Brain, Behavior, and Immunity 135 (2026) 106517

Contents lists available at ScienceDirect

Brain Behavior and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Review Article

Regular cannabinoid use and inflammatory biomarkers: Systematic review and hierarchical meta-analysis

Martino Belvederi Murri [a,1,*], Riccardo Guglielmo [b,1], Alessio Zizzi [b], Angela Muscettola [a], Maria Giulia Nanni [a], Manuela Dall'Oro [b], Gianluca Serafini [b], Alberto Inuggi [b], Andrea Escelsior [b], Mario Amore [b], Luigi Grassi [a]

[a] Institute of Psychiatry, Department of Neuroscience and Rehabilitation, University of Ferrara, Italy
[b] Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, and Mother-Child, School of Medical and Pharmaceutical Sciences, University of Genoa, Italy

ARTICLE INFO

Keywords:
Cannabis
Inflammation
Cytokines
Psychosis
Addiction
Neuroinflammation
CBD
THC
Endocannabinoid
Immune system

ABSTRACT

Background: Cannabis use is rising, with both therapeutic and harmful uses that might involve inflammation. Preclinical studies and findings in humans are inconsistent. It remains unclear whether cannabinoids affect inflammation in healthy populations or individuals with psychiatric disorders. We examined the association between cannabinoid use and peripheral inflammatory biomarkers.

Methods: We systematically searched multiple databases from inception to October 2025. Eligible studies compared inflammatory biomarkers between cannabinoid users and non-users. Bayesian multilevel cross-classified *meta*-analyses were used to pool effect sizes, accounting for clustering within studies and biomarkers.

Results: We included 46 studies (54,382 participants); 190 effect sizes from 40 studies were pooled in three meta-analyses (n = 178 effects from cross-sectional and case-control studies, n = 2 prospective studies, n = 10 RCTs). In observational studies, cannabis use was associated with higher levels of anti-inflammatory (Standardized Mean Difference (SMD) = 0.298; 95% CrI, 0.052, 0.536, PD = 99%) and pro-inflammatory biomarkers (SMD = 0.166; 95% CrI, 0.122, 0.209, PD = 100%), with credible differences by demographic factors, study design, synthetic cannabinoids and recency of use. RCTs of cannabidiol suggested small increase of pro-inflammatory markers (SMD 0.15; 95% CrI, −0.07 to 0.36; PD 90.9%). No consistent effects were observed in prospective studies. There was no evidence of major publication bias.

Conclusions: Cannabinoid use is associated with concurrent pro- and anti-inflammatory modulation in non-medical populations, consistent with immunomodulatory effects rather than a uniform pro- or anti-inflammatory shift. Understanding the immunological impact of cannabinoids remains critical to anticipate long-term health consequences and guide therapeutic development.

1. Introduction

Cannabis use is increasing worldwide, particularly in youth, driven by changing legislation and reduced perception of risk (Connor et al., 2021; D'Souza, 2023). Despite this, the health and biological consequences of chronic cannabis exposure remain largely unknown (Hoch and Lorenzetti, 2020).

Cannabis occupies a paradoxical role in modern medicine and public health. On one hand, it is among the substances most consistently associated with psychiatric, cognitive, and functional harms (Curran et al., 2016; Volkow et al., 2016; Belvederi Murri et al., 2025); on the other, several of its components are being explored for a range of therapeutic applications, including pain, epilepsy, and inflammation (Solmi et al., 2023). This contrast has intensified interest in its immunomodulatory properties, which date back to first evidence of anti-inflammatory and analgesic effects (Berdyshev, 2000).

Cannabinoids modulate immune activity via CB1, CB2 and other receptors expressed on innate and adaptive immune cells. Preclinical studies have shown suppression of pro-inflammatory cytokines (e.g., Interleukin-6 (IL-6), Interleukin-1 beta (IL-1β), Tumour Necrosis Factor-

* Corresponding author at: Institute of Psychiatry, Department of Neuroscience and Rehabilitation, University of Ferrara, Via Fossato di Mortara 64a, 44121 Ferrara, Italy.
E-mail address: martino.belvederimurri@unife.it (M. Belvederi Murri).
[1] These authors contributed equally to this manuscript.

https://doi.org/10.1016/j.bbi.2026.106517
Received 21 May 2025; Received in revised form 12 February 2026; Accepted 21 February 2026
Available online 23 February 2026
0889-1591/© 2026 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

alpha (TNF-α)) but also upregulation of anti-inflammatory mediators (e.g., Interleukin-10 (IL-10)) (Giacobbe et al., 2021; Klein, 2005). First reports, however, were mostly based on studies in patients with chronic inflammatory diseases, such as multiple sclerosis (Lima et al., 2021), leaving uncertainty on the effects in healthy subjects. In addition, these effects may vary by compound, with Δ9-tetrahydrocannabinol (THC) showing both pro- and anti-inflammatory effects, and cannabidiol (CBD) generally regarded as an anti-inflammatory and immunomodulatory agent. Most evidence to date derives from in vitro or animal models of physical disease; translation to humans remains also largely unknown (Henshaw et al., 2021). Previous human studies have yielded conflicting or inconclusive results (Doggui et al., 2021; Moshfeghinia et al., 2024). Some report increases in cytokines or indices such as the Neutrophil-to-Lymphocyte Ratio (NLR), while others show no association or selective anti-inflammatory effects. Prior *meta*-analyses, however, were limited by narrow biomarker focus (e.g., only IL-6 or few other biomarkers) or inclusion of a small number of studies (Candeloro et al., 2025; Doggui et al., 2021; Moshfeghinia et al., 2024).

Peripheral inflammation is recognized as a cornerstone pathophysiological mechanism contributing to cardiovascular, metabolic, neurodegenerative, and psychiatric conditions (Furman et al., 2019; Miller, 2020; Thylur and Goldsmith, 2022). Given the widespread use of cannabinoids and their emerging therapeutic applications (Whiting et al., 2015), it is imperative from a public health perspective to clarify their impact on inflammation, yet this remains complicated by overlapping lifestyle factors, psychiatric comorbidity, and heterogeneous biological mechanisms. This study aimed to synthesize the association between regular cannabinoid use and peripheral inflammatory biomarkers in humans, integrating data across biomarkers, populations, and different study designs, and accounting for methodological and clinical sources of heterogeneity.

2. Methodology

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021).

2.1. Eligibility criteria

Eligible studies were observational and experimental, assessing the association between cannabinoid use and inflammatory biomarkers in peripheral blood, serum, or plasma (see Supplementary Paragraph S1 for the full search strategy) of physically healthy participants, participants with substance addictions or psychiatric disorders.

Regarding cannabinoid use, we aimed at identifying studies focusing on regular, either recreational, therapeutic or experimental, use of any type of cannabinoid compound, without restrictions based on route of administration or time since last use. We did not impose restrictions based on the presence/absence of a cannabis-related diagnosis (e.g. dependence, misuse). Similarly, we did not restrict inclusion on the presence/absence of other psychiatric or substance use disorders, as these conditions are often comorbid with cannabis use. However, we sought to reduce the risk of confounding by excluding studies or data from participant subgroups suffering from physical diseases, especially of infectious, inflammatory, or chronic types. We also excluded studies conducted in samples with other conditions that might affect inflammatory status, such as pregnancy or exercise. This was expected to filter out a substantial stream of literature examining therapeutic applications of medical cannabinoids (Solmi et al., 2023).

We adopted the additional following eligibility criteria: (1) participants had to be aged ≥18 years; (2) regular cannabinoid use needed to be reported or documented, or experimentally administered; (3) studies had to explicitly compare inflammatory biomarker levels between Cannabinoid Users (CU) and Cannabinoid Non-Users (CNU), or between epochs of use and non-use (e.g., in crossover Randomized Controlled Trials (RCTs)); (4) studies had to be published in peer-reviewed publications in English.

2.2. Search strategy, information sources, search strategy, selection process

We searched PubMed, Scopus, PsycINFO, ClinicalTrials.gov and the Cochrane library up to December 2023 (search strategies reported in Supplementary Paragraph S1). Reference lists of included records and relevant reviews were also screened for additional citations. Two reviewers (RG and AZ) independently screened titles, abstracts, and full texts using the Rayyan platform (Ouzzani et al., 2016). Discrepancies were resolved through discussion with a third reviewer (MBM).

2.3. Data collection process

Two reviewers (MBM and AZ) independently extracted data using a standardized template. For each study, we recorded bibliographic information (first author, publication year), study design (case-control, cross-sectional, prospective, experimental), and participant groups (e.g., healthy controls, clinical or other populations). Demographic and clinical descriptors included group sample sizes, mean age and standard deviation, proportion of male participants, Body Mass Index (BMI), and prevalence of cigarette and alcohol use.

Cannabinoid exposure was classified as cannabis only, cannabis plus other substances, or synthetic cannabinoids. Recency of use was coded as recent or past, and assessment method as self-report or toxicological screening. Inflammatory biomarkers were grouped as pro-inflammatory or anti-inflammatory, and extracted alongside units and transformation status (e.g., raw or log-transformed values). We also documented whether analyses were unadjusted or adjusted for covariates. Discrepancies in extraction were resolved through consensus.

2.4. Study risk of bias assessment

Two reviewers (RG and AZ) independently assessed the methodological quality of included studies using the National Heart, Lung, and Blood Institute (NHLBI) Quality Assessment Tools appropriate for each study design (e.g., case–control, cross-sectional, cohort, randomized). Discrepancies were resolved through discussion. Attention was given to the methods used for diagnostic classification, blinding of exposure assessors, and the handling of potential confounding variables in the statistical analysis.

2.5. Effect measures

For each eligible comparison, raw data on inflammatory biomarker levels and corresponding variability (e.g., standard deviation) were extracted for cannabis users, non-users, and relevant subgroups. We computed Standardized Mean Differences (SMDs) with 95% Confidence Intervals (95% CI) as the primary effect measure for cross-sectional and case-control studies, as well as for RCTs comparing cannabinoid versus placebo groups at study endpoint. Where required, effect sizes were derived from alternative data sources, including author correspondence, digital extraction from figures (Drevon et al., 2017), or transformation from other metrics (e.g., regression coefficients) using established formulas (Harrer et al., 2021). For prospective studies, the most frequently reported metric—standardized beta regression coefficients—was used to capture the association between baseline cannabis exposure (i.e., joint-years) and follow-up biomarker levels (i.e. log-transformed C-Reactive Protein, CRP). For randomized controlled trials, we computed SMDs from between-group differences at the study endpoint (cannabinoid vs placebo). Adjusted effect size estimates were also extracted, where available.

2.6. Synthesis methods

Effects were pooled using a Bayesian framework, which represents uncertainty across effect sizes. Separate analyses were conducted by study design (cross-sectional/case–control, prospective, RCTs).

We fitted a hierarchical Bayesian *meta*-analysis, anticipating that studies would report non-overlapping subsets of inflammatory biomarkers and would vary in methodological quality. Multilevel *meta*-analysis was preferred to exploit all available information while accounting for the nested data structure, improving variance partitioning, retaining all effect sizes without aggregation, and allowing precise estimation of moderator effects (Fernández-Castilla et al., 2020). Models were estimated with the R package *brms*, using effect size and precision as the dependent variable (Bürkner, 2017). We tested random effect structures with effect sizes nested within studies, with additional clustering by biomarker type (Shu et al., 2024), study design, and sample type. Model selection was based on predictive accuracy with Pareto-Smoothed Importance Sampling Leave-One-Out Cross-Validation (PSIS-LOO-CV) and prior sensitivity analysis.

Interpretation of results was based on Average Marginal Predictions (AMPs) and Average Marginal Effects (AMEs). AMPs represent the predicted average effect size (SMD) for observations at a specific covariate level, maintaining other covariates at their observed distribution (Arel-Bundock et al., 2024; Heiss, 2022). AMEs estimate the average change in SMD when switching between covariate levels or after a unit change for continuous moderators, while holding other variables constant. These marginal estimates differ from conditional effects, which fix covariates at reference values. For all estimates we report the Probability of Direction (PD), i.e. the probability that the effect sizes (or effect size differences) does not cross zero with their 95% Credible Intervals (CrI) (Makowski et al., 2019).

Sensitivity analyses included: (1) a robust hierarchical model based on Student t distribution, (2) models restricted to pro-inflammatory biomarkers and to non-clinical samples, (3) models using constrained priors, and (4) independent *meta*-analyses of each biomarker using Bayesian model-averaged *meta*-analysiswith metaBMA (Heck et al., 2017), without hierarchical pooling. Studies that met eligibility criteria but lacked sufficient data for *meta*-analysis were included in a qualitative synthesis, grouped by study design, biomarker type, and direction of association. The supplement reports further information on data synthesis.

2.7. Reporting bias assessment

Reporting bias was assessed through visual inspection of the funnel plot and tested using Egger's regression intercept.

