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The association between cannabis use and paranoia: Meta-analysis of experimental and observational studies

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ABSTRACT

Paranoia is common and has negative implications at clinical and societal levels. Cannabis may cause paranoia, although conflicting evidence exists. We reviewed studies on the association between cannabinoid use and paranoid symptoms. PubMed was searched from inception to July 2023, seeking experimental and observational studies that measured paranoid symptoms with specific assessments. Data of 13 studies (n = 13.559 participants) were pooled using Bayesian Model-Averaged Meta-Analysis, hierarchical Bayesian meta-analyses and Robust Bayesian Meta-Analysis. Effect size measures were Standardized Mean Difference (SMD) or Odds Ratio (OR). Five experimental studies showed that participants receiving cannabinoids developed more severe paranoid symptoms than those receiving placebo (SMD = 0.47; 95 % CI, 0.13 – 0.48, Posterior Probability of Inclusion, PPI: 94 %). Studies using TCH-prevalent cannabinoids detected higher effects than those administering mixed THC-CBD or CBD- prevalent cannabinoids. In four cross-sectional studies from the general population, the odds of displaying paranoid symptoms in cannabinoid users was higher than in non-users (OR: 1.75, 95 % CI, 1.43–2.07, PPI: 99 %), with effects increasing with the percentage of males in the sample. The pooled effect was not significant in studies recruiting patients with psychiatric disorders. Results of three prospective studies also suggest that cannabis is associated with the subsequent onset of paranoid symptoms. In conclusion, converging evidence from experimental and observational studies suggest that cannabinoids are associated with, and may cause paranoid symptoms. Preventive and therapeutical actions may be warranted, considering the implications of paranoia, and the dramatic increase in cannabis use worldwide.

1. Introduction

Paranoia has negative consequences at the clinical (Freeman, 2016), pre-clinical (Arribas et al., 2024) and societal (Neidhart et al., 2024) levels. Manifestations of paranoia range in severity from persecutory delusions - seen during the course of major psychotic illnesses - to paranoid symptoms as heightened suspiciousness and interpersonal hypersensitivity, especially common, but not exclusive to youth. Paranoid symptoms, including suspiciousness and mistrust, can deteriorate interpersonal functioning, hinder work and academic performance, even result in social withdrawal (Bebbington et al., 2013; Freeman et al., 2005). Paranoia can also impact on health-related decisions, like reducing help-seeking for medical and mental health issues, or impede the receipt of healthcare interventions. Notably, paranoid and conspiracy-related ideas contributed to the recent widespread refusals of vaccines during the recent COVID-19 pandemic (Freeman et al., s.d)

Paranoia has multiple causes, largely rooted in social and environmental factors, such as familial ties (Sood et al., 2022; Freeman and Loe 2023), bullying (Singham et al., 2017) or virtual social interactions (Suthaharan and Corlett, 2023). However, it is common knowledge that substance use, particularly cannabis, might also cause or exacerbate paranoid symptoms (Talbott, 1969). This effect is supported by studies examining participants after cannabinoid administration (Freeman et al., 2015), but also retrospective and prospective reports investigating

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the levels of paranoid experiences among cannabis users (Freeman et al., 2013; Sharma et al., 2021).

Research into the link between cannabis and paranoia dates back to early reports (Talbott and Teague, 1969) suggesting a potential causal effect. Since then, the association between cannabis use and psychotic disorders has been extensively studied (Di Forti et al., 2019; Hasan et al., 2020) but paranoia has received comparatively less attention, and has rarely been considered as a distinct or main study outcome. This historical bias may have limited our understanding of paranoia-specific mechanisms and epidemiological trends, despite potentially far-reaching implications for both clinical and general populations.

Cannabis use is in fact peaking at a global scale: in Europe, around 8 % (22.6 million) of adults aged 15–64 have reported using it in the previous year (Manthey et al., 2021). Its legalization is leading to further increases, although with possible differences according to age groups (Hasin et al., 2023; Anderson et al., 2024). Also, the introduction of novel cannabis-based products, such as synthetic cannabinoids, delta-8 tetrahydrocannabinol and high-potency extracts, raises concern for their possible acute and chronic effects, which also include a wide array of paranoid experiences (Zangani et al., 2020; LoParco et al., 2023). Such reactions may be particularly frequent and severe, including risk of harm to the self- and others (Hobbs et al., 2018; Escelsior et al., 2021). Finally, there may be dramatic differences in terms of physical and psychological effects of cannabinoids, according to their type, "potency" or composition in THC, CBD and other active principles (Solmi et al., 2023; Murray et al., 2016). In particular, CBD use may cause lower rates of paranoia than THC, or even counteract the onset of paranoia due to THC (Englund et al., 2013). Cannabis is often used by individuals with established mental health issues or risk for specific disorders. In addition cannabinoids, especially strains with high CBD content, have been considered as a potential intervention for specific conditions, such as autism (Aran and Cayam Rand, 2024; Solmi et al., 2023). If it was confirmed that cannabinoid use is associated with paranoia, or causes increases of paranoid symptom severity, this would have far-reaching societal and clinical implications.

The aim of this study was to review the available evidence on the association between cannabinoid use and paranoia, including both experimental and observational studies.

2. Methods

This review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Page et al., 2021).

2.1. Eligibility criteria

Eligible studies were written in English, reporting on at least one assessment of participant cannabinoid use. We used an inclusive approach for assessment (self-, observer-report or toxicological examination), type (hashish, Marijuana, synthetic cannabinoids or others), composition (prevalence or percentage of THC, CBD and other active principles) route (smoked, intravenous (IV), inhaled, enteral) and pattern of use (lifetime, daily, occasional use, current vs past use). To be included, studies had to report at least one assessment of paranoia and/or paranoid symptoms, either defined by standardized diagnostic criteria or a standardized definition or assessment (e.g. rating scale severity scores), while we excluded those reporting only on positive symptoms. We required a measure of association between cannabinoid use and paranoid symptoms or disorders: for instance, we excluded those reporting only on associations with substance use defined generically, or other substances. Inclusion was not restricted by study design: experimental (e.g. randomized studies of cannabis administration in healthy subjects) or observational (e.g. cross-sectional, case-control or prospective design). We did not impose restrictions based on the recruitment setting or characteristics of the included populations (e.g. healthy subjects, individuals with Cannabis Use Disorder (CUD) or psychiatric disorders). However, we planned to conduct sensitivity analyses based on participant characteristics.

2.2. Search strategy

Eligible studies were identified searching PubMed with search terms related to cannabis and paranoia (search string in the supplement par. **S1.1**). The search period covered from inception to July 1st, 2023.

2.3. Selection process

Two independent reviewers (S.Ce. and S.Ca.) independently screened the title and abstract of retrieved citations, then the full-texts of potentially relevant articles. Conflicts were solved by discussion and consulting a third reviewer (F.F.). The bibliographies of retrieved studies were also checked for additional eligible citations. We managed the screening process using the Rayyan literature review software (Ouzzani et al., 2016).

2.4. Data extraction

We coded studies by their design (Randomised Controlled Trials (RCTs), cross-sectional, longitudinal and case-control studies). For each study, three reviewers (S.Ca., S.Ce and A.M.) independently extracted data: study characteristics (author, year of publication, country of origin, study design); sample size, setting of recruitment; participant characteristics (gender composition, mean age), presence/absence of psychiatric disorders, medical illnesses; cannabinoid use assessment, type and composition (ratio of THC to CBD content, percentage of THC or CBD), route of administration, timing of exposure (for experimental use), pattern and frequency of use (for observational studies), diagnostic criteria of paranoid disorders; rating scale to assess paranoid symptoms.

