety disorders (Mustonen et al., 2021). Between the ages of 15-64 years, the prevalence of cannabis use has been reported to be 4%, with an increase in use in recent years (Canton, 2020; Hasin et al., 2015) . There is rising concern about the long-term and chronic use of cannabis starting at a young age, which is associated with negative consequences on health, particularly mental health (Copeland et al., 2013; Hall & Degenhardt, 2009; Karila et al., 2014; Silins et al., 2014). There is some evidence that earlier onset and higher frequency of cannabis use are significantly associated with developing depression and anxiety(Hayatbakhsh et al., 2007). Although many reports experiencing a calming effect from the use of cannabis, acute anxiety is reported to be one of the most common side effects (Crippa et al., 2009).

Research is expanding in order to better understand the relationship between cannabis use and various aspects of health (Lev-Ran et al., 2014b; Marconi et al., 2016; Schoeler et al., 2016). In line with the current research, studies have also studied the relationship between cannabis use and suicide (Armoon et al., 2021; Francesco Bartoli et al., 2019; F. Bartoli et al., 2019; Bartoli et al., 2018; Borges et al., 2016; Breet et al., 2018; Carvalho et al., 2022; Escelsior et al., 2021; Fresán et al., 2022; Gabriella Gobbi et al., 2019; Leite et al., 2015; Poorolajal et al.,

2016). However, previous reviews have not comprehensively and comparatively analyzed other dimensions of suicide; the prevalence rate of suicide-related outcomes needs to be investigated, suicide mortality has not been reviewed or meta-analyzed, and the suicide plan has also not been examined. Furthermore, there is a need to assess gender differences in both cannabis use and suicide (Canetto & Sakinofsky, 1998).

The aim of this systematic review and meta-analysis is to investigate the relationship between cannabis use and suicide-related outcomes, such as suicidal ideation, suicide attempts, suicide mortality, suicidality, suicide plans, and self-injury (both suicidal and non-suicidal). This study also examines the gender differences in the relationship between cannabis use and suicide.

Materials and Methods

A systematic review of the literature was carried out to gather all relevant primary studies. The collected data was then synthesized using a correlational meta-analysis, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. (Page et al., 2021). The review protocol is registered in the PROSPERO Register of Systematic Reviews (Registration number CRD42023396757).

Eligibility criteria

Inclusion criteria

Studies that investigated the relationship between cannabis use and suicide-related outcomes and were included in this meta-analysis. 1) Eligible study designs were: longitudinal, cross-sectional, case-control, and retrospective cohort. 2) The presence of a reference group compared to the cannabis use group was an inclusion criterion. 3) Original research articles published in the English language (Appendix 1).

Exclusion criteria

Articles retrieved were excluded based on the following criteria to eliminate potential quality or methodological issues. 1) Studies in which cannabis use was defined as an outcome of suicide-related outcomes. 2) Case studies, reviews, letters to the editor, and clinical trial studies were not included. 3) To reduce selection bias, studies with small numbers of participants were excluded. 4) Studies, where the presented results were not adjusted, were excluded. 5) Studies that had a mixed exposure or a mixed outcome were not included. 6) The studies that were from the same database were not eligible, only one study with the highest quality was selected from among these studies. 7) Studies that did not report sufficient data to calculate the odds ratio between the exposure variable and the outcomes or if their results were not deductible, were further excluded. 8) Synthetic cannabinoids, like Delta-8 or Delta-10 were not eligible.

Database search

The authors (SA, MK) searched electronic databases for relevant studies that investigated the relationship between cannabis use and suicide-related outcomes. The database included five databases from time of inception to December 2022: PubMed, Web of Science, Scopus, Google Scholar, and Research Gate. The search strategy included relevant key terms: “Cannabis" OR "Marijuana" OR "Hashish" OR "Marijuana Abuse" OR "Drug Abuse" OR "Substance-Related Disorders" OR "Substance Use" OR "Drug Dependence" OR "Drug Use Disorder" ” AND "Suicide" OR "Suicidal Ideation" OR "Suicide Attempted" OR "Suicide Attempts" OR "Suicide thoughts" OR "Suicide Plan" OR "Suicide Behavior" OR "Self-Injurious Behavior" OR "Death wishes" OR "Self-Harm" OR "Self-Injury" OR "Self-Destructive.". Additional relevant studies were identified by manually reviewing the reference lists of the retrieved papers and reviews. The complete search strategy can be found in Appendix 2.