3. Results

3.1. Study selection

The study selection process is detailed in the supplement, with the PRISMA flow diagram (Fig. S1). The first electronic search yielded 5174 records, a second updated search, 3675. After removal of duplicates, screening of titles and abstracts, 225 full-text records were assessed for eligibility, 175 records were excluded (see Supplementary Table S1) leaving 50 reports included in the review, corresponding to 46 studies.

3.2. Study characteristics

Fifty included reports corresponded to 46 studies, of which 25 had a cross-sectional or case-control design (29 reports), 10 case–control, 5 prospective design and 6 reported clinical trials (Table 1). In total, the studies involved 54,382 participants: 37,797 in cross-sectional or case–control designs, 16,099 in prospective cohort studies, and 486 in RCTs.

Six studies were retained for qualitative synthesis only, leaving 40 studies for inclusion in three *meta*-analyses, 34 for the larger one of case-control and cross-sectional studies, 2 studies for the *meta*-analysis of longitudinal studies and 4 studies for the *meta*-analysis of RCTs. Among reports included in the larger *meta*-analyses, 21 compared Cannabis Users (CU) to Cannabis Non-Users (CNU) in populations of healthy individuals, with or without cannabis use or other substance use (Alasmari et al., 2021; Alshaarawy, 2019; Alshaarawy et al., 2019; Alshaarawy and Anthony, 2015; Andersen et al., 2021; Bayazit et al., 2017; Guler et al., 2020; Guzel et al., 2017; Ibarra-Lecue et al., 2022; Keen et al., 2015, 2014; Lisano et al., 2020; Muniyappa et al., 2013; Ngueta et al., 2015; Okafor et al., 2020; Orum and Kara, 2020; Pacifici et al., 2007, 2003; Rajavashisth et al., 2012; Ribeiro et al., 2021; Stewart et al., 2024), 11 reports compared individuals with schizophrenia who used cannabis (SCZ-CU) to those with schizophrenia who did not (SCZ-CNU) (Fond et al., 2017, 2016; Fridman et al., 2023; Gibson et al., 2020; Goetz and Miller, 2019; Ibarra-Lecue et al., 2022; Miller et al., 2018; Romeo et al., 2024, 2022; Sehlikoğlu et al., 2024; Szabo et al., 2020), one compared individuals with bipolar disorder who used cannabis (BD-CU) to those who did not (BD-CNU) (Szabo et al., 2020), 3 compared individuals with alcohol use disorder with or without comorbid cannabis use (Fuster et al., 2020; Grodin et al., 2024; Karoly et al., 2018), two compared individuals with first-episode psychosis (FEP-CU vs FEP-CNU) (Di Nicola et al., 2013), one from a longitudinal study (Kreis et al., 2025). Three studies examined populations with various psychiatric disorders, including depressive anxiety disorders and posttraumatic stress disorder (PTSD) (Llorca-Bofí et al., 2024; Mongan et al., 2023; Rajasekera et al., 2025).

Five prospective cohort studies were included (Costello et al., 2013; Ferguson et al., 2019; Kreis et al., 2025; Meier et al., 2019, 2016), but one did not report the association between baseline cannabis use and inflammatory biomarker levels at follow-up (Kreis et al., 2025). Two allowed to examine baseline association between cannabis use and biomarkers (Ferguson et al., 2019; Kreis et al., 2025).

Six controlled trials compared cannabidiol (CBD) to placebo (Bryan et al., 2025; Flores et al., 2023; Lisano et al., 2025; Mastrofini et al., 2024; Morissette et al., 2021; R. Wang et al., 2023), of which four reported extractable data, and were also randomized, thus were included in the *meta*-analysis.

3.3. Risk of bias

Most studies were rated to be of fair quality. The most frequent methodological limitations included non-representative sampling, unclear or biased selection of cases and controls, low participation rates, and insufficient control for key confounders such as tobacco or alcohol use. Of the four longitudinal studies, three were rated as good quality and one as fair. Half of the RCTs were rated as fair, two good and one poor. Risk of bias assessments are summarized in Supplementary Tables S2–S9. Inter-rater agreement between the two assessors was 88%.

3.4. Effect sizes

A total of 178 effect sizes were extracted from cross-sectional and case–control studies (Supplementary Table S11). Of these, 158 were relative to pro-inflammatory biomarkers and 20 to anti-inflammatory biomarkers. The most frequently reported pro-inflammatory markers were CRP (n = 29), IL-6 (n = 19), White Blood Cell (WBC, n = 11), Monocyte percentage (n = 10), Neutrophil percentage (n = 10), TNF-α (n = 9), IL-8 (n = 7), IL-1 beta (n = 6). Among anti-inflammatory markers, IL-10 (n = 7), Interleukin-1 Receptor Antagonist (IL-1RA) (n = 3), Soluble Glycoprotein 130 (sgp130) (n = 3), Soluble Tumour Necrosis Factor receptor (sTNFr) (n = 3). Most effects were relative to non-clinical (healthy) samples (75), while 38 effects were from participants with schizophrenia, 20 from subjects with various psychiatric disorders, 14 from subjects with alcohol-related disorders. 8 with bipolar disorder, and 7 with first-episode psychosis.

Table 1
Study characteristics.

Study	Study Design	Risk of Bias [1]	Population (% male, mean age ± sd)	Duration of cannabinoid use	Inflammatory marker, measurement	Main findings (effect size [2], comment)
Case-control and cross-sectional						
Alasmari et al., 2021 [2]	Case-control	Fair	10 CUD, 100% male, age 24.4 ± 3.6; 10 CNU, 100% male, age 30.4 ± 4.3	Current: urinalysis Cannabis use history: 2-5y: 4 6-10y: 3 ≥11y:3	Untargeted proteomic analysis of serum samples: 2D-DIGE, Peptide mass fingerprints (PMFs) and Ingenuity Pathway Analysis (IPA)	The study identified 121 proteins, 55 upregulated and 66 downregulated in CUD patients compared with CNU. IPA suggested variance in the expression of free radical scavenging (reduced), cellular compromise, inflammatory proteins (stimulated Acute Phase Response proteins, reduced Tumor Necrosis Factor Alpha-Induced Protein 3), atherosclerosis signaling (reduced). The study did not control for anti-inflammatory drug history.
Alshaarawy et al., 2015; 2019	Cross-sectional	Fair	20–59-year-old participants from the National Health and Nutrition Examination Surveys, 2005–2010Cannabis smoking (%) : • Never 4150 (39.8) • Former 3891 (48.0) • Recently active 1115 (12.2)	Recently active cannabis use (assessed via confidential Audio Computer Assisted Self-Interviews	−CRP −Blood sample (latex-enhanced nephelometry) −WBC	Lower serum CRP levels for recently CU among adults age 20–59 years old, as compared with US community residents of the same age who had never smoked cannabis, with no appreciable variation in relation to covariates or subgroups studied. Total WBC count was higher among heavy cannabis users than in never users. The study did not control for anti-inflammatory drug history.
Alshaarawy et al., 2019b	Cross-sectional	Fair	5115 participants enrolled in 1985—–1986, and followed up for over 25 years. Cannabis smoking: • Never 907 • Former 2699 • Recently active 701	Cannabis use history assessment and blood sample	−Fibrinogen (year 5) −CRP (year 7, 15, 20, 25) −IL-6 (year 20) Fibrinogen: Clauss method; nephelometry-based assay CRP: nephelometry-based assay; At Y25 Roche latex-particle enhanced immunoturbidimetric assay IL-6: ultra-sensitive ELISA	Compared to never use, recent cannabis use was not associated with any biomarker after adjusting for potential confounders. Former cannabis use was inversely associated with fibrinogen levels, whereas the associations were weaker for serum CRP.
Andersen et al., 2021	Cross-sectional	Poor	62 young adults 37% male, age 30.7 ± 1.2; 11% only nicotine smokers 11% only CU 20% nicotine smokers + CU	Self-reported scaled cannabis use (average use over the past year on a zero to two scale). Current serum cotinine or THC positivity	− GPR15, CRP, Ratio of pro-inflammatory to anti-inflammatory cytokines. Blood samples: ELISA, Flow Cytometry; Bio-Plex Pro Human Cytokine 17-Plex Immunoassay	There were significant correlations between GPR15 + Th cell percent and self-reported nicotine smoking intensity and CU intensity. GPR15 + Th cell percent was significantly correlated with serum THC positivity. CRP was significantly negatively correlated with male gender and positively correlated with BMI but not with cannabis or tobacco use. The ratio of pro- to anti-inflammatory cytokines was positively correlated with cigarettes per day and showed a trend-level association with self-reported CU, but was not correlated with serum cotinine or THC. The study controlled for the use of NSAIDs in the past month.
Bayazit et al., 2017	Case-control	Good	34 CUD, 100% male, age 26 ± 9;	Current use: urinalysis	- IL-1β, IL-6, IL-8, IL-12p70, IFN-γ, TNF-α	Levels of IL-1-β, IL-6, IL-8, TNF-α, TOS, OSI were higher

(*continued on next page*)

Table 1 (*continued*)

Study	Study Design	Risk of Bias [1]	Population (% male, mean age ± sd)	Duration of cannabinoid use	Inflammatory marker, measurement	Main findings (effect size [2], comment)
			34 CNU 100% male age 26 ± 8	Mean duration of cannabis use: 55 ± 7 months	- Plasma: ELISA - Serum Total Antioxidant Status (TAS), Total Oxidant Status (TOS) and Oxidative Stress Index (OSI, calculated as the TOS/TAS ratio) (ad-hoc automated colorimetric method)	in CUD subjects vs CNU, but not those of IL-12p70, IFN-γ- and TAS. IL-6 levels correlated significantly with TOS (R = 0.41) and OSI levels (R = 0.41). No significant correlation between TAS, TOS, OSI, IL-12, and IFN-γ levels in patients. Although the study did not control for a history of anti-inflammatory drug use, taking any medications was one of the exclusion criteria for participants.
Di Nicola et al., 2013	Case-control	Fair	24 first-episode psychotic patients: 66% male, age 28.1 ± 1.1 24 CNU: 62,5% male age 29.6 ± 0.9	Current use	IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, TNF-a, IFN-γ, VEGF, EGF, MCP-1 Serum: Chemiluminescent immunoassay Leukocyte m-RNA expression analyses – real time PCR	CU patients had significantly lower serum levels of IL-2 and mRNA levels of IL-1α, but higher serum levels of MCP-1 compared with CNU patients. The study did not examine the effect of cannabis on cytokines levels in healthy controls. The study did not control for anti-inflammatory drug history.
Fond et al., 2016; 2017	Cross-sectional	Fair	Year 2016: 219 SZ: 75,3% male, age 31.6 ± 10.6 Year 2017: 345 SZ: 73% male, age 32.3 ± 9.8	Interview with the Structured Clinical Interview for Mental Disorders	- CRP Hs CRP measured with nephelometry (Dade Behring)	2016 study: CRP levels significantly associated with cannabis use in univariate, but not multivariate analysis 2017 study: no significant association between cannabis use disorder and chronic peripheral inflammation.
Fridman et al., 2023	Cross-sectional	Fair	34 SCZ-CU, 97% male, age 36.6 ± 10.2; 110 NO-SCZ-CU, 70.9% male, age 39.5 ± 10.5	Use at least once in the last month (either reported by the patient or confirmed by a positive urine toxicology test)	– NLR – Blood samples (analysis method not reported)	No significant differences in NLR between SCZ-CU and NO-SCZ-CU. All other blood count parameters showed no statistical significance. The study did not control for anti-inflammatory drug history.
Fuster et al., 2020	Cross- sectional	Fair	289 inpatients with AUD 77.5% male, age 43.5 ± 57, of which: 220 nicotine smokers 67 cocaine use 64 CU 32 cocaine + cannabis 14 opioids use	Current use; Urinalysis at admission	– Blood plasma: sCD163, sCD14, IL-6 –CD163, CD164: Quantikine ELISA – IL-6: Cytometric Bead Array	CU was associated with higher sCD163 levels, but not with IL-6 or sCD14 levels. The study did not control for anti-inflammatory drug history.
Gibson et al., 2020	Cross-sectional	Fair	59 SCZ-CU, 67.7% male, age 32.9 ± 10.4; 60 SCZ-CNU, 70% male, age 39 ± 12.9	Current use Urinalysis at the admission	– CRP, IL-21, IL-6, IFN-γ, IL-12, sil-2ra, IL-2, IL-1β, TNFα, sIL-2Ra, IL-8, IL-10; – Blood samples collected in sodium heparin tubes. Cytokines levels were measured with commercially available multiplex cytokine/chemokine panels: – Mean number of days between hospital admission and sample collection was 2.3 days (SD = 1.8 days).	IFN-γ levels were lower in CU compared to CNU, but not significantly after adjusting for covariates or multiple comparisons. No other significant differences in inflammatory markers between groups.IL-6 levels negatively correlated with PANSS total score, as well as negative and positive subscale scores in patients with CU.CU subjects were significantly younger, had lower BMIs andtrend-level lower rates of medical conditions that may impact inflammation. The study did not control for anti-inflammatory drug history.
Goetz et al., 2019	Cross-sectional	Fair	18 SCZ-CU 61.1% male age 35.4 ± 11.4	Current use	– WBC, lymphocytes, monocytes, neutrophiles,	There were no significant differences in total or other

