Received: 7 August 2024 | Accepted: 31 March 2025

DOI: 10.1111/add.70080

RESEARCH REPORT

ADDICTION SSA

Effects of legal access versus illegal market cannabis on use and mental health: A randomized controlled trial

Lavinia Baltes-Flueckiger[1] | Regine Steinauer[2] | Maximilian Meyer[3] | Adrian Guessoum[3] | Oliver Herrmann[3] | Christoph Felix Mosandl[3] | Jens Kronschnabel[1] | Eva-Maria Pichler[1] | Marc Vogel[3] | Marc Walter[1,4]

[1]Psychiatric and Psychotherapeutic Clinic, Psychiatric Services Aargau, Windisch, Switzerland

[2]Health Department, Basel, Switzerland

[3]Psychiatric University Clinics Basel, University of Basel, Basel, Switzerland

[4]Faculty of Medicine, University of Basel, Basel, Switzerland

Correspondence
Lavinia Baltes-Flueckiger, Psychiatric and Psychotherapeutic Clinic, Psychiatric Services Aargau, Königsfelderstrasse 1, 5210 Windisch, Switzerland.
Email: lavinia.baltes@pdag.ch

Funding information
This work was supported by the Canton Basel-Stadt, Switzerland (Nr. 21/30/19; P211352)

Abstract

Aims: We measured the effects of public health-oriented cannabis access compared with the illegal market on cannabis use and related mental health outcomes in adult cannabis users.

Design: This was a two-arm, parallel group, open-label, randomized controlled trial. Follow-up outcome measurement took place after 6 months.

Setting: The study was conducted in Basel-Stadt, Switzerland.

Participants: A total of 378 adult (aged ≥18 years) cannabis users were enrolled and randomized between August 2022 and March 2023, although only 374 users who completed baseline measures could be included.

Intervention and Comparator: Participants were randomly assigned to the intervention group with public health-oriented recreational cannabis access in pharmacies (regulated cannabis products, safer use information, voluntary counseling, no advertisement; 189/188) or the illegal market control group (continued illicit cannabis sourcing; 189/186).

Measurements: The primary outcome was self-reported severity of cannabis misuse after 6 months, as measured by the Cannabis Use Disorders Identification Test – Revised (range 0–32). Secondary outcomes involved depressive, anxiety, and psychotic symptoms, cannabis consumption amount, alcohol, and drug use.

Findings: Ten participants were not followed (2.7%). Primary analysis included those with complete data (182 vs. 182). There was some evidence of a difference in cannabis misuse between the legal cannabis intervention group (mean [M] = 10.1) and the illegal market control group (M = 10.9; β = −0.69, 95% confidence interval [CI] = −1.4 to 0.0, P = 0.052). These results were supported by an intention-to-treat multiple imputation analysis (n = 374). Additional sub-group analysis by whether the participant used other drugs or not suggested that any reduction in cannabis misuse was confined to those in the legal cannabis intervention group who used other drugs ($P_{Interaction}$ < 0.001). We found no statistically significant changes in any of the secondary outcomes.

Conclusions: Public health-oriented recreational cannabis access may decrease cannabis use and cannabis-related harms, especially among those using other drugs.

KEYWORDS
cannabis legalization, cannabis misuse, cannabis use, mental health, randomized controlled trial, recreational cannabis

INTRODUCTION

In 2022, approximately 228 million people globally used cannabis [1]. Many individuals use cannabis without adverse health outcomes. However, cannabis use is associated with an increased risk of mental disorders, including psychotic, affective and substance use disorders [2–5]. Up to 33% of those who regularly use cannabis are estimated to develop cannabis use disorder [6]. Cannabis use disorder substantially contributes to the global burden of disease [7].

Despite prevailing prohibition, cannabis remains the most widely used illicit substance [8]. Efforts to address this global challenge have increasingly focused on alternative regulatory frameworks [9]. Several countries, such as Canada, Uruguay, Germany and various United States (US) states have legalized cannabis for recreational use and multiple countries are considering taking this step. Among the diverse aims of recreational cannabis laws (RCL), a key objective is reducing cannabis related harms [9–11]. Essential measures in RCL that aim to reduce cannabis use and to improve mental health include regulated cannabis products, as well as facilitating access to preventive information, counseling, treatment and harm reduction [11].

The body of literature from countries with RCL is rapidly growing [12–21], but data on the effects on cannabis use and related mental health outcomes are inconsistent. Moreover, previous studies on the health effects of RCL were principally based on observational designs comparing regions with and without RCL or regions before and after RCL [12–18]. These study designs are highly informative at the population level, but causal inferences on the individual level are limited, because observed (e.g. age, gender) and unobserved factors (e.g. social norms, unmeasured genetic factors) cannot be disentangled and may bias the observed association between RCL and health outcomes. Additionally, and aside from cannabis use and cannabis use disorders, research is scarce on cannabis related mental health outcomes such as depression or anxiety [22]. Therefore, experts have called for more experimental and controlled research on RCL effects [10, 17, 23–25] as well as for a broader range of potentially impacted mental health outcomes [26].

This study seeks to address these issues using a randomized controlled trial that compared the effects of public health-oriented access to recreational cannabis with continued illegal market use, with respect to cannabis use and a broad range of related mental health outcomes in cannabis users.

METHODS

Study design

This open-label, parallel-group, randomized controlled trial was designed to evaluate the effects of a legal cannabis intervention versus illegal market in individuals who already use cannabis. The 6 months monocenter trial was conducted in the canton Basel-Stadt in Switzerland from August 2022 to July 2023. After the 6 months of randomized controlled trial, a 2-year observational study of providing legal cannabis to all participants has followed and will last until July 2025. The randomized controlled trial is the basis for the present article. Data of the currently ongoing observational period will be published in future articles.

The trial protocol was approved by the local ethics committee 'Ethikkomission Nordwest-und Zentralschweiz' (protocol number 2021–01670) as well as the Federal Office of Public Health (approval number 2022/000001). The trial was prospectively registered at ClinicalTrials.gov NCT05522205 on 30 August 2022. A study protocol has been published [27]. Additionally, the study was designed in agreement with the Declaration of Helsinki, the International Council for Harmonisation Good Clinical Practice guidelines and the national law, in particular the amendment of the Federal Act on Narcotics and Psychotropic Substances [28]. Cannabis for recreational use is prohibited in Switzerland. However, in 2021, a legislative amendment allowed pilot trials of recreational cannabis use in adults, and this amendment defined various conditions for these trials such as the maximum tetrahydrocannabinol (THC)-content of the legal products [28]. This unique legal setting allowed us to conduct a randomized controlled trial within this legal framework that—spatially and temporally limited—evaluates the health impacts of legal cannabis access in a restricted sample of registered users, and in which users without legal access serve as controls.

