

Continued versus discontinued cannabis use in patients with psychosis: a systematic review and meta-analysis



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Summary

Background Although the link between cannabis use and development of psychosis is well established, less is known about the effect of continued versus discontinued cannabis use after the onset of psychosis. We aimed to summarise available evidence focusing on the relationship between continued and discontinued cannabis use after onset of psychosis and its relapse.

Methods In this systematic review and meta-analysis, we searched MEDLINE for articles published in any language from the database inception date up until April 21, 2015 that included a sample of patients with a pre-existing psychotic disorder with a follow-up duration of at least 6 months. We used a combination of search terms for describing cannabis, the outcome of interest (relapse of psychosis), and the study population. We excluded studies if continued cannabis use or discontinued cannabis use could not be established. We compared relapse outcomes between those who continued (CC) or discontinued (DC) cannabis use or were non-users (NC). We used summary data (individual patient data were not sought out) to estimate Cohen's *d*, which was entered into random effects models (REM) to compare CC with NC, CC with DC, and DC with NC. Meta-regression and sensitivity analyses were used to address the issue of heterogeneity.

Findings Of 1903 citations identified, 24 studies (16565 participants) met the inclusion criteria. Independent of the stage of illness, continued cannabis users had a greater increase in relapse of psychosis than did both non-users ($d_{CC-NC}=0.36$, 95% CI 0.22–0.50, $p<0.0001$) and discontinued users ($d_{CC-DC}=0.28$, 0.12–0.44, $p=0.0005$), as well as longer hospital admissions than non-users ($d_{CC-NC}=0.36$, 0.13 to 0.58, $p=0.02$). By contrast, cannabis discontinuation was not associated with relapse ($d_{DC-NC}=0.02$, –0.12 to 0.15; $p=0.82$). Meta-regression suggested greater effects of continued cannabis use than discontinued use on relapse ($d_{CC-NC}=0.36$ vs $d_{DC-NC}=0.02$, $p=0.04$), positive symptoms ($d_{CC-NC}=0.15$ vs $d_{DC-NC}=-0.30$, $p=0.05$) and level of functioning ($d_{CC-NC}=0.04$ vs $d_{DC-NC}=-0.49$, $p=0.008$) but not on negative symptoms ($d_{CC-NC}=-0.09$ vs $d_{DC-NC}=-0.31$, $p=0.41$).

Interpretation Continued cannabis use after onset of psychosis predicts adverse outcome, including higher relapse rates, longer hospital admissions, and more severe positive symptoms than for individuals who discontinue cannabis use and those who are non-users. These findings point to reductions in cannabis use as a crucial interventional target to improve outcome in patients with psychosis.

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Introduction

Cannabis is the most commonly used illicit drug in patients with an existing psychotic disorder.¹ In some studies, about one of every four patients with psychosis meets the criteria for cannabis dependence,^{2,3} with rates of use especially high in young people presenting with their first psychotic episode.² These rates are much higher than those of the general population⁴ or those of people with other psychiatric diagnoses.⁵ Although the association between cannabis use and onset of psychotic disorders is well established,^{6,7} suggesting that cannabis use is a component cause of the disorder,⁸ its effect on the course of psychosis after onset is less clear. This lack of clarity seems mainly related to limitations of study design such as cross-sectional approach, underpowered samples, and no consideration of potential confounders.⁹ Some studies^{10–12} implicate cannabis use as a potential risk factor for relapse of psychosis as indexed by

readmission to hospital, with some evidence supporting a dose–response association.¹¹ Other studies report worsening of positive psychotic symptoms^{14,15} or less time to symptom re-emergence¹⁶ in cannabis-using patients with psychosis compared with non-users. These findings are in line with experimental pharmacological challenge studies reporting that Δ -9-tetrahydrocannabinol (THC), the main psychoactive constituent in cannabis, can induce transient psychotic experiences in healthy individuals and worsen existing symptoms in patients with pre-existing psychosis.^{17–20}

If cannabis use were associated with worse outcomes in individuals with established psychosis, then we would expect that those who continue using cannabis would have far worse outcomes compared with those who stop. However, although some evidence suggests that discontinuation of cannabis use might lead to a reduction in readmission rates^{21,22} and improvement in symptomatic

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and functional outcomes of psychosis,^{15,22–26} other research suggests that this scenario might not necessarily be the case.^{1,10,27,28} Nevertheless, about 30–50% of cannabis users stop using the drug after the onset of their psychotic illness,^{15,21–23,29} suggesting that this issue might be clinically relevant. Conclusions from individual studies need to be treated with caution in view of the modest sample sizes. Meta-analytic techniques offer a method of overcoming the sample size problem by statistically integrating the results from several separate studies thereby improving the power to detect significant effects.³⁰ Considering the conflicting evidence from individual studies investigating the relation between continued cannabis use and relapse and from studies looking at discontinued use and outcome, we have attempted to quantitatively summarise the present evidence. We aimed to establish whether continuing cannabis use is associated with poor outcome in established psychosis and establish the magnitude of this effect by pooling together the results of all available studies using a meta-analytic approach. We focused on outcome defined as relapse of psychosis, operationalised as either readmission to hospital or investigator-established psychotic relapse. Because cannabis use is potentially amenable to treatment and a substantial proportion of patients with psychosis continue using the drug after onset of their illness, estimation of the effect of continuing cannabis use on a robust measure of outcome indicative of relapse, such as admission to hospital, is needed. This outcome is a reliably estimated measure, with substantial implications for the cost of health care.³¹ Although previous meta-analyses have investigated the association between continued and discontinued cannabis use and outcome in psychosis, they have mainly focused on symptomatic outcome measures such as positive and negative symptoms or depression scores, whereas outcome indexed by hospitalisation was considered only in the context of the effects of substance use in general.^{32–34} We therefore aimed to investigate whether continued use of cannabis after the onset of psychosis is associated with worse relapse outcome relative to non-users, whether discontinued use of cannabis subsequent to the onset of psychosis is associated with a similar relapse outcome compared to non-users, and whether discontinued use of cannabis is associated with a better relapse outcome compared with continued use. Furthermore, we investigated whether the effect of cannabis use on outcome was consistent across different outcome measures by also examining the effect on measures such as length of admission to hospital, symptom severity, and level of functioning.