(*continued on next page*)

Table 1 (*continued*)

Study	Study Design	Risk of Bias [1]	Population (% male, mean age ± sd)	Duration of cannabinoid use	Inflammatory marker, measurement	Main findings (effect size [2], comment)
			24 SCZ-Cocaine 62.5% male age 39.1 ± 11.4 43 SZ 62.8% male age 39.6 ± 12.6	Urine drug screen within 48 h of admission	eosinophils. – Blood sample. Total and differential WBCs were analyzed using a COULTER LH 750 Haematology Analyzer.	differential WBC counts based on marijuana use.Post -hoc analysis: SCZ-CU women had significantly higher lymphocyte and a trend for higher monocyte counts versus SZ. By contrast, in men there were no significant differences in total or other differential WBC counts based on marijuana use. The study did not control for anti-inflammatory drug history.
Grodin et al., 2024	Cross-sectional	Fair	149 people with AUD 60,9% male, age 40.14 ± 11.83 - N = 133 either no recent cannabis use (n = 72) or recent cannabis use (n = 61). - N = 16 participants reported inconsistent cannabis use and were excluded	Cannabis use severity over past 6 months assessed with the Cannabis Use Disorder Identification Test	–IL-6 Plasma levels evaluated with Meso Scale Discovery MULTI-SPOT Assay System	Recent cannabis use moderated the relationship between alcohol consumption and IL-6 levels. Cannabis appeared to reduce the inflammatory effect of alcohol.
Guler et al., 2020	Case-Control	Poor	40 CU (synthetic cannabinoids), 100% male, age 31.2 ± 5.8; 40 CNU, 100% male, age 31.2 ± 5.8	At least 2 years (authors did not specify if the last 2 years)	– IL-1β, IL-6, TNFα, MPO, TT, NT, TOS, TAS, OSI; –Plasma: ELISA	Lymphocyte DNA damage, TOS, MPO activity, disulfide, OSI levels, IL-1β, IL-6, and TNF-α levels were significantly higher in the CU group than in the CNU. TAS and NT levels were significantly lower in CU vs CNU. The study did not control for anti-inflammatory drug history.
Guzel et al., 2017	Case-Control	Fair	40 CUD (synthetic cannabinoids), 95% male, age 28.5 ± 7.1; 40 CNU, 95% male, age 30.8 ± 6.3	Current use: urine-analysis Consumption: more than one year	– WBC, lymphocytes, monocytes, neutrophils, eosinophils, basophils, NLR –Blood samples: hemogram parameters were measured using aperture impedance technology.	WBC, MCH, RDW, MCV, neutrophils, monocytes, UIBC, TIBC, and NLR were significantly higher in CUD patients compared to the CNU. MPV and lymphocytic parameters were significantly lower in CUD patients compared to the CNU The study did not control for anti-inflammatory drug history.
Ibarra-Lecue et al., 2022	Case-control	Poor	13 SCZ-CU, 92.3% male age, 38 ± 2.9; 26 CUD, 80.7% male, age 32.5 ± 1.9; 22 SCZ-CNU, 59% male, age 48.4 ± 1.8; 36 CNU, 83.3% male, age 33.9 ± 3.1	Current useToxicologic blood test (TCNU was found in the blood of 25 CUD patients, 2 CUD_SZ subjects and 1 SZ patient)	– IL-6 – Plasma: ELISA	No difference in IL-6 between CUD and SCZ-CU vs CNU.In people with SCZ-CNU, IL-6 levels were significantly higher vs CUD, SCZ-CU and CNU. The study did not control for anti-inflammatory drug history.
Karoly et al., 2018	Cross-sectional	Fair	66 regular drinkers (any level of drinking over the past 3 months) male 48.5%, age 30,08 ± 4.7 32 CNU 32 CU 2 Other substances	Current use Cannabis days in the last 90 days assessed by the Timeline Follow back (TLFB) = 23.61 day	–IL-6, IL-1β, IL-8 –Plasma: Quantikine HS ELISA	IL-1β: CU had a significant negative effect on IL-1β levels. Drinks Per Drinking Day did not have a significant impact on IL-1β. IL-6: an alcohol by cannabis interaction predicting circulating IL-6 was found. CNU demonstrated a significant positive association between alcohol consumption and IL-6, whereas CU showed no

(*continued on next page*)

Table 1 (*continued*)

Study	Study Design	Risk of Bias [1]	Population (% male, mean age ± sd)	Duration of cannabinoid use	Inflammatory marker, measurement	Main findings (effect size [2], comment)
						association. IL-8: No significant effects on IL-8 levels were found from any of the factors examined (alcohol or CU). The study did not control for anti-inflammatory drug history.
Keen et al., 2014	Cross-sectional	Fair	46 CU, 67.4% male, age 41.3 ± 11.7; 45 CU + drugs, 60% male, age 48.6 ± 7.5; 78 CNU, 33.3% male, age 46.6 ± 13	Lifetime: self-report	− IL-6 − Serum: ELISA	IL-6 levels were lower in CU compared to CNU. No other significant differences were observed between CU vs NO-CU as well as CU vs CU + drugs. The authors did not specifically control for anti-inflammatory drugs, as they lacked information on the intended use or names of the medications, except for the exclusion criteria related to psychological disorders and brain trauma.
Keen et al., 2015	Cross-sectional	Fair	46 CU, 67.4% male, age 41.3 ± 11.7; 45 CU + drugs, 60% male, age 48.6 ± 7.6; 77 CNU, 32.5% male, age 46.6 ± 13	Lifetime: self-report	−TNF, IL-1α −Serum: ELISA	CU was not significantly associated with IL-1α levels adjusting for demographic and physiological variables. CNU were more likely to have higher TNF levels than CU. The authors did not specifically control for anti-inflammatory drugs
Kopczynska et al., 2019 [2]	Case-control	Fair	136 First Episode Psychosis – ICD codes F20–29 and F30–33. (94 CU, 83 CU + nicotine smokers) 71,11% male, age 32.51 ± 10.12, 42 CNU (14 CU, 9 CU + nicotine smokers) 45.24% male, age 37.55 ± 14.44,	Lifetime: self-report	CRP −Serum: ELISA	CRP did not significantly differ between CU and CNU The study did not control for immediate previous history of infectious illness or anti-inflammatory drug history.
Lisano et al., 2020	Cross-sectional	Fair	15 CU, 66.6% male, age 23.4 ± 4.4; 15 CNU, 66.6% male, age 23.4 ± 4.4	≥1time/week last 6 month: self-report (average 18.00 ± 10.12 days over the past 30-days with 1.67 ± 0.72 uses per day used); Average CU duration: 6.87 ± 3.94 years.	− IL-6, CRP − Serum: ELISA	Serum IL-6 and CRP did not significantly differ between CU and CNU The study did not control for anti-inflammatory drug history.
Llorca-Bofi et al., 2024	Cross-sectional	Good	- 719 individuals with psychiatric dx with negative toxicology, age 44.93 ± 16.16, male 49% - 208 individuals with psychiatric dx with positive toxicology test: o 168 cannabinoids, age 33.89 ± 10.25, 46% male o 13 opiods, age 42.95 ± 15.12, 31% male o 27 cocaine, age 38,93 ± 9,22, 59% male	Toxicology test (blood and urine)	− WBC count − CRP − NLR, MLR, PLR Flow cytometry	Cannabis-positive patients exhibited higher WBC, neutrophil, monocyte, counts and lower PLR versus cannabis-negative individuals, with moderating effects of age, diagnosis, and benzodiazepine use; effects were most pronounced in psychotic disorders.
Miller et al., 2018	Cross-sectional	Fair	Data from CATIE schizophrenia trial dataset. 47 SCZ-CU, 83.7% male, age 32.8 ± 10.2; 19 SCZ-Cocaine, 78.9% male, age 37.4 ± 10.2; 490 SZ, 73.3% male, age 40.2 ± 11.4	Current use: Urine drug screening	− Total and differential WBC, CRP, IL-6, E-selectin, intercellular adhesion molecule 1 (ICAM-1), and vascular cell adhesion molecule 1 (VCAM-1), adiponectin and leptin. − Plasma: Luminex bead-based	CU had lower IL-6 than CNU, but post-hoc analysis did not confirm a significant difference. Plasma CRP did not significantly differ between CU and CNU. The study did not control for

(*continued on next page*)

Table 1 (*continued*)

Study	Study Design	Risk of Bias [1]	Population (% male, mean age ± sd)	Duration of cannabinoid use	Inflammatory marker, measurement	Main findings (effect size [2], comment)
					assays.	anti-inflammatory drug history.
Mongan et al., 2023	Cross-sectional	Fair	781 participants - 377 cases with psychiatric disorders age 24.1 ± 0.8, male 24.9% (n = 42 with CU); - 35 with psychotic disorder - 202 with depressive disorders; - 268 with GAD - 404 controls age 24.0 ± 0.0, male 47.3% (n = 13 with CU)	Regular cannabis use; NR	−IFN-γ, TNF-α, IL1-β −IL2, IL4, IL6, IL8, IL10, IL13 −CRP From peripheral blood samples	Did not directly analyse the association between cannabis use and inflammation.
Muniyappa et al., 2013	Cross-sectional	Fair	30 CU 60% male, age 27 ± 8; 30 CNU 60% male, age 27 ± 7	At least 4 days per week for the last 6 months. Years of use: 12 ± 9 Joints per day: 9.5 ± 8.4	−hsCRP − Plasma: Method not reported	This study found no significant differences in hsCRP levels between CU and CNU The study did not control for anti-inflammatory drug history.
Ngueta et al., 2015	Cross-sectional	Fair	335 CNU 25% male, age 43.3 ± 0.7; 451 CU 60.2% male Age 32.2 ± 0.6	Last 12 months: Self-report	− hsCRP, IL-6, TNFα −Plasma hsCRP: highly sensitive CRP assay; − Plasma IL-6, TNFα: ELISA	Cannabis use not associated with significant differences of inflammatory marker levels. The study did not control for anti-inflammatory drug history.
Okafor et al., 2020	Cross-sectional	Fair	Wave 1 (2013–2014) of the Population Assessment of Tobacco and Health study. N = 5,363 adults, median age 38, 50.7% male. N = 315 reported CU	Recent cannabis use (past 30 days) Self-report	−hsCRP −IL-6 −Fibrinogen −Serum or plasma using the Cardiac C-reactive Protein Sensitive immunoturbidimetric assay on the automated Roche/Hitachi cobas c 311 modules. −ELISA	CU associated with lower levels of systemic inflammatory markers. Specifically, past 30-day cannabis use showed an inverse association with hsCRP in crude and fully adjusted models, which remained significant after adjustment for sociodemographic factors, health behaviours, and BMI. Similarly, recent cannabis use associated with lower IL-6 and fibrinogen levels in bivariate analyses; however, these associations were attenuated and became non-significant after multivariable adjustment. No significant associations were observed for less recent cannabis use; no sex interactions were detected.
Örüm et al., 2020	Case-control	Good	56 CUD, 100% male, age 23.7 ± 5.5; 56 OUD, 100% male, age 23.6 ± 5.3; 56 CNU, 100% male, age 26.2 ± 4.8	Urine toxic screening test negative for the last 4 weeks.	− CBC, MLR, PLR, NLRMONO% − Peripheral venous blood sample: CELL-DYN 3700 SL analyser	Monocytes number was significantly higher in CUD compared with CNU and OUD (p = 0.018).MLR was significantly higher in the CUD compared to OUD (p = 0.049). PLR was significantly different from the other two groups in the OUD group. The study did not control for anti-inflammatory drug history.
Pacifici et al., 2003; 2007	Cross-sectional	Fair	2003 study: 32 CNU 72% male age 22, 13 occasional CU 92%	Use during the previous 6 months Occasional CU: eventual to	− IL-2, IL-10, TGF-β1 − Plasma: ELISA	Cannabis use was associated with a decrease in IL-2 levels, and an increase in levels of IL-10 and TGF-β1.

