Association between cannabis use and symptom dimensions in schizophrenia spectrum disorders: an individual participant data meta-analysis on 3053 individuals

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Summary

Background The association between cannabis use and positive symptoms in schizophrenia spectrum disorders is well documented, especially via meta-analyses. Yet, findings are inconsistent regarding negative symptoms, while other dimensions such as disorganization, depression, and excitement, have not been investigated. In addition, meta-analyses use aggregated data discarding important confounding variables which is a source of bias.

Methods PubMed, ScienceDirect and PsycINFO were used to search for publications from inception to September 27, 2022. We contacted the authors of relevant studies to extract raw datasets and perform an Individual Participant Data meta-analysis (IPDMA). Inclusion criteria were: psychopathology of individuals with schizophrenia spectrum disorders assessed by the Positive and Negative Syndrome Scale (PANSS); cannabis-users had to either have a diagnosis of cannabis use disorder or use cannabis at least twice a week. The main outcomes were the PANSS subscores extracted via the 3-factor (positive, negative and general) and 5-factor (positive, negative, disorganization, depression, excitement) structures. Preregistration is accessible via Prospero: ID CRD42022329172.

Findings Among the 1149 identified studies, 65 were eligible and 21 datasets were shared, totaling 3677 IPD and 3053 complete cases. The adjusted multivariate analysis revealed that relative to non-use, cannabis use was associated with higher severity of positive dimension (3-factor: Adjusted Mean Difference, aMD = 0.34, 95% Confidence Interval, CI = [0.03; 0.66]; 5-factor: aMD = 0.38, 95% CI = [0.08; 0.63]), lower severity of negative dimension (3-factor: aMD = –0.49, 95% CI [–0.90; –0.09]; 5-factor: aMD = –0.50, 95% CI = [–0.91; –0.08]), higher severity of excitement dimension (aMD = 0.16, 95% CI = [0.03; 0.28]). No association was found between cannabis use and disorganization (aMD = –0.13, 95% CI = [–0.42; 0.17]) or depression (aMD = –0.14, 95% CI = [–0.34; 0.06]).

Interpretation No causal relationship can be inferred from the current results. The findings could be in favor of both a detrimental and beneficial effect of cannabis on positive and negative symptoms, respectively. Longitudinal designs are needed to understand the role of cannabis is this association. The reported effect sizes are small and CIs are wide, the interpretation of findings should be taken with caution.

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Keywords: Cannabis; Schizophrenia; PANSS; Individual participant data; Symptom dimensions; Meta-analysis

Introduction

Cannabis is a widely used psychotropic substance, with a highly prevalent usage in people with schizophrenia spectrum disorders.[1] Specifically, 42% of people with schizophrenia present a lifetime use of cannabis,[2] and 26% suffer from a comorbid cannabis use disorder (CUD).[3] Among people with a First-Episode Psychosis (FEP), the estimated rate of cannabis use is 38%.[4] Cannabis use was shown to precipitate schizophrenia onset,[4] where cannabis-users have a disease onset 2–3 years earlier than non-users.[5] Cannabis use is also associated with a two-fold risk of developing psychosis in vulnerable individuals[5,6] and with a poorer prognosis in individuals with an established vulnerability to psychotic disorders.[6]

At the symptom level, an association between cannabis use and higher severity of positive symptoms (e.g., delusions, hallucinations) is well documented. This has been reported in people with schizophrenia,[7–9] as well as people with recent onset psychosis[10] and in individuals with schizotypal traits.[11,12] A recent review of existing meta-analyses and reviews has confirmed the potentiating role of cannabis use on the severity of positive symptoms.[13] Regarding negative symptoms (e.g., blunted affect and avolition), a consensus has been more difficult to reach. In individuals with schizophrenia,

Research in context

Evidence before this study

Cannabis use plays a critical role in increasing the risk for developing psychosis and is one of the most observed comorbidities in individuals with such disorders. Previous reviews have consensually reported a significant positive association between cannabis use and the severity of psychotic symptoms. There is no consensus regarding negative symptoms, and none of these previous reviews have investigated the association with other symptom dimensions described in schizophrenia spectrum disorders. In addition, accounting for individual confounding variables is impossible when using published aggregated data, while it is of great importance to ensure reliable results.

Added value of this study

This analysis employs individual participant data and refined statistical methods which together ensure robust and generalizable findings. It is the first of its kind to explore cannabis use in relation to the severity of multiple symptom dimensions. We report significant effect-size estimates using two empirically validated PANSS structures, revealing the higher severity of positive and excitement symptoms, along with the lower severity of negative symptoms, in the presence of cannabis use in individuals with schizophrenia and related disorders. The risk of bias is reported and considered low.

Implications of all the available evidence

Our findings along with existing evidence suggest that continuing to raise public awareness regarding the harmful effects of cannabis is appropriate. In addition, thorough research encompassing clinical trials on subcomponents of cannabis and longitudinal study designs are needed to understand if cannabis or its subcomponents play a role in the lower severity of negative symptoms. Future studies should consider accounting for all possible biasing variables as the findings appear to be sensitive to their inclusion.

results appear inconsistent. Although one study on 3500 participants reported a positive association between cannabis use and negative symptoms severity,[14] other large studies found no association[7–10] or even a negative association, where patients using cannabis presented less severe negative symptoms[15] (11 studies). Similarly, a study on 18 patients with FEP found that CUD was associated with lower negative symptoms severity.[16]