See Online for appendix

Methods

Search strategy and selection criteria

We used a systematic search strategy to identify all relevant studies, following the methods recommended by the Cochrane Handbook³⁵ and in accordance with the

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.³⁶ First, we searched the MEDLINE database for studies published in any language from the database inception date using a combination of search terms describing cannabis (“marijuana/marihuana”, “cannabis”, “illicit substance”), the outcome of interest (“outcome, hospital*”, “relapse”, “readmission”), and the study population (“psycho*”, “bipolar”, “schizophrenia”), with the final search done on April 21, 2015. After the database search, bibliographies of the identified publications and previous published meta-analyses were hand-searched to identify additional studies that met the inclusion criteria but were missed by the database search. Studies were selected if they included a sample of patients with a pre-existing psychotic disorder (schizophrenia, schizoaffective, or bipolar if outcome was reported as number of psychotic episodes),⁷ with a follow-up duration of at least 6 months. The primary predictor variables⁷ were defined as continued cannabis use (yes or no) after onset of psychosis and discontinued cannabis use after onset (yes or no). Only a subset of the total pool of studies that examined the effect of continued cannabis use on outcome also examined the effect of discontinuation of the drug. We excluded studies if continued cannabis use (CC) or discontinued cannabis use (DC) could not be established (eg, studies^{38–41} that assessed cannabis use only around the onset of psychosis and studies^{42–45} that only reported lifetime cannabis use). The primary outcome was defined as relapse of psychosis, which was indexed as either readmission to hospital, investigator-established relapse (operationalised in this Article as a psychotic episode or exacerbation of psychotic symptoms),^{16,22,46} or investigator-established relapse without any reported criteria for operationalisation.⁴⁷ If the identified studies reported symptom scores (positive or negative), length of time admitted to hospital, or level of functioning (as measured with the Global Assessment of Functioning Scale⁴⁸) alongside the relapse information, this data was also extracted and used in separate outcome analyses.

Quality assessment and data extraction

We used a modified seven-point strength-of-reporting scale, which has been used in previous meta-analyses done in a related topic of research.^{32,34} This scale is based on items describing methodological aspects in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)⁴⁹ checklist. Studies with a score of more than 5 were classified as higher quality studies (appendix).

An initial data extraction protocol was drafted in 2013 and data extraction was piloted from studies identified through a systematic search by at least two independent researchers (TS and RB) to finalise the selection criteria and variables of interest. Summary data were extracted by two independent researchers (TS and AM or MBS). In case of missing data, contact was made with the authors.

	Definition of cannabis use	Definition of cannabis non-use	Relapse outcome	Length of illness at follow-up (years); illness stage* (early vs chronic)	Follow-up (years); matched (yes/no)	Participants	d (95% CI)	Odds ratio (95% CI)
Continued cannabis use								
Baeza et al (2009); ³⁸ Spain	Cannabis use during 1 month before follow-up assessment (n=15)	No history of cannabis use (n=69)	Number of hospital readmissions in 6 months follow-up	1; early stage	CAN+ 0.5; CAN- 0.5; yes	84	0 (-0.57 to 0.57)	N/A
Barrowclough et al (2013); ³⁷ UK	Cannabis use (any) in previous 90 days (n=160)	No cannabis use in previous 90 days (n=167)	Hospital admission (yes/no) in previous year	12; chronic	CAN+ 1; CAN- 1; yes	327	0.33 (0.11 to 0.55)	1.82 (1.22 to 2.71)
Bersani et al (2002); ⁴¹ Italy	Present user (C-NS; n=54)	No history of cannabis use (n=71)	Number of previous hospital admissions	10; chronic	CAN+ 8; CAN- 13; no	125	-0.07 (-0.43 to 0.29)	N/A
Caspari (1999); ⁴² Germany	Cannabis misuser (n=27)†	Non-misuser (n=26)	Number of hospital readmissions after index hospital admission	7; chronic	CAN+5; CAN-6; yes	53	1.04 (0.56 to 1.52)	N/A
Faridi et al (2012); ⁴³ Spain	Presence of CUD at follow-up (n=28)	Absence of CUD at follow-up (n=20)	Relapse (yes/no) in 1-year follow-up (R-NS)	1; early stage	CAN+ 1; CAN- 1; yes	48	0.04 (-0.55 to 0.63)	1.08 (0.37 to 3.13)
González-Pinto et al (2009); ²¹ Spain	Continued use throughout 7 years of follow-up (n=25)	No history of cannabis use (n=40)	Number of hospital admissions during 8 years of follow-up	8; chronic	CAN+ 8; CAN- 8; yes	65	0.58 (0.06 to 1.10)	N/A
Isaac et al (2005); ⁴⁴ UK	Positive UDS at admission (n=69)	Negative UDS at admission (n=46)	Number of previous hospital admissions	N/A	Not reported	115	0.62 (0.24 to 1.01)	N/A
Jockers-Scherubl et al (2007); ⁴⁴ Germany	Presence of CUD (n=19)	Cannabis use <5 times in their lifetime (n=20)	Number of previous hospital admissions	7; chronic	CAN+ 6; CAN- 9; no	39	-0.40 (-1.05 to 0.26)	N/A
Koenders et al (2014); ⁴⁶ Netherlands	Presence of CUD (n=80)	Cannabis use ≤5 times in their lifetime (n=33)	Number of previous psychotic episodes (R-NS)	1; early stage	CAN+ 1; CAN+ 1; no	113	0.12 (-0.43 to 0.39)	N/A
Linszen et al (1994); ⁴⁵ USA	Presence of CUD during 1-year follow-up (n=24)	Absence of CUD during 1-year follow-up (n=69)	Relapse (yes/no) (exacerbation of psychotic symptoms)† in 1-year follow-up	3; early stage	CAN+ 1; CAN- 1; yes	93	0.45 (0.07 to 0.88)	2.27 (1.05 to 4.89)
Maremmani et al (2004); ⁴⁴ Italy	Lifetime CUD and positive UDS (n=43)	No history of cannabis use (n=45)	Number of previous hospital admissions	10; chronic	CAN+ 7; CAN- 12; no	88	-0.08 (-0.51 to 0.34)	N/A
Martinez-Arevalo et al (1994); ⁴² Spain	Cannabis use during 1-year follow-up (not specified C-NS; n=14)	No history of cannabis use (n=24)	Hospital admission (yes/no) in 1-year follow-up	2; early stage	CAN+ 1; CAN- 1; yes	38	0.46 (-0.23; 1.14)	2.29 (0.66 to 7.91)
Negrete et al (1986); ³⁵ Canada	Cannabis use during 6 months before follow-up assessment and/or positive UDS (n=25)	No history of cannabis use (n=61)	Number of previous hospital admissions	10; chronic	CAN+ 6; CAN- 13; no	86	0.8 (0.31 to 1.29)	N/A
Peralta and Cuesta (1992); ⁴⁴ Spain	Cannabis use >1 time per week 1 year before follow-up assessment (n=23)	Cannabis use ≤1 time per week 1 year before follow-up assessment (n=72)	Number of previous hospital admissions	5; early stage	CAN+ 5; CAN- 6; yes	95	-0.14 (-0.62 to 0.34)	N/A
Rehman and Farooq (2007); ⁴⁹ Pakistan	Cannabis use during 1 year before follow-up assessment (n=50)	No use during 1 year before assessment (n=50)	Number of previous hospital admissions	5; early stage	CAN+ 4; CAN-5; yes	100	0.40 (-0.002 to 0.80)	N/A
Rentzsch et al (2011); ²⁹ Germany	Present user (≥5 days/week for ≥1 year; n=27)	Cannabis use ≤5 times in their lifetime (n=26)	Number of previous hospital admissions	6; chronic	CAN+ 5; CAN- 7; no	53	0.25 (-0.31 to 0.80)	N/A
Ringen et al (2010); ²⁷ Norway	Cannabis use during 6 months before follow-up assessment (C-NS; n=41)	No use during 6 months before follow-up assessment (n=232)	Number of previous hospital admissions	8; chronic	CAN+ 7; CAN- 9; no	273	0.20 (-0.13 to 0.54)	N/A
Salyers and Mueser (2001); ²⁷ USA	Cannabis use ≥1 time during 6 months before follow-up assessment (n=363)	Never used during 6 months before follow-up (n=41)	Number of hospital admissions within 2 years before follow-up assessment	8; chronic	CAN+2; CAN- 2; yes	404	0.37 (0.04 to 0.69)	N/A
San et al (2013); ⁴¹ Spain	Cannabis use during 4 years before follow-up assessment (n=553)	No use during 4 years before follow-up assessment (n=1093)	Hospital admission (yes/no) in 1-year follow-up	≥10 for 57% of the sample; chronic	CAN+ 1; CAN- 1; yes	1646	0.25 (0.13 to 0.36)	1.56 (1.27 to 1.92)