Selection process

To process the selection of manuscripts, Figure 1 was used as a guide for screening studies in systematic review and meta-analysis. At first, all the studies were stored in the Endnote software, and then the duplicates were identified and screened by two Authors (MK, SA). After screening the studies based on the title and abstract, the studies were screened based on the full text. Finally, all eligible studies were identified based on the inclusion and exclusion criteria. Any discrepancies between selections were later resolved by discussion.

Main Outcomes and Measures

The present study investigated the relationship between cannabis use and its various forms such as marijuana and hashish with suicide-related outcomes. The measurement of cannabis consumption involved various techniques, including self-reporting, disease classification, physical diagnostic information, and registry-based data.

The outcome variables for this study included suicidal ideation, suicide attempts, suicide mortality, suicidality (a combination of suicidal ideation and suicide attempt), suicide plans, and self-injury, which included self-harm and non-suicidal self-injury. These outcomes were defined and diagnosed using multiple methods, including diagnostic and psychiatric interviews, medical diagnoses, self-reports, and registry data.

Data extraction

For each of the eligible studies, thirteen sets of data were extracted from the manuscripts, the details of which are listed in Table 1. The data include the authors of each manuscript and the year of its publication, country, population, study design, age, sex, Sample size, cannabis use measure, suicide and suicide measure. The exposure variables and the outcome of each study, the qualitative evaluation of the studies and the results of each study.

Study risk of bias assessment

The Effective Public Health Practice Project Quality Assessment Tool was used to evaluate all included studies. Using this tool, bias assessment can be improved by examining four types of biases: selection bias, confounder bias, data collection method bias, withdrawal bias, and dropout bias (Armijo-Olivo et al., 2012; Thomas, 2003). The selected articles were scored by two authors (MK and SA). Any disagreement between the authors was then resolved by a third assessor (NM).

Effect measures

For most of the studies included in this study, the odds ratio (OR) was the commonly reported effect size for the association between cannabis use and suicide-related outcomes. A few studies used the hazard ratio, the risk ratio, or the relative risk to determine the effect size. In this meta-analysis, the effect size was calculated based on the odds ratio with a 95% confidence interval. Using Stata software (version 14.0, Stata Corp, College Station, TX, USA), the random-effect model was utilized to calculate the pooled odds ratio and its corresponding 95% confidence interval (CI).

Data Synthesis and Statistical Analysis

For each of the studies included in this research, the extracted results for the relationship between cannabis use and suicide-related outcomes were analyzed

separately for each outcome measure, including suicidal ideation, suicide attempts, suicide mortality, suicidality, a suicide plan, and self-injury. Additionally, women and men were analyzed separately. In studies with multiple independent subgroups, a fixed-effects method was used to pool the subgroups to obtain the odds ratio and 95% confidence interval.The results were analyzed by calculating the odds ratio and 95% confidence interval for each relationship, followed by performing a meta-analysis using the random-effects method. The heterogeneity of the results was measured using the heterogeneity chi-squared test and I^2 (Higgins & Thompson, 2002; Ioannidis et al., 2007).

To investigate publication bias, a funnel plot, Egger's test, and the trim-and-fill method were used (Begg & Mazumdar, 1994; Duval & Tweedie, 2000; Egger et al., 1997). Publication bias was only investigated in subgroups with >10 studies. Using Stata software (version 14.0, Stata Corp, College Station, TX, USA), the random-effect model was utilized to calculate the pooled standardized mean difference (SMD) and its corresponding 95% confidence interval (CI).

