Title: Differential effects of continued versus discontinued cannabis use on outcome in patients with psychosis: A meta-analysis

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Abstract

Background

Although the link between cannabis use and development of psychosis is well established, less is known about the impact of continued versus discontinued cannabis use after the onset of the illness. No meta-analysis has as yet summarized the evidence focusing on the relationship between continued and discontinued cannabis use following onset of psychosis and its relapse.

Methods

Studies were identified through a systematic literature search. Relapse outcomes were compared between those who continued (CC) or discontinued (DC) cannabis use or were non-users (NC). Cohen's *d* was estimated and entered into Random Effects Models (REM) to compare (1) CC-NC, (2) CC-DC and (3) DC-NC. Meta-regression and sensitivity analysis were employed to address the issue of heterogeneity.

Findings

Twenty-four studies (N=16565) were included. Independent of the stage of illness, continued cannabis users had significantly ($p \leq 0{\cdot}05$) worse relapse outcome than both non-users ($d_{CC\text{-}NC}=0{\cdot}36$) and discontinued users ($d_{CC\text{-}DC}=0{\cdot}28$), as well as longer hospitalizations ($d_{CC\text{-}NC}=0{\cdot}32$). In contrast, cannabis discontinuation was not associated with relapse ($d_{DC\text{-}NC}=0{\cdot}02$, $p=0{\cdot}82$). Meta-regression indicated greater effects of continued compared to discontinued cannabis use ($p \leq 0{\cdot}05$) on relapse, positive symptoms and level of functioning but not negative symptoms.

Interpretation

Continued cannabis use after onset of psychosis predicts adverse outcome, including higher relapse rates, longer hospitalizations and more severe positive symptoms - adverse effects that are absent in those who discontinue use of cannabis. 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 out of every four patients with psychosis meet 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 population [4] or those with other psychiatric diagnoses [5]. While 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 following onset is less clear. This lack of clarity seems mainly related to limitations of study design such as cross-sectional approach, underpowered samples and lack of consideration of potential confounders (reviewed here [9]). However, more recent studies implicate cannabis use as a potential risk factor for relapse of psychosis as indexed by readmission to hospital [10-12], with some evidence supporting a dose-response relationship [13]. Other studies reported worsening of positive psychotic symptoms [14,15] or shorter time to symptom re-emergence [16] in cannabis-using patients with psychosis. These findings are in line with experimental pharmacological challenge studies reporting that delta-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 really associated with worse outcome in those with established psychosis, then one would expect that those who continue using cannabis would have far worse outcome compared to those who stop. However, while some evidence suggests that discontinuation of cannabis use may lead to a reduction in readmission rates [21,22] and improvement in symptomatic and functional outcome of psychosis [15,22-

[26], others suggest that this may not necessarily be the case [1,10, 27,28]. Although, about 30-50% of cannabis users stop using it after the onset of their psychotic illness [15,21-23,29] suggesting that this may be a clinically relevant issue worth exploring, there is lack of clarity in terms of existing evidence as outlined earlier. Furthermore, conclusions from the individual studies need to be treated with caution in light of the relatively modest sample sizes. Meta-analytic techniques offer a method of overcoming the sample size issue by statistically integrating the results from a number of separate studies thereby improving the power to detect significant effects[30]. Considering the conflicting evidence from individual studies investigating the relationship between continued cannabis use and relapse and from studies looking at discontinued use and outcome, we have attempted to quantitatively summarize the current evidence. We aimed to (a) establish whether ongoing cannabis use is associated with poor outcome in established psychosis and (b) establish the magnitude of this effect by pooling together the results of all available studies using a meta-analytic approach. In particular, we focused on outcome defined as 'relapse of psychosis', operationalized as either readmission to hospital or based on investigator-determined psychotic relapse. Since cannabis use is potentially amenable to treatment and given that a substantial proportion of patients with psychosis continue using the drug following onset of their illness, there is a particular need to estimate the effect of ongoing cannabis use on a robust measure of outcome which is indicative of relapse, such as hospitalization. This is a reliably estimated measure, with significant implications for the cost of healthcare [31]. Although previous meta-analyses have investigated the association between continued and discontinued cannabis use and outcome in psychosis, these have mainly focused on symptomatic outcome measures such as positive and negative symptoms or depression scores, while outcome indexed

by hospitalization was only considered in the context of the effects of substance use in general.[32-34]. We therefore set out to investigate whether (i) continued use of cannabis following the onset of psychosis is associated with worse relapse outcome relative to non-users, (ii) discontinued use of cannabis subsequent to the onset of psychosis is associated with a worse relapse outcome comparable to non-users and (iii) discontinued use of cannabis is associated with a better relapse outcome compared to continued use. Furthermore, we investigated whether the effect of cannabis use on outcome was consistent across different outcome measures by also examining effect on measures such as length of hospitalization, symptom severity and level of functioning.