Although numerous studies have investigated the influence of cannabis use on positive or negative symptoms, only few studies have investigated the influence of cannabis use on other symptom dimensions in schizophrenia. However, there is evidence that cannabis use is associated with higher severity of disorganization,[17] depression,[18] and excitement.[19,20] Besides disorganization, these associations have never been investigated in individuals with schizophrenia. In addition, psychotic symptoms may be also influenced by many other factors than just cannabis use such as sex,[21,22] illness duration,[23] long exposure to stimulants,[24] childhood trauma,[21] etc. The main goal of the current study is to thoroughly investigate the influence of cannabis across the global psychopathology and take into account other variables that may influence symptoms severity using a meta-analytic approach with individual participant data (IPD) on a large sample of individual-level data collected from previously published studies. Given the widespread use of the Positive and Negative Syndrome Scale (PANSS) to parse and measure psychotic symptoms,[25] we specifically selected studies using the PANSS as to maximize data homogeneity. This allows to better capture the influence of cannabis on the complex symptomatology of psychosis using the 3-factor as well as the 5-factor structure of the PANSS at the individual level.[26]

Methods

The methods and results of our Individual Participant Data Meta-Analysis (IPDMA) are reported according to the Preferred Reporting Items for Systematic Review and Meta-analysis on Individual Participant Data (PRISMA-IPD).[27] An IPDMA -also known as mega-analysis- relies on one main principle: extracting individual-level data from published studies to compute fine-grained analyses. This kind of analysis can be conducted in one stage or two stages. The method employed in the current study is based on a two-stage framework.[28] The protocol for conducting this IPDMA was preregistered on PROSPERO, accessible via the ID CRD42022329172.

Information sources

Publications were identified using PubMed, ScienceDirect and PsycINFO databases. Contact with original research teams was also used to identify additional publications. The last search was conducted on September the 27th, 2022. Publications were screened using the following search syntax: ["positive and negative syndrome scale" OR "PANSS" AND "cannabis"]. The filter "research articles" was used on ScienceDirect.

Eligibility criteria

Studies were eligible if: 1) CUD was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases (ICD); or data on cannabis use was collected using validated tools such as questionnaires (Appendix, Scales and Questionnaires, p.5); 2) participants were diagnosed with schizophrenia spectrum disorders (i.e., schizophrenia and subtypes such as paranoid, undifferentiated, disorganized; schizophreniform disorder, schizoaffective

disorder, psychosis not otherwise specified) or FEP according to DSM or ICD criteria, with no restriction on age; 3) individual data could be divided into two groups, i.e., patients using and not-using cannabis at assessment; 4) symptoms were assessed using the PANSS. Studies were not eligible if: 1) cannabis use was not investigated; 2) subcomponents of cannabis were administered to individuals as part of the protocol; 3) publication was not in English language. If a study reported data for several groups of patients with multiple diagnoses (e.g., patients with schizophrenia spectrum disorders, bipolar disorder, depression), only the data concerning the groups of interest were requested (i.e., patients with schizophrenia spectrum disorders). In cases of follow-up studies, only the baseline data was retrieved to avoid the influence of any interventions realized as part of the study protocol.

At the patient-level, the criteria for being included in the cannabis-using group were: 1) Diagnosis of CUD; or 2) frequency of use of at least twice a week; or 3) presenting an "at-risk" consumption as assessed via questionnaires. Criteria for belonging to the non-using group was no or sporadic cannabis use (less than twice a week) during the three previous months.

Identifying studies

Two independent reviewers (MA, MN) conducted the literature search. Each reviewer checked the relevance of the different studies through their titles and abstracts. Full texts were then read to determine eligibility (MA). Disagreements were resolved through referral to third authors (BR). Subsequently, datasets were collected following a two-step process. First, the corresponding author from each selected study was contacted via an email proposing a scientific collaboration. If no response was received after 2 weeks, a reminder was sent. In addition, co-authors were also contacted to maximize the chances of receiving a response. Then, a template excel file was sent to all authors who responded to collect anonymous homogenous datasets according to General Data Protection Regulation (GDPR).[29] IPD were cross-checked with the published data and any inconsistencies were discussed and resolved with corresponding authors.

The variables that were collected were predefined according to their putative respective influence on psychotic symptoms. To this end, we used a Directed Acyclic Graph (DAG) that was consensually established during a meeting that gathered a psychiatrist (BR), two researchers in neuroscience (GS and JB) and a biostatistician (MN), based on their expertise (Appendix, Figure S1, p.3). The predefined minimal adjustment confounding set was extracted by DAGitty, an online algorithm[30] (Appendix, Table S1, p.4).

Risk of bias

The risk of bias in individual studies was assessed using the Quality Assessment Tool for Observational Cohort and Cross-sectional studies, a recommended tool for cross-sectional studies.[31] Publication bias was assessed by visually inspecting funnel plots and testing for its asymmetry using Egger's test.[32]

Statistics

Choices regarding the most appropriate statistical analyses were based on an Individual Participant Data Meta-Analysis (IPDMA) methods handbook.[33] Analyses were conducted using R version 4.1.1 for statistical computing. A two-stage meta-analysis was planned to synthesize IPD. This approach allows for an estimation of the mean difference (MD) and its 95% confidence interval (CI) in PANSS scores between patients using and not-using cannabis for each study. Both univariate and multivariate analyses were conducted, using two sets of outcomes: 1) 3-factor PANSS with the positive, negative and general subscores; 2) 5-factor PANSS with positive (P1, P3, P5, P6, G9), negative (N1, N2, N3, N4, N6, G7, G16), disorganization (or neurocognitive) (P2, N5, G11, N7, G5, G10, G13, G15), depression (or affect, or anxiety) (G1, G2, G3, G4, G6), and excitement (or hostility, or resistance) (P4, P7, G8, G14) subscores.[26] Detailed items included in each factor is available in the Appendix, Figure S10, p.15.