Participants

Recruitment occurred through a media conference in August 2022 that informed the public about the current study. Interested participants could register at a study-specific website. After initial screening by telephone, potential participants were invited to a face-to-face screening with the study physician, to check inclusion and exclusion criteria. From August 2022 to March 2023, we screened 665 participants for eligibility and randomly assigned 378 participants, 189 (50%) to the legal cannabis intervention group and 189 (50%) to the illegal market control group (Figure 1). Eligible participants used cannabis at least once per month during the last 6 months (including a positive THC-urine sample); were 18 years or older; had basic German language skills; resided in the canton Basel-Stadt; and had internet access to answer on-line-surveys. Potential participants were excluded if they were currently pregnant or breast-feeding; were in current inpatient psychiatric treatment; had acute psychosis or suicidal ideation; suffered from severe cognitive impairment that prevented them from understanding the study information or to follow the study procedure; or had any intention to move away from Basel-Stadt within the

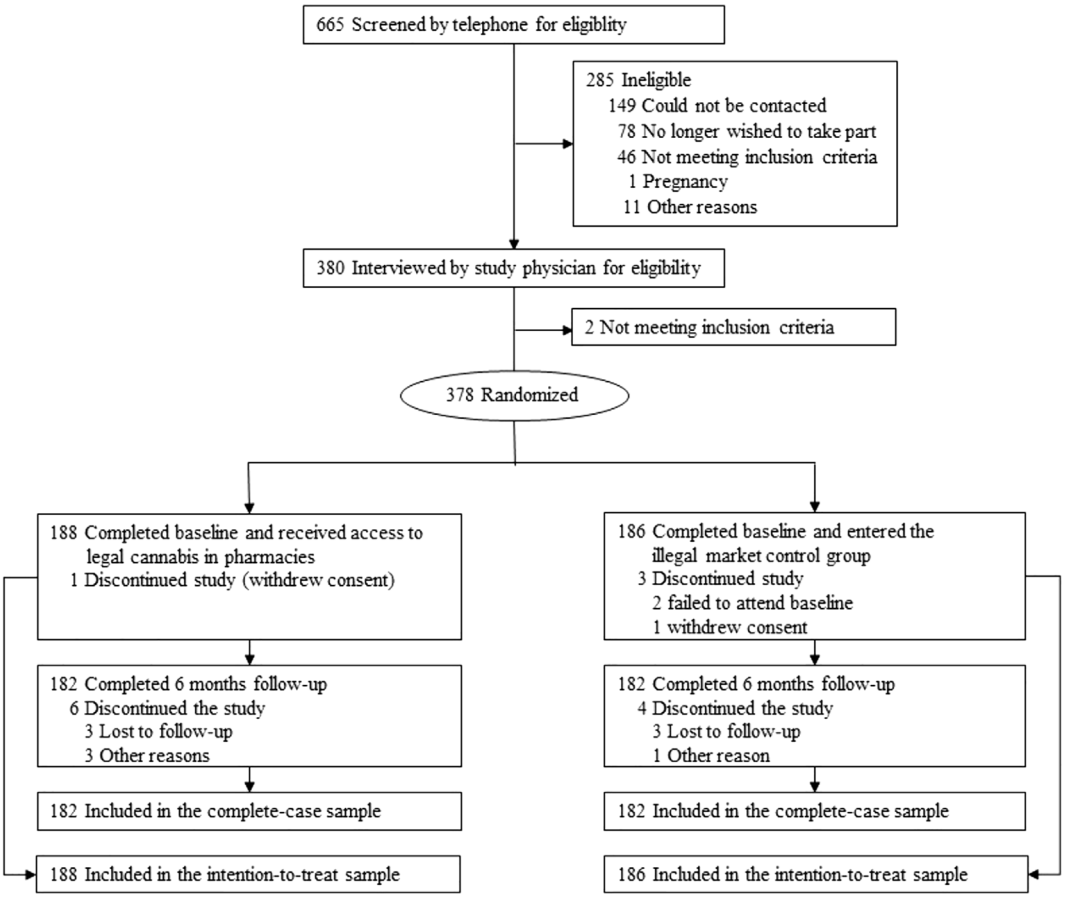

FIGURE 1 Flow diagram from screening to 6-months follow-up assessment. Participants who were lost to follow-up were those whom we were unable to contact. Other reasons included moving from the canton, dissatisfaction with cannabis quality and financial difficulties.

subsequent 12 months. All included participants provided informed written consent before any study procedures occurred.

Study start was originally planned for 15 September 2022. However, since cannabis products did not meet quality requirements, the beginning of the study (baseline assessment and cannabis access in pharmacies) had to be postponed to 30 January 2023. A total of 14 drop outs were recorded. Four participants dropped out before legal cannabis access started (3 in the illegal market control group; 1 in the legal cannabis intervention group), so that four additional participants were re-recruited. Another 10 (3%) participants (4 in the illegal market control group, 6 in the legal cannabis intervention group) did not complete the survey at the 6 months follow-up in July 2023. The main reason for loss to follow-up was failure to reach participants after discharge—despite repeated calls (Figure 1).

Study procedures

After enrolment, a study nurse randomly assigned participants to the legal cannabis intervention group or to the illegal market control group. The randomization allocation was conducted by a random-number table through REDCap that was created by an independent statistician, who was not involved in the rest of the trial.

Participants assigned to the legal cannabis intervention group had access to legal cannabis in nine pharmacies from the baseline. The illegal market control group was denied legal cannabis access and had to continue to obtain their cannabis from illegal sources, as is the current legal situation in Switzerland. The legal cannabis intervention consisted of several measures to mitigate risks of cannabis use [11]. First, participants were provided with six regulated cannabis products free from contaminants. Products had to meet quality standards in production that were defined by law (e.g. organic cannabis cultivation, maximum content of contaminants such as microbiological contaminants, mycotoxins or pesticides). Products included four flower and two hash products with different THC and cannabidiol (CBD) concentrations, but with an upper THC limit of 20%, as is required by law [28]. Participants were free to choose between the products. Furthermore, participants were allowed to purchase a maximum of 10 grams of total THC per month, allowing larger quantities of products with lower THC content [28]. All cannabis purchases were registered in a specific 'track and trace' software, to track the maximum amount of 10 grams of total THC per month per participant. Cannabis products are listed in Appendix S1. Product prices were derived by a user survey from 2021 so that they were comparable to illegal market prices. Prices were also THC dependent, with lower THC content being more affordable. Packaging was labelled with THC/CBD concentration and preventive

information (safety and legal warnings, lower risk use information, symbols of product strength). Detailed lower risk use information was available on-line that could be accessed via QR-code on the packaging. There was no advertisement of the study products. Voluntary counseling by the study physician (by e-mail or by telephone) and the vending staff (face-to-face in pharmacies) was available during the entire study. Vending staff in pharmacies were trained in guidelines on lower risk of use [11], identification of vulnerable users, triage to drug counseling, treatment institutions and prevention services. Brochures with counseling and treatment institutions were provided by the vending staff and study physician. Therefore, prevention, early intervention and treatment were facilitated in pharmacies. Moreover, participants were able to contact study physicians for any medical concerns.