2.5. Risk of bias assessment

Two review authors (S.Ca. and S.Ce) assessed the risk of bias independently using the 2018 version of the Mixed Methods Appraisal Tool (MMAT) (Hong et al., 2018). Discordances were solved by discussion with a third author (A.M.). The MMAT assesses the methodological quality for systematic reviews of mixed studies (i.e. qualitative, quantitative and mixed methods studies). The five key MMAT criteria are: appropriate randomization, comparability of baseline groups, completeness of outcome data, blinding of outcome assessors, and adherence of participants to assigned interventions. Reviewers independently assessed the risk of bias of all selected articles using the MMAT rating each item as "*addressed*", "*partially addressed*" or "*not addressed*". A score of to each of the eleven items as follows: 1 = 'yes'; 0 = 'can't say/partially' or 'no', for a total score ranging from 0 to 5. Studies with MMAT scores lower than three were considered at high risk of bias.

2.6. Effect measures and synthesis methods

For quantitative analyses of the strength of the association between cannabis use and paranoia, we extracted and pooled measures of association (Standardized Mean Difference, SMD and Odds Ratio, OR), based on study design (details in **Supplement Paragraph S2**) whenever the number of studies allowed it (2 or more). Meta-analyses were conducted within a Bayesian framework. We pooled study results using the Bayesian Model-Averaged (BMA) Meta-Analysis based on the *metaBMA* R package 0.6.9 version (Gronau et al., 2021). This approach averages over a fixed-effect meta-analysis (assuming no between-study heterogeneity of the true effect "d") and a random-effect model (assuming the effect is normally distributed across studies, with a standard deviation "tau" representing between-study heterogeneity). The BMA

Meta-Analysis takes into account what model (fixed or random) is more likely given the data and computes an estimate giving more weight to the model supported by stronger evidence. BMA Meta-analysis uses empirical prior distributions based on the Cochrane Database of Systematics Reviews. It has favourable properties such as taking in account the uncertainty of estimates, discriminating between evidence of absence of an effect, from an absence of evidence (inconclusive data). Given the high expected heterogeneity across studies, we chose the Bayesian model-averaged approach to adaptively balance fixed- and random-effects models—thus providing more reliable estimates of uncertainty in meta-analytic estimates (Gronau et al., 2021).

For each meta-analysis we report the mean and median estimate, its 95 % Credible Interval and the Posterior Probability of Inclusion (PPI), i.e. the probability the estimated effect is non-zero. Model-Averaged meta-analysis assume that each study effect is independent, thus in the main analyses we removed effects from the same study (Gronau et al., 2021). However, we conducted sensitivity, subgroup and meta-regression analyses to fully use their information.

To examine the role of methodological and clinical factors, we conducted a series of meta-regressions with the 2.21.0 version of *brms* (Bürkner, 2017). This approach is based on a hierarchical random-effect model, and allows to retain multiple effects from the same study as well as modelling the effects of continuous, categorical and ordinal predictors (moderators) with monotonic effects (Bürkner and Charpentier, 2020). For each group of meta-analyses modelled the effects of sample size, population type (healthy participants vs. suffering from mental disorders vs. medically ill), sample mean age, percentage of females, cannabinoid composition (ordinal variable: low or none THC vs. mixed CBD and THC vs. THC prevalent), methodological quality. For each predictor we report the probability that it is positively or negatively associated with the effect size (Makowski et al., 2019).

We assessed reporting and small-study bias by inspecting the Funnel Plot, conducting the Egger test and evaluation with the Robust Bayesian Meta-Analysis approach (Maier et al., 2023). This approach quantifies evidence in favour of the absence of publication bias, and performs well under high heterogeneity. It combines inference from PET-PEESE and an ensemble of 36 selection models (PSMA), providing bias-adjusted robust estimates.

The overall confidence in the evidence provided by studies was adjudicated by considering the level of evidence for each design type (RCTs were considered more indicative of cannabis – paranoia causality than cross-sectional studies), the level of uncertainty provided by meta-analyses/sensitivity analyses and the difference between model-averaged estimates and bias-corrected estimates.

3. Results

3.1. Study selection

The study selection process is summarized in the PRISMA flow diagram (Fig. 1, Supplementary Tables S1, S2). The search string yielded 229 articles that were screened for inclusion on the basis of their titles, abstracts or the full text. The total final number of included studies was 16, of which seven had an experimental design (RCTs), six cross-sectional and three prospective design. The total number of participants was 14.750.

According to the MMAT all seven experimental studies scored higher than three, indicating that none were at high risk of bias; among cross-sectional studies, one was classified at high risk of bias. Among prospective studies, one was at high risk of bias (Supplementary Tables S3, S4 and S5).

3.2. Experimental studies

3.2.1. Study characteristics

Seven experimental studies (Table 1) reported the effects of cannabinoid administration on paranoia based on a RCT design, with a total number of 449 participants (Drennan et al., 2021; Englund et al., 2013; Freeman et al., 2015; Gibson et al., 2022; Hundal et al., 2018; Spindle et al., 2020; Aragona et al., 2009). Among participants, 121 were included in THC-only cannabinoid studies, 32 in CBD-only studies, and 296 in studies using both THC- and CBD-based cannabinoids. No study examined synthetic cannabinoids or delta-8 THC.

Five studies included participants from the general population with previous cannabis use, one recruited participants with multiple sclerosis and one with subclinical paranoia. With the exception of the study on MS patients, the mean age was of young age, around 30 years. Participants were balanced in terms of gender. No study was at high risk of bias.

Paranoia was assessed using various measures, ranging from the SCL-

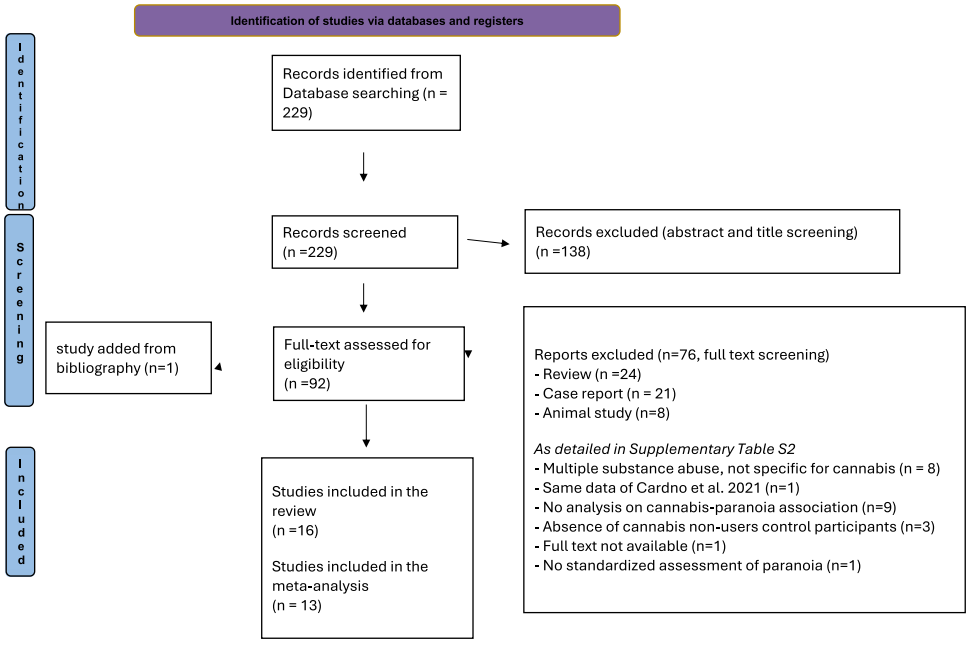

Fig. 1. PRISMA flow chart.