2. Methods

Study selection

A systematic search strategy was used to identify all relevant studies, following the methods recommended by the Cochrane Handbook [35] and in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [36]. Firstly, the MEDLINE database was searched for English language studies using a combination of search terms describing the cannabis terms (marijuana/marihuana, cannabis, illicit, substance), the outcome of interest (outcome, hospital*, relapse, readmission) and the study population (psycho*, bipolar, schizophrenia), with the final search conducted on the 21st of April 2015. Following this, bibliographies of the identified publications and previous published meta-analyses were hand-searched in order to identify additional studies that met the inclusion criteria but might have been missed by the database search. Studies were selected if they included a sample of patients with a pre-existing psychotic disorder (schizophrenia, schizoaffective, bipolar if outcome was reported as number of

psychotic episodes [e.g. Ringen et al. (2010)[37]]), with a follow-up duration of at least 6 months. The primary predictor variables were defined as (1) continued cannabis use (yes/no) after onset of illness and (2) discontinued cannabis use after onset (yes/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)/ 'discontinued cannabis use' (DC) could not be established, e.g. studies that assessed cannabis use only around the onset of illness [38-41] and studies that only reported lifetime cannabis use [42-45]. The primary outcome was defined as 'relapse of psychosis', which was indexed as either (1) readmission to hospital, (2) investigator-determined relapse [operationalized in manuscript as 'psychotic episode' or exacerbation of psychotic symptoms [16,22,46]] or (3) investigator-determined relapse but without any reported criteria for operationalization [47] (cf. *Table 1.*). If the identified studies reported symptom scores (positive, negative), length of hospitalization (time spent in hospital) or level of functioning (as measured with the Global Assessment of Functioning Scale [48]) alongside the relapse information, this data was also extracted and used in separate outcome analyses. 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 to finalize the selection criteria and variables of interest. Data was extracted by two independent researchers (TS and one other researcher). Disagreements were resolved through discussion between the researchers extracting data and a senior researcher (SB).

Quality assessment

We used a modified seven-point 'strength of reporting scale' which has been employed in previous meta-analyses conducted in a related area 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 >5 were classified as higher quality studies (cf. *sTable 1.*, supplementary material).

Statistical analysis

Analyses were conducted with R and its package metaphor [50], using random effects models (REM) [51] that assume that effect sizes vary from study to study [52]. Effect sizes were estimated using Cohen's *d,* where *d*-values of 0·2 represent small effects, *d*-values between 0·4 and 0·6 represent moderate effect and *d*-values of 0.8 or higher indicate large effects [53]. *d* per study was calculated for the comparisons (1) continued cannabis use vs. non-user (CC-NC), (2) continued use vs. discontinued use (CC-DC) and (3) discontinued use vs. non-user (DC-NC). The R-package Compute.es [54] was used, which allows data from included studies to be entered in the form of means and standard deviations [37], *p*-values for mean comparisons or chi square statistics to reach an approximated *d*. In addition, the package allowed the estimation of *d* for those studies that reported odds ratios [11,12]. In those cases where the SD was not reported [55,56], 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 *d*'s between the groups CC-NC and DC-NC for outcome (relapse, length of hospitalization, positive symptoms, negative symptoms, functioning). In addition, meta-regression was used to test whether the effect of cannabis was confounded by the stage of illness of participants in the studies included [i.e. early psychosis vs. chronic psychosis, with chronic psychosis referring to those subjects with an illness length of more than 5 years as classified in previous studies [57]]. Finally, meta-regression for continuous moderators was used to test the effect of

gender (percentage of sample being male) and age at the time of study assessment. The possibility of publication bias was examined using funnel plots, followed by the Egger's linear regression test [58] to test funnel plot asymmetry for significance. Homogeneity of the distribution of weighted effect sizes was tested with the *Q* test, and degree of heterogeneity was quantified using the I^2 test, which describes the percentage of observed heterogeneity that would not be expected by chance [59]. I^2 values between 0 and 25% suggest small heterogeneity, while I^2 values in the range 25% and 50% suggest moderate heterogeneity, and those >50% indicate large heterogeneity.