Measures

Primary outcome

The primary outcome was self-reported severity of cannabis misuse, measured as total score at 6 months follow-up on the Cannabis Use Disorders Identification Test - Revised (CUDIT-R) [29]. This 8-item scale assesses frequency of use; hours stoned during days of use; inability to stop using; failure to meet expectations; time spent getting, using, or recovering from cannabis; memory or concentration problems after cannabis use; use in hazardous situations (e.g. driving, caring for children); and desire to stop/reduce cannabis use. Scores range from 0 to 32, with higher scores indicating more severe cannabis misuse and with a score of 13 or greater as recommended threshold for potential cannabis use disorder. However, authors note that lower scores can still be considered as problematic use [29].

Secondary outcomes

Secondary outcomes included self-reported depressive, anxiety and psychotic symptoms as well as self-reported amount of cannabis consumption, as well as alcohol and drug use at 6 months follow-up. Depressive symptoms were assessed with the 9-item Patient Health Questionnaire (PHQ-9) [30]. Scores range from 0 to 27 and higher scores represent more severe symptoms, with a score of 10 or greater indicating moderate to severe depression [30]. Generalized anxiety symptoms were assessed with the 7-item Generalized Anxiety Disorder Assessment (GAD-7), with scores ranging from 0 to 21 and a score of 10 or greater being the recommended threshold for moderate to severe generalized anxiety disorder [31]. Psychotic symptoms were measured with a short version of the Early Recognition Inventory Checklist including seven items on early psychosis, with scores ranging from 0 to 7 (higher scores indicate more severe psychotic symptoms) [32]. Amount of cannabis consumption was assessed separately for legal and illegal cannabis. To facilitate the specification of the amount of cannabis consumption, participants were provided with pictures of different amounts of cannabis flower and hashish in relation to a coin. Alcohol use was measured with the 3-item Alcohol Use Disorders Identification Test - Consumption (AUDIT-C) [33]. Scores range from 0 to 12, with a score of 3 or more for women and a score of 4 and more for men as indicative of hazardous alcohol use [33]. Drug use was assessed with one question of the Alcohol, Smoking and Substance Involvement Screening Test, which asked participants how often they had used cocaine, amphetamine-type stimulants, inhalants, sedatives, hallucinogens, opioids and other drugs during the preceding 6 months [34]. Scores of these seven items range from 0 to 42. Whereas a score of 0 indicates no drug use during the preceding 6 months, higher scores indicate more frequent drug use.

Baseline characteristics

At baseline the following socio-demographic characteristics were assessed: Sex, age, Swiss nationality, marital status, education and employment status. Additionally, the age of onset cannabis use, cannabis use days per month, lifetime nicotine use ('Have you smoked more than 100 cigarettes or a comparable amount of other tobacco products in your life? Yes/No') as well as cigarette use days per month were assessed.

Further measures

Additional exploratory outcomes of substance use (e.g. medication), physical health (e.g. respiratory symptoms, physical symptoms and physical activity) and mental health (sleep, positive and negative affect) were also collected at baseline and at 6 months. These outcomes will be published in future articles and will be interpreted as secondary outcomes.

Adverse events

Serious adverse events including hospitalization of more than 24 hours and life-threatening events were assessed every 2 months via an on-line-survey. Additionally, participants were advised to contact the study team immediately in the event of a serious adverse event.

Baseline and follow-up assessment at 6 months included primary and all secondary outcomes as well as safety measures. The assessments were collected via on-line-surveys in REDCap and were self-reported. If participants did not answer the on-line-survey, they were reminded (first reminder via e-mail, second and third reminder by call). Baseline and follow-up assessments were mandatory to be permitted legal cannabis in pharmacies.

Statistical analysis

Assuming a two-sided α of 5%, power of 80% and 20% attrition, 374 participants were estimated to be required to detect a benefit of

two points in CUDIT-R score after 6 months in favor of the legal cannabis intervention. A change of two points or greater in mean CUDIT-R is defined as reliable change in cannabis misuse [35].

Categorical variables are presented as numbers (%) and continuous variables as means (SD) when normally distributed or median [interquartile range (IQR)] when not. The primary analysis was a multivariable regression of CUDIT-R score at 6 months regressed on intervention allocation, adjusted for baseline CUDIT-R score as a covariate. The full analysis set contains all participants who were randomly assigned and who completed baseline assessment. Because only a very limited number of observations was missing (10 participants; 3%), the analyses were conducted on complete cases, assuming that values were missing completely at random. For the primary outcome, an additional sensitivity analysis was conducted following the intention-to-treat principle, which assumed that missingness was not at random and which imputed the follow-up value from the participants' baseline value (assuming no change over time).

For the primary outcome, additional exploratory analyses were conducted. First, the change from baseline to 6 months follow-up was analyzed for each of the CUDIT-R items, to explore whether the

TABLE 1 Baseline demographic and clinical characteristics.