Table 1
RCTs examining the effects of the administration of cannabinoids on paranoia.

Study	Sample size, mean age, % females	Study design (duration, arms, allocation concealment, delay[a])	Interventions (compounds [active or inactive controls], doses)	Paranoia measure	Main findings; Risk of Bias (RoB) score
Aragona et al., (2009)	n = 17 Multiple Sclerosis patients; mean age: 49.8 (6.6); %F: 65 %	Crossover RCT, double-blind; 3 weeks intervention, 2 weeks washout	1) Sativex (Δ−9-THC 27 mg/mL, CBD 25 mg/mL) sublingual spray 2) Placebo sublingual spray	Symptom Checklist−90 (SCL−90) "paranoid ideation"	No significant difference in paranoid ideation or cognitive impairment in Sativex arm vs placebo groups. Positive correlation between blood THC levels and paranoia scores (z = 0.36, P = 0.72).
Englund et al., (2013)	n = 48 previous CU > 1 lifetime; mean age: 25.5 (3.5); %F: 44 %	Between-group RCT, double-blind, First assessment *after 3 h from CBD/Placebo, second assessment 2 h* after THC	*Pretreatment CBD 600 mg vs placebo (baseline) 1st paranoia assessment comparison:* 1) Oral CBD (600 mg) 2) Placebo *THC 1.5 mg IV infusion (3.30 h after baseline) 2nd paranoia assessment comparison:* 1) CBD + IV THC (1.5 mg) 2) Placebo + IV THC (1.5 mg)	SSPS	CBD + THC had lower SSPS scores than Placebo + THC: CBD pretreatment inhibited THC-elicited paranoia. Episodic memory (Hopkins Verbal Learning Test-Revised) was higher in the CBD group, as PANSS (Positive and Negative Syndrome Scale) positive score, although not statistically significant.
Freeman et al., (2015)	n = 121 CU; mean age: 29.7 (8.9); %F: 43.8 %	Between-group RCT, double-blind, over 3 h	1) THC (Dronabinol, 1.5 mg) IV 2) THC IV + 5 min educational module preparing participants to the effects of THC (cognitive awareness) 3) Placebo IV	1) Baseline: Paranoid VAS from six VASs; 2) 5 min after administration: hospital tour and reassessment with 6 VAS (Social Situation Paranoia); 3) 5 min in an immersive VR social environment, assessed with SSPS and VAS VR Hostile and PANSS Suspiciousness item 4) CAPE referred to overall experience Outcome measure: Principal Component Analysis (PCA) score of 6 measures of paranoia	THC significantly increased paranoia compared to Placebo (THC coefficient = 0.91, SE = 0.43, t = 2.15, P = .034). Addition of Cognitive Awareness module was associated with higher paranoia scores (not stat. significant, p = 0.25) THC also increased CAPE self-reported anomalous experiences and negative affect (acting as full mediators of the effect on paranoia) and decreased working memory (not acting as mediator). The cognitive awareness module decreased component 8 (catastrophizing and jumping to conclusions).
Hundal et al., (2018)	n = 32 with subclinical paranoia (Green Paranoid Thoughts Scale Part B score >21), mean age: placebo 25 (8); CBD 26 (9); %F: 50 %	Between-group RCT, double-blind, over 3 h	130 min prior to entering VR: 1) CBD capsules (600 mg) vs. 2) Placebo Then, 4 min session of immersive social VR environment.	SSPS upon exit from VR session; CAPE; University of Wales Institute of Science and Technology Mood Adjective Checklist (UMACL); Beck Anxiety Inventory (BAI); MATRICS Consensus Cognitive Battery (MCCB); cortisol	Single dose of CBD (600 mg) increased anxiety and paranoia but not significantly. SSPS scores were higher but not significantly in the CBD arm (p = 0.15). Statistical trend for a Session × Treatment interaction on BAI scores, higher under VR following CBD (p = 0.09). No effect of CBD on arousal, hedonic tone, cognitive functions, physiological measures.
Spindle et al., (2020)	n = 18 with past CU but no cannabis use for ≥ 30 days prior to study; mean age: 31; %F: 50 %	Crossover RCT, double-blind, over 3 h (8 h total)	1) 100 mg oral CBD and vaporized placebo cannabis; 2) oral placebo and 100 mg vaporized CBD; 3) oral placebo and vaporized CBD-dominant cannabis (100 mg CBD, 3.7 mg THC); 4) oral placebo and vaporized placebo cannabis	21 VAS item Drug Effect Questionnaire (subjective effects); Divided Attention Task (DAT); Digit Symbol Substitution Task (DSST); Paced Serial Addition Task (PASAT); blood pressure and Heart rate; blood THC and CBD levels	Repeated measure analysis did not reveal significant group x time interactions between CBD (vaporized or oral) and placebo for paranoia ratings. CBD-dominant cannabis with low THC was associated with stronger pleasant subjective effects and increased heart rate. Similar cognitive and physiological effects across dosing conditions.
Drennan et al., (2021)	n = 54 CU ≤ 4/month plus previous high-potency CU; mean age: THC-D 29.86 (8.7), CBD-D 29.88 (10.5); %F: 42.9 % (THC-D), 53.8 % (CBD-D)	Between-group RCT, double-blind, 5-day ad libitum use, 1 day off, measures taken while acutely intoxicated and after 1 h	1) THC-D (84.99 % THC + THCa, <1 % CBD) Inhaled 2) CBD-D (74.7 % CBD, 4.1 % CBDa, 4.5 % THC + THCa) Inhaled	Profile of Mood States (POMS) revisited; item paranoia	THC-D group showed higher intoxication and paranoia immediately after use, returning to baseline within an hour, vs CBD-D. CBD-D group had more positive mood effects and reduced intoxication, lower side effects than THC-D. Paranoia induced by THC was short-lived.

(*continued on next page*)

Table 1 (*continued*)

Study	Sample size, mean age, % females	Study design (duration, arms, allocation concealment, delay[a])	Interventions (compounds [active or inactive controls], doses)	Paranoia measure	Main findings; Risk of Bias (RoB) score
Gibson et al., (2022)	n = 159 CU > 4/month plus previous high-potency CU 4/month; mean age: 36, %F: 40.9 %	Between-group RCT, double-blind, 5-day ad libitum use, 1 day off, measures taken acutely intoxicated and after 1 h.	1) THC-D (24 % THC, 1 % CBD) orally; 2) Mixed THC + CBD (9 % THC, 10 % CBD) orally; 3) CBD-D (1 % THC, 23 % CBD) orally	POMS revisited; item paranoia	THC-D reported higher paranoia and anxiety compared to both mixed THC+CBD and CBD-D groups. Also, THC-D had higher plasma THC levels. Authors argued that CBD compound levels may reduce THC plasma levels and mitigate the negative psychotomimetic effects of THC

Abbreviations:
RCT = Randomized Controlled Trial; Δ-9-THC = Delta-9-tetrahydrocannabinol; CBD = Cannabidiol; THC = Tetrahydrocannabinol; CU = Cannabis Users; SSPS = State Social Paranoia Scale; VAS = Visual Analogue Scale; VR= Virtual Reality; VAS VR Hostile = Visual Analogue Scale for Virtual Reality Hostility; CAPE = Community Assessment of Psychic Experiences; THC-D: THC-dominant; CBD-D= CBD-dominant; THCa = Tetrahydrocannabinolic Acid; CBDa = Cannabidiolic Acid; IV: intravenous

[a] delay between cannabinoid administration and paranoia measurement

90 "Paranoid Ideation" subscale, the SSPS, a Visual Analogue Scale, the PANSS Suspiciousness item, or the CAPE subscale. Only four studies used a measure of paranoia as the primary outcome, three of which using assessment instruments specific for paranoia.