(*continued on next page*)

Table 1 (*continued*)

Study	Study Design	Risk of Bias [1]	Population (% male, mean age ± sd)	Duration of cannabinoid use	Inflammatory marker, measurement	Main findings (effect size [2], comment)
			male, age 21, 16 regular CU 37% male, age 23 2007 study: 37 MDMA + CU 51% male age 23.5 ± 3.5, 23 CU, 35% male age 22 ± 1.9, 34 CNU 27% male age 22 ± 2.6	monthly use; Regular CU: weekly to daily use; Urinalysis		The study did not control for anti-inflammatory drug history. MDMA + CU showed a significant increase in anti-inflammatory TGF-β1 and a decrease in pro-inflammatory IL-2, indicating a shift towards an immunosuppressive profile. In contrast, cannabis-only users exhibited no significant difference in TGF-β1 but had reduced IL-2 levels, though to a lesser extent than MDMA–CU. The study did not control for anti-inflammatory drug history.
Rajasekera et al., 2025	Case-control	Fair	88 participants with PTSD (50% male); mean age 37; n = 6 with CUD; 85 HC (mean age 38); n = 0 with CUD	ICD-10 Diagnosis of CUD	− CRP, IL-1β, IL-6, IL-8, IL-18, TNFα −Immunoassay multiplex Stable isotope dilution liquid chromatography/tandem mass spectrometry	Did not primarily examine association between cannabis and inflammatory biomarkers. Analysis of primary data provided by authors did not yield significant association.
Rajavashisth et al., 2012	Cross-sectional	Fair	10,896 adults, Age 20—–59 years: 6667 CNU 42.9% male. 3346 past CU: 53.6% male 883 current CU: 64.4% male	Lifetime: self-report Past CU: not used marijuana in the past month Light current use (<4 days per month): 557 Heavy current use (>5 days per month): 326	− CRP − Serum: latex-enhanced nephelometry	CRP: d = -0.374 (95% CI −0.460—0.287) CRP: d = 0.390 (95% CI 0.278 0.501) CRP: d = -4.946 (95% CI −5.027—4.866) All marijuana users had a higher prevalence of CRP < 0.5 mg/dl ($p < 0.0001$); Serum CRP was significantly ($p < 0.001$) lower in past marijuana users compared to current and non marijuana users suggesting lower inflammation in past marijuana users. The study did not control for anti-inflammatory drug history.
Ribeiro et al., 2021	Cross Sectional	Poor	21 CU, 100% male, age 28.6 ± 8.5; 12 Cocaine users, 100% male, age 38.7 ± 4.9; 27 CUD + cocaine, 100% male, age 32.3 ± 7.9; 21 CNU, 100% male, age 33.4 ± 9.7	Current use: urinalysis	− CRP, TNFα, IL-6, IL-10 − Serum CRP: turbidimetric assay − Plasma TNFα, IL-6, IL-10: ELISA	CRP: higher in CU + cocaine compared to CNU and CU. TNF-α: Significantly lower in CU compared to CNU.IL -6: Lower in CU compared to CNU. Higher in CU + Cocaine compared to CU.IL -10: No significant differences among groups. The study did not control for anti-inflammatory drug history.
Romeo et al., 2022; 2024	Cross-sectional	Fair	2022 study of acutely ill inpatients: 17 psychotic CU, age 32.7 ± 8.2, 94% male 21 psychotic CNU, age 38.5 ± 11.4, 85,7% male 2024 study:102 psychotic inpatients (including SZ, SZ-AFF, FEP, delusional, bipolar disorder and psychotic MDD) ;	Urinalysis at baseline (current use) and 4 weeks after cessation	− hsCRP, Monocytes	2022 study: CU patients had lower CRP and higher lymphocyte counts compared with non-users. Following cannabis cessation, CRP and lymphocyte levels increased, abolishing between-group differences at follow-up, except for persistently higher lymphocyte counts in former users.

(*continued on next page*)

Table 1 (*continued*)

Study	Study Design	Risk of Bias [1]	Population (% male, mean age ± sd)	Duration of cannabinoid use	Inflammatory marker, measurement	Main findings (effect size [2], comment)
			65 psychotic CU, 69% male, age 40.4 ± 13.7; 37 psychotic CNU, 78% male, age 32.1 ± 9.85			2024 study: Baseline: psychotic CU showed higher total WBC and monocyte vs psychotic CNU. Result became non-significant after adjusting for age, gender, smoking status, BMI and diagnosis After 4 weeks of cessation: psychotic CU showed higher WBC and monocyte counts vs psychotic CNU. Difference persisted adjusting for age, gender, smoking status, BMI and diagnosis.The study controlled for the use of NSAIDs (non-steroidal anti-inflammatory drugs) in the past month.
Sehlikoğlu et al., 2024	Case-control	Fair	Outpatients from alcohol and drug addiction treatment centre 76 CU and Meth users, age 28.9 ± 7.1, male 100% 78 HC, age 26.7 ± 5.6, male 100%	Precedent diagnosis and report	- WBC; Monocytes. Venous blood samples; NR - Neutrophil; BLR; NLR; MLR; SIII; SIRI	WBC, neutrophils, monocytes, SIII and SIRI were higher in methamphetamine and CU compared to controls
Stewart et al., 2024	Cross-sectional	Good	88 patients with substance use disorder, age 18–56, 48% male 96 patients without substance use, age 18–56, 19% male	Urine drug and breathalyzer screen	– CRP – IL-8 – IL-10 Neuroinflammation Panel 1 Human Kit	Among women with SUDs, CRP levels were lower than those without SUD; no significant difference in IL-8 and IL-10 levels.
Szabo et al., 2020	Cross-Sectional	Fair	60 SZ_CU, 73.3% male, age 26 ± 7.7; 37 BD_CU, 51.4% male, age 29.2 ± 9.3;341SZ (including schizophrenia, schizoaffective, schizophreniform), 52.8% male, age 31.9 ± 10.5;205 BD (Including type I, type II and not otherwise specified), 39% male, age 35.5 ± 12.6	Use in the last 6 months prior to blood sampling Urinalysis	– SGP130, YKL40, CatS, sTNFR1, BDNF, IL-1RA, CXCL16, vWF, OPG, and PTX3; – Plasma: ELISA mRNA expression measurements: gene expression microarray	The circulating levels of sgp130 were significantly higher among cannabis users in the SCZ group after adjustment for the number of tests performed ($p = 0.002$). No significant difference in sgp130 levels between usersand non-users was observed in the BD group ($p = 0.87$). No significant differences were found with respect to the other markers. Changes in the plasma concentrations of sgp130, were not accompanied by corresponding changes at the gene expression level indicating limited contribution from peripheral immune cell modulation. The study did not control for anti-inflammatory drug history.
Longitudinal						
Costello et al., 2013 [2]	Prospective; FU period: 5–6 years	Good	N = 1334, 51% male; age 14.1 ± 7.9; 7.5% CU 3.8% CUD	Substance use was defined as use of Cannabis in the past 3 months CUD was defined by DSM-IV	– CRP – Bloodspots collected and assayed for CRP with biotin–streptavidin based immune-fluorometric system	Higher CRP levels were observed in cannabis users and individuals with CUD, but the prospective association between baseline cannabis use and follow-up CRP levels was not statistically significant after adjusting for co-occurring substance use and other covariates. Whereas higher CRP levels predicted cannabis use and nicotine dependence at the next assessment, but the association was non-

(*continued on next page*)

Table 1 (*continued*)

Study	Study Design	Risk of Bias [1]	Population (% male, mean age ± sd)	Duration of cannabinoid use	Inflammatory marker, measurement	Main findings (effect size [2], comment)
						significant after adjustment. The study did not control for anti-inflammatory drug history.
Ferguson et al., 2019	Prospective; FU period: 6 years	Fair	N = 13155, 50% male; 2156 CU, 62% male, 10,999 CNU, 46.7% male	Lifetime Past 30 day marijuana use was assessed in Waves III and IV and past year marijuana use was also assessed at Wave IV of the National Longitudinal Study of Adolescent to Adult Health	– CRP – Blood samples: ELISA	Marijuana use was associated with lower CRP, but the effect became non-significant adjusting for gender, BMI, and non-steroidal anti-inflammatory drug use.
Kreis et al., 2025	Prospective; FU period: 10 years	Good	N = 320 FEP, median age 25, 58% male 71 CU, 242 NCU Lost to follow- up n = 188	At baseline, self-reported past 6-months cannabis use (yes/no)	– CRP – IL-1RA – sIL-2R – sgp130 – sTNFR1 enzyme immunoassays	No significant baseline differences in any inflammatory marker between CU and CNU. The study did not directly examine the prospective association between cannabis use and inflammatory biomarkers. Significant cannabis-dependent interactions emerged for biomarkers predicting psychiatric outcomes. For instance, in CU, higher baseline CRP and IL-1RA levels were associated with lower risk of readmission over 10 years, while no associations were observed in non-users.
Meier et al., 2016	Prospective; FU period: 20 years	Good	N = 1037, 52% male, age: 18. Analyses in 947 participants with laboratory health data: 265 CU 675 CNU 171 CUD	Lifetime CU and CUD assessed at ages 18, 21, 26, 32, and 38 Cumulative joint-years was estimated using self-reported frequency of cannabis use over the past year. One joint-year reflects the equivalent of daily cannabis use for 1 year. CUD: DSM	– hsCRP – Plasma: immunoturbidimetric assay	Cannabis use was not associated with CRP levels. The study controlled for the use of NSAIDs (non-steroidal anti-inflammatory drugs) in the past month.
Meier et al., 2019	Prospective; FU period: 20 years	Good	N = 253, 100% male, Age at recruitment: 6.9 years 198 CU 55 CNU	Lifetime CU was assessed yearly from approximately ages 12 to 20 years and again at approximately ages 26, 29, and 32 years. Cannabis joint-years was estimated based on reported frequency of CU for the past year at approximately ages 12 to 20, 26, 29, and 32 years. One cannabis joint-year is equivalent to daily CU for 1 year.	– IL-6, hsCRP – Blood samplesIL-6 (ELISA); hsCRP (immunoturbidimetric assay)	The results of the study indicate that cannabis use from approximately age 12 to 32 years was not associated with differences in IL-6 or hsCRP, but with lower cardiometabolic risk factors. The study controlled for the use of NSAIDs (non-steroidal anti-inflammatory drugs) .
Randomized Controlled Trials	Registration, design, length		Study sample	Trial design	Inflammatory biomarker	Main findings
Bryan et al., 2025 [2]	NCT04114903; Pseudo-RCT, 4 wk	Fair	97 CU (>weekly use/> 8 use per month for > 12 months) for age 21–40 pseudo-randomized to: • THC group n = 47, 66% male • CBD group n = 9, 44% male • THC + CBC group n = 41, 66% male, • CNU comparison group n = 28 non-randomized; 43% male	Previous CU for 4 weeks self reported	– TNFα, IL-1b, IL-4, IL-6, IL-10, IL-12, IFNG, MCP-1 used to compute latent inflammatory index – Quanterix Simoa CorPlex Cytokin Panel and Quanterix Chemokine Panel. ELISA	CU associated with a reduced inflammatory profile already at baseline, compared with CNU. More frequent use was associated with less inflammation. Difference in overall inflammation persisted at 4 weeks with no significant between-group differences (THC-dominant, THC + CBD, and CBD-dominant). No differences in insulin sensitivity. IL-10 was

(*continued on next page*)

Table 1 (*continued*)

Study	Study Design	Risk of Bias [1]	Population (% male, mean age ± sd)	Duration of cannabinoid use	Inflammatory marker, measurement	Main findings (effect size [2], comment)
						consistently non-significant; MCP-1 increased over time in THC and CBD groups (with users > nonusers at 4 weeks), but not in THC + CBD or CNU group. Individuals CU had higher physical activity levels than CNU.
Flores et al., 2023	NCT04881539; RCT, 8 wk	Poor	48 Healthy individuals, 50% male, age 25 ± 623 CBD (50 mg)25 Placebo (225 mg of medium-chain triglyceride)	8-Week RCT of 50 mg CBD daily vs placebo. 6 weeks of abstinence from cannabis (either tetrahydrocannabinol (THC) and/or CBD), and no chronic alcohol and/or drug use	– CRP – Serum: ELISA	No significant between-group differences in CRP levels post-CBD. The study controlled for the use of NSAIDs in the previous month.
Lisano et al., 2025 [2]	NCT03491384; Pseudo-RTC, 4 wk	Fair	171 subsample of trial on anxiety individuals (GAD-7 score > 5), mean age 31.4 ± 12.3, 45% male: NCU non-randomized n = 24, age 31.75 ± 11.8, 33% male ● THC n = 44, age 32.70 ± 13.40, 48% male ● CBD n = 52, age 29.67 ± 11.39, 44% male ● THC + CBD n = 51, age 31.71 ± 12.66, 49% male	4 weeks THC + CBD: 12% THC / 12% CBD THC-dominant: 24% THC / <1% CBD CBD-dominant: <1% THC / 24% CBD Use at libitum	– IL-1a – IL-1b – IL-6 – IL-8 – IL-12 – TNFα – Ciraplex Human Cytokine 10-plex Array, Ciraplex Human Cytokine 10-plex Array, or the Ciraplex Human Cytokine 7-plex Legacy Array	No group-dependent change in cytokine composite over 4 weeks (group x time interaction). Baseline inflammatory state displayed moderation group x time changes in negative affect (DASS-21) and sleep quality (PSQI)
Mastrofini et al., 2024	NCT05212402; RCT, 12 wk	Fair	54 HC, age 25 ± 7, 50% male: • 27 placebo group (1 lost to follow up) • 27 CBD 50 mg/ml (1 lost to follow up)	13 weeks RTC of CBD 50 mg/ml/day. Checks on baseline, 30 days, 60 days and 90 days.	– TNFα – IL-6 – IL-10 – WBC – NEU – MONO – Blood sample, NR	Over 12 weeks there were no group, time, or group × time effects on inflammatory biomarkers (TNF-α, IL-6, IL-10), indicating no detectable anti-inflammatory effect of CBD. Exploratory sex-stratified analyses reported lower cytokine levels in placebo among men, which the authors attribute to baseline imbalance rather than treatment effect.
Morissette et al., 2021	NCT02559167; RCT, 13 wk	Good	48 cocaine use disorder (up to 2 weeks prior admission), 81.2% male, age 46 ± 11 • 24 CBD (800 mg) • 24 Placebo	13-week RCT of CBD 400 mg/day on days 2 and 3; then increased to 800 mg/day from day 4; CBD 800 mg daily vs placebo; 12 wk 10 days of cocaine detoxification before being enrolled.	– IL-6, VEGF-A, monocytes – Plasma: Fluorescent flow cytometry e electroluminescent assay	CBD was associated with lower IL-6, VEGF-A and intermediate monocytes (CD14 + CD16 +) levels. No significant differences for IL-16, T cells, B cells and NK. Lower number of activated mature NK cells ($CD56^{neg}CD16^{hi}$) with poor cytotoxic activity in the CBD arm. Lymphocyte subpopulations of CD25 + CD4 + T was significantly higher in CBD than PLB. This increase was caused by higher levels of CD25 + CD4 + Tem, CD25 + CD4 + Temra and CD25 + CD4 + Tn. The sensitivity analysis excluding participants who were taking anti-inflammatory drugs, revealed similar results
Wang et al., 2023	NCT01747850; RCT, 12 wk	Good	40 individuals with CUD randomized to: • Placebo n = 20, age 35.3 ± 13.1, 70% male (6 lost to follow up) • Nabiximols n = 20 age 30.7 ± 10.4, 75% male (7 lost to follow up)	Nabiximols is cannabinoid buccal spray (27 mg/ml THC and 25 mg/ml CBD) licensed for multiple sclerosis. 12-week; max dose of 105 mg/day	– WBC – Blood sample	Subchronic high dose nabiximols had no significant impact on WBC. No differential change over time (treatment × time), like other liver, renal, or haematological biomarkers