Results

Study selection

A total of 36,655 articles were found in the primary search (Figure 1), of which 327,591 were deleted after duplicate checking and records screening. Based on title and abstract, 599 articles were retrieved for screening. A total of 169 publications were selected for full-text screening, of which 106 were omitted due to insufficient reporting of outcome measures. The quantitative meta-analysis and subgroup analyses included 63 articles (Table 1) (Afifi et al., 2007; Agrawal, Nelson, et al., 2017; Agrawal, Tillman, et al., 2017; Arendt et al., 2013; Arenliu et al., 2014; Artenie et al., 2015; Beautrais et al., 1999; Bohnert et al., 2011; Bohnert et al., 2017; Bolanis et al., 2020; Borges et al., 2017; Borowsky et al., 2001; Borschmann et al., 2014; Bovasso, 2001; Carrico et al., 2007; Carvalho et al., 2019; Cheref et al., 2019; Davis et al., 2020; Delfabbro et al., 2016; Denissoff et al., 2022; du Roscoät et al., 2016; Fresán et al., 2016; Giletta et al., 2012; Greene & Ringwalt, 1996; Greene et al., 2020; Halladay et al., 2019; Hill et al., 2021; Huas et al., 2008; Kahn & Wilcox, 2022; Kassie et al., 2022; Katapally, 2022; Kelly et al., 2004; Kimbrel et al., 2018; Kimbrel et al., 2017; King et al., 2001; Kung et al., 2003; Lückhoff et al., 2014; Mars et al., 2019; McGee et al., 2005; Moller et al., 2013; Muula et al., 2007; Naji et al., 2018; Oppong Asante & Meyer-Weitz, 2017; Østergaard et al., 2017; Pedersen, 2008; Price et al., 2009; Quarshie et al., 2020; Rasic et al., 2013; Robinson et al., 2009; Rossow et al.,

2009; Sakamoto et al., 2020; Sampasa-Kanyinga et al., 2021; Shalit et al., 2016; Silins et al., 2014; Silva et al., 2014; Smith et al., 2021; Spears et al., 2014; Sundin et al., 2011; Taliaferro et al., 2019; Tetteh et al., 2020; Turner et al., 2022; Waterreus et al., 2018; Wilcox & Anthony, 2004).

Study characteristics

The studies included in this research had a range of research designs, including longitudinal, cross-sectional, retrospective, and case-control studies.

Most of the studies included in this research included both men and women, and the percentage for these is listed in Table 1. The number of studies included in this study from Europe and America was higher than other continents. The studies enrolled more than 5.9 million participants.

Risk of bias in studies

The studies were reviewed based on four dimensions of quality assessment to assess the bias of the studies. These bias measurement dimensions included: selection bias, confounders' bias, data collection method bias, and withdrawals and dropouts bias. Eight of the studies were found to have a moderate risk of selection bias, while the remaining studies had a low risk of such bias. For confounders' bias, 27 studies had a low risk, 25 had a moderate risk, and 11 had a high risk. Data collection method bias was deemed low in 17 studies, moderate in 47 studies, and high in none. As for withdrawals and dropouts bias, 597 studies had a low risk, three had a moderate risk, and one had a high risk. The results of the quality assessment of the studies by the researchers are listed in Table 1.

Results of individual studies

For the relationship between exposure and outcome in this meta-analysis, the odds ratio or risk ratio (or relative risk) or hazard ratio has been extracted from each of the studies, and their 95% confidence interval has also been reported, which is included in Table 1. In studies with several subgroups, these results were extracted for each of the subgroups. The extracted results include adjusted results.

Results of synthesis

Figure 2 shows the relationship between cannabis use and suicidal ideation. The obtained results show that cannabis use is associated with an increased odd of suicidal ideation [odd ratio=1.63; 95% confidence interval=1.44-1.85; Z=7.91; P<0.001; I^2=95.8%].

Figure 3 shows the relationship between cannabis use and suicide attempts. The obtained results show that cannabis use is associated with an increased odd of suicide attempts [odd ratio=1.93; 95%confidence interval=1.56-2.37; Z=6.17; P<0.001; I^2=98.5%].

Figure 4 shows the relationship between cannabis use and suicide plan, suicide mortality, self-injury, and suicidality. The obtained results show that cannabis use is associated with an increased odd of suicide plan [odd ratio=1.84; 95% confidence interval=1.15-2.95; Z=2.54; P=0.011; I^2=97.3%]. The obtained results show that cannabis use is associated with an increased odd of suicide mortality [odd ratio=1.66; 95%confidence interval=1.13-2.44; Z=2.57; P=0.010; I^2=94.9%]. The obtained results show that cannabis use is associated with

increased odds of self-injury [odd ratio=1.54; 95%confidence interval=1.30-1.83; Z=4.97; P<0.001; I^2=49.7%]. The obtained results show that cannabis use is associated with an increased odd of suicidality [odd ratio=1.89; 95% confidence interval=1.63-2.19; Z=8.50; P<0.001; I^2=0%].