Sensitivity analysis

Given the heterogeneity in the definition of relapse employed 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 [60]. Similarly, in the light of variation in follow-up duration between cannabis users and non-users in the studies (cf. *Table 1.*), we carried out subset analyses by including only those studies in which cannabis users were matched to the non-users with respect to their follow up duration (indicated as "Matched = YES" if the difference was not more than 1 year between the groups, *cf. Table 1.*).

2.1 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 paper.

3. Results

Study selection

Out of 1903 identified studies, 24 met inclusion criteria, comprising 5849 individuals with continued cannabis use following psychosis onset and 10308 who were classified as non-users (cf. Flow Chart, *Figure 1.*). Screening of studies published in languages other than English (n=126) did not yield any additional studies meeting our inclusion criteria (cf. *sFigure 1.*, supplementary material). A subset (n=6) of the included studies included an additional group of patients that were classified as discontinued cannabis users (408 discontinued users, 268 continued users and 496 non-users).

Figure 1 (Flow chart) about here

Table 1. Effects of cannabis continuation after onset and discontinuation after onset on relapse outcome

Continued Cannabis use

Study / Country	Definition continued cannabis use	Definition cannabis non-user	Relapse outcome	Length of Illness (LI) in years at FU; Illness stage (Early vs Chronic)	FU duration (years) [Matched YES/No]	N	*d* [95% CI]	OR [95% CI]
Baeza, Graell (2009)[26] / Spain	Use in 1 month prior FU assessment (n=15)	No cannabis history (n=69)	Number of re-hospitalizations in 6 months FU	LI: 1 Early stage	0·5 (CAN +) 0·5 (CAN -) [YES]	84	0 [-0.57; 0.57]	N/A
Barrowclough, Emsley (2013)[1] / UK	Use (any) in previous 90 days (n=160)	No use in previous 90 days (n=167)	Hospitalization (y/n) in previous year	LI: 12 Chronic	1 (CAN +) 1 (CAN -) [YES]	327	0·33 [0.11; 0.55]	1.82 [1.22; 2.71]
Bersani et al. (2002)[61] / Italy	Current user (NS) (n=54)	No cannabis history (n=71)	Number of previous hospitalizations	LI: 10 Chronic	8 (CAN +) 13 (CAN -) [NO]	125	-0·07 [-0.43; 0.29]	N/A
Caspari (1999)[62] / Germany	Cannabis abuser (n=27) [c]	Non-abuser (n=26)	Number of rehospitalizations following index hospitalization	LI: 7 Chronic	5 (CAN +) 6 (CAN -) [YES]	53	1·04 [0.56; 1.52]	N/A
Faridi, Joober (2012)[47] / Spain	Presence of CUD at FU (n=28)	Absence of CUD at FU (n=20)	Relapse (y/n) in 1 year FU (NS)	LI: 1 Early stage	1 (CAN +) 1 (CAN -) [YES]	48	0·04 [-0.55; 0.63]	1.08 [0.37; 3.13]
González-Pinto, Alberich (2009)[21] / Spain	Continued use throughout 7 years FU (n=25)	No cannabis history (n=40)	Number of hospitalizations in 8 years FU	LI: 8 Chronic	8 (CAN +) 8 (CAN -) [YES]	65	0·58 [0.06; 1.10]	N/A
Isaac et al. (2005)[63] / UK	+ve UDS (n=69) at admission	-ve UDS (n=46) at admission	Number of previous hospitalizations	N/A	NOT REPORTED	115	0·62 [0.24; 1.01]	N/A
Jockers-Scherubl et al. (2007)[64] / Germany	Presence of CUD (n=19)	No Use $\leq$ 5 times/ lifetime (n=20)	Number of previous hospitalizations	LI:7 Chronic	6 (CAN +) 9 (CAN -) [NO]	39	-0·40 [-1.05; 0.26]	N/A
Koenders, Machielsen (2014)[46] / Netherlands	Presence of CUD (n=80)	Use $\leq$ 5 times/ lifetime (n=33)	Number of previous psychotic episodes (NS)	LI: 1 Early stage	1 (CAN +) 1 (CAN -) [YES]	113	0·12 [-0.43; 0.39]	N/A
Linszen et al. (1994)[65] / US	Presence of CUD (n=24) in 1 year FU	Absence of CUD (n=69) in 1 year FU	Relapse (y/n) (exacerbation of psychotic symptoms[b]) in 1 year FU	LI: 3 Early stage	1 (CAN +) 1 (CAN -) [YES]	93	0·45 [0.07; 0.88]	2.27 [1.05; 4.89]
Maremmani et al. (2004)[66] / Italy	Lifetime CUD and +ve UDS (n=43)	No cannabis history (n=45)	Number of previous hospitalizations	LI: 10 Chronic	7 (CAN +) 12 (CAN -) [NO]	88	-0·08 [-0.51; 0.34}	N/A
Martinez-Arevalo et al. (1994)[67] / Spain	Use during 1 year FU (NS) (n=14)	No cannabis history (n=24)	Hospitalization (y/n) in 1 year FU	LI: 2 Early stage	1 (CAN +) 1 (CAN -)	38	0·46 [-0.23;	2.29 [0.66;