(Table continues on next page)

	Definition of cannabis use	Definition of cannabis non-use	Relapse outcome	Length of illness at follow-up (years); illness stage* (early vs chronic)	Follow-up (years); matched (yes/no)	Participants	d (95% CI)	Odds ratio (95% CI)
<i>(Continued from previous page)</i>								
Sara et al (2014); ²⁷ Australia	Presence of CUD during 5 years of follow-up (n=3946)	Absence of CUD in 5 years follow-up (n=7672)	Number of hospital readmissions during 5 years of follow-up	>7; chronic	CAN+ 5; CAN- 5; yes	11 618	0.92 (0.89 to 0.96)	N/A
Sorbara et al (2003); ¹¹ France	Presence of CUD within 2 years after psychosis onset (n=9)	Absence of CUD in 2 years after psychosis onset (n=49)	Hospital admissions (yes/no) in 2 years after psychosis onset	2; early stage	CAN+ 2; CAN- 2; yes	58	0.62 (0.01 to 1.24)	3.1 (1.01 to 9.4)
van Dijk et al (2012); ²³ Netherlands	Cannabis use ≥ 4 times during 1 year follow-up or use 1 month before follow-up assessment (n=68)	Cannabis use <4 times during 1-year follow-up or no use 1 month before follow-up assessment (n=77)	Number of hospital admissions in 1-year follow-up	14; chronic	CAN+ 1; CAN- 1; yes	145	0.38 (0.05 to 0.71)	N/A
van der Meer and Velthorst (2015); ²⁷ Netherlands	Cannabis use ≤5 times during 3-year follow-up (n=146)	No history of cannabis use (n=257)	Number of relapses (hospital admission and/or exacerbation of psychotic symptoms)‡ in 3-year follow-up	4; early stage	CAN+ 3; CAN- 3; yes	403	0.23 (0.03 to 0.43)	N/A
Wade et al (2006); ²⁴ Australia	Presence of CUD during follow-up (n=40)	Absence of CUD during follow-up (n=48)	Relapse (yes/no) (exacerbation of psychotic symptoms)§	1.3; early stage	CAN+ 1.3; CAN- 1.3; yes	88	0.87 (0.41 to 1.33)	4.87 (2.09 to 11.32)
Discontinued cannabis use								
Baeza et al (2009); ²⁸ Spain	Cannabis use at baseline but no use 1 month before follow-up assessment (n=16)	No history of cannabis use (n=69)	Number of hospital re-admissions in 6 months follow-up	..	CAN+ 0.5; CAN- 0.5; yes	85	0 (-0.57 to 0.57)	N/A
González-Pinto et al (2009); ²¹ Spain	Stopped cannabis use between psychosis onset and during 7 years of follow-up (n=27)	No history of cannabis use (n=40)	Number of hospital admission during 8 years of follow-up	..	CAN+ 8; CAN- 8; yes	67	0.25 (-0.25 to 0.75)	N/A
Maremmani et al (2004); ²⁶ Italy	Lifetime CUD but negative UDS (n=23)	No history of cannabis use (n=45)	Number of previous hospital admissions	..	CAN+ 9; CAN- 12; no	68	-0.08 (-0.60 to 0.43)	N/A
Martinez-Arevalo et al (1994); ⁴² Spain	No cannabis use during 1-year follow-up but previous use (n=25)	No history of cannabis use (n=24)	Hospital admission (yes/no) in 1-year follow-up	..	CAN+ 1; CAN- 1; yes	49	0.02 (-0.56 to 0.60)	1.03 (0.36 to 2.95)
Negrete et al (1986); ⁴⁴ Canada	History of cannabis use but no use during 6 months before follow-up assessment (n=51)	No history of cannabis use (n=61)	Number of previous admissions to hospital	..	CAN+ 9; CAN+ 13; no	112	0.22 (-0.16 to 0.60)	N/A
van der Meer and Velthorst (2015); ²⁷ Netherlands	Past cannabis use >5 times/lifetime but no use during 3 years of follow-up (n=266)	No history of cannabis use (n=257)	Number of relapses (hospital admission and/or drop score on symptom scale) in 3-year follow-up	..	CAN+ 3; CAN- 3; yes	523	-0.04 (-0.21 to 0.13)	N/A