Both univariate and multivariate analyses were conducted following a two-stage approach. The following procedure describes the first stage of the univariate analysis: for each study, linear regression models were fitted independently to the PANSS subscores and adjusted for cannabis use as a binary variable (yes/no) and confounding factors as defined in the DAG (Appendix, Figure S1, p.3), using the lm () function. The mean differences between cannabis-users and non-users and their estimated variances were extracted from each study and used in the second stage. For the second stage, a random-effect meta-analysis was performed. Between-study heterogeneity was evaluated with tau^2 and I^2. $I^2 < 25\%$, $25\% < I^2 < 75\%$, $I^2 > 75\%$ are considered as low, moderate and high heterogeneity, respectively.[34] Tau^2 was estimated by the Restricted Maximum Likelihood. In addition, Hartung-Knapp adjustment was applied to the 95% CI of the global MD to reduce the chances of false positive.[35] The multivariate analysis follows the same procedure as the univariate analysis. In the first stage, PANSS subscores were jointly fitted in one linear regression model per study to extract covariance estimates between subscores. The second stage was performed including these covariances in a random-effect meta-analysis using the mixmeta () function.[36] This multivariate model allows for the correlation between subscores to be accounted for. Primary outcomes to be investigated in this study are the PANSS subscores using the 3-factor and 5-factor structures, in a multivariate analysis framework.

Two post-hoc sensitivity analyses were performed because of specific features found in some datasets.

Reasons for conducting these analyses and results are reported in the results.

Role of the funding source

The funder had no role in study design, data collection, data analyses, interpretation, or writing of report.

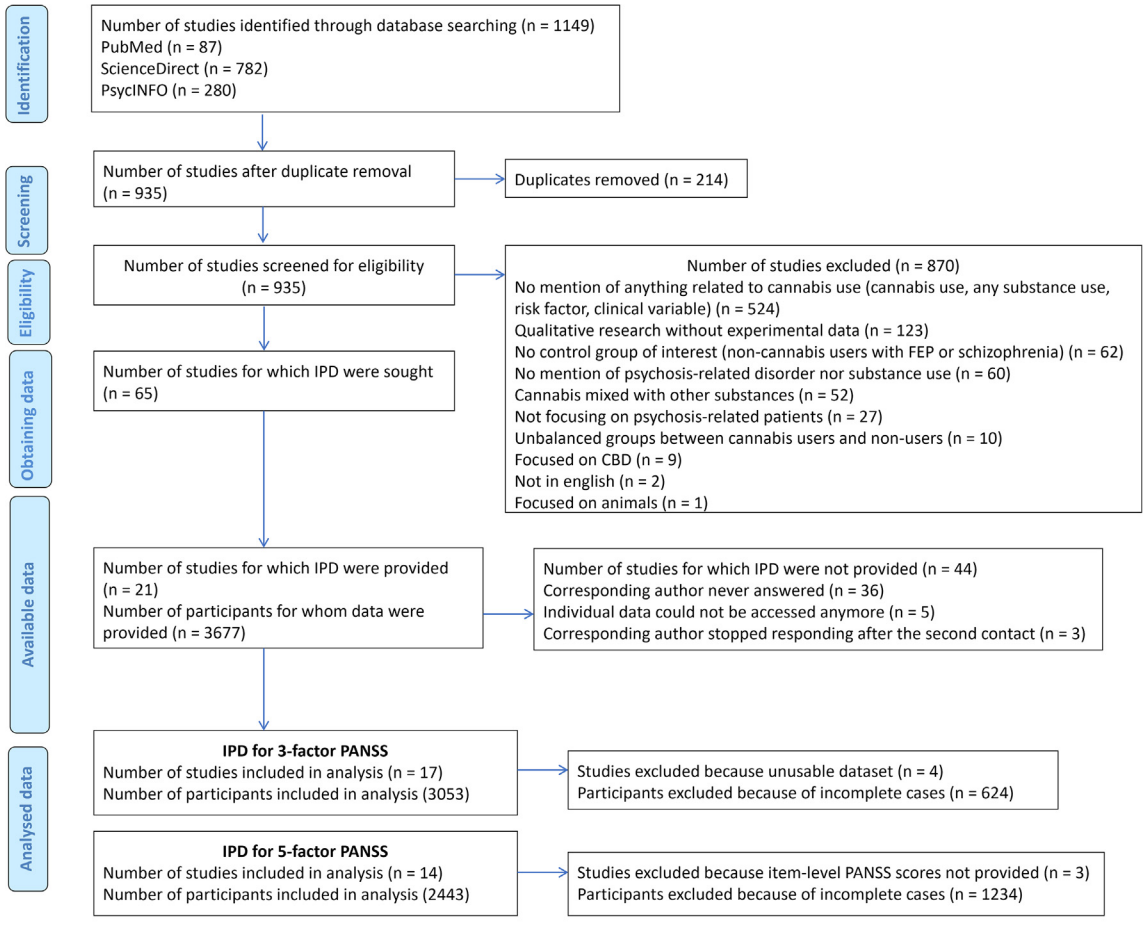
Results

Study selection and data extraction

A total of 1149 studies were retrieved following the databases search and contact with authors. Finally, 72 publications were eligible, corresponding to 65 independent datasets. Twenty-one datasets were extracted. All came from primary studies following a cross-sectional design except four that were longitudinal.[37–40] In those cases, cross-sectional baseline data was shared to maintain homogeneity across study designs. Issues were identified in 4 datasets. One was composed solely of cannabis-using patients,[41] and another did not provide data on the general symptomatology subscale.[42] These studies could not be included in the analyses. Two others included very few cannabis-users as compared to non-users so the mean difference between both groups could not be adjusted for covariates.[43,44] These two datasets were included in a post-hoc sensitivity analysis. Seventeen datasets were thus included in the main analysis. The screening and selection process is presented in the PRISMA flow diagram (Fig. 1) and in the Appendix, p.20–22 for details.