Across the seven RCTs, four featured a THC-only or THC-dominant arm (Freeman et al., 2015; Englund et al., 2013; Drennan et al., 2021; Gibson et al., 2022), four included a CBD-only or CBD-dominant arm (Englund et al., 2013; Hundal et al., 2018; Spindle et al., 2020; Gibson et al., 2022), and three tested mixed THC–CBD formulations (Aragona et al., 2009; Spindle et al., 2020; Gibson et al., 2022). Across studies the THC doses ranged from a single 1.5 mg oral (dronabinol) or intravenous THC dose (Freeman et al., 2015; Englund et al., 2013) up to ad libitum use of very high-potency cannabis with around 85 % THC (Drennan et al., 2021). CBD doses similarly varied from 100 mg (Spindle et al., 2020) to 600 mg (Englund et al., 2013; Hundal et al., 2018) in single-administration designs, as well as ad libitum use of high-CBD

Table 2
Meta-analyses of the association between cannabis use and paranoia (RCTs and cross sectional studies).

Randomized clinical trials (SMD)	Mean	sd	95 % CrI low	median	95 % CrI high	PPI	k
Paranoia in cannabinoid (any) vs placebo[a]	**0.472**	**0.126**	**0.180**	**0.484**	**0.690**	**93.5 %**	**5**
Robust estimate	*0.370*		*0.000*	*0.430*	*0.630*	*86.2 %*	*5*
Sensitivity analysis; healthy population[b]	0.435	0.172	0.042	0.450	0.757	77.9 %	3
THC- vs CBD-cannabinoids	**0.409**	**0.215**	**−0.048**	**0.414**	**0.843**	**67.6 %**	**2**
CBD-cannabinoids vs placebo	**0.404**	**0.139**	**0.067**	**0.422**	**0.633**	**86.1 %**	**3**
Mixed THC-CBD cannabinoids vs placebo	**0.303**	**0.182**	**−0.114**	**0.313**	**0.629**	**60.3 %**	**2**
Meta-regressions (cannabinoid vs placebo)	*B*	*SE*	*95 % CrI low*		*95 % CrI high*	*PPI*	*k*
Sample size	*0.003*	*0.004*	*−0.004*	-	*0.01*	*87.0 %*	*6*
Age	*−0.00*	*0.06*	*−0.12*	-	*0.11*	*52.5 %*	*6*
Percentage of females	*−0.01*	*0.07*	*−0.15*	-	*0.12*	*62.8 %*	*6*
Mixed THC-CBD vs CBD-only[c]	*0.48*	*0.29*	*0.02*	-	*0.97*	*100.0 %*	*6*
THC-only vs Mixed THC-CBD[c]	*0.48*	*0.29*	*0.02*	-	*0.97*	*100.0 %*	*6*
Route: IV vs inhalation	*0.30*	*0.36*	*−0.43*	-	*1.03*	*85.5 %*	*6*
Route: oral vs inhalation	*0.01*	*0.16*	*−0.31*	-	*0.32*	*52.3 %*	*6*
Methodological quality	*−0.05*	*0.40*	*−0.80*	-	*0.81*	*60.0 %*	*6*
Cross-sectional studies (OR)	**Mean**	**sd**	**95 % CrI low**	**median**	**95 % CrI high**	**PPI**	**k**
Paranoia; general population[d]	**1.745**	**1.098**	**1.432**	**1.751**	**2.071**	**98.7 %**	**4**
Robust estimate	*1.679*		*1.000*	*1.729*	*2.070*	*91.9 %*	*4*
Paranoia; psychiatric population[e]	**1.141**	**1.357**	**0.654**	**1.120**	**2.265**	**23.2 %**	**2**
Robust estimate	*1.012*		*0.519*	*1.000*	*1.463*	*17.6 %*	*2*
Paranoia in cannabis users vs non-users (all studies)[f]	1.715	1.404	0.890	1.673	3.857	71.5 %	6
Meta-regressions	*B*	*SE*	*95 % CrI low*	-	*95 % CrI high*	*PPI*	*k*
Sample size	*−1.95e−05*	*0.0001*	*−0.0003*	-	*0.0002*	*58.0 %*	*8*
Age	*0.014*	*0.020*	*−0.023*		*0.053*	*76.0 %*	*8*
Percentage of females	*−0.026*	*0.0093*	*−0.045*	-	*−0.008*	*100.0 %*	*8*
Sample with psychiatric disorders	*0.303*	*0.482*	*−0.607*	-	*1.274*	*73.0 %*	*8*
Methodological quality	*−0.356*	*0.490*	*−1.346*	-	*0.640*	*81.0 %*	*8*

Posterior Probability of Inclusion (PPI) or Probability of Direction (PD)

[a] this analysis is conducted on independent effects, thus we excluded one effect from the study of Spindle et al., (2020) [CBD-only cannabinoid] and kept the effect relative to the comparison between CBD- and THC- cannabinoid (#3 in Table 1)

[b] this sensitivity analysis excludes the effect from the study examining patients with multiple sclerosis (Aragona et al., 2009), and one study on individual with high levels of subclinical paranoia (Hundal et al., 2018)

[c] monotonic ordinal predictor (levels: CBD-only, Mixed THC-CBD, THC-only). The positive value of the predictor indicates that increasing concentrations of THC were associated with a higher effect size;

[d] this analysis retains only studies conducted in the general population, excludes one study from juvenile detention [Colins et al., (2009)], two effects from psychiatric samples [Newman-Taylor et al., (2020) and Boydell et al., (2007)]

[e] this analysis is conducted on effects obtained from psychiatric samples [Boydell et al., (2007) and Newman-Taylor et al., (2020)]

[f] this analysis is conducted on independent effects, thus we excluded one effect from the study of Colins et al., (2009) [past year cannabis use] and one from Newman-Taylor et al., (2020) [psychiatric sample]

preparations (e.g., ~75 % CBD; Drennan et al., 2021). Balanced or mixed THC–CBD formulations ranged from oromucosal spray (Sativex) containing 27 mg/mL THC and 25 mg/mL CBD (Aragona et al., 2009) to herbal cannabis at approximately 9–10 % THC/CBD (Gibson et al., 2022).