							1.14]	7.91]
Negrete, Knapp (1986)[55] / Canada	Use in 6 months prior to FU assessment and/or +ve UDS (n=25)	No cannabis history (n=61)	Number of previous hospitalizations	LI: 10 Chronic	6 (CAN +) 13 (CAN -) [NO]	86	0·8 [0.31; 1.29]	N/A
Peralta and Cuesta (1992)[68] / Spain	Use > 1 time/week in year prior to assessment (n=23)	Use ≤ 1 time/week in year prior assessment (n=72)	Number of previous hospitalizations	LI: 5 Early stage	5 (CAN +) 6 (CAN -) [YES]	95	-0·14 [-0.62; 0.34]	N/A
Rehman and Farooq (2007)[69] / Pakistan	Use in 1 year prior assessment (n=50)	No use in year prior assessment (n=50)	Number of previous hospitalizations	LI: 5 Early stage	4 (CAN +) 5 (CAN -) [YES]	100	0·40 [-0.002; 0.80]	N/A
Rentzsch et al. (2011)[70] / Germany	Current user (≥ 5 days/week for≥ 1 year) (n=27)	Use ≤ 5 times/ lifetime (n=26)	Number of previous hospitalizations	LI: 6 Chronic	5 (CAN +) 7 (CAN -) [NO]	53	0.25 [-0.31, 0.80]	N/A
Ringen, Vaskinn (2010)[37] / Norway	Use in 6 months prior FU assessment (NS) (n=41)	No use in 6 months prior FU assessment (n=232)	Number of previous hospitalizations	LI: 8 Chronic	7 (CAN +) 9 (CAN -) [NO]	273	0·20 [-0.13; 0.54]	N/A
Salyers and Mueser (2001)[71] / US	≥1 time during 6 months prior FU assessment (n= 363)	Never used in 6 months prior FU (n=41)	Number of hospitalizations in 2 years prior FU assessment	LI: 8 Chronic	2 (CAN +) 2 (CAN -) [YES]	404	0·37 [0.04; 0.69]	N/A
San, Bernardo (2013)[11] / Spain	Use in 4 years prior FU assessment (n=553)	No use in 4 years prior FU assessment (n=1093)	Hospitalization (y/n) in 1 year FU	LI: ≥10 years for 57% of the sample Chronic	1 (CAN +) 1 (CAN -) [YES]	1646	0·25 [0.13, 0.36]	1.56 [1.27; 1.92]
Sara et al. (2014)[72] / Australia	Presence of CUD in 5 years FU (n=3946)	Absence of CUD in 5 years FU (n=7672)	Number of rehospitalizations in 5 years FU	LI: > 7 Chronic	5 (CAN +) 5 (CAN -) [YES]	11618	0·92 [0.89; 0.96]	
Sorbara, Liraud (2003)[12] / France	Presence of CUD in 2 years following onset (n=9)	Absence of CUD in 2 years following onset (n=49)	Hospitalization (y/n) in 2 years following onset	LI: 2 Early stage	2 (CAN +) 2 (CAN -) [YES]	58	0·62 [0.01; 1.24]]	3.1 [1.01; 9.4]
van Dijk et al. (2012)[73] / Netherlands	≥ 4 times during 1 year FU or use 1 month prior FU assessment (n=68)	< 4 times during 1 year FU or no use 1 month prior FU assessment (n=77)	Number of hospitalizations in 1 year FU	LI: 14 Chronic	1 (CAN +) 1 (CAN -) [YES]	145	0·38 [0.05; 0.71	N/A
van der Meer and Velthorst (2015)[22] / Netherlands	Use ≤ 5 times/ in 3 year FU (n=146)	No cannabis history (n=257)	Number of relapses (hospitalization and/or exacerbation of psychotic symptoms[a]) in 3 year FU	LI: 4 Early stage	3 (CAN +) 3 (CAN -) [YES]	403	0·23 [0.03; 0.43]	N/A
Wade et al. (2006)[74] / Australia	Presence of CUD during FU (n=40)	Absence of CUD during FU (n=48)	Relapse (y/n) (exacerbation of psychotic symptoms[b])	LI: 1.3 Early stage	1.3 (CAN +) 1.3 (CAN -) [YES]	88	0.87 [0.41; 1.33]	4.87 [2.09; 11.32]