Data harmonization

All collected datasets were merged into one, clustering patients by study. Regarding socio-demographic data, education could not be standardized according to International Standard Classification of Education (ISCED) levels as planned. The type of medication and its related dose (mg/day) was transformed into



The PRISMA IPD flow diagram

Fig. 1: PRISMA IPD flow diagram of study selection. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; IPD, Individual Participant Data; CBD, Cannabidiol; FEP, First-Episode Psychosis; PANSS, Positive and Negative Syndrome Scale.

chlorpromazine equivalents.[45] Similarly, multiple substances were reported across datasets. It was decided to pool them under stimulants (e.g., cocaine, amphetamines), depressants (e.g., alcohol, benzodiazepines) or hallucinogens (e.g., psilocybin). Illness duration was obtained by subtracting the age of the patient and the onset of the psychotic disorder, defined as the observation of the first symptoms or the first hospitalization. All studies provided item-level PANSS scores except 3,[46–48] allowing for the calculation of 5-factor PANSS subscores in 14 datasets.

First-stage

The total number of cases that were shared amounts to 3677. Due to missing data, the total number of useable cases was 3053 (Table 1). Education level was unstandardized and thus not included in the regression models. Table 2 shows the variables fitted in linear regression models for each dataset. Results obtained after the first stage are shown in Table 4 (3-factor PANSS outcomes) and 5 (5-factor PANSS outcomes) (Appendix, Tables S4–S5, p.11–12). Within-study covariances between outcomes extracted from joint modeling are reported in Tables 4–6 (Appendix, Tables S4–S6, p.11–13).

Second stage–3-factor outcomes

The second stage of this analysis was then performed, incorporating the data presented in Tables 4–6 (Appendix, Tables S4–S6, p.11–13). As shown in Table 3, the univariate and unadjusted analysis indicates that the severity of positive (MD = 0.30, 95% CI = [–0.01; 0.61]), negative (MD = –0.22, 95% CI = [–0.61; 0.16]), and general symptoms (MD = –0.05, 95% CI = [–0.54; 0.45]) do not differ significantly between cannabis-users and non-users. The heterogeneity for each outcome is low to moderate. When the models are adjusted for covariates presented in Table 2, the same tendencies are found for positive (MD = 0.22, 95% CI = [–0.08; 0.52]), negative (MD = –0.38, 95% CI = [–0.80; 0.04], and general (MD = –0.10, 95% CI = [–0.56, 0.36]) symptoms. Similarly, none of the effect sizes are significant.

In the adjusted multivariate analysis, the influence of cannabis use is significant on positive (MD = 0.34, 95% CI = [0.03; 0.66]), and negative (MD = –0.49, 95% CI [–0.90; –0.09]) symptoms. This indicates that cannabis-users present significantly more severe positive symptoms, and significantly less severe negative symptoms than non-users. General symptomatology did not significantly differ between groups (MD = –0.12, 95%

Study	Country	Retrieved cases	Available data										Complete cases
			Cannabis	Age	Gender	Education	Onset	Frequency	Medication	SUDs	Item-level PANSS scores	PANSS global scores	
Pencer 2003[40]	Norway	372	✓	✓	✓	✓	✓	–	✓	✓	✓	✓	319
Amoretti 2022[49]	Spain	209	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	187
Baudin 2016[50]	France	366	✓	✓	✓	–	✓	–	–	✓	✓	✓	312
Carra 2017[42]	England	122	Not used[a]										
Cookey 2020[46]	Canada	99	✓	✓	✓	–	–	–	–	✓	–	✓	77
Devos 2020[51]	Germany	97	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	79
Dragogna 2014[43]	Italy	12	Not used in main analysis[b]										
Hajkova 2021[52]	Czech Republic	86	✓	✓	✓	✓	✓	–	✓	✓	✓	✓	81
Herzig 2015[53]	Switzerland	62	✓	✓	✓	–	–	✓	✓	✓	✓	✓	35
Huber 2016[37]	Germany	52	✓	✓	✓	✓	✓	–	–	✓	✓	✓	52
Kline 2022[54]	USA	246	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	188
Mallet 2017[55]	France	61	✓	✓	✓	✓	✓	–	–	✓	✓	✓	59
Rabin 2013[48]	Canada	54	✓	✓	✓	✓	–	✓	–	✓	–	✓	54
Rabin 2017[41]	Canada	20	Not used[a]										
Ricci 2021[56]	Italy	62	✓	✓	✓	–	✓	–	–	✓	✓	✓	62
Ringen 2013[57]	Norway	1107	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	876
Schaub 2008[58]	Switzerland	39	✓	✓	✓	✓	–	–	–	✓	✓	✓	34
Scheffler 2021[39]	South Africa	130	✓	✓	✓	✓	–	✓	✓	–	✓	✓	125
Schnell 2009[59]	Germany	35	✓	✓	✓	✓	✓	✓	–	✓	✓	✓	34
Vilabadia 2020[44]	Spain	70	Not used in main analysis[b]										
Wobrock 2013[47]	European countries and Israel	498	✓	✓	✓	✓	–	✓	✓	✓	–	✓	479
Total number of useable cases: 3053													

Abbreviations: SUDs, substance use disorders [a]Datasets which could not be included for reasons explained in the Results section. [b]Datasets which were included in sensitivity analyses due to biasing issues (Results section and Appendix, Tables S9 and S10, p.16).

Table 1: **Characteristics of included datasets.**

Study/variables	Cannabis	Age	Sex	Illness duration	CPE	Depressants	Stimulants	Hallucinogens
Pencer 2003[40]	✓	✓	✓	✓	✓	✓	Insufficient data to create two groups (users and non-users)	
Amoretti 2022[49]	✓	✓	✓	✓	✓			
Baudin 2016[50]	✓	✓	✓	✓				
Cookey 2020[46]	✓	✓	✓					
Devos 2020[51]	✓	✓	✓	✓				
Hajkova 2021[52]	✓	✓	✓	✓	✓			
Herzig 2015[53]	✓	✓	✓					
Huber 2016[37]	✓	✓	✓	✓				
Kline 2022[54]	✓	✓	✓	✓	✓			
Mallet 2017[55]	✓	✓	✓	✓				
Rabin 2013[48]	✓	✓						
Ricci 2021[56]	✓	✓	✓	✓				
Ringen 2013[57]	✓	✓	✓	✓	✓			
Schaub 2008[58]	✓	✓						
Scheffler 2021[39]	✓	✓	✓		✓			
Schnell 2009[59]	✓	✓	✓	✓				
Wobrock 2013[47]	✓	✓	✓		✓			

Abbreviation: CPE, chlorpromazine equivalents.