	Total (*n* = 374)	Legal cannabis (*n* = 188)	Illegal market (*n* = 186)
Sex (*n* = 370), no. (%)			
Male	299 (81)	149 (81)	150 (81)
Female	65 (17)	34 (18)	31 (17)
Non-binary	6 (2)	2 (1)	4 (2)
Age (*n* = 370), mean (SD), y	35.8 (11.4)	36.0 (11.8)	35.6 (11.1)
Swiss nationality (*n* = 370), no. (%)	277 (75)	139 (75)	138 (75)
Marital status (*n* = 370), no. (%)			
Married or in a partnership	53 (14)	32 (17)	21 (11)
Single	288 (78)	133 (72)	155 (84)
Separated or widowed	29 (8)	20 (11)	9 (5)
Education, no. (%)			
Obligatory school	36 (10)	18 (10)	19 (10)
Basic vocational school	113 (30)	51 (27)	62 (33)
University qualification	57 (15)	35 (19)	22 (12)
Higher vocational education	28 (8)	15 (8)	13 (7)
University degree	136 (36)	68 (37)	68 (36)
Other	4 (1)	1 (1)	3 (2)
Employment status, no. (%)			
Paid employment	281 (75)	139 (74)	142 (76)
Unemployed	20 (5)	10 (5)	10 (5)
Non-working (retired, home maker, training)	73 (20)	39 (21)	34 (18)
Age of onset cannabis use (*n* = 372), mean (SD), years	16.6 (3.5)	16.6 (3.6)	16.6 (3.4)
Cannabis use days per month (*n* = 364), median (IQR)	21 (7, 30)	20 (8, 30)	25 (7, 30)
Nicotine use (yes), no. (%)	264 (71)	140 (75)	124 (67)
Cigarette use days per month (*n* = 228), median (IQR)	30 (20, 30)	30 (20, 30)	30 (20, 30)
Primary and secondary measures			
CUDIT-R (possible range 0–32), mean (SD)	11.02 (4.58)	10.90 (4.29)	11.15 (4.85)
PHQ-9 (possible range 0–27), median (IQR)	4.00 (3.00–7.00)	4.00 (3.00–8.00)	4.00 (3.00–7.00)
GAD-7 (possible range 0–21), median (IQR)	3.00 (1.00–5.00)	3.00 (1.00–5.00)	3.00 (1.25–5.00)
Psychotic symptoms (possible range 0–7), median (IQR)	0.00 (0.00–1.00)	0.00 (0.00–1.00)	0.00 (0.00–1.00)
Cannabis amount per use day (*n* = 358), median (IQR), gram	0.50 (0.20–2.00)	0.50 (0.20–1.50)	0.78 (0.20–2.00)
AUDIT-C (possible range 0–12), mean (SD)	3.68 (2.53)	3.59 (2.33)	3.78 (2.72)
Drug use (*n* = 373, possible range 0–42), median (IQR)	0.00 (0.00–0.57)	0.00 (0.00–0.57)	0.00 (0.00–0.57)

Note: Data are no. (%), mean (SD), or median (IQR). No. of participants for whom data were available at baseline for each measure are given where different from the total for the group.

Abbreviations: AUDIT-C, Alcohol Use Disorders Identification Test - Consumption; CUDIT-R, Cannabis Use Disorders Identification Test - Revised; GAD-7, General Anxiety Disorder Assessment; IQR, interquartile range; PHQ-9, Patient Health Questionnaire; SD, standard deviation.

intervention had differential effects on individual items. Second, adjusting covariates were included in the primary analysis. Potential covariates were baseline demographic and clinical characteristics and were included into the model as adjusting covariates, when they were predictors of the primary outcome at $P < 0.1$. Third, an additional exploratory interaction analysis served to evaluate whether the intervention effect may be different for some individuals. We estimated a single two-way interactions model between the intervention allocation with substance use at baseline (CUDIT-R, AUDIT-C and other drug use).

The intervention effect for secondary outcomes was analyzed in the same way as the primary outcome conducting a multivariable regression of the secondary outcome at 6 months regressed on intervention allocation, adjusted for baseline secondary score as a covariate. To correct for multiple testing across the analyses of the six secondary outcomes, we computed Bonferroni-corrected CI [100% − (5%/6) = 99.2%]. Primary and secondary baseline variables were included as continuous variables in the model and were mean centered before entering the model.

All analyses were carried out in R version 4.3.2 (2023-10-31) or higher, and based our results on the *lm* and *summary.lm* function in base R.

RESULTS

Study participants

The study population including 374 participants had a mean age of 35.8 years (SD = 11.4) and 81% participants were men, 17% women and 2% non-binary. Participants assigned to both groups were mostly comparable at baseline. The illegal market control group had a slightly higher proportion of singles than the legal cannabis intervention group (Table 1). A total of 109 (30%) participants reported daily cannabis use. The mean CUDIT-R score at baseline was 11.02 (SD = 4.58) and 126 (34%) participants exceeded the threshold for potential cannabis use disorder. For further details on baseline characteristics, see Table 1.

Four participants had missing values in sex, age, nationality and marital status. Additionally, 11 participants reported unrealistic values in the amount of cannabis consumption (10 participants; >10 g per consumption day) and other drug use (one participant), and were, therefore, recoded as missing values.

Primary outcome

In the legal cannabis intervention group, participants' self-reported cannabis misuse declined from a mean of 10.9 (SD = 4.29) at baseline to 10.1 (SD = 4.39) at 6 months. In the illegal market control group, the CUDIT-R score declined from a mean of 11.2 (SD = 4.85) at baseline to 10.9 (SD = 4.79) at 6 months. Therefore, results for the primary analysis showed that the CUDIT-R score was estimated to be 0.69 (95% CI = −1.38 to 0.01, $P = 0.052$) lower in the legal cannabis intervention group compared to the illegal market control group at 6 months follow-up [Table 2, Figure 2(a)]. Model residuals were close to normal and therefore, no transformation was applied.

For the primary outcome, the additional sensitivity analysis assuming that missingness was not at random showed similar results

TABLE 2 Primary and secondary outcomes at 6 months and model results.

	Legal cannabis (n = 188)	Illegal market (n = 186)	Intervention effect β (95% CI[a])	P value
Primary outcome				
Complete-case analysis (MCAR, n = 364)				
CUDIT-R, mean (SD)	10.08 (4.39)	10.94 (4.79)	−0.69 (−1.38 to 0.01)	0.052
Sensitivity analysis (ITT, MNAR, n = 374)				
CUDIT-R, mean (SD)	10.11 (4.36)	10.94 (4.77)	−0.66 (−1.34 to 0.01)	0.055
Secondary outcomes				
PHQ-9, median (IQR)	4.00 (3.00–7.00)	3.00 (2.00–6.00)	0.46 (−0.40 to 1.32)	0.154
GAD-7, median (IQR)	2.00 (1.00–4.75)	3.00 (1.00–5.00)	0.18 (−0.56 to 0.93)	0.510
Psychotic symptoms, median (IQR)	0.00 (0.00–1.00)	0.00 (0.00–1.00)	0.09 (−0.10 to 0.28)	0.218
Cannabis amount per use day (n = 353), median (IQR)	0.83 (0.25–1.65)	0.60 (0.20–2.00)	0.17 (−0.13 to 0.47)	0.135
AUDIT-C (n = 363), mean (SD)	3.46 (2.46)	3.83 (2.55)	−0.25 (−0.66 to 0.16)	0.101
Drug use (n = 362), median (IQR)	0.00 (0.00–0.29)	0.00 (0.00–0.29)	−0.03 (−0.11 to 0.06)	0.406

Note: Data are n (%), mean (SD) or median (IQR). No. of participants for whom data were available at 6 months are given where different from the total for the group. For all outcomes, higher scores reflect worse outcomes. The sensitivity analysis for the primary outcome was conducted, assuming that missingness was not at random and imputing the follow-up value by participants' baseline value.