3.2.2. Results of meta-analyses

Five studies compared cannabinoids with placebo. All but one (Aragona et al., 2009) found that cannabinoid administration caused significantly higher levels of paranoia than placebo. In line with the high expected heterogeneity across studies, model averaged meta-analyses relied more on random-effect models, as reflected in distinctly broader credibility intervals (Table 2). The pooled effect suggested that individuals receiving cannabinoids displayed levels of paranoia about half standard deviation higher than those receiving placebo (k = 5; SMD: 0.47; 95 % CrI: 0.180–0.690, PPI 94 %, Fig. 2). Inspection of the funnel plot asymmetry and the result of the Egger test (Intercept: −2.99; SE: 1.31; p = 0.08) suggested the possibility of small study effects (Figure S6). The PSMA analysis, however, suggested that asymmetry was likely due to heterogeneity. The bias-corrected robust estimate was lower, but still significant at the 95 % credibility level (SMD: 0.271, 95 % CrI: 0.000–0.630, PPI 86 %) (Figure S1). Excluding effects from patients with multiple sclerosis and with subclinical paranoia did not significantly affect the results. Two studies directly compared THC-prevalent vs CBD-prevalent cannabinoids, with a less credible difference in levels of paranoia (k = 2; SMD: 0.409, 95 % CrI: −0.048–0.843, PPI 68 %) (Figure S2). Three studies directly compared CBD-prevalent cannabinoids vs placebo, suggesting that those receiving CBD displayed higher paranoia than those receiving placebo (k = 3; SMD: 0.404, 95 % CrI: 0.067–0.633, PPI 86 %) (Figure S3). Finally, two studies directly compared mixed THC-CBD cannabinoids vs placebo with a non-significant effect (k = 2; SMD: 0.303, 95 % CrI: −0.114–0.629, PPI 60 %) (Figure S4).

Meta-regression analyses suggested that the magnitude of the effect of cannabis on paranoia increased with larger sample sizes (PPI: 87 %, Fig. 2). The effect was also larger among studies administering cannabinoid that contained exclusively THC, than those using mixed THC-CBD content, and the latter yielded higher effects than studies based on CBD-only cannabinoids (PPI of both monotonic effects of 100 %). There was a higher probability to observe a higher effect on paranoia in studies with IV route of administration, compared to the oral route (PPI: 85 %).

3.3. Cross-sectional studies

3.3.1. Study characteristics

A total of six studies (Table 2) examined the association between cannabinoids and paranoia within a cross-sectional design, with a total number of 13.110 participants (1.751 users and 11.359 non-users) (Boydell et al., 2007; Cardno et al., 2021; Colins et al., 2009; Freeman et al., 2013; Mackie et al., 2021; Newman-Taylor et al., 2020). Of these, four studies recruited participants from the general population. Four studies did not exclude participants with psychiatric disorders, and in two cases provided data to compute effect sizes for this subpopulation.

Paranoia was assessed using different instruments including the Cross Paranoia Measure, the Operational Criteria Checklist for Psychotic Illness (OPCRIT), the DISC-IV interview, the Paranoid Thoughts Scale Part B (16 items), the Paranoia Scale (20 items), and the Specific Psychotic Experiences Questionnaire (SPEQ) for psychotic-like experiences (PLEs), consisting of 15 items. Only two studies employed assessment instruments that are specific of paranoia as the outcome, as opposed to a single or subset of items from a rating scale intended for other clinical

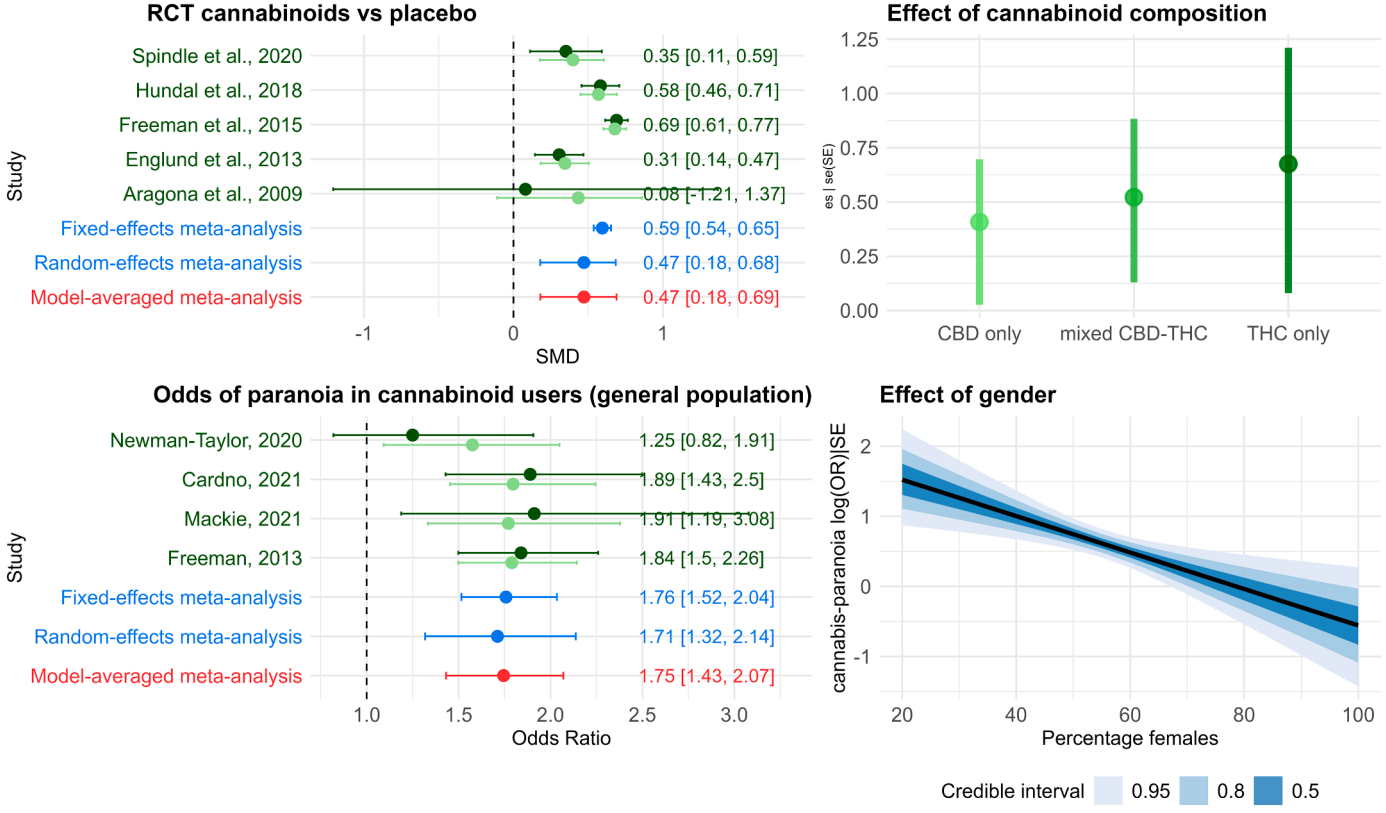

Fig. 2. Meta-analyses and meta-regressions of paranoia levels. Upper left panel. Forest plot of RCT of cannabinoid administration (cannabinoids vs placebo). Upper right panel. Meta-regression: cannabinoid composition (THC and CBD content) as a moderator of the effects of cannabinoids on paranoia in RCTs. Lower left panel. Forest plot of cross-sectional studies conducted on healthy participants. Lower right panel. Meta-regression: gender as a moderator of the association between cannabis use and paranoia.

dimensions (e.g. cannabis-related experiences, or psychotic-like experiences).