Table 2: **First stage: covariates included in linear regression models.**

CI = [–0.52, 0.29]). Forest plots are presented in Figs. 2–4.

Second stage—5-factor outcomes

In the adjusted univariate model, positive (MD = 0.27, 95% CI = [–0.02; 0.55]) and negative (MD = –0.42, 95% CI = [–0.89; 0.05]) symptoms did not significantly differ between cannabis-users and non-users. Similarly, disorganization (MD = –0.03, 95% CI = [–0.34; 0.27]) and depression (MD = –0.14, 95% CI = [–0.37; 0.09]) severity were similar between both groups. The excitement factor presented a significantly higher severity for cannabis-users (MD = 0.13, 95% CI = [0.01; 0.25]) even though the effect size was small. Heterogeneity for each factor was considered low (Table 4).

In the adjusted multivariate model, cannabis-users presented a significantly higher severity of positive symptoms (MD = 0.38, 95% CI = [0.08; 0.63]), and significantly less severe negative symptoms (MD = –0.50, 95% CI = [–0.91; –0.08]) relative to non-users. These results are in accordance with those presented for the 3-factor adjusted multivariate analysis. Disorganization did not significantly differ between users and non-users (MD = –0.13, 95% CI = [–0.42; 0.17]), and so did the depression dimension (MD = –0.14, 95% CI = [–0.34; 0.06]). Excitement severity was significantly higher for cannabis-users relative to non-users, with a small effect size (MD = 0.16, 95% CI = [0.03; 0.28]). The heterogeneity was considered low for all factors. Correlation matrices between the estimates for both sets of outcomes are reported in Appendix, Tables S7–S8, p.14. Interestingly, positive and negative as well as depression and excitement dimensions are inversely correlated in both PANSS structures. In the 5-factor PANSS, excitement is the only dimension that is positively correlated with the positive dimension. Forest plots are presented in Appendix, Figures [S11–S15], p.17–19.

Model	Outcome	Summary cannabis effect [95% CI]	p-value	Heterogeneity I^2	Tau^2
Unadjusted univariate	Positive	0.30 [–0.01; 0.61]	0.06	34.5%	0.05
	Negative	–0.22 [–0.61; 0.16]	0.23	39.6%	0.12
	General	–0.05 [–0.54; 0.45]	0.84	36%	0.14
Adjusted univariate	Positive	0.22 [–0.08; 0.52]	0.14	28.5%	<0.0001
	Negative	–0.38 [–0.80; 0.04]	0.07	42.9%	0.19
	General	–0.10 [–0.56; 0.36]	0.63	21.4%	0.04
Adjusted multivariate	Positive	0.34 [0.03; 0.66]	0.03[a]	28.6%	–
	Negative	–0.49 [–0.90; –0.09]	0.02[a]	42.9%	
	General	–0.12 [–0.52,0.29]	0.57	23%	

[a]$p < 0.05$.

Table 3: **Summary results of univariate and multivariate models using the 3-factor PANSS structure—unadjusted and adjusted.**

Model	Outcome	Summary cannabis effect [95% CI]	p-value	Heterogeneity I^2	Tau^2
Adjusted univariate	Positive	0.27 [−0.02; 0.55]	0.07	19.5%	<0.0001
	Negative	−0.42 [−0.89; 0.05]	0.08	39.7%	0.19
	Disorganization	−0.03 [−0.34; 0.27]	0.81	10.4%	0.007
	Depression (Affect—anxiety)	−0.14 [−0.37; 0.09]	0.22	10.4%	<0.0001
	Excitement/Activity (Resistance)	0.13 [0.01; 0.25]	0.03[a]	<1%	<0.0001
Adjusted multivariate	Positive	0.38 [0.08; 0.63]	0.01[a]	19.9%	–
	Negative	−0.50 [−0.91; −0.08]	0.02[a]	39.7%	
	Disorganization	−0.13 [−0.42; 0.17]	0.41	10.6%	
	Depression (Affect – anxiety)	−0.14 [−0.34; 0.06]	0.16	11.1%	
	Excitement/Activity (Resistance)	0.16 [0.03; 0.28]	0.02[a]	<1%	

[a]$p < 0.05$.

Table 4: **Summary results of adjusted univariate and multivariate analysis model using the 5-factor PANSS structure.**

Overall, the effect sizes that were found in this study using both PANSS structures are relatively small, while their confidence intervals are relatively wide.

Results of individual studies

Additional analyses

The planed one-stage IPDMA could not be performed as the number of covariates overlapping between datasets was not sufficient to provide reliable results. Also, the three planned subgroup analyses were not conducted. Indeed, the first subgroup analysis (FEP, schizophrenia and schizo-affective disorders) was not performed as the number of patients and studies per subgroup was insufficient (Appendix, Table S2, p.4). Data required for the other two subgroups analyses (frequency of use and other substance use) was too sparse across datasets to be used.