Figure 5 shows the relationship between cannabis use and suicidal ideation in men and women. The obtained results show that cannabis use is not associated with an increased odd of suicidal ideation in men [odd ratio=1.45; 95% confidence interval=0.97-2.17; Z=1.82; P=0.068; I^2=73%]; but this relationship is associated with an increased odd of suicidal ideation in women [odd ratio=1.62; 95%confidence interval=1.15-2.29; Z=2.74; P=0.006; I^2=58.6%].

Figure 6 shows the relationship between cannabis use and suicide attempts in men and women. The obtained results show that cannabis use is not associated with an increased odd of suicide attempts in men [odd ratio=1.79; 95% confidence interval=0.86-3.73; Z=1.55; P=0.121; I^2=98.8%] and women [odd ratio=1.75; 95% confidence interval=0.84-3.61; Z=1.50; P=0.132; I^2=98.6%].

Figure 7 shows the relationship between cannabis use and suicide mortality, and suicidality in men and women. The obtained results show that cannabis use is associated with an increased odd of suicidality in men [odd ratio=2.06; 95% confidence interval=1.69-2.51; Z=7.20; P<0.001; I^2=0%] and women [odd ratio=1.63; 95% confidence interval=1.12-2.37; Z=2.54; P=0.011; I^2=38.3%]. The obtained results show that cannabis use is not associated with an increased odd of suicide mortality in men [odd ratio=1.29; 95% confidence interval=0.85-

1.96; Z=1.20; P=0.228; I^2=86.2%] and women [odd ratio=2.24; 95% confidence interval=0.49-10.38; Z=1.03; P=0.301; I^2=38.3%].

Reporting biases

The association between cannabis use and suicidal ideation funnel plot showed publication bias (Appendix 2). The Egger test confirmed the publication bias (P=0.050). The trim-and-fill (Duval & Tweedie, 2000) showed that there are three missing studies in this regard. With the imputed of these three studies, the adjusted result was equal to OR=1.80 [CI=1.54-2.10]. The level of heterogeneity in the included studies in this regard was equal to I^2=95.8% which indicates high heterogeneity(Higgins et al., 2003) and another test was to check the heterogeneity of chi-square, which showed that it is equal to 646.88 (d.f=27; p<0.001).

The association between cannabis use and suicide attempts funnel plot showed publication bias (Appendix 3). The Egger test confirmed the publication bias (P=0.100). The trim-and-fill (Duval & Tweedie, 2000) showed that there are three missing studies in this regard. With the imputed of these three studies, the adjusted result was equal to OR=2.13 [CI=1.69-2.68]. The level of heterogeneity in the included studies in this regard was equal to I^2=98.5% which indicates high heterogeneity (Higgins et al., 2003) and another test was to check the heterogeneity of chi-square, which showed that it is equal to 2547.35 (d.f=37; p<0.001).

Discussion

A systematic review and meta-analysis were conducted to examine the relationship between cannabis use and suicide-related outcomes, including suicidal ideation, suicide attempts, suicide mortality, suicidality, a suicide plan, .and self-injury, which included non-suicidal self-injury

According to the results of this meta-analysis, cannabis use is associated with all suicide-related outcomes. The highest risk was associated with suicide attempts, followed by suicide plans and suicide mortality. The results also suggest that cannabis use can have both direct and indirect effects on suicide-related outcomes.

Cannabis can have a direct effect on suicide-related outcomes is by altering consciousness. Research shows that cannabis use alters Δ-9 tetrahydrocannabinol (THC) levels in the brain (Murray & Srinivasa-Desikan, 2022; Zaytseva et al., 2019) causing an alteration in consciousness. Cannabis effects can impair a person's ability to consciously process their behaviors, which can lead to suicide-related outcomes. Additionally, many studies have shown that cannabis can directly influence suicide-related outcomes by affecting the structural and functional composition of the brain. (Campolongo et al., 2007; Gleason et al., 2012; Rubino et al., 2009).