Abbreviations: AUDIT-C, Alcohol Use Disorders Identification Test - Consumption; CUDIT-R, Cannabis Use Disorders Identification Test - Revised; GAD-7, General Anxiety Disorder Assessment; ITT, Intention -to-treat; IQR, interquartile range; MCAR, missing completely at random; MNAR, missing not at random; PHQ-9, Patient Health Questionnaire; SD, standard deviation.

[a]For secondary analyses CI were Bonferroni-corrected for multiple testing (CI = 99.2%).

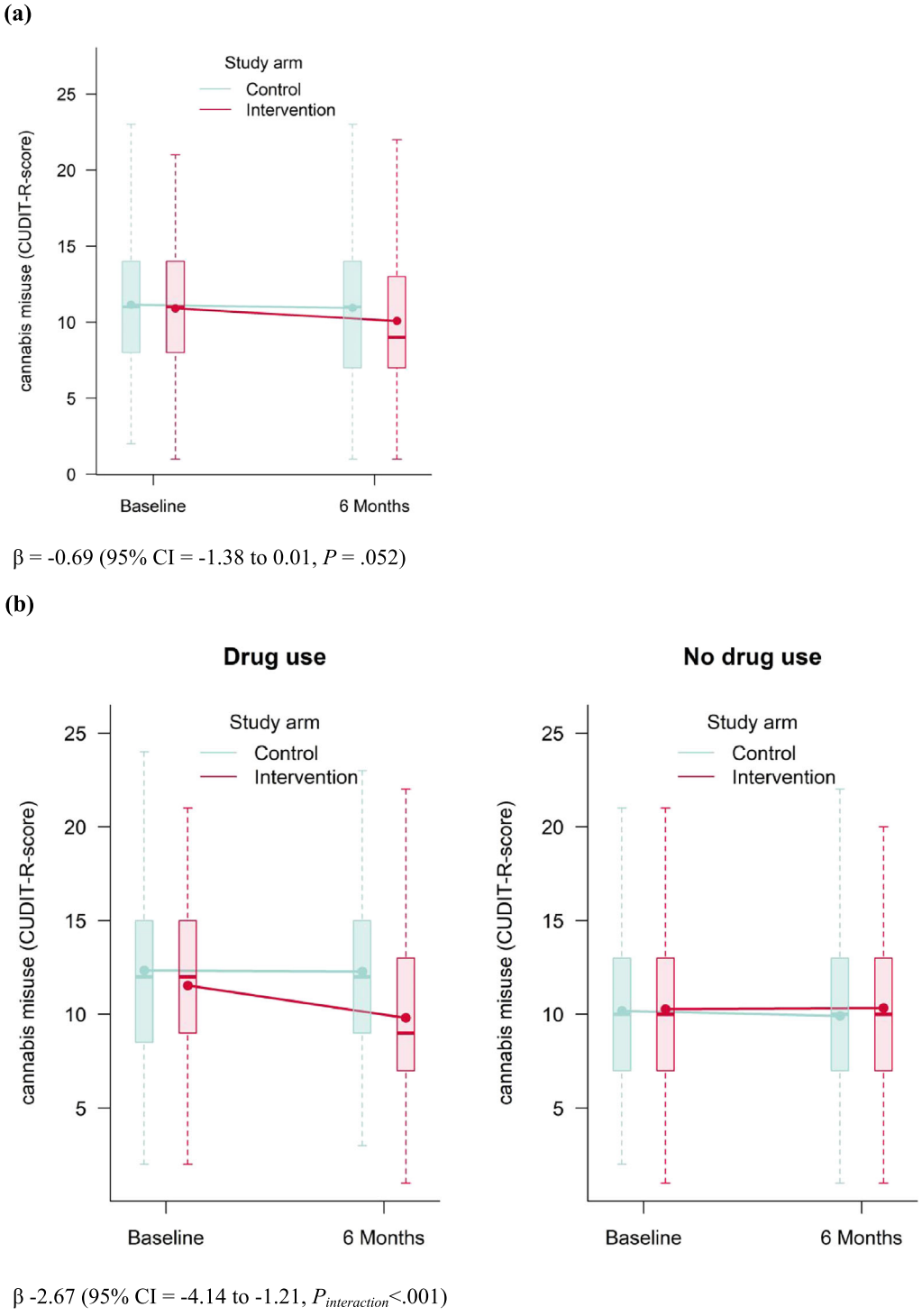

FIGURE 2 Change of cannabis misuse over the study period. (a) Shows cannabis misuse at baseline and at 6 months follow-up for the total study population (a) (*n* = 364) and (b) stratified for participants with other drug use and those without other drug use at baseline (b) (*n* = 362). The interaction model was analyzed with other drug use as continuous variable. For illustrative purposes in this figure the variable was dichotomized into participants using other drugs (score > 0; *n* = 162) and participants not using other drugs (score = 0; *n* = 200) at baseline.

to those from the complete case primary analysis. Findings are shown in Table 2.

The additional exploratory analysis evaluating the change in each individual CUDIT-R item stratified by group allocation showed that the item concerning time spent for getting, using and recovering was lower in the legal cannabis intervention group than in the illegal market control group. None of the other items was affected by the intervention. Results are shown in Appendix S2.

As a further exploratory analysis of the primary outcome, variables of Table 1 that predicted the primary outcome CUDIT-R at

$P < 0.1$ were included into the primary analysis as adjusting covariates. These adjusting covariates were sex, cigarette use days per month, anxiety (GAD-7) and psychotic symptoms. Results of the primary analysis including these four adjusting covariates were comparable to the original primary analysis. Detailed results are shown in Appendix S3.

An additional exploratory analysis examined the interaction between a number of drug use-related variables (CUDIT-R, AUDIT-C and other drug use) at baseline and the intervention effect. The analysis suggested that the intervention effect was moderated by drug use at baseline. In particular, the results suggested that participants in the legal cannabis intervention group with a higher drug use score showed a larger reduction in the CUDIT-R score at 6 months than participants with a lower drug use score, while this difference was not present in the illegal market control group ($\hat{I}^2 = -2.67$, 95% CI = −4.14 to −1.21, $P < 0.001$) [Figure 2(b), Table 3]. The intervention effect appeared to be 1.96 points in the CUDIT-R score stronger for participants with other drug use compared to participants with no other drug use. This difference is close to the two-points difference considered to be a reliable change [35]. No clear interaction effects appeared for the moderators CUDIT-R score and AUDIT-C score at baseline. Model results of the exploratory interaction analysis are shown in Table 3. A further exploratory interaction analysis between group allocation with not only substance use, but also mental health at baseline on cannabis use at 6 months follow-up did not result in any clear effects, and findings were comparable to the original interaction model (Appendix S4).