Two post-hoc sensitivity analyses were conducted. The first sensitivity analysis excluded one dataset from the main analysis.[52] Indeed, the description of the cannabis-using group differed somewhat from the a priori criteria established in the protocol. Cannabis-users were defined as using cannabis with a frequency of at least a few times per year for several years (>2 years) or daily for more than one month prior to the onset of the disorder. Moreover, data on the frequency

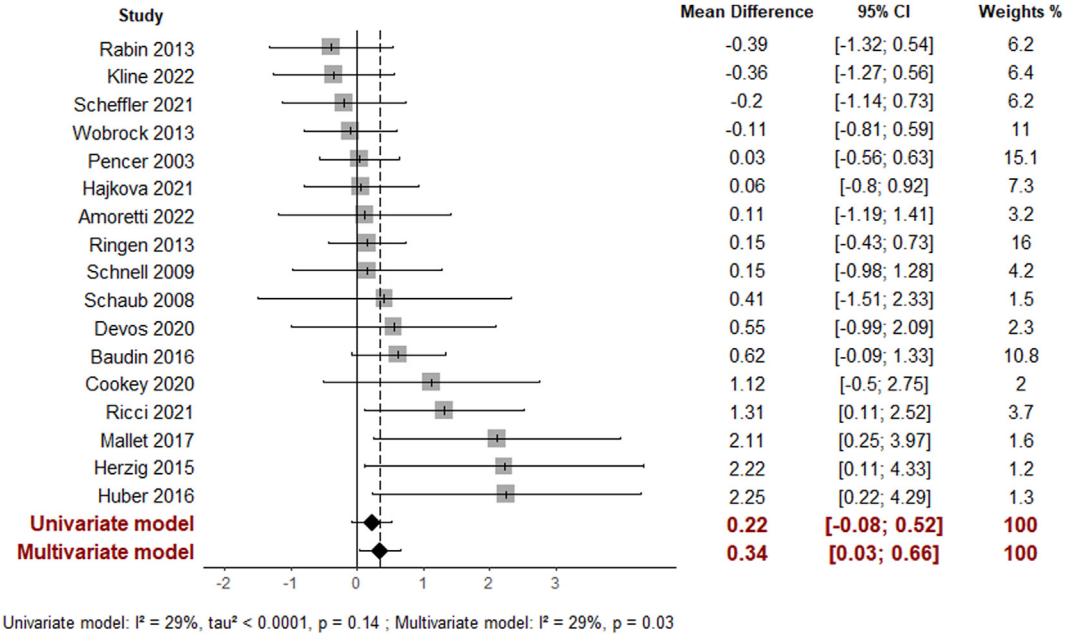


Fig. 2: Forest plot of the final stage of the meta-analysis indicating results from univariate and multivariate models comparing cannabis-users and non-users for the Positive dimension of the 3-factor PANSS. Mean differences with corresponding 95% CI are shown. Heterogeneity and p-values for both models are reported. CI, Confidence Interval; I^2 and tau^2, measures of heterogeneity; p, p-value.

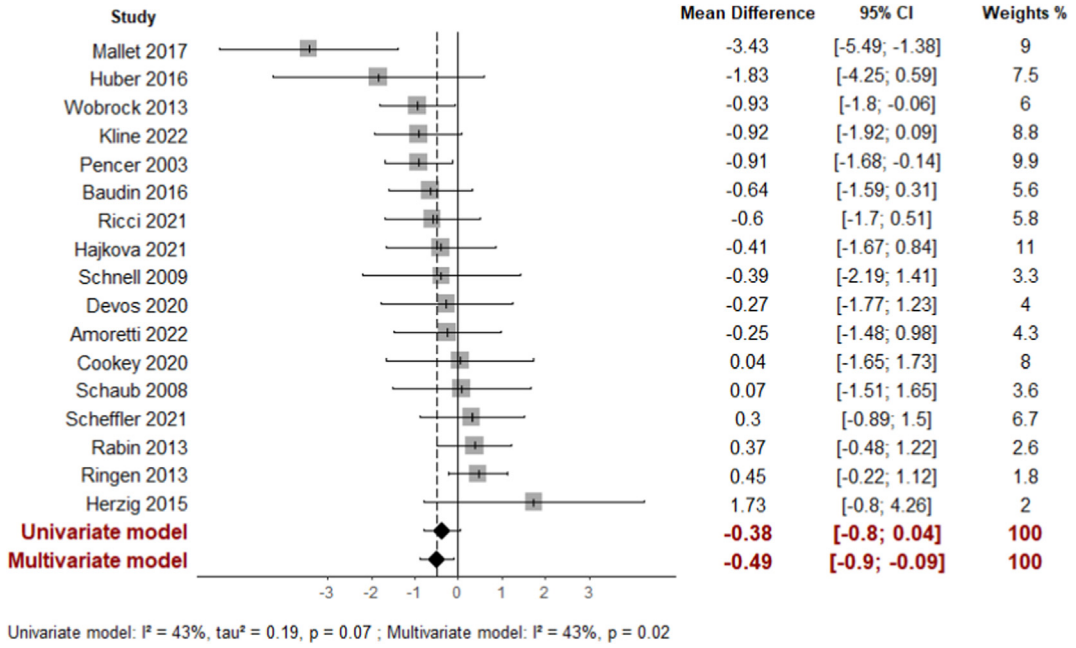


Fig. 3: Forest plot of the final stage of the meta-analysis indicating results from univariate and multivariate models comparing cannabis-users and non-users for the Negative dimension of the 3-factor PANSS. Mean differences with corresponding 95% CI are shown. Heterogeneity and p-values for both models are reported. CI, Confidence Interval; I^2 and tau^2, measures of heterogeneity; p, p-value.

and recency of use of each patient could not be extracted, preventing the categorization of patient on their frequency of use. The removal of this study did not impact the results, and it was thus decided to keep it in the main analyses. The second sensitivity analysis included the two additional datasets marked as "not