d=effect size Cohen's d with p value for random effects model. C-NS=further information regarding classification of cannabis user not specified. R-NS=further information about relapse definition not specified. CUD=cannabis use disorder (diagnosis of cannabis abuse or dependence based on the DSM or ICD). UDS=urine drug screen. Matched=yes if difference in follow-up between cannabis users [CAN(+)] and non-users [CAN(-)] is not more than 1 year, No-if difference more than 1 year. N/A=not applicable. *Early stage of illness defined as illness duration ≥5 years; chronic stage of illness defined as illness duration 6 years. †Based on rating scale: Comprehensive Assessment of Symptoms and History. ‡Based on rating scale: Brief Psychiatric Rating Scale. §Diagnosed if consumed regularly for several months and if this interfered with social functioning or was prominent during therapy; patients with occasional use were not included.

Table 1: Effects of cannabis continuation and discontinuation after psychosis onset on relapse outcome, by study and country

Disagreements were resolved through discussion between the researchers (TS and AM or MBS) extracting data and a senior researcher (SB).

Data analysis

Analyses were done with R and its package metaphor,³⁰ using random effects models (REM)³¹ that assume that effect sizes vary from study to study.³² Effect sizes were

estimated using Cohen's d, in which d values of 0.2 or lower represent small effects, d values between 0.4 and 0.6 represent moderate effects, and d values of 0.8 or higher represent large effects.³³ d per study was calculated for the following comparisons: continued cannabis use versus non-user (CC-NC), continued use versus discontinued use (CC-DC), and discontinued use versus non-user (DC-NC). We used the R package Compute.es,³⁴

which allows data from included studies to be entered in the form of means and standard deviations (SD),³⁷ p values for mean comparisons, or χ^2 statistics to reach an estimated d. Additionally, the package allowed the estimation of d for the studies that reported odds ratios.^{38,32} In cases in which the SD was not reported,^{35,36} the SD was extrapolated from other studies with similar outcome and sample characteristics. We carried out meta-regression analysis for categorical variables to compare the estimated ds between the groups CC–NC and DC–NC for outcome (relapse, length of time admitted to hospital, positive symptoms, negative symptoms, and functioning). We also used meta-regression to test whether the effect of cannabis was confounded by the stage of illness of participants in the studies included (ie, early psychosis versus chronic psychosis, with chronic psychosis referring to participants with an illness duration of more than 5 years, as classified in previous studies³⁷). Finally, we used meta-regression for continuous moderators to test the effect of sex (percentage of sample being male) and age at the time of study assessment. We examined the possibility of publication bias using funnel plots, followed by the Egger's linear regression test³⁸ to test funnel plot asymmetry for significance. We tested homogeneity of the distribution of weighted effect sizes with the Q test, and degree of heterogeneity was quantified using the I² test, which describes the percentage of observed heterogeneity that would not be expected by chance.³⁹ I² values between 0%

and 25% suggest small heterogeneity, whereas I² values in the range 25% and 50% suggest moderate heterogeneity, and those of more than 50% suggest large heterogeneity.

Because of the heterogeneity in the definition of relapse used by the studies, we carried out sensitivity analyses restricting the studies to only those investigating hospital admissions, which has been reported to be a valid measure of relapse in psychosis.⁴⁰ Similarly, in view of the variation in follow-up duration between cannabis users and non-users in the studies, we carried out subset analyses by including only those studies in which cannabis users were matched to the non-users in terms of their follow-up duration (denoted as matched=yes if the difference was not more than 1 year between the groups).

Role of the funding source

The funder of the study had no role in study design or collection, analysis and interpretation of data, or writing of the report. All authors had access to the data and have approved the final version of the report.

Results

24 of 1903 identified studies met the inclusion criteria (table), comprising 5849 individuals with continued cannabis use after psychosis onset and 10 308 who were classified as non-users (figure 1). Screening of 126 studies