Abbreviations: 2D-DIGE, Two-Dimensional Differential Gel Electrophoresis; AUD, Alcohol Use Disorder; BD, Bipolar Disorder; C1inh, C1 Inhibitor; C1q, Complement Component 1q; C3, Complement Component 3; C4, Complement Component 4; C5, Complement Component 5; CatS Cathepsin S; CBC, Complete Blood Count; CBD, Cannabidiol; CNU, Non-Cannabis-Use/Users; CU, Cannabis-Use/Users; CUD, Cannabis Use Disorder; CXCL16, Chemokine C-X-C Motif Ligand 16; DSM-IV, Diagnostic And Statistical Manual Of The American Psychiatric Association, Fourth Ed; EGF, Epidermal Growth Factor; ELISA, Enzyme-Linked Immunosorbent Assay; FB, Factor B; FH, Factor H; FHR1/2/5, Factor H Related Proteins 1, 2, And 5; Cr1 Complement Receptor 1; GPR15, G-Protein Coupled Receptor 15; hsCRP, High-Sensitivity C-Reactive Protein; IFN-ɣ, Interferon-ɣ;IL-1RA, Interleukin 1 Receptor Antagonist; IL-1β, Interleukin 1 Beta; IL-6, Interleukin 6; MCH, Mean Corpuscular Hemoglobin; MCP-1, Monocyte Chemotactic Protein-1; MCV, Mean Red Blood Cell Volume; MDMA, 3,4-Methylenedioxy-Methamphetamine; MIP-1, Macrophage Inflammatory Protein; MCP-1, Monocyte Chemoattractant Protein-1; MLR, Monocyte-To-Lymphocyte Ratio; MONO%, Monocyte Percentage; NEU, Neutrophils; NLR, Neutrophil-To-Lymphocyte Ratio; NT, Native Thiol; MPO, Myeloperoxidase; OPG, Osteoprotegerin; OSI, Oxidative Stress Index; OUD, Opioid Use Disorder; PLR, Platelet-To Lymphocyte Ratio; PTX3, Pentraxin 3; RCT, Randomized Controlled Trial; RDW, Red Blood Cell Distribution Width; SIII, Systemic-immune inflammatory index; SIRI, Systemic-inflammation response index; sgp130, Soluble Gp130; sTNFR1, Soluble Tumor Necrosis Factor Receptor 1; TAS, Total Antioxidant Status; TCC, Terminal Complement Complex; TGF-B1, Transforming Growth Factor; TIBC, Total Iron-Binding Capacity; TNF-A, Tumor Necrosis Factor-Alpha; TNF-A, Tumor Necrosis Factor-Alpha; TOS, Total Oxidant Status; TT, Total Thiol; UIBC, Unsaturated Iron-Binding Capacity; VEGF-A, And Vascular Endothelial Growth Factor-A; vWF, Willebrand Factor; wk, Weeks; YKL40, Chitinase-3-Like Protein.
Risk Of Bias Assessed With NIH Quality Assessment Tool (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools); see Supplementary Materials for details: Risk of bias; Not included in meta-analyses.

Twelve effect sizes were extracted from four prospective studies (Table S11). All estimates referred to CRP, but differed in predictor type, effect metric, transformation of the outcome, and model adjustment. Ten effect sizes were extracted from four RCTs, reflecting between-group differences in CRP, IL-6 and IL-16 and other biomarkers following CBD and nabiximols administration (Table S12).

3.5. *Multilevel meta-analysis and meta-regression of cross-sectional and case-control studies*

Hierarchical *meta*-analysis and *meta*-regression models converged well. To ensure comparability across models, missing socio-demographic moderator data for two studies (age and gender) were imputed at the mean sample value. After comparing incremental models, the final model had a cross-classified random effect structure, with independent varying effects for *study, nested within sample type,* and *biomarker*, and included a series of fixed effects for methodological, demographic and cannabis-related moderators (Supplementary Table S13). The model converged well and was robust to the power-scaling sensitivity analysis. It had the best out-of-sample predictive accuracy (57.3% cases with Pareto k values below 0.7; Fig. S2) and explained 67.6% of the variance in effect sizes (Bayesian R^2), 49.3% excluding random effects.

Average Marginal Predictions (AMPs) showed that, compared with CNU, CU are likely to display a consistent increase in inflammatory markers across all categories (Fig. 1, Table 2). Predicted SMDs were significantly above zero for both anti-inflammatory (SMD = 0.298; 95% CrI, 0.052, 0.536, PD = 99%) and pro-inflammatory biomarkers (SMD = 0.166; 95% CrI, 0.122, 0.209, PD = 100%), indicating a robust overall association with cannabis use, slightly higher and with larger uncertainty for anti-inflammatory markers. The corresponding marginal effect (AME = –0.132; PD = 83%) suggested a possible difference in effect

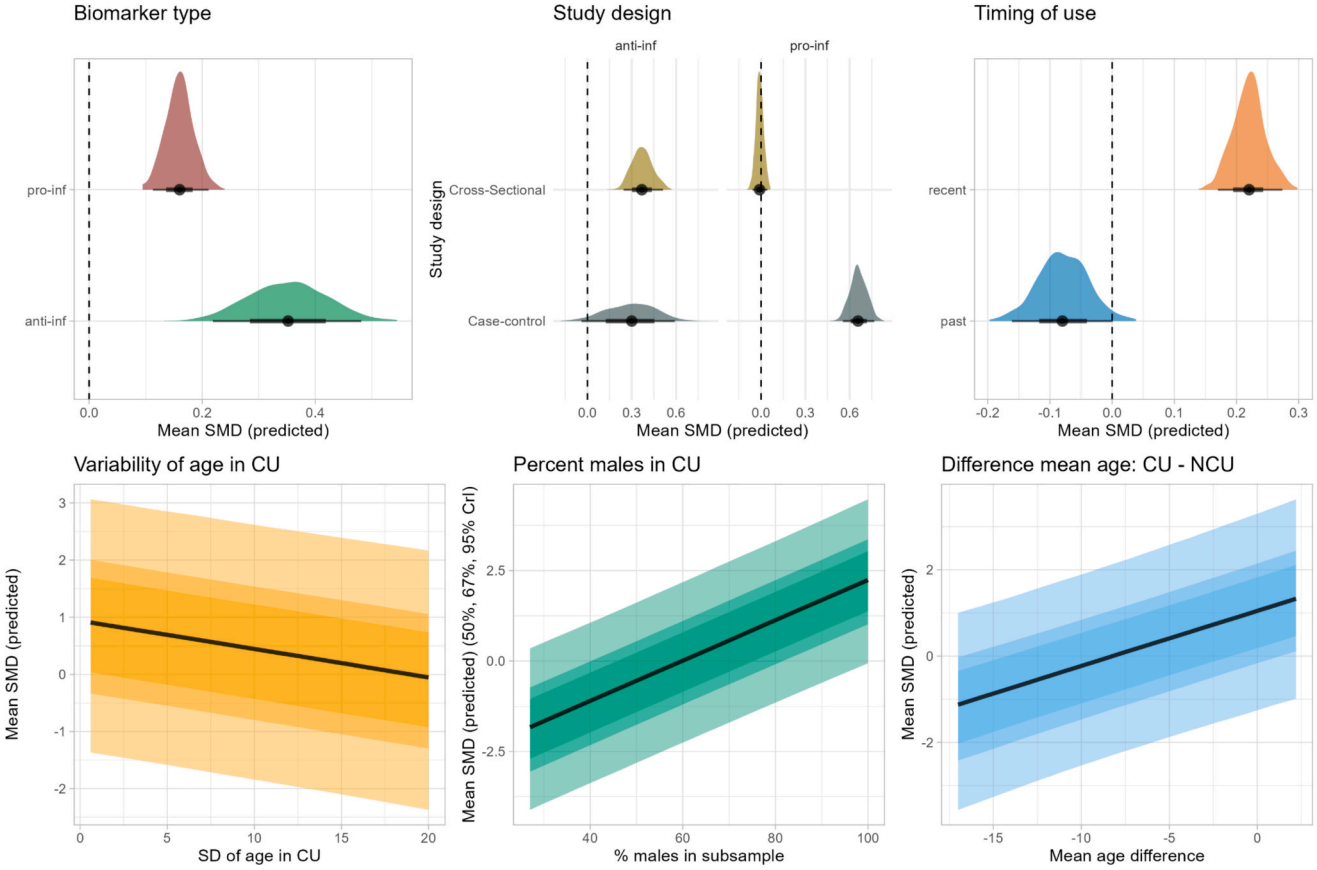

Fig. 1. Marginal predictions of effect size: hierarchical *meta*-regression analysis.

Table 2
Marginal predictions and marginal effects from the multilevel *meta*-analysis of cross-sectional and case-control studies.

Average Marginal Predictions [a]	Estimate	CrI low	CrI high	PD	Average Marginal Effects [b]	Estimate	95% CrI	PD
Anti-inflamm.	0.298	0.052	0.536	99.04%				
Pro-inflamm.	0.166	0.122	0.209	100%	Pro-inflamm. − Anti-inflamm.	−0.132	[-0.40, 0.14]	83.17%
Case-control / pro-inflamm.	0.655	0.578	0,733	100%				
Case-control / anti-inflamm.	0.292	0.089	0.492	100%				
Cross-Sectional / pro-inflamm.	−0.008	−0.043	0.026	67.91%				
Cross-Sectional / anti-inflamm.	0.367	0.277	0.457	100%	Cross-Sectional − Case-control	1.498	[0.35, 2.72]	99.3%
Healthy	0.240	−0.281	0.751	82.73%				
Clinical	0.119	−0.422	0.668	67.25%	Other − Clinical	−0.122	[-1.17, 0.95]	59.27%
Cannabis	0.150	−0.021	0.325	95.81%				
Cannabis/alcohol	−0.020	−1.603	1.576	51.03%	Cannabis/alcohol − Cannabis	−0.170	[-1.78, 1.45]	58.49%
Synthetic C.	1.550	−0.087	3.214	96.78%	Synthetic C. − Cannabis	1.400	[-0.35, 3.17]	94.29%
Cannabis/methamphetamine	−0.530	−2.837	1.738	68.22%	Cannabis/meth − Cannabis	−0.677	[-3.12, 1.73]	71.62%
Past	−0.347	−0.399	−0.294	100%				
Recent	0.259	0.227	0.291	100%	Recent − Past	0.606	[0.56, 0.65]	100%
Self-report	0.257	−0.257	0.763	84.22%				
Toxicological screening	0.129	−0.215	0.477	77.2%	Tox. – Self-report	−0.129	[-0.98, 0.73]	62.02%
Poor	0.148	−0.539	1.058	70.35%				
Fair	0.171	0.028	0.266	98.77%	Fair − Poor	0.014	[-0.94, 0.72]	54.67%
Good	0.209	−0.356	1.010	82.04%	Good − Poor	0.076	[-1.26, 1.36]	54.67%
Continuous moderators								
Average Marginal Predictions [c]	Estimate	CI_low	CI_high	PD	Average Marginal Effects [b]	Estimate	95% CrI	PD
Study year min (2003)	0.570	−1.060	2.153	76.2%				
Study year max (2025)	0.055	−0.453	0.577	58.8%	1 year increase	−0.023	[-0.12, 0.07]	68.9%
Mean age in CU min (22)	0.500	0.013	1.071	97.8%				
Mean age in CU max (50)	−0.541	−1.819	0.558	82.7%	1 year increase	−0.037	[-0.10, 0.02]	89.8%
Age variability in CU min (0.6)	0.547	0.369	0.725	100%				
Age variability in CU max (11.7)	−0.413	−0.701	−0.125	99.8%	1 year increase	−0.049	[-0.07, −0.03]	100%
% males in CU min (35)	−2.184	−2.575	−1.793	100%				
% males in CU max (100)	1.897	1.612	2.180	100%	1 percent increase	0.056	[0.05, 0.07]	100%
Diff. mean age min (CU − CNU) (−11.1)	−1.497	−2.362	−0.765	100%				
Diff. mean age max (CU − CNU) (0)	0.976	0.626	1.391	100%	1 year increase	0.129	[0.07, 0.20]	100%
Diff. in age variability min (CU − CNU) (−3.85)	0.726	0.561	0.888	100%				
Diff. in age variability max (CU − CNU) (1.1)	−0.169	−0.276	−0.062	99.9%	1 year increase	−0.106	[-0.14, −0.07]	100%
Diff. in % males min (CU − CNU) (−10)	−0.009	−0.496	0.471	51.4%				
Diff. in % males max (CU − CNU) (35.2)	0.364	−0.101	0.837	93.6%	1 percent increase	0.003	[-0.01, 0.01]	77.8%