Discontinued Cannabis use								
Study / Country	**Definition discontinued cannabis use**	**Definition cannabis non-user**	**Relapse definition**	**Length of Illness (LI) in years at FU; Illness stage (Early vs Chronic)**	**FU duration (years) [Matched YES/No]**	**N**	***d* (*p*)**	
Baeza, Graell (2009)[26] / Spain	Use at baseline but no use 1 month prior FU assessment (n=16)	No cannabis history (n=69)	Number of Rehospitalizations in 6 months FU	LI: 1 Early stage	0·5 (CAN +) 0·5 (CAN -) [YES]	85	0 [-0.57; 0.57]	N/A
González-Pinto, Alberich (2009)[21] / Spain	Stopped use between onset and 7 years FU (n=27)	No cannabis history (n=40)	Number of hospitalizations in 8 years FU	LI: 8 Chronic	8 (CAN +) 8 (CAN -) [YES]	67	0·25 [-0.25; 0.75]	N/A
Maremmani, Lazzeri (2004)[66] / Italy	Lifetime CUD but -ve UDS / (n=23)	No cannabis history (n=45)	Number of previous hospitalizations	LI: 9 Chronic	9 (CAN +) 12 (CAN -) [NO]	68	-0·08 [-0.60; 0.43]	N/A
Martinez-Arevalo, Calcedo-Ordo (1994)[67] / Spain	No use during 1 year FU but previous use (n=25)	No cannabis history (n=24)	Hospitalization (y/n) in 1 year FU	LI: 2 Early stage	1 (CAN +) 1 (CAN -) [YES]	49	0·02 [-0.56; 0.60]	1.03 [0.36; 2.95]
Negrete, Knapp (1986)[55] / Canada	History of use but no use in 6 months prior FU assessment (n=51)	No cannabis history (n=61)	Number of previous hospitalizations	LI: 11 Chronic	9 (CAN +) 13 (CAN -) [NO]	112	0·22 [-0.16; 0.60]	N/A
van der Meer and Velthorst (2015)[22] / Netherlands	Past use $\leq$ 5 times/ lifetime but no use in 3 year FU (n=266)	No cannabis history (n=257)	Number of relapses (hospitalization and/or drop score on symptom scale) in 3 year FU	LI: 5 Early stage	3 (CAN +) 3 (CAN -) [YES]	523	-0·04 [-0.21; 0.13]	N/A

CI = Confidence interval; CUD = Cannabis use disorder (DSM or ICD based diagnosis of cannabis abuse or dependence); *d* = Effect size Cohen's *d* with *p*-value for Random Effects Model; FU = Follow up; LI = Length of illness in years at time of follow up assessment; Matched = YES if difference in follow up between CAN(+) and CAN(-) not more than 1 year, NO = if difference more than 1 year; NS = Not specified; N/A = Not applicable; OR = Odds Ratio; UDS = Urine drug screen; Stage of illness = Early stage (illness less $\leq$ 5 years), Chronic (illness $\geq$ 6 years).