3.3.2. Results of meta-analyses

In samples from the general population, cannabis users had higher odds of displaying paranoia than non-users (k = 4; OR: 1.745, 95 % CrI: 1.430 – 2.071; PPI 98.7 %, Fig. 2). Inspection of the funnel plot asymmetry and the result of the Egger test (Intercept: 0.89; SE: 2.27; p = 0.71) did not suggest the probability of small study effects (Figure S7): similar results were obtained using robust estimates. In the two samples with psychiatric disorders, the association between cannabis use and paranoia was non-significant (k = 2; OR = 1.14, 95 % CrI: 0.654 – 2.265; PPI 23.2 %) (Figure S5). In the analysis of combined samples (general population and subjects with psychiatric conditions), the odds of paranoia in cannabis users was not significantly different from non-users, and associated with greater uncertainty (k = 6; OR: 1.715; 95 % CrI: 0.890 – 3.857; PPI 71.5 %). In meta-regression analyses, a higher percentage of females was associated with lower risk of paranoia induced by cannabinoid use (PPI 100 %, Fig. 2).

3.4. Prospective studies

Three studies investigated the association between cannabis use and paranoia prospectively (Albertella and Norberg, 2012; Mason et al., 2008; Sharma et al., 2021), with a total number of 1191 participants (1.829 users and 12.271 non-users) (Table 3).

Albertella et al. examined cannabis use and paranoia levels in adolescents before and after a residential treatment programme for substance use. They did not detect associations between changes of cannabis use and changes of levels of paranoia (Albertella and Norberg, 2012). Sharma et al. examined a cohort of adolescents over 5 years and found a dose-dependent relationship between cannabis use and increased risk of paranoid and schizotypal symptoms (Sharma et al., 2021). Mason and colleagues compared participants over two occasions 3–5 days apart (cannabis use vs. abstinence), and found that cannabis use at baseline was associated with an acute onset of psychotomimetic experiences including paranoia (Mason et al., 2008).

Paranoia was assessed using the Paranoia item of the Brief Symptom Inventory (BSI), the Paranoid and Schizotypal subscales of the Personality Questionnaire (PQ) and the paranoia subscale of the Psychotomimetic States Inventory (PSI). Only the study by Sharma et al., used an entire rating scale that is intended for paranoia."

4. Discussion

This meta-analysis examined the relationship between cannabis use and paranoia. Surprisingly few studies have examined this association, given the potential implications of paranoia as a social and clinical phenomenon, and the widespread, increasing use of cannabis. Nevertheless, pooled estimates from experimental and observational studies are largely convergent and suggest that cannabinoid use is associated with heightened paranoid symptoms, particularly among males from the general population, especially, but not exclusively, after use of THC-prevalent compounds. Whereas, this effect may be not generalizable to individuals with established mental disorders.

Numerous studies suggest a causal association between cannabis and psychosis (D'Souza et al., 2022) or depression (Gobbi et al., 2019), but the specific dimension of paranoid symptoms remained relatively understudied despite its importance. Paranoid symptoms are more complex to define and operationalize: they may range across an intensity continuum from interpersonal worries, to mistrust, ideas of reference and frank delusional thinking (Neidhart et al., 2024). The low end of severity in the spectrum of paranoid experiences are common in the general population, while the severe end is generally observed among individuals diagnosed with psychotic, personality and other disorders, and among those who will progress to develop such conditions (Ellett et al., 2023; Elahi et al., 2017; Freeman and Loe 2023). The manifestations of paranoia, irrespective of their severity, are associated with negative affect, low self-esteem and cognitive biases, such as thinking inflexibility and the tendency to jump to conclusions. Negative interpersonal experiences, like bullying or trauma, can predispose individuals to expect hostility from others (Sloan et al., 2024; Taylor et al., 2022; Sood et al., 2022) and maintain vicious cycles of distress and poor interpersonal and occupational functioning (Freeman et al., 2005; Garety et al., 2021).

Although the causes of paranoia are numerous and complex, this review suggests that: (1) cannabinoid administration within the experimental setting causes the onset of more severe paranoid experiences than placebo, and that (2) cannabinoid use is associated with an increased probability of observing paranoid symptoms cross-sectionally and longitudinally. Given the widespread, increasing use of cannabis, especially in adolescents (Gobbi et al., 2019), and the size of the effects detected by our meta-analysis (OR = 1.75 among cross-sectional studies), a prevalence of significant paranoid symptoms of about 5 % would translate to a large population fraction attributable to cannabinoids of 3.5 %. These estimates may be conservative, since people affected by more severe degrees of paranoia may avoid seeking help or to participate in studies, remaining unrecognized. Similarly, cannabis users may minimise self-report of use (King et al., 2024; Freeman and Loe 2023). To our knowledge, no study has yet quantified the extent of such selection bias. Also, the effects of contextual factors may not be specifically linked with the subjective effect of cannabis (Ayyagari et al., 2024)

The meta-analysis of RCTs found a credible, robust effect of cannabinoid administration on the development of acute paranoid experiences, across different modalities of administration – particularly intravenous, type of cannabinoid and assessment tools. Such results converge with those of cross-sectional studies conducted on the general population, and with the results of two out of three longitudinal studies. These findings may be considered initially supportive of a causal relationship between cannabis use and paranoia, but caution is advised due to the lack of other lines of evidence (e.g. Mendelian Randomization studies) (Treur et al., 2021) and the possibility of confounding by other common environmental factors responsible for both cannabis use and paranoia (Shakoor et al., 2015). Data from six RCTs provided some insight into the differential effects of THC- and CBD-based cannabinoids, suggesting that THC was more frequently and strongly associated with paranoia than CBD, which aligns with findings related to positive symptoms (Ganesh et al., 2020). The finding that CBD compounds, however, were also associated with the onset of paranoid symptoms, although to a lesser degree than THC-based ones, may be relevant for safety concerns on cannabinoids, both as recreative and medicinal agents. As shown by a recent umbrella review, CBD is considered generally safe from a mental health perspective, but its effects on paranoia had not been examined in detail yet (Solmi et al., 2023; Freeman et al., 2019). At this stage, however, we strongly advise caution before drawing firm conclusions, since this finding is based on a subgroup analysis of only three studies that drew direct comparisons between CBD and placebo, and there is limited general knowledge on the standardization of cannabinoid content and CBD-THC ratios to guide clinical management (Zeyl et al., 2020). Some studies even suggested that CBD administration may counteract the onset of THC-induced paranoia (Englund et al., 2013) and other psychotic symptoms, but others (Englund et al., 2023) and recent reviews failed to detect univocal pharmacologic interactions (Freeman et al., 2019), or clear protective effects against positive or negative symptoms (Hindley et al., 2020). Also, CBD could not reverse the acute brain effects of THC-dominant cannabinoids (Lorenzetti et al., 2023). Interestingly, when we considered the two studies comparing mixed CBD-THC cannabinoids vs placebo, we did not detect a significant effect on paranoia. Overall, CBD may be generally safer than THC inducing paranoia and psychosis, but available evidence does not suggest efficacy to treat cannabis-related

Table 3
Observational studies on cannabinoid use and levels of paranoia.