a. Average Marginal Predictions (AMPs): Average effect size (SMD) predicted by the model at each level of a categorical variable (e.g., anti- vs. pro-inflammatory biomarkers) and at the minimum/maximum observed value of continuous predictors. b. Average Marginal Effects (AMEs): Expected change of the SMD that would be associated with the change of level of a categorical variable, or with a 1-unit increase in a continuous predictor, around the mean (e.g., per year or percentage point). The AMEs are averaged across the entire dataset, while maintaining all other covariates fixed at the observed value.

size between biomarker classes. Considering study design, case-control studies yielded variable negative effects (SMD: −0.938; 95% CrI, −1.848, −0.077, PD 98%), while cross-sectional designs showed positive estimates (SMD: 0.559; 95% CrI, 0.265, 0.868, PD = 99.9%), with a significant AME for the contrast between designs (PD = 99%). Cannabis users recruited from non-clinical samples showed higher AMPs than those from populations with psychiatric disorders, but the difference did not reach high certainty as AME (0.240 vs 0.119; AME: –0.122, PD = 59%).

Among substance types, predicted effects were non-zero for synthetic cannabinoids (SMD = 1.550; 95% CrI, −0.097, 3.214, PD = 97%), and cannabis alone (SMD: 0.150; PD = 96%), but more uncertain for cannabis plus alcohol (SMD: –0.02; PD = 51%) and cannabis plus methamphetamine (SMD: −0.530; PD: 68%). Only the AME contrasting synthetic cannabinoids with cannabis alone was highly credible (PD 94%). Predicted effects in studies with recent cannabis use were positive, unlike those in studies reporting past use (SMD = 0.259 vs –0.347), with a significant AME (0.606, PD: 100%), indicating that shifting from past to recent cannabis use is associated with higher biomarker levels. When cannabis use was ascertained by toxicological confirmation a slightly smaller effect was detected compared with studies relying on self-report, but the difference was uncertain (SMD: 0.129 vs 0.257; AME = −0.129; PD for AME = 62%). There was no apparent association between methodological quality and the effect size, possibly due to a low variability in methodological quality. Most studies rated as “fair” yielded highly credible effect (SMD = 0.171, PD: 99%), of similar mean magnitude of those rated as “good” (SMD = 0.21, PD: 82%).

Continuous moderators were associated with variable effects of cannabis on inflammatory biomarkers (Table 2). Increases of cannabis users age and age variability were associated with smaller effect sizes (AME for age: −0.037 per year; PD: 90%; AME for age variability: −0.05 per year of standard deviation; PD: 100%). In contrast, higher percentage of males in CU samples (AME = 0.056 per 1% increase, PD = 100%) and greater CU – CNU difference in age (0.13 per year difference increase, 100%) were associated with higher biomarker levels. Finally, differences between CU and CNU in age variability were also negatively associated with inflammation (−0.106 per year difference increase, 100%). For study year, predicted effects were not conclusive.

In case-control studies, cannabis use was associated with higher levels of several pro-inflammatory markers, most notably IL-1β (SMD = 2.58), TNF-α (1.74), IL-8 (1.20), IFN-γ (0.86), and IL-6 (0.75) (Fig. 2). Increases were also seen for inflammation-related hematologic indices, including Red cell Distribution Width (RDW) (0.72), WBC count (0.58), neutrophils (0.56), monocytes (0.64), Systemic immune-inflammation index (SII) (0.52), and Systemic inflammation response index (SIRI) (0.48). IL-2 (−0.42) showed a negative association. Among anti-inflammatory markers, TGF-β1 (1.16), IL-12p70 (0.50), and IL-10 (0.29) were elevated, while TGF-β (−0.78) was reduced. In cross-sectional studies, associations were generally smaller and more heterogeneous, with positive effects for Chemokine (C-X-C motif) ligand 16 (CXCL16) (SMD = 0.49), Monocyte Chemoattractant Protein-1 (MCP-1) (0.53), Pentraxin 3 (PTX3) (0.47), YKL-40 (0.52), Soluble Urokinase Plasminogen Activator Receptor (suPAR) (0.44), and Soluble Intercellular Adhesion Molecule-1 (sICAM-1) (0.20), alongside modest increases in monocytes (0.27) and neutrophils (0.19). In contrast, several markers showed negative associations, including CRP (−0.29), PLR (−0.32), IL-

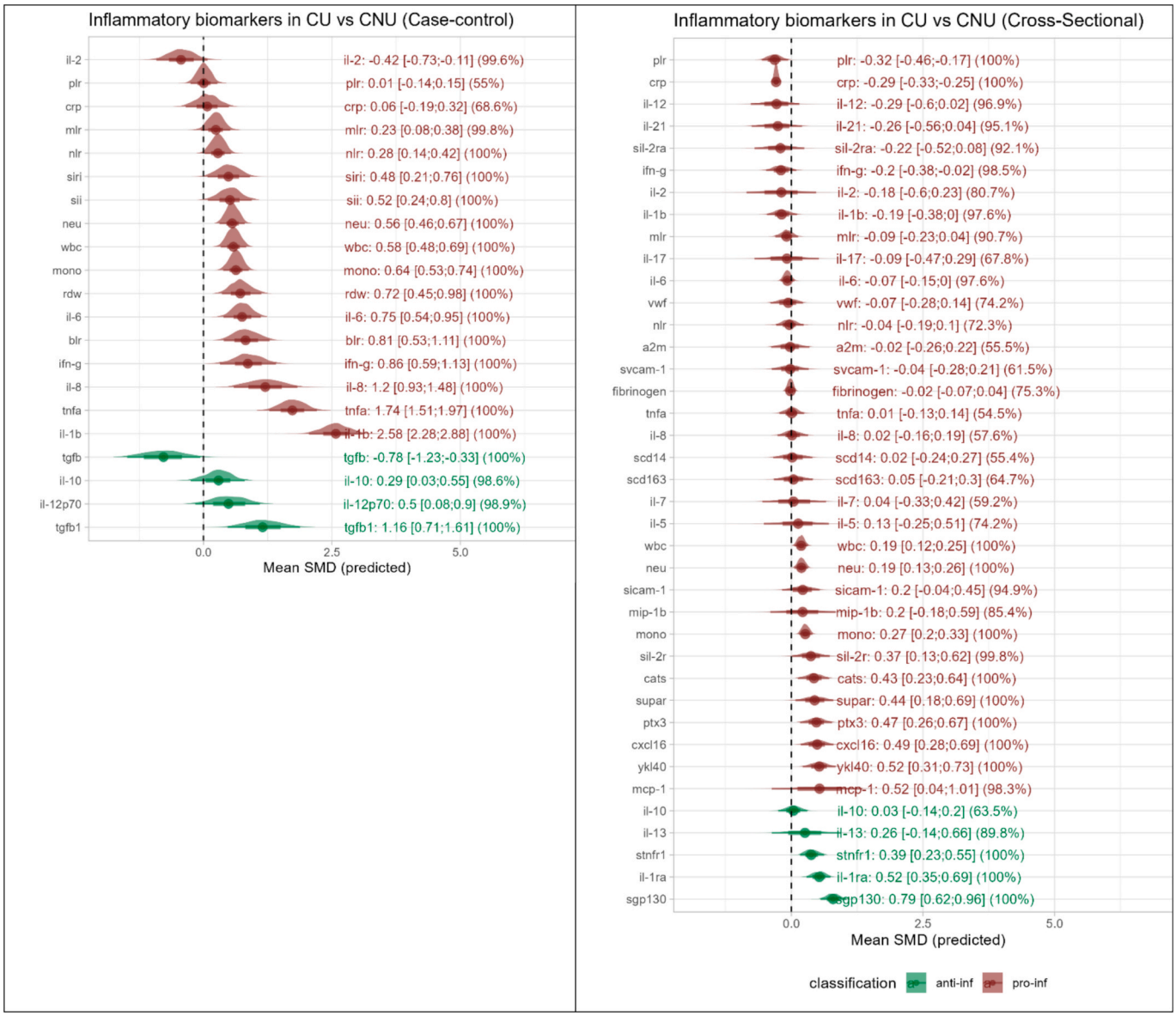

Fig. 2. Marginal predictions of effect sizes by cytokine comparison: CU vs CNU. CATS, Cartilage acidic protein 1; sCD14, Cluster of differentiation 14 (soluble); sCD163, Cluster of differentiation 163 (soluble); CRP, C-reactive protein; CXCL16, C-X-C motif chemokine ligand 16; IL-8, CXCL8 / Interleukin-8; PTX3, High-sensitivity pentraxin-3; IFN-γ, Interferon-gamma; IL-1β, Interleukin-1 beta; IL-1ra, Interleukin-1 receptor antagonist; IL-2, Interleukin-2; IL-5, Interleukin-5; IL-6, Interleukin-6; IL-7, Interleukin-7; IL-10, Interleukin-10; IL-12, Interleukin-12; IL-12p70, Interleukin-12p70; IL-13, Interleukin-13; IL-17, Interleukin-17; IL-21, Interleukin-21; sIL-2Rα, Interleukin-2 receptor alpha (soluble); MCP-1, Monocyte chemoattractant protein-1; MLR, Monocyte-to-lymphocyte ratio; MONO, Monocytes (percentage); MIP-1β, Myeloid differentiation primary response 88-binding protein 1 beta; NLR, Neutrophil-to-Lymphocyte Ratio; NEU, Neutrophils (percentage); PLR, Platelet-to-lymphocyte ratio; RDW, Red cell distribution width; sgp130, Soluble glycoprotein 130; sTNFR1, Soluble tumor necrosis factor receptor 1; TGF-β, Transforming growth factor beta; TGF-β1, Transforming growth factor beta 1; TNF-α, Tumor necrosis factor alpha; vWF, Von Willebrand factor; YKL-40, chitinase-3-like protein 1.

12 (−0.29), IL-21 (−0.26), IFN-γ (−0.20), and IL-1β (−0.19). Anti-inflammatory biomarker differences included increases in sgp130 (0.79), sTNFr1 (0.39), and IL-1RA (0.52). Notably, CRP differed by design (slightly positive in case-control vs negative in cross-sectional).

3.6. Sensitivity analyses

Sensitivity analyses confirmed the robustness of the main findings on cross-sectional/case-control studies. Use of informed priors and *meta*-analysis with Student t likelihood produced similar estimates. Subgroup analyses of pro-inflammatory markers and healthy samples plus substance users revealed consistent patterns, though some estimates were attenuated. Full results, including Bayesian diagnostics and extended model outputs, are reported in Supplementary Tables S13–S15 and Figs. S3–S4. Independent, non-hierarchical *meta*-analyses of selected biomarkers (e.g., IL-6, CRP, TNF-α, IL-1β) in general population samples yielded uncertain or null effects, while a separate analysis in schizophrenia samples showed lower IL-6 levels among cannabis users.