Furtehrmore, cannabis use can also indirectly influence suicide-related outcomes in several ways. The use of cannabis can affect a person's mental health and may predispose them to suicidal behavior. One of the most important factors

contributing to suicide is depression, and (Ribeiro et al., 2018)cannabis use has been linked to depression in many studies (Gobbi et al., 2019; Lev-Ran et al., 2014b; Manrique-Garcia et al., 2012). Evidence suggests that cannabis use disorder can have a causal influence on developing major depressive disorder (MDD) (Smolkina et al., 2017) and it is known from psychological autopsy studies that MDD is the most common psychiatric disorder seen in suicide victims (Cheng et al., 2000). This implies cannabis use can affect suicide-related outcomes through depression. Cannabis use is also associated with other mental disorders, such as schizophrenia (Vaucher et al., 2018), and schizophrenia is also associated with suicide (Palmer et al., 2005). It is possible that the association of cannabis use with mental health disorders may be because of underlying mechanisms, such as the production and regulation of the corticotropin-releasing hormone (CRH) or other neurotransmitters. For example, endocannabinoids are associated with both anxiety and drug addictions (Rodríguez de Fonseca et al., 2005). The role of CRH has also been well-studied in the maintenance of drug addictions, including cannabis (Bruijnzeel & Gold, 2005). Interestingly, increased expression levels of CRH have also been associated with suicide among patients with depression (Zhao et al., 2015).

Cannabis use and suicide-related outcomes may be mediated by other individual dimensions such as emotional regulation problems. Studies indicate that cannabis use affects various aspects of mental health, including suicide, which can be mediated by emotional dysregulation (Ghorbani et al., 2017; Orr et al., 2020).

Some have previously hypothesized under the self-medication model of depression and aggression, that among individuals already suffering from depression and behavioural issues, cannabis is used to alleviate the negative symptoms experienced. However, Arendt et al. (2007) found that individuals with depression reported using cannabis for the same reasons as others, i.e., not for self-medication, but to experience an exaggerated adverse symptom from cannabis use (Arendt et al., 2013). It has also been reported that experiencing depression and anxiety among cannabis users increases their likelihood of developing psychotic experiences (Radhakrishnan et al., 2022). All of these findings may be mediating factors in understanding the link between cannabis and suicide.

This study also examined how cannabis use and suicide-related outcomes differ by gender. Prior research has shown that men are more likely than women to commit suicide and that suicidal ideation is prevalent than suicide death (Borges et al., 2010; Department of Veterans, 2014; Nock et al., 2008). Interestingly, our findings show a similar relationship: cannabis use is associated with increased odds of suicidal ideation in women and suicidality in men and women. When observing these gender differences it is important to examine the mechanisms behind them. Cannabis use may affect each gender differently, thus resulting in a different attitude toward suicide among men and women. Further research could aim towards understanding how cannabis affects gender differently, and how these effects influence suicide outcomes.

To our knowledge, this review was the first to examine all types of suicide outcomes at a comprehensive level, including an analysis on gender differences relating to cannabis use and suicide outcomes. A rigorous selection process was used to determine the studies that would be included in the meta-analysis, reducing bias potential. A major strength of this meta-analysis was the large population included. However, it is important to note that this meta-analysis also has some limitations. In order to investigate the causal relationship between cannabis use and suicide, prospective cohort studies are required. There were cross-sectional studies and other types of studies in this research that did not provide this possibility. As research continues to expand in this field, future meta-analyses can prioritize prospective cohort studies. Most of the studies included in this study were conducted in developed countries, which needs to be considered when interpreting and generalizing the findings. Due to limitations and a lack of sufficient data, the severity of cannabis use and its relationship to suicide outcomes cannot be explored in this current study. Methodological limitations in the meta-analysis include heterogeneity in the studies included. Heterogeneity in research can originate from two main sources: clinical inhomogeneity and statistical heterogeneity. In this study, attempts were made to determine homogeneity through subgroup analysis and the use of random effects, which had a limited effect. However, heterogeneity remained high in some cases. Nonetheless, subgroup analysis was successful in reducing heterogeneity in

certain instances. Such limitations must be considered when interpreting the results.

Conclusion

Cannabis use and suicide-related outcomes were found to be related in this study, and persons who use cannabis were found to be more likely to experience suicide-related outcomes than non-cannabis users. Further research is necessary to better educate the public about the potential consequences resulting from cannabis use, especially in light of the findings in this review and meta-analysis. This research could have substantial public health implications and dictate policy and prevention programs.

Registration and protocol

The review protocol is registered in the PROSPERO Register of Systematic Reviews (Registration number CRD42023396757). The present research protocol was based on standards preferred reporting items for systematic reviews and meta-analyses (Page et al., 2021).

Support

No funding was used in this study.

Competing interests

None to declare.

Availability of data, code, and other materials

Data is available on request from the first and the corresponding authors.

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