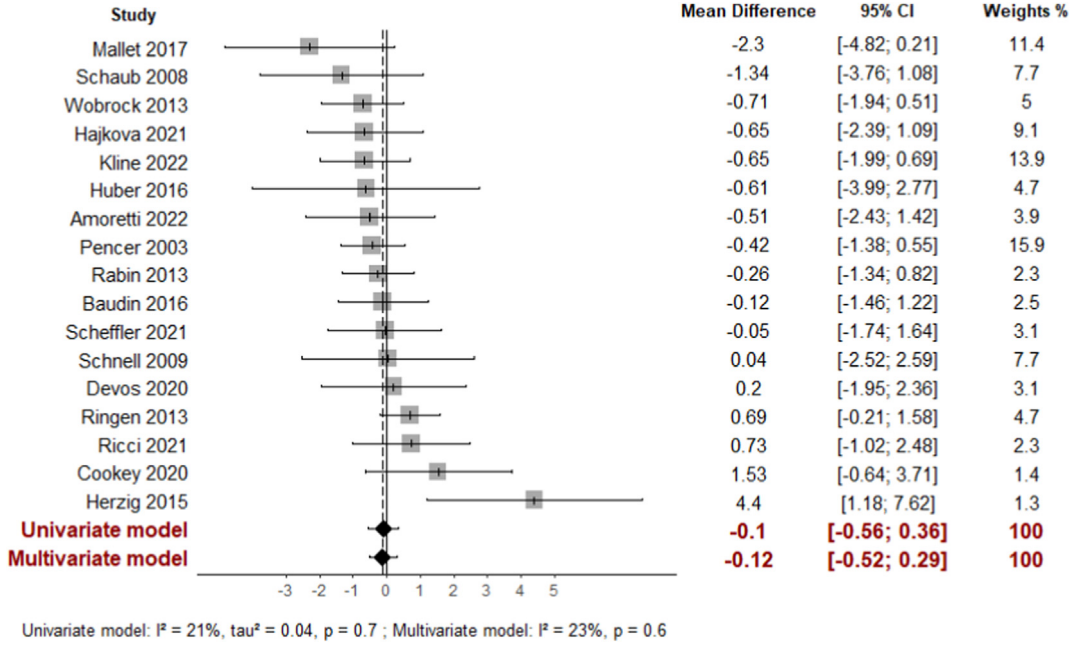


Fig. 4: Forest plot of the final stage of the meta-analysis indicating results from univariate and multivariate models comparing cannabis-users and non-users for the General dimension of the 3-factor PANSS. Mean differences with corresponding 95% CI are shown. Heterogeneity and p-values for both models are reported. CI, Confidence Interval; I^2 and tau^2, measures of heterogeneity; p, p-value.

used in main analysis" in Table 1.[43,44] Indeed, these two datasets each contained very few cannabis-users (two and six respectively). The linear regression could thus not be adjusted for covariates, introducing potential bias. The inclusion of these datasets did not impact the results for the 3-factor PANSS. Interestingly, it did not yield the same findings regarding negative symptoms in the 5-factor PANSS structure, where this dimension was not significantly associated with cannabis use anymore. Reasons for this change are discussed below. Other findings remained similar in both sensitivity analyses compared with the findings reported in the main analysis. Results of both analyses are presented in Appendix, Table S9 and S10, p.16.

Risk of bias

The overall risk of bias was considered low: 2 studies were judged as of "poor" quality in the context of the current study,[39,52] that of 8 as "fair",[37,47,49,53–56,58] and that of 7 as "good"[45,46,48,50,51,57,59] (detailed rating in Appendix, Table S3, p.5). A risk for publication bias was found at the visual inspection of the funnel plot and the Egger's test for the positive dimension of both 3 and 5-factor PANSS (Appendix, Figures [S2–S5], p.6–8). Using trim and fill method,[60] the corrected effect sizes of cannabis use were lower for the positive 3-factor (MD = 0.13, 95% CI [–0.2; 0.47]) and the positive 5-factor outcomes (MD = 0.19, 95% CI [–0.13; 0.5]) than the ones reported in the univariate analysis: MD = 0.22, 95% CI [–0.08; 0.52] and MD = 0.27, 95% CI [–0.02; 0.55] for positive 3 and 5-factor outcome respectively. No publication bias was reported for the other outcomes.

Discussion

This meta-analysis used IPD to provide refined results on the association between cannabis use and the psychopathology of schizophrenia spectrum disorders. Using two empirically validated PANSS structures, cannabis use was found to be associated with a higher severity of positive symptoms. This observation strengthens previous reports showing the same association between cannabis use and positive symptoms.[8,9,13] A review of longitudinal studies investigated the causal role of cannabis on the higher severity of positive symptoms and highlighted the consistent findings supporting this causal role.[61] However, it was also mentioned that the magnitude of this effect could be overstated in some studies, for example when not accounting for confounding variables. The presented results showed a decrease in the effect size when adjusting for confounding variables, in line with this observation. However, considering the consistent effect found in cross-sectional and longitudinal reviews, it supports the hypothesis of cannabis use being one of the causes of the higher severity of positive symptoms.

Similarly, negative symptoms in both PANSS structures were found to be decreased for cannabis-users, in accordance with two previous studies[15,16] but divergent from a larger number of published reviews.[7–9] In line with the already mentioned review of longitudinal studies,[61] confounding variables were shown to impact the results. The difference between unadjusted and adjusted analyses showed that adding these variables increased the negative association of cannabis use with negative symptoms severity, suggesting that omitting these variables could understate the association. Again, no causal role of cannabis can be implied from the current results. The lower severity of negative symptoms among cannabis-users supports both the self-medication hypothesis and the possibility that patients with fewer negative symptoms are more prone to substance use.[62] To date, no study can provide a definitive answer to this question. A recent longitudinal study reported that cannabis could be causally linked to detrimental effects on diminished expression but not apathy, two subdimensions of negative symptoms.[63,64] More studies employing longitudinal designs are needed to ascertain the causal role of cannabis on global negative symptoms.