Secondary outcomes

Secondary outcome analyses showed that the legal cannabis intervention group did not differ to the illegal market control group with respect to change in depressive symptoms (PHQ-9), anxiety symptoms (GAD-7) and psychotic symptoms (Table 2). Furthermore, no significant difference was found at 6 months between the legal cannabis intervention group and the illegal market control group in amount of cannabis consumption, alcohol use (AUDIT-C) and drug use (Table 2).

As residuals for some secondary variables were not close to normal, sensitivity analyses with log-transformed outcomes were performed for all secondary outcomes. The transformation improved the model performance for depressive and anxiety symptoms, as well as drug use. Whereas the residuals for these variables were close to normal after transformation, the residuals for psychotic symptoms were not normal even after transformation. Therefore, a logistic regression on a dichotomization of psychotic symptoms (0 vs. >0) was performed as an additional sensitivity analysis. None of the sensitivity analyses showed any qualitatively different results to the original analyses (Appendix S5).

Of the 182 participants in the legal cannabis intervention group, 93 (51%) reported having used illegal cannabis. Hence, additional per-protocol analyses were conducted for primary and secondary outcomes excluding participants in the legal cannabis intervention group who also used illegal cannabis. The results did not differ substantially from the results of the original complete-case analyses (Appendix S6).

We recorded 10 serious adverse events, eight in the legal cannabis intervention group and two in the illegal market control group. The proportion of participants who reported a serious adverse event did not differ by allocation group [X^2 (1, n = 374) = 2.51, P = 0.113). None of the serious adverse events was classified as being possibly related to the study product. The serious adverse events are described in Appendix S7.

DISCUSSION

The present study is the first to provide randomized controlled trial evidence comparing the impacts of RCL to the illegal market on cannabis use and a broad range of related mental health outcomes. Our results showed no evidence that public health-oriented RCL increased the severity of self-reported cannabis misuse and related mental health outcomes at 6 months compared to the illegal market. Instead, there was some evidence that cannabis misuse was reduced.

TABLE 3 Interaction analysis between group allocation with substance use at baseline on cannabis misuse at 6 months follow-up.

	Intervention effect β	95% CI	*P* value
CUDIT-R (n = 362)			
Group allocation	−0.65	−1.33 to 0.03	0.059
Baseline CUDIT-R	0.68	0.58–0.78	<0.001
Baseline AUDIT-C	0.20	0.02–0.38	0.026
Baseline drug use	1.51	0.43–2.59	0.006
Baseline CUDIT-R by group	−0.02	−0.18 to 0.13	0.756
Baseline AUDIT-C by group	−0.24	−0.52 to 0.03	0.085
Baseline drug use by group	−2.67	−4.14 to −1.21	<0.001

Note: The model includes CUDIT-R, AUDIT-C and drug use score at baseline as well as group allocation as predictors and CUDIT-R at 6 months follow-up as outcome. Each of the moderators was centered, but not scaled, before entering the model. All variables were used as continuous variables. Variance inflation factors studying multicollinearity of the interaction model was not problematic.
Abbreviations: AUDIT-C, Alcohol Use Disorders Identification Test - Consumption. CUDIT-R, Cannabis Use Disorders Identification Test - Revised.

Moreover, there was evidence that cannabis users in the legal cannabis intervention group with other drug use had reduced cannabis misuse compared to those without other drug use. This differential effect was not present in the illegal market control group. Taken together, our results suggest that public health oriented RCL might differ in its benefits on cannabis misuse across different populations.

Our finding that RCL did not increase the severity of cannabis misuse is partly in line with previous observational studies from the United States, Canada and Uruguay that reported no relation between RCL and cannabis use disorder among pre-existing users [15]. There is little evidence with which we could compare our findings of the secondary analyses that show no impact of RCL on mental health outcomes. In accordance with the present study, existing observational studies identified no link between RCL and psychotic symptoms [36], psychosis-related emergency visits and health insurance claims [15, 22]. There is no published evidence on the association between RCL with depression and anxiety. Moreover, our result of no differential effects in alcohol use between the two groups further enlightened the current inconclusive evidence on RCL and alcohol use [16]. It is noteworthy that the period of 6 months follow-up in the current study might be too short to detect any changes in substance use and mental health outcomes. Continued follow-up of 2 years is underway to enhance our understanding of the longer-term effects of legal cannabis access.

Hypothesized mechanisms through which RCL could potentially improve users' health include regulated cannabis products, social contact and facilitated access to prevention, treatment and harm reduction and are comparable to existing opioid harm reduction policies [9, 10]. Vulnerable participants using other drugs might benefit from the brief conversations with the vending staff in pharmacies. Furthermore, a voluntary counseling service by the study physician and the vending staff was available. These factors might have reduced cannabis-related stigma, which is a considerable barrier for help-seeking and negatively affects clinical and personal recovery outcomes [37].

It must be born in mind that cannabis legalization takes various forms ranging from strict control to free commercial markets. The present study evaluated a model with a strong focus on public health and involving no advertisement, maximum THC content, THC dependent prices and facilitated access to prevention, treatment and harm reduction. Public health efforts compete with commercial interests and modifying the regulative factors could improve some outcomes while worsening others. Therefore, it is essential that future research should compare the effects of different forms of RCL and should consider contextual differences, to better understand the benefits and harms of each model [24, 38].

Strengths and limitations

The randomized controlled study design allowed for the possibility of drawing causal inferences. Furthermore, the present study elucidated the impact of RCL on a broad range of cannabis-related outcomes within individuals. Despite these two major strengths, the study has limitations. The sample's representativeness is limited, since individuals with acute psychosis, suicidal ideation, severe cognitive impairment or current inpatient treatment were excluded. Further factors might have deterred from study participation, such as fear of loss of anonymity (cannabis is still prohibited in Switzerland) or the face-to-face interview, which might especially pose a barrier for individuals at risk for cannabis use disorder or mental disorders. Therefore, the representativeness to more diverse clinical populations may be limited. Furthermore, our study sample consisted predominantly of men and this may also affect the generalizability of the findings. Moreover, the present study investigated legal cannabis access via pharmacies and this type of vendor might not be attractive for some users. Future research should investigate and compare alternatives such as social clubs or specialized shops. Moreover, outcome measures used in this study were based solely on self-report questionnaires. Self-reported data carry the risk of socially desirable answers and, therefore, may bias the results. This bias might be intensified by the open-label study design because participants of the legal cannabis intervention group may be motivated to answer in favor of the intervention. Future research should validate the self-reported data with biological measures such as exposure to cannabinoids in blood. Furthermore, serious adverse events were solely assessed via self-report. Future research should track and document all serious adverse events, including self-reported data as well as independent hospitalization data, to improve the quality of data assessment. In addition, although the dropout rate was low, approximately half of the legal cannabis intervention group continued to acquire cannabis from the illegal market, as is comparable with data from Uruguay and Canada [39, 40]. This result indicates that the regulation model in the present study imposed barriers for participants in completely abandoning the illegal market and underlines the importance of thoroughly evaluating the framework of RCL before implementation in a specific country. Finally, our results showed that a subgroup of cannabis users, in particular users with other drug use, could benefit from legal cannabis access. Future research should evaluate whether additional subgroups might benefit from a public health-oriented RCL.