[a] Based on rating scale: Comprehensive Assessment of Symptoms and History [75]

[b] Based on rating scale: Brief Psychiatric Rating Scale [76]

[c] 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

Random Effects Model: Effect of ongoing cannabis use on relapse

As shown in *Figure 2.* (cf. *sTable 2.,* supplementary material*)*, continued cannabis use post-onset of illness was significantly associated with relapse of psychosis (d_{CC-NC}=0·36, p<0·0001 [95% CI 0·22; 0·50]). An effect of a similar magnitude was found on length of hospitalization after onset (d_{CC-NC}=0·36, p=0·02[95% CI 0·13; 0·58]). For a subset of studies (k=4, n=688) we were able to calculate the number of days spent in hospital per year of illness following onset, estimated as the weighted mean difference (WMD) (cf. supplementary material, *sMethods1.* for method description). The results indicated that cannabis users spent an additional 8·47 days in hospital per year of illness, although this difference was statistically not significant (p=0·20) which may reflect the lack of power (cf. *sTable 3.* supplementary material). Among the studies that examined the risk of relapse (k=7, n=2298, cf. *Table 1.*), the pooled odds were 1·97[95% CI 1·46; 2·65] times greater among those who continued to use cannabis compared with those who did not (p<0·0001). Limiting analysis to only those studies that reported on relapse rates in individuals with the three patterns of cannabis use of interest in this context, i.e. continued cannabis user, discontinued user and non-user (CC-DC-NC, k=6; N=1172) revealed that this adverse effect of cannabis in continued users remained when compared to those who discontinued (d_{CC-DC}=0·28, p=0·0005, [95% CI 0·12; 0·44]). In contrast, those who discontinued cannabis use did not significantly differ from the non-users in their relapse outcome (d_{DC-NC}=0·02, p=0·82[95% CI -0·11; 0·15]) (cf. *Figure 3*. for a summary). 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) also confirmed that the effect-sizes were significantly different between the two sets of comparisons (p=0·04; cf. *sTable 2*,

supplementary material). Egger's test and funnels plot (cf. *sFigure 2* and *sTable 2*, supplementary material) indicated evidence of funnel plot asymmetry for relapse (p=0·0002), but the trim-and-fill method (R_0 estimator) did not indicate missing studies, suggesting that the asymmetry may be due to other causes such as study heterogeneity [77,78].

Figure 2 about here

Figure 3 about here

Random Effects Model: Effects of ongoing cannabis use on other outcome measures

As summarized in *Figure 4.,* continued cannabis use significantly predicted positive symptom severity ($d_{CC\text{-}NC}$=0·15, p=0·04[95% CI 0·01; 0·29]). These effects on positive symptoms were not present in those who discontinued using the substance ($d_{DC\text{-}NC}$=-0·30, p=0·39[95% CI -0·99; 0·38]) and meta-regression indicated that the effect-sizes ($d_{CC\text{-}NC}$ vs. $d_{DC\text{-}NC}$) were significantly different (p=0·05). Interestingly, while continued cannabis users showed comparable levels of functioning when compared to the non-users ($d_{CC\text{-}NC}$=0·04, p=0·68[95% CI -0·14; 0·21]), those who discontinued using cannabis had significantly higher levels of functioning when compared to non-users ($d_{DC\text{-}NC}$=-0·49, p=0·002[95% CI -0·81; -0·17]). This difference in effect-size ($d_{CC\text{-}NC}$ vs. $d_{DC\text{-}NC}$) was significant as indicated by meta-regression (p=0·0075). Continued cannabis use was not a significant predictor for negative symptomatology ($d_{CC\text{-}NC}$=-0·09, p=0·37[95% CI -0·30; 0·11]) and there was a trend for reduced negative symptoms in those who discontinued compared to non-users ($d_{DC\text{-}NC}$=-0·31, p=0·10[95% CI -0·67; 0·05]). However, the difference in effect size ($d_{CC\text{-}NC}$ vs. $d_{DC\text{-}NC}$) was not significant (meta-regression, p=0·41). This is also in

accordance with the direct comparison between continued and discontinued users (CC-DC*, cf. Table 4.*), which suggested that those who continued smoking cannabis had higher levels of negative symptoms than those who discontinued. However, this was only significant at a trend level (p=0·07) and generalizability may be limited due to the few studies included in this analysis (k=2, n=83).