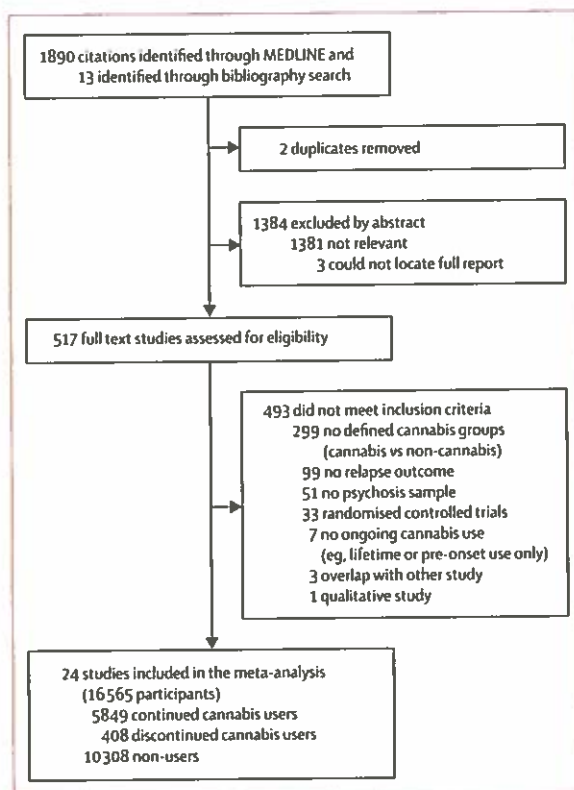


Figure 1: Study selection

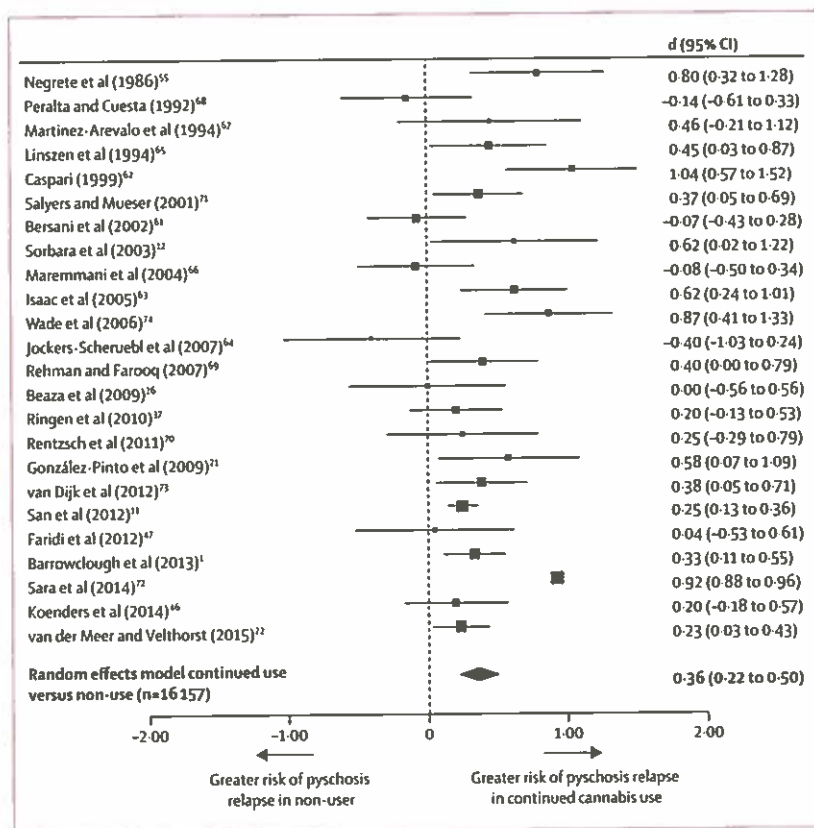


Figure 2: Random effects model of relapse and continued cannabis use versus non-use

published in languages other than English did not yield any additional studies meeting our inclusion criteria (appendix). Six of the included studies had an additional group of patients who were classified as discontinued cannabis users (408 discontinued users, 268 continued users, and 496 non-users). Continued cannabis use after onset of illness was associated with a low-to-moderate increase in relapse of psychosis compared with non-users ($d_{CC-NC}=0.36$, 95% CI 0.22 to 0.50, $p<0.0001$; figure 2, appendix). An effect of a similar magnitude was reported on length of time admitted to hospital after onset ($d_{CC-NC}=0.36$, 0.13 to 0.58, $p=0.02$). For four studies (688 participants) we were able to calculate the number of days spent in hospital per year of illness since the onset of psychosis (estimated as the weighted mean difference [WMD]; appendix). The results suggest that cannabis users spent an additional 8.47 days (-4.56 to 21.50) in hospital per year of having psychosis, although this difference was not significant ($p=0.20$), which might be attributable to the lack of power (appendix). In the seven studies (2298 participants) that examined the risk of relapse (table), the pooled odds were 1.97 (95% CI 1.46 to 2.65, $p<0.0001$) times greater in people who continued to use cannabis than they were in those who did not use cannabis. Limiting analysis to include only the six studies ($n=1172$) that reported on relapse rates in individuals with the three patterns of cannabis use of interest in this

context (ie, CC, DC, and NC) showed that this adverse effect of cannabis in continued users remained when compared with those who discontinued ($d_{CC-DC}=0.28$, 0.12 to 0.44, $p=0.0005$). By contrast, individuals who discontinued cannabis use did not significantly differ from the non-users in their relapse outcome ($d_{DC-NC}=0.02$, -0.12 to 0.15; $p=0.82$, figure 3). Including all identified studies in meta-regression to compare the difference in effect size d between continued cannabis users and those who discontinued relative to corresponding non-user groups ($d_{CC-NC}=0.36$ vs $d_{DC-NC}=0.02$) confirmed that the effect sizes were significantly different between the two sets of comparisons ($p=0.04$; appendix). Egger's test and funnel plots (appendix) suggest evidence of funnel plot asymmetry for relapse ($p=0.0002$), but the trim-and-fill method (R_0 estimator used for estimating the number of missing studies) did not show missing studies, suggesting that the asymmetry might be due to other causes such as study heterogeneity.^{77,78}

Continued cannabis use predicted positive symptom severity ($d_{CC-NC}=0.15$, 95% CI 0.01 to 0.29, $p=0.04$; figure 4). These small but significant adverse effects on positive symptoms were not present in participants who discontinued using cannabis ($d_{DC-NC}=-0.30$, -0.99 to 0.38, $p=0.39$) and meta-regression suggested that the effect sizes (d_{CC-NC} vs d_{DC-NC}) were different ($p=0.05$). Notably, although continued cannabis users showed similar levels of functioning when compared with the non-users ($d_{CC-NC}=0.04$, -0.14 to 0.21, $p=0.68$), those who discontinued using cannabis had higher levels of functioning than did non-users ($d_{DC-NC}=-0.49$, -0.81 to -0.17, $p=0.002$). This difference in effect-size (d_{CC-NC} vs d_{DC-NC}) was significant, as shown by meta-regression ($p=0.0075$). Continued cannabis use was not a significant predictor for the presence of negative symptoms ($d_{CC-NC}=-0.09$, -0.30 to 0.11, $p=0.37$) or reduction in negative symptoms in individuals who discontinued use compared with non-users ($d_{DC-NC}=-0.31$, -0.67 to 0.05, $p=0.10$); the difference in effect size (d_{CC-NC} vs d_{DC-NC}) was not significant by meta-regression ($p=0.41$). This finding is in accordance with the direct comparison between continued and discontinued users (CC-DC; appendix), which suggested that individuals who continued smoking cannabis had higher levels of negative symptoms than did those who discontinued. However, this association was not significant ($p=0.07$) and generalisability might be restricted owing to the few studies included in this analysis (two studies, $n=83$).