Other symptom dimensions were investigated using the 5-factor PANSS. Disorganization and depression subscores severity were not associated with cannabis use. The findings regarding disorganization are not in line with a meta-analysis which found a positive association between cannabis use and Formal Thought Disorder (comprising disorganization) severity.[17] However, this meta-analysis is focused on positive Formal Thought Disorder whereas the current study represents positive and negative dimensions together. A finer analysis would require studying both dimensions separately, using adequate tools. Excitement dimension was found to be more severe for cannabis-users. To date, no previous review had investigated this association, and no findings are reported from longitudinal designs. The observed decrease of heterogeneity between the two sets of outcomes can be caused by the better clustering of symptoms offered by the 5-factor PANSS, encouraging its use in clinical settings. Overall, the results show some slight sensitivity to the addition of confounders, as demonstrated by the unadjusted analysis (Table 3) and sensitivity analysis (Appendix, Table S10, p.16). This change might occur because including confounders to regression models helps refining levels of association between variables, stressing the importance of including those biasing factors when studying the association between cannabis use and the severity of symptom dimensions.

The current study has several strengths. First, the use of IPD and adjustment for confounding variables allowed to provide refined results on a major health issue. The interpretation of the findings is not limited by a small sample-size, and more robust results can be

obtained relative to classic meta-analysis designs. In addition, results from this IPDMA can be generalized to multiple populations as individuals from 12 countries around the world are represented in this sample. The restrictive criteria on using the PANSS exclusively allowed us to maximize the homogeneity of the results and enabled us to investigate the association between cannabis use and other symptom dimensions. Finally, the extraction of homogeneous outcomes allowed to perform a multivariate analysis, considered to be robust and reliable.[33]

This study also has some limitations. Indeed, no causal role of cannabis can be implied because of the cross-sectional nature of the analyses. In addition, not all relevant confounding factors could be included as such exhaustive datasets can rarely be collected. The influence of other illicit substances on psychopathology along with common socioeconomic or heritable factors could not be ruled out. Moreover, cannabis users as defined in this study included individuals with various frequencies of use. The binary variable used in the current study for cannabis use (yes or no) does not account for the potential dose–effect relationship between the frequency of use and the severity of symptoms. Also, there is large variability in symptom profiles encountered along the schizophrenia spectrum. In particular, individuals diagnosed with schizophrenia vs schizoaffective disorder present a few striking differences. In the latter disorder, individuals are more prone to experiencing affective symptoms such as depression or mania.[65] Interestingly, the risk for psychotic depression and bipolar disorder is increased by cannabis use.[66] Thus, while our results did not support an association between cannabis use and the depression/affect dimension, individuals with a schizo-affective disorder only accounted for 9% of the sample and were scattered across studies (Appendix, Table S2, p.4). Future studies should consider investigating this association in affective psychotic disorders. Finally, the counterpart of focusing on studies including the PANSS is the exclusion of studies that have used alternative scales to assess similar symptoms (such as the Brief Psychiatric Rating Scale, Scale for the Assessment of Positive Symptoms, or the Scale for the Assessment of Negative Symptoms). Hence, the clinical constructs investigated in this study are solely characterized through the lens of the PANSS and cannot be generalized to symptoms assessed via the mentioned alternative scales, as they convey considerable clinical differences.[67] Future studies should consider extending these results to related symptoms as characterized in these other scales. Moreover, future research could consider replicating these results using scales that deeply assess specific symptom dimensions. The reported results thus must be interpreted in the context of these limitations.

Considering previous knowledge along with the current findings on positive and excitement dimensions, raising public health awareness on the harmful effects of cannabis is appropriate. Indeed, a high severity of these symptoms tends to disrupt the therapeutic alliance and puts individuals with schizophrenia spectrum disorders who are using cannabis especially at-risk for the discontinuation of their treatment and poor clinical outcomes.[13] However, the lower severity of negative symptoms for cannabis-users cannot be ignored. The presented results support both the self-medication and toxicity hypotheses of cannabis use, with differential effects on positive and negative symptoms. More longitudinal designs are needed to fully understand the role of cannabis use on symptom dimensions. In addition, the composition of cannabis needs to be acknowledged as its two main components, THC and CBD, were shown to have differential impacts on healthy individuals, THC inducing both positive and negative symptoms.[68] A recent review highlighted the need for trials to investigate this issue among patients with schizophrenia, as the few available trials are insufficient to bring evidence for an effect of THC or CBD on the global symptomatology in this population mainly due to the high heterogeneity between trials (e.g., in dose, length of treatment).[69] The presented findings reflect the complexity of the interaction between cannabis use and the symptomatology of schizophrenia spectrum disorders and allowed to disentangle its association with multiple symptom dimensions. Its opposite association regarding negative and positive symptoms provides interesting perspectives for future longitudinal designs and clinical trials.

Contributors

Each author contributed to the current article according to the following description: Conceptualization: BR, GS, MA, MN. Data collection: MA, GS, BR, MN, JB, GB, MS, RR, TS, PR, OA, JA, PB, AB, TW, TSA, DH, RVB, JM, VR, KK, JC, FS, GRC, SA, CH, HT, EK. Data curation and check of the underlying data: MA, MN. Formal analysis: MA, MN. Investigation: MA, BR, GS. Methodology: MA, MN, GS, BR, JB. Supervision: BR, GS. Writing and editing/reviewing: MA, GS, BR, MN, JB, EF, RJ, GB, MS, RR, TS, PR, OA, JA, PB, GD, AB, TW, TSA, DH, CM, RVB, JU, JM, VR, GM, KK, MR, JC, PT, FS, GRC, SA, CH, HT, EK, LA. All authors reviewed, edited, and approved the final version of the manuscript.

Data sharing statement

The dataset used in this study can be made available to researchers who provide a justified hypothesis and after the signing of a dataset user agreement. Specifically, the dataset from Stellenbosch University is not readily available due to ethical and legal restrictions. Requests to access this dataset should be directed to Laila Asmal (laila@sun.ac.za). The authors are open to collaborating and sharing data within the limits of ethical review restrictions and data transfer policies of Stellenbosch University.

Declaration of interests

OA received consulting fees from Cortechs. ai, and payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Janssen, Sunovion, Lundbeck (all to him personally). EF received consulting fees; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events; support for attending meetings and/or travel; participation on a Data Safety Monitoring Board or Advisory Board from Boehringer-

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102199.

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