Cross-sectional studies

Study	Sample size, mean age, % females	Sample (Setting of Recruitment, Inclusion Criteria)	Inclusion of Psychiatric Disorders, Cannabis Use, Medical Illnesses (Yes/No)	Cannabis Measure	Paranoia Measure (n. items)	Type of Statistical Analysis for Paranoia; Contrast	Main findings
Boydell et al., (2007)	Total: 757; *Users:* 182 (24 %) Age: < 40 years 164 (90 %), Age: > 40 years 18 (10 %), Sex: 35 (10 %) F; *Non-users:* 552 (73 %) Age < 40 years 373 (68 %), Age > 40 years 175 (32 %), Sex: 294 (90 %) F; *Not classified:* 23 (3 %)	*Setting*: Camberwell Case Register, presented to psychiatric services with any possible psychotic illness between 1965 and 2004. *Inclusion Criteria:* Research Diagnostic Criteria (RDC) of schizophrenia	Yes, Yes, No	NA	Operational Criteria Checklist for Psychotic Illness (OPCRIT)	Univariate analysis; Logistic regression modelling Cannabinoid Users vs. non-users	No significant differences in presentation of paranoid delusions between c. users and non-users; Cannabis users had a greater tendency towards distraction, lower presence of organized delusions and abusive auditory hallucinations; No significant differences in family history of schizophrenia between the two groups.
Colins et al., (2009)	Total: 231; Age: 12–18 years, %F: 0 %, *Users*: 192 (83.1 %), *Non-users*: 39 (16.9 %)	*Setting*: Randomly selected from three Youth Detention Centres (YDC) in Flanders. *Inclusion criteria:* 1) Belgian or Moroccan origin, 2) in YDC for at least 1 month, 3) sufficient knowledge of Dutch.	Yes, Yes, Yes	Substance Use module of the Diagnostic Interview Schedule for Children, fourth edition (DISC-IV)	DISC-IV interview (5 items related to paranoia, 9 to other psychotic symptoms, 6 hallucinatory)	Logistic regression model; forward conditional selection method Cannabinoid users vs. non-users	Both lifetime and intense past year use of marijuana were associated with an increased likelihood of having paranoia experiences.
Freeman et al., (2013)	Total: 1713; Mean Age: 37.6 years (SD:17.4, median: 32.0 (18−95); %F: 55.8 % *Sub-sample of patients reporting mental illness*: Total: 260; Mean age: 39.73 (SD 13.06); %F: 36.7 %; *Users*: 38; *Non-users*: 22.	*Setting*: Individuals from the general population recruited via distribution of leaflets to local postcodes and local radio adverts in Oxfordshire, UK. Screening questionnaires completed online or by post.	Yes, Yes, No	self-report questions for cannabis use	Paranoid Thoughts Scale Part B (16 items)	Logistic regression; chi-square tests Cannabinoid Users vs. non-users	lifetime use of cannabis was associated with significantly higher levels of persecutory ideation vs non-use; The association of cannabis use with paranoia scores held after controlling for demographic variables. Estimated three point additional increase in paranoia scores associated with cannabis use in individuals with a family history of psychosis.
Newman-Taylor et al., (2020)	Total: 296; Mean age: 16.45 (SD:11.2); %F: 65 %; *Users*: 181; *Non-users*: 115. *Sub-sample of psychotic patients*: Total: 60; Mean age: 39.73 (SD 13.06); %F: 36.7 %; *Users*:	*Setting*: *Study 1.* General population sample recruited via university, public-access research, and crowd sourcing websites. *Study 2.* Subsample of cannabis-users *Study 3.* Psychotic patients recruited from community mental health	Yes, Yes, No	Cannabis-use items, including frequency and reasons for use	Paranoia Scale (20 items)	MANOVA, MANCOVA, mediation analysis, including variables like gender, history of childhood sexual abuse, age of first cannabis use, schizotypy, and using cannabis to cope with negative affect 1) recent cannabis use (past 3 months)	*Study 1:* levels of paranoia, psychotic-like experiences, and distress were higher in cannabis users compared to non-users. "cognitive fusion" coping mediated the relationship between cannabis use and paranoia *Study 2:* "cognitive

(*continued on next page*)

Table 3 (*continued*)

Cross-sectional studies							
Study	**Sample size, mean age, % females**	**Sample (Setting of Recruitment, Inclusion Criteria)**	**Inclusion of Psychiatric Disorders, Cannabis Use, Medical Illnesses (Yes/No)**	**Cannabis Measure**	**Paranoia Measure (n. items)**	**Type of Statistical Analysis for Paranoia; Contrast**	**Main findings**
	38; *Non-users*: 22.	services in southern England				vs. Non-use; 2) Cannabis Users lifetime vs. non-users	fusion" coping mediated the relationship between schizotypy and cannabis-related paranoia in users *Study 3:* No difference in paranoia between psychotic-users and non-users, but higher scores of psychosis. Mediation analyses were repeated based on self-medicating cannabis use (i.e. to manage negative affect). Self-medicating cannabis-users was associated with higher paranoia. This association was mediated by external attribution and cognitive fusion
Mackie et al., 2021	Total = 467 mean age 16.8 (SD 7 months), %F: 43.9 %; *Non-users* n = 323, Mean age 16.8 (0.76) %F: 57.9 % *Herbal only* n = 69, Mean age 16.9 (0.85), %F: 60.9 %; *Skunk only* n = 30, Mean age 17.0 (0.81) %F: 32.3 %, *Mixed* n = 45, Mean age 16.8 (0.76) %F: 51.1 %	*Inclusion criteria:* Students aged 16–17 years	No, Yes, No	Self-report questionnaire; Marijuana Motives Measure (MMM)	Specific Psychotic Experiences Questionnaire (SPEQ) (15 items) for PLEs	Latent class analysis to identify patterns of cannabis use, with support for three groups (herbal only 47.9 %, skunk only 20.8 %, mixed 31.3 %). ANOVAs and Chi-square tests examining the association between class and paranoid /psychotic experiences Cannabis users vs. non-users	Skunk-only use, but not mixed use was associated with increases of paranoia compared to non-cannabis use (OR = 2.45, 95 % CI = 1.29–4.63). Monthly cannabis use and consuming 2 or more joints on one occasion were associated with a 2-fold increase in hallucinations (OR = 2.2, 95 % CI = 1.0–4.8 and OR = 1.9, 95 % CI = 1.2–3.2). Cognitive disorganization also associated with skunk only, but not mixed use
Cardno et al., (2021)	Total: 9646; Mean age: 16.3 (SD 0.68); 55 % F; *Users*: 404; *Non-users*: 4692	*Setting*: Twins from the Twins Early Development Study (TEDS) assessed longitudinally across childhood and adolescence *Inclusion Criteria:* 1) born in England and Wales 2) born in 1994–1996,	No, Yes, No	Cannabis use within checklist for substance use	SPEQ (15 items) for PLEs	Examination of the strength of association between risk factors for schizophrenia and individual PLEs. Comparison between effects for individual PLEs vs clustered PLEs (paranoia plus hallucinations, plus negative symptoms, plus cognitive disorganization) Logistic regression analysis accounting for twin clustering Cannabis users vs. non-users	Cannabis use was associated with individual PLEs and clusters, along with bullying victimization, and lower life satisfaction. Cannabis use had the strongest effect sizes for co-occurring PLE groups with ORs between 2.61 and 3.15
Prospective studies							

(*continued on next page*)

Table 3 (*continued*)