Figure 4 about here

Sensitivity Analysis

There was substantial heterogeneity in the effect of continued cannabis use on relapse (83·62%, p<0·0001[95% CI 68·04%; 92·89%]). Hence, sensitivity analysis was carried out with more homogeneous groups of studies (for a summary see *sTable 4.*, supplementary material): Studies were selected if they matched the follow up duration between continued cannabis users and non-users (cf. *Table 1.*, "Matched=YES") (k=17, n=15371, $d_{CC\text{-}NC}$=0·42, p<0·0001[95% CI 0·26; 0·57]), were rated as "high quality" (k=10, n=1366, $d_{CC\text{-}NC}$=0·50, p<0·0001[95% CI 0·32; 0·68], included either only early stage psychosis (k=10, n=1120, $d_{CC\text{-}NC}$=0·30, p=0·0004[95% CI 0·13; 0·47]) or chronic psychosis (k=13, n= 14922, $d_{CC\text{-}NC}$=0·37, p=0·0006[95% CI 0·16; 0·58]) and defined relapse as hospital admission (k=19, n=15412, $d_{CC\text{-}NC}$=0·36, p<0·0001[95% CI 0·19; 0·52]). Effect-sizes estimated for studies including only patients with non-affective psychosis (k=9, n=1280, $d_{CC\text{-}NC}$=0·34, p=0·0036[95% CI 0.11; 0.58]) and those including only affective psychosis (k=15, n=14877, $d_{CC\text{-}NC}$=0·37, p<0·0001[95% CI 0·19; 0·55] were not significantly different (p=0·89). Gender and age at follow up assessment did not significantly (p=0·87 and p=0·38) reduce the heterogeneity in relapse outcome, as indicated by meta-regression.

4. Discussion

To our knowledge, this is the first meta-analysis to demonstrate that, regardless of the stage of their psychotic disorder, patients who continue using cannabis are more likely to suffer from a relapsing course when compared both to non-using patients (d_{CC-NC}=0·36) and to patients who discontinue using the substance after onset (d_{CC-DC}=0·28). Furthermore, considering that those who discontinue do 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 may resolve following discontinuation of its use. Gradient in the effect of cannabis use (continued use > discontinued use > non-use) on outcome in psychosis observed in the present analysis is consistent with that noted in other studies not included here [15,24], with the effect on outcome being most adverse in those who continue to use the drug. This is also compatible with other epidemiological evidence of the adverse effects of cannabis being dose-dependent [13,65] and with evidence that the magnitude of cognitive impairments associated with cannabis exposure tend to diminish following abstinence [79]. Additionally, our results suggest that continued cannabis users suffered significantly longer hospitalizations following their onset than non-users (d_{CC-NC}=0·36), which may suggest perhaps more severe relapses requiring longer inpatient care to stabilize. It is worth noting that longer hospital stay may also be related to other factors unrelated to the severity of the illness, such as lack of suitable accommodation for the patient to be discharged to.

In terms of symptomatic outcome, continued cannabis users experienced more severe positive psychotic symptoms at follow-up assessment. This effect was not present in those who discontinued using the substance (d_{CC-NC}=0·15 vs. d_{CC-DC}=-0·30). This is consistent with other follow-up studies that compared positive symptom levels

between continued users, discontinued users and non-users of cannabis [22-25] and a report from a longitudinal population-based sample suggesting that continuation of cannabis use predicted subsequent persistence of psychotic symptoms [80]. Other studies have reported a temporal association between changes in cannabis use and subsequent changes in psychotic symptom severity, both in the short [81] and long-term [14]. Evidence that cannabis use has a particularly harmful effect on different outcome measures of psychosis (relapse, psychotic symptoms) when use is continued compared to when one stops using is intuitive and consistent with effects of cannabis use on cognition [79]. However, the effect of cannabis and continuity of its use was not observed across certain other domains of outcome in the present meta-analysis: continued cannabis users did not differ from the non-user groups in their negative symptomatology ($d_{CC\text{-}NC}$=-0·09, p=0·37). A similar result was reported in a separate meta-analysis focusing on symptoms [32]. Discontinued users also did not differ significantly from non-users ($d_{DC\text{-}NC}$=-0·31, p=0·10), though they had less negative symptoms when compared directly with continued users ($d_{CC\text{-}DC}$=0·41, p=0·07). This may appear to contradict the results of the meta-regression suggesting no difference between the effects of continued and discontinued use on negative symptoms. However, it is worth noting that meta-regression compared the estimates from two different random effects models (i.e., $d_{CC\text{-}NC}$ and $d_{DC\text{-}NC}$) examining effect on negative symptoms, rather than a direct comparison between discontinued and continued cannabis users. Furthermore, while the direct comparison involved data from only two studies, the meta-regression compared data from a larger sample of studies. Nevertheless, it is worth noting that the general direction of effect in different groups is consistent across all comparisons. Continued cannabis users showed similar levels of functioning when compared to the non-users ($d_{CC\text{-}NC}$=0·04, p=0·68), while