We noted substantial heterogeneity in the effect of continued cannabis use on relapse (83.62%, 95% CI 68.04-92.89, $p<0.0001$). Hence, we did sensitivity analyses with more homogeneous groups of studies (appendix); studies were selected if they matched the follow-up duration between continued cannabis users and non-users (17 studies, $n=15371$; $d_{CC-NC}=0.42$, 95% CI 0.26-0.57, $p<0.0001$), were rated as high quality (ten studies, $n=1366$; $d_{CC-NC}=0.50$, 0.32-0.68, $p<0.0001$),

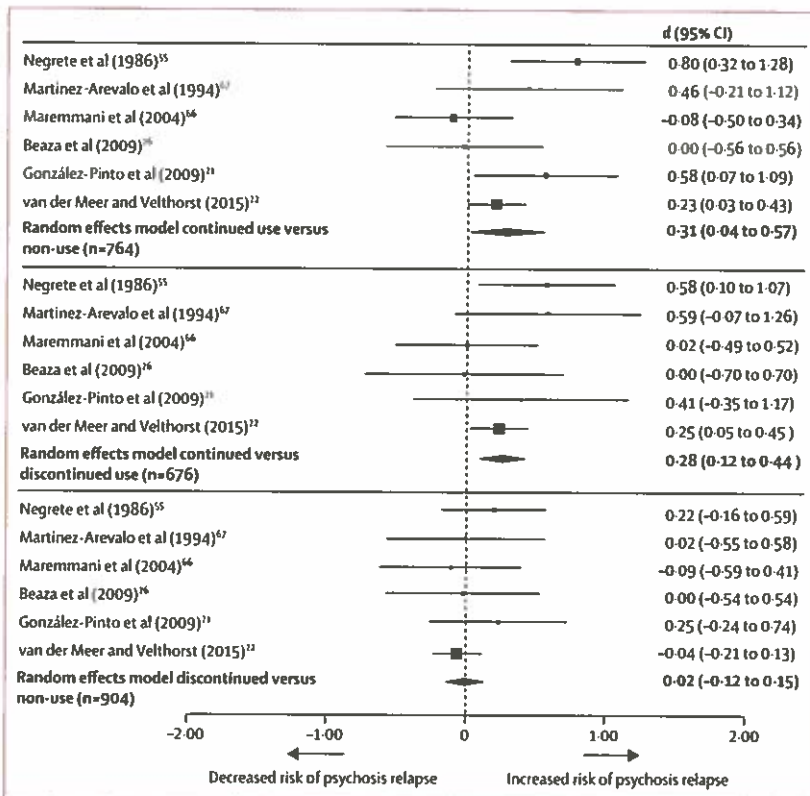


Figure 3: Random effects model of relapse (continued versus discontinued versus non-use of cannabis)

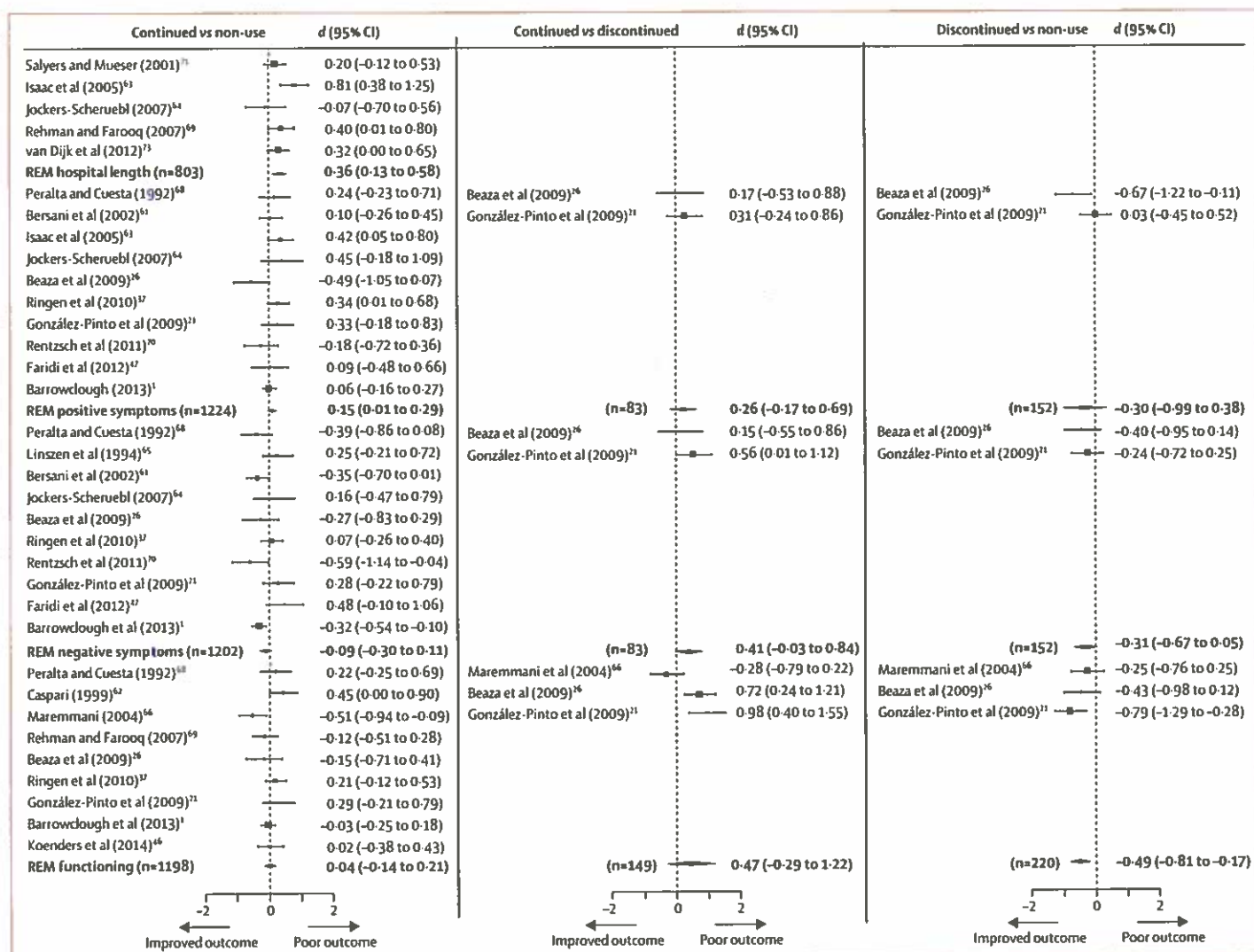


Figure 4: Random effects model of relapse-related outcome (continued versus discontinued versus non-use of cannabis)

if they included either only early stage psychosis (ten studies, $n=1120$; $d_{CC-NC}=0.30$, $0.13-0.47$, $p=0.0004$) or chronic psychosis (13 studies, $n=14922$; $d_{CC-NC}=0.37$, $0.16-0.58$, $p=0.0006$), and defined relapse as hospital admission (19 studies, $n=15412$; $d_{CC-NC}=0.36$, $0.19-0.52$, $p<0.0001$). Effect sizes estimated for studies including only patients with non-affective psychosis (nine studies, $n=1280$; $d_{CC-NC}=0.34$, $0.11-0.58$, $p=0.0036$) and those including only affective psychosis (15 studies, $n=14877$; $d_{CC-NC}=0.37$, $0.19-0.55$, $p<0.0001$) were not different ($p=0.89$). Sex and age at follow-up assessment did not reduce the heterogeneity in relapse outcome, as shown by meta-regression (sex $p=0.87$ and age $p=0.38$).