CONCLUSIONS

In this randomized controlled study, a public health-oriented RCL did not lead to an increase in cannabis use and cannabis related harms, while cannabis users with other drug use could benefit in terms of a significant reduction in self-reported cannabis misuse. Our results indicate that public health-oriented RCL could be an effective policy model to make cannabis safer without increasing cannabis use and cannabis-related harms. These results contribute to an evidence-based cannabis policy and inform policy makers, clinicians and the public.

AUTHOR CONTRIBUTIONS

Lavinia Baltes-Flueckiger: Conceptualization (equal); data curation (equal); formal analysis (equal); funding acquisition (equal);

methodology (equal); project administration (equal); supervision (supporting); validation (lead); writing—original draft (lead); writing—review and editing (lead). **Regine Steinauer:** Funding acquisition (equal); project administration (equal); writing—review and editing (supporting). **Maximilian Meyer:** Investigation (equal); writing—review and editing (equal). **Adrian Guessoum:** Investigation (equal); writing—review and editing (supporting). **Oliver Herrmann:** Investigation (equal); writing—review and editing (supporting). **Christoph Felix Mosandl:** Investigation (equal); writing—review and editing (supporting). **Jens Kronschnabel:** Methodology (supporting); writing—review and editing (equal). **Eva-Maria Pichler:** Project administration (equal); writing—review and editing (supporting). **Marc Vogel:** Project administration (equal); writing—review and editing (equal). **Marc Walter:** Conceptualization (equal); funding acquisition (equal); project administration (equal); supervision (lead); writing—review and editing (equal).

ACKNOWLEDGEMENTS

We thank the staff from the Clinical Trial Unit Basel for their contribution to the study through recruitment, support in study conduction and monitoring of the study—in particular, Silke Purschke, Fauzia Mughal, Klaus Ehrlich, Marielle Rutquist and Tamara Zeschky. Furthermore, we thank the police of the canton Basel-Stadt, the cannabis producer and the pharmacies for their cooperation. Finally, we thank all participants.

DECLARATION OF INTERESTS

The authors declare that they have no competing interests. The funder had no role in considering the study design or in data collection, analysis, interpretation of data and writing of this manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

CLINICAL TRIAL REGISTRATION

ClinicalTrials.gov NCT05522205 Date submitted for registration 8 August 2022; date registered 30 August 2022.

ORCID

Lavinia Baltes-Flueckiger https://orcid.org/0009-0007-9541-6998
Maximilian Meyer https://orcid.org/0000-0003-1183-1195

REFERENCES

1. United Nations. World drug report 2024 [internet] United Nations: Office on Drugs and Crime; 2024[cited 2024 Jul 26]. Available from: https://www.unodc.org/
2. Moore TH, Zammit S, Lingford-Hughes A, Barnes TR, Jones PB, Burke M, et al. Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. Lancet. 2007;370(9584):319–28. https://doi.org/10.1016/S0140-6736(07)61162-3
3. Hasin DS, Kerridge BT, Saha TD, Huang B, Pickering R, Smith SM, et al. Prevalence and correlates of DSM-5 cannabis use disorder, 2012-2013: findings from the National Epidemiologic Survey on alcohol and related conditions–III. Am J Psychiatry. 2016;173(6):588–99. https://doi.org/10.1176/appi.ajp.2015.15070907
4. Solmi M, De Toffol M, Kim JY, Choi MJ, Stubbs B, Thompson T, et al. Balancing risks and benefits of cannabis use: umbrella review of meta-analyses of randomised controlled trials and observational studies. BMJ. 2023;e072348. https://doi.org/10.1136/bmj-2022-072348
5. Hines LA, Heron J, Zammit S. Incident psychotic experiences following self-reported use of high-potency cannabis: results from a longitudinal cohort study. Addiction. 2024;119(9):1629–34. https://doi.org/10.1111/add.16517
6. Leung J, Chan GCK, Hides L, Hall WD. What is the prevalence and risk of cannabis use disorders among people who use cannabis? A systematic review and meta-analysis. Addict Behav. 2020 Oct;109:106479. https://doi.org/10.1016/j.addbeh.2020.106479
7. GBD 2016 Risk Factors Collaborators. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2016: a systematic analysis for the global burden of disease study 2016. Lancet. 2017;390:1345–422.
8. Room R, Reuter P. How well do international drug conventions protect public health? Lancet. 2012;379(9810):84–91. https://doi.org/10.1016/S0140-6736(11)61423-2
9. Csete J, Kamarulzaman A, Kazatchkine M, Altice F, Balicki M, Buxton J, et al. Public health and international drug policy. Lancet. 2016;387(10026):1427–80. https://doi.org/10.1016/S0140-6736(16)00619-X
10. Englund A, Freeman TP, Murray RM, McGuire P. Can we make cannabis safer? Lancet Psychiatry. 2017 Aug;4(8):643–8. https://doi.org/10.1016/S2215-0366(17)30075-5
11. Fischer B, Robinson T, Bullen C, Curran V, Jutras-Aswad D, Medina-Mora ME, et al. Lower-risk cannabis use guidelines (LRCUG) for reducing health harms from non-medical cannabis use: a comprehensive evidence and recommendations update. Int J Drug Policy. 2022;99:103381. https://doi.org/10.1016/j.drugpo.2021.103381
12. Hall W, Stjepanović D, Caulkins J, Lynskey M, Leung J, Campbell G, et al. Public health implications of legalising the production and sale of cannabis for medicinal and recreational use. Lancet. 2019;394(10208):1580–90. https://doi.org/10.1016/S0140-6736(19)31789-1
13. Hall W, Stjepanović D, Dawson D, Leung J. The implementation and public health impacts of cannabis legalization in Canada: a systematic review. Addiction. 2023;118(11):2062–72. https://doi.org/10.1111/add.16274
14. Athanassiou M, Dumais A, Zouaoui I, Potvin S. The clouded debate: a systematic review of comparative longitudinal studies examining the impact of recreational cannabis legalization on key public health outcomes. Front Psych. 2023;13:1060656. https://doi.org/10.3389/fpsyt.2022.1060656
15. Manthey J, Hayer T, Jacobsen B, Kalke J, Klinger S, Rehm J, et al. Effects of legalizing cannabis [internet] Hamburg, Germany: Institut für interdisziplinäre Sucht- und Drogenforschung; 2023[cited 2023 Dec 20]. Available from: https://www.drugsandalcohol.ie/38753/
16. Pacula RL, Smart R, Lira MC, Pessar SC, Blanchette JG, Naimi TS. Relationships of cannabis policy liberalization with alcohol use and co-use with cannabis: a narrative review. Alcohol Res. 2022;42(1):06. https://doi.org/10.35946/arcr.v42.1.06
17. Smart R, Pacula RL. Early evidence of the impact of cannabis legalization on cannabis use, cannabis use disorder, and the use of other substances: findings from state policy evaluations. Am J Drug Alcohol Abuse. 2019;45(6):644–63. https://doi.org/10.1080/00952990.2019.1669626
18. Hall W, Lynskey M. Assessing the public health impacts of legalizing recreational cannabis use: the US experience. World Psychiatry. 2020;19(2):179–86. https://doi.org/10.1002/wps.20735
19. Caulkins JP. Changes in self-reported cannabis use in the United States from 1979 to 2022. Addiction. 2024;119(9):1648–52. https://doi.org/10.1111/add.16519