3.7. Prospective studies

We were able to pool the effects of two prospective studies that examined the association between cumulative cannabis joint-years at baseline and log-transformed CRP levels at follow-up (Meier et al., 2019, 2016). This non-hierarchical *meta*-analysis yielded a highly uncertain estimate of the beta coefficient, with no clear direction of effect (beta:

0.033; 95% CrI: −0.129; 0.166; Table S13, Fig. S5). In the other studies, one reported an initial inverse association between cannabis use and CRP levels, which became non-significant after adjusting for gender, BMI, and use of anti-inflammatory medications (Ferguson et al., 2019). The other found elevated CRP levels among cannabis users and those with Cannabis Use Disorder, although these associations were not significant after controlling for nicotine use and other substance dependence (Costello et al., 2013). Another study found no baseline differences in CRP, IL-1RA, soluble interleukin-2 receptor (sIL-2R), sgp130, or sTNFr1 between CU and CNU, but did not report cannabis-related changes in biomarkers over follow-up; instead, immune markers predicted psychiatric outcomes interacting with cannabis use (Kreis et al., 2025).

3.8. Controlled trials

Clinical trials on cannabinoid administration were mostly based on CBD but also included other compounds. One RCT on healthy individuals found no significant difference in CRP levels between the CBD and placebo arms following 8 weeks of administration (Flores et al., 2023). In contrast, participants admitted for cocaine use disorder, after detoxification, had significantly lower IL-6 and intermediate monocytes if they were randomized to CBD vs placebo (Morissette et al., 2021). In a 4-week pseudo-RCT, frequent cannabis users displayed a lower inflammatory profile than nonusers already at baseline, with no differential effects across THC-dominant, THC + CBD, or CBD-dominant strains on the overall inflammatory index at follow-up; MCP-1 increased over time in the THC and CBD groups only (Bryan et al., 2025). A similar study was also conducted on anxious individuals: 4 weeks of cannabis use (THC + CBD, THC-dominant, or CBD-dominant) was not associated with changes in circulating pro-inflammatory index (Lisano et al., 2025). In a 12-week RCT in healthy adults, CBD (100 mg/day) versus placebo showed no evidence of anti-inflammatory effects on TNF-α, IL-6, or IL-10 (Mastrofini et al., 2024). In a double-blind RCT of high-dose nabiximols for cannabis dependence, white blood cell count showed no evidence of a treatment effect (Wang et al., 2023a).

The two pseudo-randomized studies contrasting different types of cannabinoids did not allow to extract effect sizes (Bryan et al., 2025; Lisano et al., 2025). Whereas, the available RCTs allowed to extract 10 effect sizes, mostly relative to end-study SMD between placebo and CBD groups (supplementary Table S12) (Flores et al., 2023; Mastrofini et al., 2024; Morissette et al., 2021; Wang et al., 2023a). Of these, nine were relative to pro-inflammatory markers and were pooled in a smaller hierarchical model with random intercepts for study and biomarker. The pooled averaged predicted effect was positive, but small (SMD 0.10; 95% CrI, −0.11 to 0.31; PD 83%). Between-study and between-biomarker heterogeneity were modest (SD study 0.24; SD biomarker 0.16). As expected, biomarker-specific marginal predictions were small and imprecise, with variable PD values ranging from 66% (IL-6) to 84% (TNF-α). Excluding the study on individuals undergoing cocaine detoxification (Morissette et al., 2021) slightly increased the pooled estimate and the credibility of a small pro-inflammatory effect of CBD (SMD 0.15; 95% CrI, −0.07 to 0.36; PD 90.9%), while not substantially affecting between-study and between-biomarker heterogeneity (SD study 0.23; SD biomarker 0.14).

3.9. Reporting biases

The funnel plots of effect sizes showed a generally symmetrical distribution of studies around the pooled effect size, with some asymmetry among small studies with large positive effects (Fig. S6). The Egger tests were however not statistically significant (Cross-sectional/case-control: beta = 1.37, standard error (SE) = 1.09, $p = 0.21$; RCTs: − 1–46, SE = 1.11, p = 0.23), excluding evidence of small study effects.

4. Discussion

This *meta*-analysis is the first to examine the association between cannabinoid use and peripheral inflammatory biomarkers by integrating evidence from healthy and clinical samples, across study designs. Few available randomized trials suggest that CBD administration in healthy individuals might cause small increases of pro-inflammatory markers. A larger body of observational literature indicates that regular cannabis use is associated with higher peripheral levels of both pro- and anti-inflammatory biomarkers compared with non-use, and that the magnitude of associations varies systematically by sociodemographic characteristics, study design, co-occurring substance use and recency of use. These findings would have been missed conducting non-hierarchical *meta*-analyses.

The effects of cannabinoids on inflammatory biomarkers have been previously examined by other *meta*-analyses, but no clear pattern had emerged. Two recent *meta*-analyses pooled results from few available studies comparing peripheral pro- and anti-inflammatory biomarker levels between cannabis users and non-users, and did not detect significant differences, while acknowledging the possible presence of publication bias (Candeloro et al., 2025; Doggui et al., 2021). Another *meta*-analysis summarized results from five studies measuring haematological indices of inflammation, such as NLR (Moshfeghinia et al., 2024): results suggested that cannabis use was not associated with significant differences in NLR, but with increases of other pro-inflammatory indices, such as Platelet-to-Lymphocyte Ratio (PLR) (Moshfeghinia et al., 2024). Our analyses combined data from all available biomarkers (Fernández-Castilla et al., 2020), and detected consistent associations between cannabinoid use and increased levels of both pro- and anti-inflammatory markers. No strong indication of publication bias emerged, supporting the robustness of the findings. These patterns point to complex immunomodulatory effects, likely influenced by multiple factors across experimental and observational evidence.

Early preclinical studies were largely based on acute inflammatory disease models (colitis, encephalomyelitis, lung injury, diabetes) and characterized cannabinoids – particularly THC and other agonists – as predominantly *anti-inflammatory*, with reduced immune-cell activation, suppression of pro-inflammatory cytokines and increases of anti-inflammatory cytokines (Klein, 2005). These effects were typically attributed to CB2-mediated signalling in immune cells, alongside multiple CB-independent mechanisms (Rakotoarivelo et al., 2024). This framework led to investigate specific cannabinoids formulations with therapeutic anti-inflammatory potential. Subsequent animal work showing that CBD reduces pro-inflammatory cytokines – centrally or peripherally – prompted further clinical studies in humans (Candeloro et al., 2025; Henshaw et al., 2021; Jantsch et al., 2025; Wang et al., 2023b). By contrast, THC was not found to exert anti-inflammatory actions, or even to determine dose- and exposure-dependent increases of pro-inflammatory biomarkers, especially when accompanied by pathogen exposure or Lipopolysaccharide (LPS) stimulation (Klein, 2005; Mitchell et al., 2019).

Translation to human peripheral biomarkers has been variable, especially for populations without pre-existing medical conditions. The randomized trials synthesized here—mostly testing CBD in healthy individuals over short follow-up— did not support a consistent anti-inflammatory signal and instead suggested small increases in peripheral pro-inflammatory markers. Likewise, few quasi-experimental studies in humans examining different cannabis chemovars showed limited evidence of short-term biomarker changes or systematic differences by THC/CBD ratio, although baseline differences and adherence may limit causal inference (Bryan et al., 2025; Lisano et al., 2025).

Results of the *meta*-analysis of observational studies extend these findings by suggesting that regular cannabinoid use is associated with increases of both pro- *and anti-inflammatory* biomarkers concurrently. This “mixed” profile is compatible with immunomodulatory effects rather than a uniform anti-inflammatory shift, and aligns with some

recent results from *in vitro* studies, showing that CB2 receptor activation increased the levels of both IL-6 and IL-10 in human primary leukocytes (Saroz et al., 2019). Importantly, much of the preclinical literature demonstrating anti-inflammatory effects relies on acute inflammatory challenge models, whereas our synthesis focused on peripheral biomarkers in predominantly non-acute human samples. Differences in dosing, exposure duration, route of administration, and measurement site also limit direct comparison across experimental and observational evidence.

In observational *meta*-analysis, cannabinoids were variably associated with inflammatory biomarkers depending on methodological and demographic factors. For instance, mean age imbalances were associated with inflated CU − CNU contrasts, while age heterogeneity—within CU or relative to CNU—was associated with reduced cannabis-related differences. These patterns are consistent with effect modification by demographic and co-occurring factors (e.g. BMI, tobacco smoking, NSAIDs use) (Olivieri et al., 2023). Of note, gender, age and other factors can plausibly function as confounders, mediators, or colliders depending on the underlying causal structure (Moriarity et al., 2023) and study design (Mésidor et al., 2025). Routine adjustment is not necessarily sufficient, or suited to recover an unbiased causal estimate of the association between cannabis and inflammation. Finally, considerable variability across biomarkers may also reflect differences in biological function, responsiveness to stimuli, and analytical properties (Menzel et al., 2021).

If confirmed, findings on the immunomodulatory effects of cannabinoids on peripheral inflammatory biomarkers would have clinically relevant implications. The context of rising cannabis use and potency, especially considering youth, increased availability of synthetic variants (ElSohly et al., 2021; Lake et al., 2025) and expanding legalization (Connor et al., 2021) suggest potential high public health impact. Because chronic low-grade inflammation contributes to increased risk for cardiovascular, metabolic, neurodegenerative, and psychiatric risk, and is linked to higher all-cause mortality (Crowe et al., 2014; Furman et al., 2019; Suárez-Pinilla et al., 2014), even small shits in inflammatory profiles could matter at the population level. At the same time, such detrimental consequences should be weighed against robust evidence of potential anti-inflammatory effects in selected contexts, or acutely ill populations, supporting distinct pharmacological applications (Lake et al., 2025; Solmi et al., 2023). Interpretation remains constrained because human studies provide limited information on cannabinoid composition, dosing and exposure duration, and we did not detect clear time-dependent trends in the available evidence.

This study is strengthened by a hierarchical modelling approach that borrowed strength across studies and biomarkers, while accounting for variability, allowing to detect patterns that would have been missed using standard methods (Fernández-Castilla et al., 2020). We additionally reported AMEs which summarize expected change in biomarkers adjusting for other covariates. This approach supports more structured interpretation of observational evidence (Gelman and Hill, 2007; Hernán and Robins, 2020). Limitations include the predominance of observational studies over experimental and longitudinal designs, limiting inference on causality and on short-vs long-term effects; the uneven availability of pro- and anti-inflammatory markers, which warrants caution interpreting individual anti-inflammatory biomarkers. Nonetheless, grouping biomarkers by their broad direction of activity—pro- or anti-inflammatory—as indicators of latent immune processes improves interpretability and prognostic utility (Shu et al., 2024). Other limitations are incomplete reporting on potential confounders (e.g. cigarette smoke, alcohol use), cannabis composition and dose. Future observational studies should account for these factors under explicit causal (Moriarity et al., 2023) and distributional assumptions (Alshaarawy and Anthony, 2015). Finally, the search strategy focused on regular and pathological patterns of cannabis use, potentially excluding relevant studies, and the protocol was not preregistered.

In conclusion, CBD use was associated with small short-term increases of peripheral pro-inflammatory biomarkers, while cannabinoid use was associated with elevated levels of both pro- and anti-inflammatory biomarkers. These findings are consistent with complex immune modulation, rather than unidirectional inflammation suppression or activation. These associations varied across population and study characteristics. Inflammatory changes, even in the absence of overt disease, may represent early stages of immune disruption and contribute to long-term health risks. As cannabis use and therapeutical applications of cannabinoids become more prevalent, understanding its immunological footprint becomes essential for anticipating downstream clinical outcomes (Fischer et al., 2020; Hoch and Lorenzetti, 2020; Solmi et al., 2023).

CRediT authorship contribution statement

Martino Belvederi Murri: Writing – review & editing, Writing – original draft, Software, Methodology, Formal analysis, Data curation, Conceptualization. **Riccardo Guglielmo:** Writing – original draft, Methodology, Conceptualization. **Alessio Zizzi:** Writing – original draft, Methodology, Investigation, Conceptualization. **Angela Muscettola:** Writing – review & editing, Investigation, Data curation. **Maria Giulia Nanni:** Writing – review & editing, Supervision. **Manuela Dall'Oro:** Investigation, Data curation. **Gianluca Serafini:** Validation. **Alberto Inuggi:** . **Andrea Escelsior:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Mario Amore:** Writing – review & editing, Validation, Supervision, Investigation. **Luigi Grassi:** Writing – review & editing, Validation, Supervision, Resources, Project administration.

Funding

Work supported by #NEXTGENERATIONEU (NGEU) and funded by the Ministry of University and Research (MUR), National Recovery and Resilience Plan (NRRP), project MNESYS (PE0000006) – A Multiscale integrated approach to the study of the nervous system in health and disease (DN. 1553 11.10.2022)

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

All authors declare they have no conflict of interest or Financial competing interests to disclose. The authors wish to deeply thank Professors Jennifer Stewart, David Mongan, Emmet Power, Primavera Spagnolo and Therese A Rajasekera for kindly providing supplementary information and data to support the meta-analysis.

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2026.106517.

Data availability

Data will be made available on request.

References

Alasmari, F., Alsanea, S., Alfadda, A.A., Alanazi, I.O., Musambil, M., Masood, A., Alqahtani, F., Fantoukh, O.I., Alasmari, A.F., Benabdelkamel, H., 2021. Serum proteomic analysis of cannabis use disorder in male patients. Molecules 26, 5311. https://doi.org/10.3390/molecules26175311.