discontinued users had better functioning scores compared to non-users ($d_{DC\text{-}NC}$=-0·49, p=0·002). In line with this, other studies have reported that those who discontinue cannabis have better functioning [22,24-26] compared to non-users and a recent meta-analysis suggested that cessation of substance use in general was associated with improvement of negative symptoms and global functioning [34]. These findings suggest that cannabis-using patients may have better functioning to begin with (though this is not something that could be tested in the present analysis). This is also compatible with the view that cannabis-using patients represent a subgroup with a less neurodevelopmental pathology [82,83]; perhaps for this reason the adverse effects of cannabis use on functioning and negative symptoms only become apparent when continued users are compared to those who discontinued use rather than non-users. Patients who are able to stop using cannabis may also represent an etiologically and clinically distinct subgroup suffering from a less severe illness with less of a need to use cannabis for self-medication. The observed association between cannabis exposure and relapse of psychosis and related outcome variables may be mediated through the effect of its key psychoactive ingredient, THC, on the neural substrates implicated in psychosis [18-20,84-86]. The observed strength of association between continued cannabis use and relapse is comparable to other identified environmental risk factors for relapse of psychosis such as high expressed emotions (d=0·31) [87], as well as the effects of interventions that prevent relapse, such as psychoeducation (d=0·21)[88] or reduce psychotic symptoms, such as antipsychotic treatment (d=0·48) [89]. Hence, these results emphasize the importance of cannabis use as a clinically relevant target for treatment development.

Limitations

Some limitations are noteworthy, which are mainly related to the methodological heterogeneity among the studies included (*cf. Table 1*). Different criteria were applied by the studies included in this meta-analysis to classify those who continued to use cannabis (e.g. presence of cannabis use disorder/use more than once in a defined time-period), or discontinued the drug (e.g. history of use but negative UDS/no use in given time period), as well as non-users (e.g. less than daily use/non-abuser/no use in given time period/never use). Follow-up durations also differed between cannabis users and non-users in some studies [e.g. 7 year relapse window for cannabis users vs. 12 year relapse window for non-users in Maremmani, Lazzeri (2004)[66]]. In fact, excluding those studies with differing follow-up windows between the participant groups as part of sensitivity analysis revealed a slightly larger effect of cannabis use on relapse than found in the main analysis (d=0·42 vs. d=0·36). The study by Baeza, Graell (2009)[26] may need to be highlighted in this context, considering that their report of absence of adverse effects of cannabis use on relapse may reflect their six months follow up, an interval perhaps too short to detect differences in relapse rates between the groups.

It may be argued that the patients differed in their stage of illness across the included studies (e.g. early stage vs. chronic psychosis), but sensitivity analysis revealed that this did not significantly influence the results. It was not possible to control for the effect of other potential confounding factors that may be associated with cannabis use such as medication adherence [1,24,25,67,69], engagement with the services [24] or other abuse of other drugs[1]. However, the present results are also consistent with studies that have systematically controlled for age, gender, alcohol and drug use, illness characteristics (e.g. duration, diagnosis, 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 analyze raw data, which limited our ability to carry out 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 may be related to the use of different types of cannabis containing differing proportion of the main ingredients such as delta-9-tetrahydrocannabinol or Cannabidiol that are known to have opposing effects[90]. However, we were unable to assess the effect of type of cannabis used, as this information was not available for the included studies. Finally, although our systematic search may have been somewhat restricted by using MEDLINE only, we aimed to address this potential limitation by screening bibliographies from previous conducted meta-analyses, systematic reviews and original studies for additional studies that may have been missed out in the database search.

Nevertheless, despite lack 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 only serves to underline the importance of addressing continued cannabis use in patients with psychosis in the clinical setting, by highlighting that outcomes are likely to be better in those who discontinue the drug.

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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 carried out 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 interest

None.

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