20. Gunadi C, Zhu B, Shi Y. Recreational cannabis legalization and transitions in cannabis use: findings from a nationally representative longitudinal cohort in the United States. Addiction. 2022;117(10):2651–9. https://doi.org/10.1111/add.15895
21. Zellers SM, Ross JM, Saunders GRB, Ellingson JM, Anderson JE, Corley RP, et al. Impacts of recreational cannabis legalization on cannabis use: a longitudinal discordant twin study. Addiction. 2023;118(1):110–8. https://doi.org/10.1111/add.16016
22. Fortier A, Zouaoui I, Dumais A, Potvin S. Effects of recreational cannabis legalization on mental health: scoping review. Psychiatr Serv. 2024;75(9):appi.ps.20230434. https://doi.org/10.1176/appi.ps.20230434
23. Rehm J, Manthey J. Cannabis and public health: a global experiment without control. World Psychiatry. 2020;19(2):192–4. https://doi.org/10.1002/wps.20740
24. Queirolo R. The effects of recreational cannabis legalization might depend upon the policy model. World Psychiatry. 2020 Jun;19(2):195–6. https://doi.org/10.1002/wps.20742
25. Trangenstein PJ, Jernigan DH. Commentary on Gunadi et al.: opportunities to design more policy-relevant evaluations of non-medical cannabis legalization. Addiction. 2022;117(10):2660–1. https://doi.org/10.1111/add.15984
26. Scheim AI, Maghsoudi N, Marshall Z, Churchill S, Ziegler C, Werb D. Impact evaluations of drug decriminalisation and legal regulation on drug use, health and social harms: a systematic review. BMJ Open. 2020;10(9):e035148. https://doi.org/10.1136/bmjopen-2019-035148
27. Baltes-Flueckiger L, Steinauer R, Meyer M, Vogel M, Walter M. Effects of cannabis regulation in Switzerland: study protocol of a randomized controlled trial. Front Psych. 2023;14:1139325. https://doi.org/10.3389/fpsyt.2023.1139325
28. Federal Council. Ordinance of pilot trials with cannabis in accordance to the federal act on narcotics and psychotropic substances (NarcA) [internet]; 2021 Available from: https://www.fedlex.admin.ch/eli/cc/2021/217/de
29. Adamson SJ, Kay-Lambkin FJ, Baker AL, Lewin TJ, Thornton L, Kelly BJ, et al. An improved brief measure of cannabis misuse: the cannabis use disorders identification test-revised (CUDIT-R). Drug Alcohol Depend. 2010;110(1):137–43. https://doi.org/10.1016/j.drugalcdep.2010.02.017
30. Kroenke K, Spitzer RL, Williams JBW. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001;16(9):606–13. https://doi.org/10.1046/j.1525-1497.2001.016009606.x
31. Löwe B, Spitzer RL, Zipfel S, Herzog W. Gesundheitsfragebogen für Patienten (PHQ D) Komplettversion Und Kurzform Testmappe Mit Manual, Fragebögen, Schablonen Pfizer; 2002.
32. Maurer K, Hörrmann F, Trendler G, Schmidt M, Häfner H, Maier W, et al. Früherkennung des Psychoserisikos mit dem early recognition inventory (ERIraos). Nervenheilkunde. 2006;25(1):11–6.
33. Bradley KA, DeBenedetti AF, Volk RJ, Williams EC, Frank D, Kivlahan DR. AUDIT-C as a brief screen for alcohol misuse in primary care. Alcohol Clin Exp Res. 2007;31(7):1208–17. https://doi.org/10.1111/j.1530-0277.2007.00403.x
34. Humeniuk R, Henry-Edwards S, Ali R, Poznyak V, Monteiro MG, World Health Organization. The alcohol, smoking and substance involvement screening test (ASSIST): manual for use in primary care Geneva: World Health Organization; 2010.
35. Adamson S, Kay-Lambkin F, Baker A, Frampton C, Sellman D, Lewin T. Measuring change in cannabis use. Addict Res Theory. 2015;23(1):43–9. https://doi.org/10.3109/16066359.2014.926895
36. Zellers SM, Ross JM, Saunders GRB, Ellingson JM, Walvig T, Anderson JE, et al. Recreational cannabis legalization has had limited effects on a wide range of adult psychiatric and psychosocial outcomes. Psychol Med. 2023;(53):1–10. https://doi.org/10.1017/S0033291722003762
37. Thornicroft G, Sunkel C, Aliev AA, Baker S, Brohan E, Chammay R e, et al. The lancet commission on ending stigma and discrimination in mental health. Lancet. 2022;400(10361):1438–80. https://doi.org/10.1016/S0140-6736(22)01470-2
38. Cousijn J, Kuhns L, Filbey F, Freeman TP, Kroon E. Cannabis research in context: the case for measuring and embracing regional similarities and differences. Addiction. 2024;119(9):1502–4. https://doi.org/10.1111/add.16460
39. Wadsworth E, Driezen P, Pacula RL, Hammond D. Cannabis flower prices and transitions to legal sources after legalization in Canada, 2019–2020. Drug Alcohol Depend. 2022;231:109262. https://doi.org/10.1016/j.drugalcdep.2021.109262
40. Queirolo R, Álvarez E, Sotto B, Cruz JM. How high-frequency users embraced CannabisRegulation in Uruguay. J Drug Issues. 2023;53(4):519–35. https://doi.org/10.1177/00220426221134902

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Baltes-Flueckiger L, Steinauer R, Meyer M, Guessoum A, Herrmann O, Mosandl CF, et al. Effects of legal access versus illegal market cannabis on use and mental health: A randomized controlled trial. Addiction. 2025;120(10):1982–92. https://doi.org/10.1111/add.70080