Discussion

To our knowledge, this is the first meta-analysis to show that, irrespective of the stage of their psychotic disorder, patients who continue using cannabis are more likely to

have a psychosis relapsing course than are both non-using patients ($d_{CC-NC}=0.36$) and patients who discontinue using cannabis after onset of psychosis ($d_{CC-DC}=0.28$). Furthermore, because individuals who discontinue cannabis use did not differ from the non-users in their relapse outcome ($d_{DC-NC}=0.02$), these results suggest that the increased relapse rate associated with cannabis use might resolve after discontinuation of its use. The gradient in the effect of cannabis use (continued use is worse than discontinued use, which is worse than non-use) on outcome in psychosis recorded in the present analysis is consistent with that noted in other studies^{15,24} not included here, with the effect on outcome being most adverse in people who continue to use the drug. This finding is also compatible with epidemiological evidence^{15,65} of the adverse effects of cannabis being dose dependent and with evidence that the magnitude of cognitive impairments associated with cannabis exposure

tend to diminish after abstinence.⁷⁹ Additionally, our results suggest that continued cannabis users underwent substantially longer admissions to hospital after their psychosis onset than did non-users ($d_{CC-NC}=0.36$), which could suggest that more severe relapses require longer inpatient care to become stabilised. Increased hospital stay might also be linked to factors unrelated to the severity of the illness, such as absence of suitable accommodation for the patient after discharge.

In terms of symptomatic outcome, continued cannabis users experienced more severe positive psychotic symptoms at follow-up assessment. This effect was not present in patients who discontinued using cannabis ($d_{CC-NC}=0.15$ vs $d_{CC-DC}=-0.30$). This result is consistent with other follow-up studies^{22,25} that compared positive symptom levels between continued users, discontinued users, and non-users of cannabis and a report³⁰ from a longitudinal population-based sample suggesting that continuation of cannabis use predicted subsequent persistence of psychotic symptoms. Other studies have reported a temporal association between changes in cannabis use and subsequent changes in psychotic symptom severity, in both the short-term³¹ and long-term.³⁴ Evidence that cannabis use has a particularly harmful effect on different outcome measures of psychosis (eg, relapse and psychotic symptoms) when it is continued compared with when it is stopped is intuitive and consistent with effects of cannabis use on cognition.⁷⁹ However, the effect of cannabis and continuity of its use was not noted across other outcomes in the present meta-analysis; continued cannabis users did not differ from individuals in the non-user group in their negative symptoms ($d_{CC-NC}=-0.09$, $p=0.37$). A similar result was reported in a separate meta-analysis focusing on symptoms.³² Discontinued cannabis users also did not differ from non-users ($d_{DC-NC}=-0.31$, $p=0.10$), although they had fewer negative symptoms when compared directly with continued users ($d_{CC-DC}=0.41$, $p=0.07$). This finding might seem to contradict the results of the meta-regression that suggest no difference between the effects of continued and discontinued use on negative symptoms. However, the meta-regression compared the estimates from two different random effects models (ie, d_{CC-NC} and d_{DC-NC}) examining the effect on negative symptoms, rather than doing a direct comparison between discontinued and continued cannabis users. Furthermore, the direct comparison included data from only two studies, whereas the meta-regression compared data from a larger sample of studies. Nevertheless, the general direction of effect in different groups is consistent across all comparisons. Continued cannabis users showed similar levels of functioning when compared with non-users ($d_{CC-NC}=0.04$, $p=0.68$), whereas discontinued users had better functioning scores than non-users ($d_{DC-NC}=-0.49$, $p=0.002$). In line with this finding, other studies^{22,24,28} have reported that individuals who discontinue cannabis use have better functioning than non-users and a 2012

meta-analysis³⁴ suggested that cessation of substance use in general was associated with improvement of negative symptoms and global functioning as measured with the Global Assessment of Functioning Scale.³⁴ These findings suggest that patients who use cannabis might have better functioning to begin with (although this hypothesis is not something that could be tested in the present analysis). This result is also compatible with the view that patients who use cannabis represent a subgroup of people with a less neurodevelopmental pathology;^{32,33} perhaps for this reason the adverse effects of cannabis use on functioning and negative symptoms become apparent only when continued users are compared with those who discontinued use rather than non-users. Patients who are able to stop using cannabis might represent a causally and clinically distinct subgroup with a less severe illness with less of a need to use cannabis for self-medication.

The reported association between cannabis exposure and relapse of psychosis and related outcome variables might be mediated through the effect of its key psychoactive ingredient, THC, on the neural substrates implicated in psychosis.^{33-23,34-36} The reported strength of association between continued cannabis use and relapse is similar to other identified environmental risk factors for relapse of psychosis, such as highly expressed emotions ($d=0.31$),³⁷ and the effects of interventions that prevent relapse, such as psychoeducation ($d=0.21$),³⁸ or reduce psychotic symptoms, such as antipsychotic treatment ($d=0.48$).³⁹ Hence, these results emphasise the importance of cannabis use as a clinically relevant target for treatment development.

Some limitations, which are mainly related to the methodological heterogeneity in the studies included (table), are noteworthy. Different criteria were used by the studies included in this meta-analysis to classify people who continued to use cannabis (eg presence of cannabis use disorder or use more than once in a defined time-period), those who discontinued the drug (eg, history of use, but negative urinary drug screen or no use in defined time period), and non-users (eg, less than daily use, non-misuser, no use in defined time period, or never use). Follow-up durations also differed between cannabis users and non-users in some studies³⁶ (eg, 7-year relapse window for cannabis users vs 12-year relapse window for non-users). Exclusion of studies with differing follow-up windows between the participant groups as part of sensitivity analysis showed a slightly larger effect of cannabis use on relapse than that reported in the main analysis ($d=0.42$ vs $d=0.36$). The study by Baeza and colleagues,²⁶ might need to be emphasised in this context, considering that their report of absence of adverse effects of cannabis use on relapse might be attributable to their 6 months follow-up, an interval perhaps too short to detect differences in relapse rates between the groups.