Cross-sectional studies

Study	Sample size, mean age, % females	Sample (Setting of Recruitment, Inclusion Criteria)	Inclusion of Psychiatric Disorders, Cannabis Use, Medical Illnesses (Yes/No)	Cannabis Measure	Paranoia Measure (n. items)	Type of Statistical Analysis for Paranoia; Contrast	Main findings
Study	**sample size, mean age, % females, % diagnoses**	**Sample (Setting of Recruitment, Inclusion Criteria)**	**Study design (duration, arms, allocation concealment)**	**Cannabis measure**	**Paranoia measure (n. items)**	**Type of statistical analysis for paranoia**	**Main findings**
Albertella and Norberg, 2012	Total: 132 adolescents; %F: 33 %; Age: 16.7 years *Users*:132; *Non-users*: 0.	*Setting*: residential programme for adolescents *Inclusion criteria*: 1) adolescents 2) cannabis-like drug use as primary concern 3) completed at least 30 days of stay/treatment	Three months, with data collected at pretreatment and three-month follow-up.	1) cannabis frequency and quantity of use items, from the Brief Treatment Outcome Measure (BTOM) 2) Severity of Dependence Scale (SDS)	Paranoia item of the Brief Symptom Inventory (BSI)	1) Poisson regression 2) Generalized Estimating Equations (GEE) relationship between BSI domains and cannabis use	1) baseline levels of paranoia were associated with *lower* cannabis use after residential treatment 2) GEE did not detect associations between changes of cannabis use and changes of paranoia
Sharma et al., (2021)	Total: 775 families, 448 adolescents; %F: 29 %; Age: 11.40 (SD = 0.91) High Average Risk (HAR): 47.1 %, Low Average Risk (LAR): 52.9 %. *Users*: 95; *Non-users*: 353.	*Setting:* General population from metropolitan area *Exclusion criteria:* 1) parents with neurological disorder, psychosis, or sensory incapacity. 2) adolescents: family history of psychosis, sensory incapacity, physical disability, neurological disorder, Intelligence Quotient (IQ) < 80	At least 5 assessment of adolescents over 7–5 years follow up (from age 12–14–19) 20 % fathers with lifetime substance use disorder (SUD) diagnosis categorized as HAR and 80 % without categorized as LAR	Items from the Drug Use Screening Inventory (DUSI) Four frequency levels for analysis: no use to > 10 times/ month	Paranoid and Schizotypal Subscales of the Personality Questionnaire (PQ) at age 19	Multiple imputation, Poisson regression models to investigate the associations between TLI score, cannabis use, demographic covariates, and paranoid or schizotypal symptoms. Moderation of effect by a TLI for SUD	1) Higher frequency of cannabis use was associated with increased risk of both paranoid and schizotypal symptoms. 2) individuals who used cannabis 3–9 times per month or higher had significantly higher levels of paranoid symptoms (IRR = 1.42, p = 0.02; IRR = 1.51, p = 0.01) and schizotypal symptoms (IRR = 1.55, p = 0.02). 4) no significant interaction with TLI Frequency of cannabis use showed a dose-dependent relationship with increased risk of paranoid and schizotypal symptoms.
Mason et al., (2008)	Total: 284 young adult participants 140 current cannabis users at least once a month; %F: 37 %; Age: 24.2 (SD = 8) years 144 healthy controls (40 past users); %F: 47 %; Age: 23.7 (SD = 8) years	*Setting:* recruitment not specified; measurements at home *Exclusion criteria:* 1) personal history of diagnosed mental illness;	Cannabis users: baseline assessment during cannabis use; Follow up 3–5 days later, after 24 h abstinence: paranoia reassessment, drug history taking, urine test Controls: similar assessment matched with users, although no drug used at baseline	NA	Psychotomimetic States Inventory (PSI) paranoia subscale	Unbalanced Repeated-measures ANOVA design, with group (cannabis vs healthy) x time (drug taking vs not) interaction	Cannabis was associated with significant effect of inducing psychotomimetic experiences including paranoia

Abbreviations

NA: Not available; SD: Standard Deviation; MANOVA: Multivariate Analysis of Variance; MANCOVA: Multivariate Analysis of Covariance; ANOVA: Analysis of Variance; OR: Odds Ratio; PLEs: psychosis-like experiences; TLI:Transmissible liability index; IRR: Incidence Rate Ratio.

paranoia or other severe psychiatric symptoms (Black et al., 2019; Solmi et al., 2023; Escelsior et al., 2021).

Few studies have specifically examined the mechanisms of cannabis-related paranoia. One seminal study showed that cannabinoids induced paranoia by increasing negative affect and inducing anomalous experiences, rather than through acute cognitive-dampening effects (Freeman et al., 2015). Animal models show that cannabis influence impulse control and reward learning (Ferland et al., 2023), which may also contribute to the development of paranoia. The modulation of endocannabinoid system activity appears a major candidate mechanism

(Zuurman et al., 2010), considering its effects on multiple neurotransmitter systems, including dopamine (Kibret et al., 2023). Altered dopaminergic activity is often called into question, as it has been implicated in paranoia due to maladaptive social belief updating following ambiguous or meaningless observations (Nour et al., 2018; Barnby et al., 2020). Indeed, acute cannabis use was shown to reduce striatal connectivity, implicated in dopamine-related reward processing and learning, but its effects on phasic dopaminergic activity remain uncertain (Lorenzetti et al., 2023; Danielsson et al., 2021; Kamp et al., 2019). In contrast, chronic cannabis use has been associated with altered frontal connectivity and cortical thinning (Thomson et al., 2022; Md et al., 2021), but with less severe psychotomimetic effects (Ganesh et al., 2020). Further studies are needed to investigate individual factors that might predispose to developing paranoia acutely and chronically after cannabis use, and to confirm observations of any compound-dose-response relationship (Robinson et al., 2023; Md et al., 2021). Research could help clarify why cannabis use may lead to observe a variety of outcomes in different people, such as paranoia, depressive symptoms, reduced motivation and/or cognitive deficits, even self-harm (Ferland et al., 2023; Volkow et al., 2016; Figueiredo et al., 2020; Escelsior et al., 2021). Variations in individual vulnerabilities, or collider bias may explain why the association between cannabis use and paranoia was not significant in populations with established psychiatric disorders.

This meta-analysis is strengthened by robust analytic methods, although its reliability crucially depends on the methodologies and number of available studies. The sensitivity analyses and the consideration of publication bias support the general validity of the association between cannabinoids and paranoia. The heterogeneity of study populations, definitions and assessments of paranoia, the variability of cannabis use and time of onset, however suggest caution in the generalization of findings.

Further, robust research is warranted to provide confirmation of these findings. In particular, studies should employ assessment instruments that are detailed enough to account for the architecture of the paranoia construct (Neidhart et al., 2024) and specifically assess the effects of the array of available cannabinoid types, with particular focus on synthetic, delta-8 THC and high-potency compounds that are still largely understudied (Bonar et al., 2014). Finally, research is needed on the biopsychosocial determinants of the vulnerability towards paranoia among cannabis users.

5. Conclusions

Experimental studies on cannabinoid administration show consistent effects of increased paranoid symptoms among healthy individuals. This effect seems particularly robust with the use of THC-prevalent compounds, but was also detected with CBD. Findings from cross-sectional and longitudinal studies converge with experimental evidence suggesting that cannabis use is associated with increased levels of paranoid symptoms. These findings call for an urgent evaluation of the clinical and societal consequences of cannabinoids based on a rigorous scientific approach.

Author contributions

All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Belvederi Murri. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: Belvederi Murri, Folesani, Catania, Centra, Muscettola. Statistical analysis: Belvederi Murri

Role of the funder/sponsor

The supporting organizations had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Data access, responsibility, and analysis

Martino Belvederi Murri.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2025.106269.

Data availability

Data will be made available on request.

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