The patients might have differed in their stage of illness across the included studies (eg, early stage vs chronic psychosis), but sensitivity analysis showed that

this discrepancy did not significantly affect the results. We could not control for the effect of other potential confounding factors that might be associated with cannabis use, such as medication adherence,^{1,24,25,67,69} engagement with services,²⁴ or misuse of other drugs.¹ However, the present results are consistent with studies that have systematically controlled for age, sex, alcohol and drug use, illness characteristics (eg duration, diagnosis, and severity), and medication adherence when measuring the effect of cannabis use on relapse.^{10–12} Another limitation inherent to the meta-analytical design relates to our inability to analyse raw data, which restricted our ability to do moderation analysis to directly test for more defined dose–response patterns such as frequency, duration, or age of onset of use or type of cannabis consumed, factors that are also likely to moderate the effect of cannabis on relapse.^{13,65} A further potential source of heterogeneity might be the use of different types of cannabis containing differing proportions of the main ingredients (such as THC or cannabidiol) that are known to have opposing effects.⁹⁰ We were unable to assess the effect of type of cannabis used because this information was not available for the included studies. Finally, although our systematic search might have been somewhat restricted by using MEDLINE only, we aimed to address this potential limitation by screening bibliographies from previously done meta-analyses, systematic reviews, and original studies for additional studies that might have been missed in the database search.

Despite the absence of more fine-grained measures, this meta-analysis detected a fairly robust pooled effect of continued cannabis exposure on relapse outcome and other measures suggestive of adverse outcome, which were absent in those who discontinued use of the drug. The fact that the effects of continued use of cannabis or its discontinuation are consistent across different measures of outcome underlines the importance of addressing continued cannabis use in patients with psychosis in the clinical setting, by emphasising that outcomes are likely to be better in those who discontinue the drug.

Contributors

SB and TS had full access to all the data in the study and take full responsibility for the integrity of the data and the accuracy of the data analysis. SB designed the study and supervised the analysis. TS did the data analysis and wrote the first draft together with SB. All other authors provided data, reviewed the results, and contributed to the final draft of the manuscript.

Declaration of interests

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Can a criminal justice alcohol abstention programme with swift, certain, and modest sanctions (24/7 Sobriety) reduce population mortality? A retrospective observational study

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Summary

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Background In the UK and USA, various jurisdictions have launched new approaches for managing alcohol-involved offenders that might have public health implications. These programmes require participants to abstain from alcohol and submit to frequent alcohol testing with swift, certain, and modest sanctions for violations, with the aim to reduce crime and keep alcohol-involved offenders in the community. In this study we examine whether the 24/7 Sobriety programme in South Dakota, USA—the largest such programme to date—is associated with reductions in mortality.

Methods With a differences-in-differences design, we used variation in the timing of 24/7 Sobriety implementation across South Dakota counties between 2005 and 2011 to estimate the association between programme introduction and county-level mortality. We used monthly, county-level, aggregate counts for mortality from January, 2000, to June, 2011. We assessed total deaths, and deaths due to external injuries, circulatory disorders, digestive disorders, and cancer (as a potential placebo).

Findings Between January, 2005, and June, 2011, 16 932 people (about 3% of the adult population) participated in the 24/7 Sobriety programme. The analysis was based on a sample size of 9108 county-month observations (ie, 66 counties × 12 months × 11.5 years). Implementation of 24/7 Sobriety was associated with a 4.2% (95% CI 1.5–6.9) reduction in all-cause adult mortality, with the largest associations among women (8.0%, 95% CI 3.9–11.8) and individuals older than 40 years (4.3%, 95% CI 1.4–7.0). Associations were most evident among circulatory disorders.

Interpretation 24/7 Sobriety might have public health benefits, which could extend beyond individuals directly enrolled in the programme. However, further research, including randomised controlled trials and analyses of individual-level data, is needed to corroborate the finding, reassess the size of these associations, and gain insight into causal mechanisms. Should a negative association be replicated, it might represent a substantial advance in our understanding of how criminal justice interventions could help shape public health.

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Introduction

Alcohol consumption can impose massive harms, with some estimates suggesting that alcohol costs the UK about £20 billion annually.¹ Mortality constitutes one of the most costly consequences of heavy alcohol use and might affect users and non-users through biological mechanisms, dependence, and intoxication.² The nature of consumption, especially heavy drinking episodes and past alcohol problems,³ and the presence of alcohol at the time of injury, play a part in mortality.⁴ Women seem to be especially sensitive to adverse outcomes associated with heavy alcohol use.⁵

Alcohol-related consequences are particularly common among alcohol-involved offenders,^{6–8} although evidence is lacking for mortality among such populations in the UK and the USA. Programmes aimed at reducing alcohol-related harms have had mixed results,^{9,10} in part based on whether they target those drinkers most likely to impose harms and the extent to which they reduce heavy drinking.

In 2003, South Dakota Governor Mike Rounds established a corrections task force focused on reducing the prison population. Because alcohol misuse was a factor

for a significant share of prisoners, there was a focus on reducing alcohol consumption. As a result of this task force—and especially the efforts of then Attorney General Larry Long—counties in South Dakota implemented a novel and targeted intervention (the 24/7 Sobriety programme) to reduce alcohol consumption for those individuals whose use threatened public health and safety.

South Dakota's 24/7 Sobriety programme (hereafter, 24/7 Sobriety) requires that alcohol-involved offenders subject to community supervision (eg, pre-trial release, probation) abstain from alcohol. The programme is intensive in that participants must submit to twice-a-day breathalyser tests, typically 12 h apart (eg, 0700–0900 h and 1900–2100 h), or wear continuous alcohol monitoring bracelets. Twice-a-day testing is unlikely to detect all drinking because alcohol passes through the body relatively quickly, but it is likely to identify heavy drinking.

Participants who test positive or skip a test are subject to an immediate, but brief jail term (typically 1 or 2 days for a failed test). 24/7 Sobriety is not ordered in lieu of treatment; judges can order individuals to