Alshaarawy, O., 2019. Total and differential white blood cell count in cannabis users: results from the cross-sectional National Health and Nutrition Examination Survey, 2005-2016. J. Cannabis Res. 1, 6. https://doi.org/10.1186/s42238-019-0007-8.

Alshaarawy, O., Anthony, J.C., 2015. Cannabis smoking and serum C-reactive protein: a quantile regressions approach based on NHANES 2005–2010. Drug Alcohol Depend. 147, 203–207. https://doi.org/10.1016/j.drugalcdep.2014.11.017.

Alshaarawy, O., Sidney, S., Auer, R., Green, D., Soliman, E.Z., Goff, D.C., Anthony, J.C., 2019. Cannabis use and markers of systemic inflammation: the coronary artery risk development in young adults study. Am. J. Med. 132, 1327–1334.e1. https://doi.org/10.1016/j.amjmed.2019.04.045.

Andersen, A.M., Lei, M.-K., Beach, S.R.H., Philibert, R.A., 2021. Inflammatory biomarker relationships with helper T cell GPR15 expression and cannabis and tobacco smoking. J. Psychosom. Res. 141, 110326. https://doi.org/10.1016/j.jpsychores.2020.110326.

Arel-Bundock, V., Greifer, N., Heiss, A., 2024. How to interpret statistical models using marginaleffects for R and Python. J. Stat. Softw. 111, 1–32. https://doi.org/10.18637/jss.v111.i09.

Bayazit, H., Selek, S., Karababa, I.F., Cicek, E., Aksoy, N., 2017. Evaluation of oxidant/antioxidant status and cytokine levels in patients with cannabis use disorder. Clin. Psychopharmacol. Neurosci. 15, 237–242. https://doi.org/10.9758/cpn.2017.15.3.237.

Belvederi Murri, M., Onofrio, A., Punzi, C., Caranci, N., Rubolino, E., Giovinazzi, F., Azzolina, D., Folesani, F., Grassi, L., Tarricone, I., Starace, F., 2025. The impact of socioeconomic factors on the incidence and characteristics of first-episode psychosis. Epidemiol Psychiatr Sci 34, e45. https://doi.org/10.1017/S2045796025100206.

Berdyshev, E.V., 2000. Cannabinoid receptors and the regulation of immune response. Chem. Phys. Lipids 108, 169–190. https://doi.org/10.1016/S0009-3084(00)00195-X.

Bryan, A.D., Skrzynski, C.J., Giordano, G., Yang, J., Stanger, M., Bidwell, L.C., Hutchison, K.E., Perreault, L., 2025. Cannabis use is associated with less peripheral inflammation but similar insulin sensitivity as nonuse in healthy adults. Am. J. Med. 138, 1285–1295. https://doi.org/10.1016/j.amjmed.2025.05.002.

Bürkner, P.-C., 2017. R Package for Bayesian multilevel models using {Stan}. J. Stat. Softw. 80, 1–28. https://doi.org/10.18637/jss.v080.i01.

Candeloro, B.M., de Oliveira, C.M., Gimenez, F.V.M., Barbosa, M.P.C.N., Soares, B.P., Ruiz, A.C.F., Folegatti, D.R.M.A., Barbalho, S.M., Oliveira, N.S., Porto, A.A., Garner, D.M., Sousa, F.H., Valenti, V.E., 2025. The pleiotropic influence of cannabidiol and tetrahydrocannabinol on inflammatory biomarkers: a systematic review and meta-analytical synthesis. Int. J. Mol. Sci. 26, 11618. https://doi.org/10.3390/ijms262311618.

Connor, J.P., Stjepanović, D., Le Foll, B., Hoch, E., Budney, A.J., Hall, W.D., 2021. Cannabis use and cannabis use disorder. Nat. Rev. Dis. Primers 7, 16. https://doi.org/10.1038/s41572-021-00247-4.

Costello, E.J., Copeland, W.E., Shanahan, L., Worthman, C.M., Angold, A., 2013. C-reactive protein and substance use disorders in adolescence and early adulthood: a prospective analysis. Drug Alcohol Depend. 133, 712–717. https://doi.org/10.1016/j.drugalcdep.2013.08.027.

Crowe, M.S., Nass, S.R., Gabella, K.M., Kinsey, S.G., 2014. The endocannabinoid system modulates stress, emotionality, and inflammation. Brain Behav. Immun. 42, 1–5. https://doi.org/10.1016/j.bbi.2014.06.007.

Curran, H.V., Freeman, T.P., Mokrysz, C., Lewis, D.A., Morgan, C.J.A., Parsons, L.H., 2016. Keep off the grass? Cannabis, cognition and addiction. Nat. Rev. Neurosci. 17, 293–306. https://doi.org/10.1038/nrn.2016.28.

Di Nicola, M., Cattaneo, A., Hepgul, N., Di Forti, M., Aitchison, K.J., Janiri, L., Murray, R. M., Dazzan, P., Pariante, C.M., Mondelli, V., 2013. Serum and gene expression profile of cytokines in first-episode psychosis. Brain Behav. Immun. 31, 90–95. https://doi.org/10.1016/j.bbi.2012.06.010.

Doggui, R., Elsawy, W., Conti, A.A., Baldacchino, A., 2021. Association between chronic psychoactive substances use and systemic inflammation: a systematic review and meta-analysis. Neurosci. Biobehav. Rev. 125, 208–220. https://doi.org/10.1016/j.neubiorev.2021.02.031.

Drevon, D., Fursa, S.R., Malcolm, A.L., 2017. Intercoder reliability and validity of webplotdigitizer in extracting graphed data. Behav. Modif. 41, 323–339. https://doi.org/10.1177/0145445516673998.

D'Souza, D.C., 2023. Cannabis, cannabinoids and psychosis: a balanced view. World Psychiatry 22, 231–232. https://doi.org/10.1002/wps.21075.

ElSohly, M.A., Chandra, S., Radwan, M., Majumdar, C.G., Church, J.C., 2021. A comprehensive review of cannabis potency in the United States in the last decade. Biol. Psych. Cogn. Neurosci. Neuroimag. 6, 603–606. https://doi.org/10.1016/j.bpsc.2020.12.016.

Ferguson, E.G., Mannes, Z.L., Ennis, N., 2019. Is marijuana use associated with lower inflammation? Results from waves III and IV of the national longitudinal study of adolescent to adult health. Drug Alcohol Depend. 198, 162–167. https://doi.org/10.1016/j.drugalcdep.2019.01.021.

Fernández-Castilla, B., Jamshidi, L., Declercq, L., Beretvas, S.N., Onghena, P., Van Den Noortgate, W., 2020. The application of meta-analytic (multi-level) models with multiple random effects: a systematic review. Behav. Res. 52, 2031–2052. https://doi.org/10.3758/s13428-020-01373-9.

Fischer, B., Bullen, C., Elder, H., Fidalgo, T.M., 2020. Considering the health and social welfare impacts of non-medical cannabis legalization. World Psychiatry 19, 187–188. https://doi.org/10.1002/wps.20736.

Flores, V.A., Kisiolek, J.N., Ramani, A., Townsend, R., Rodriguez, E., Butler, B., Stewart, L.K., 2023. Effects of oral cannabidiol on health and fitness in healthy adults: an 8-week randomized trial. Nutrients 15, 2664. https://doi.org/10.3390/nu15122664.

Fond, G., Godin, O., Brunel, L., Aouizerate, B., Berna, F., Bulzacka, E., Capdevielle, D., Chereau, I., Dorey, J.M., Dubertret, C., Dubreucq, J., Faget, C., Gabayet, F., Le Strat, Y., Micoulaud-Franchi, J.A., Misdrahi, D., Rey, R., Richieri, R., Passerieux, C., Schandrin, A., Schürhoff, F., Tronche, A.M., Urbach, M., Vidalhet, P., Llorca, P.M., Leboyer, M., 2016. Peripheral sub-inflammation is associated with antidepressant consumption in schizophrenia. results from the multi-center FACE-SZ data set. J. Affect. Disord. 191, 209–215. https://doi.org/10.1016/j.jad.2015.11.017.

Fond, G., Berna, F., Andrianarisoa, M., Godin, O., Leboyer, M., Brunel, L., Aouizerate, B., Capdevielle, D., Chereau, I., D'Amato, T., Denizot, H., Dubertret, C., Dubreucq, J., Faget, C., Gabayet, F., Llorca, P.M., Mallet, J., Misdrahi, D., Passerieux, C., Richieri, R., Rey, R., Schandrin, A., Urbach, M., Vidailhet, P., Boyer, L., Schürhoff, F., The FACE-SZ (FondaMental Academic Centers of Expertise for Schizophrenia) group, 2017. Chronic low-grade peripheral inflammation is associated with severe nicotine dependence in schizophrenia: results from the national multicentric FACE-SZ cohort. Eur. Arch. Psychiatry Clin. Neurosci. 267, 465–472. https://doi.org/10.1007/s00406-017-0771-4.

Fridman, J., Bloemhof-Bris, E., Weizman, S., Kessler, T., Porat, D., Ivry, A., Wolf, A., Stryjer, R., Shelef, A., 2023. Inflammation markers among schizophrenia patients who use cannabis. Clin. Neuropharmacol. https://doi.org/10.1097/WNF.0000000000000558.

Furman, D., Campisi, J., Verdin, E., Carrera-Bastos, P., Targ, S., Franceschi, C., Ferrucci, L., Gilroy, D.W., Fasano, A., Miller, G.W., Miller, A.H., Mantovani, A., Weyand, C.M., Barzilai, N., Goronzy, J.J., Rando, T.A., Effros, R.B., Lucia, A., Kleinstreuer, N., Slavich, G.M., 2019. Chronic inflammation in the etiology of disease across the life span. Nat. Med. 25, 1822–1832. https://doi.org/10.1038/s41591-019-0675-0.

Fuster, D., García-Calvo, X., Bolao, F., Zuluaga, P., Rocamora, G., Hernández-Rubio, A., Sanvisens, A., Tor, J., Muga, R., 2020. Cannabis use is associated with monocyte activation (sCD163) in patients admitted for alcohol use disorder treatment. Drug Alcohol Depend. 216, 108231. https://doi.org/10.1016/j.drugalcdep.2020.108231.

Giacobbe, J., Marrocu, A., Di Benedetto, M.G., Pariante, C.M., Borsini, A., 2021. A systematic, integrative review of the effects of the endocannabinoid system on inflammation and neurogenesis in animal models of affective disorders. Brain Behav. Immun. 93, 353–367. https://doi.org/10.1016/j.bbi.2020.12.024.

Gibson, C.L., Nia, A.B., Spriggs, S.A., DeFrancisco, D., Swift, A., Perkel, C., Zhong, X., Mazumdar, M., Fernandez, N., Patel, M., Kim-Schulze, S., Hurd, Y.L., 2020. Cannabinoid use in psychotic patients impacts inflammatory levels and their association with psychosis severity. Psychiatry Res. 293, 113380. https://doi.org/10.1016/j.psychres.2020.113380.

Goetz, R.L., Miller, B.J., 2019. Total and differential white blood cell counts, cocaine, and marijuana use in patients with schizophrenia. J. Nerv. Ment. Dis. 207, 633–636. https://doi.org/10.1097/NMD.0000000000001019.

Grodin, E.N., McManus, K.R., Ray, L.A., 2024. Examining the moderating role of cannabis use on the relationship between alcohol consumption and inflammation in individuals with alcohol use disorder. Addict. Biol. 29, e13431. https://doi.org/10.1111/adb.13431.

Guler, E.M., Bektay, M.Y., Akyildiz, A.G., Sisman, B.H., Izzettin, F.V., Kocyigit, A., 2020. Investigation of DNA damage, oxidative stress, and inflammation in synthetic cannabinoid users. Hum. Exp. Toxicol. 39, 1454–1462. https://doi.org/10.1177/0960327120930057.

Guzel, D., Yazici, A.B., Yazici, E., Erol, A., 2017. Alterations of the hematologic cells in synthetic cannabinoid users. J. Clin. Lab. Anal. 31. https://doi.org/10.1002/jcla.22131.

Harrer, M., Cuijpers, P., A, F.T., Ebert, D.D., 2021. Doing Meta-Analysis With R: A Hands-On Guide, 1st ed. Chapman & Hall/CRC Press, Boca Raton, FL and London.

Heck, D., Gronau, Q., Wagenmakers, E., 2017. metaBMA: Bayesian model averaging for random and fixed effects meta-analysis. Availabe at https://CRAN. R-project. org/package= metaBMA.

Heiss, A., 2022. Marginalia: A guide to figuring out what the heck marginal effects, marginal slopes, average marginal effects, marginal effects at the mean, and all these other marginal things are [WWW Document]. https://doi.org/10.59350/40xaj-4e562.

Henshaw, F.R., Dewsbury, L.S., Lim, C.K., Steiner, G.Z., 2021. The effects of cannabinoids on pro- and anti-inflammatory cytokines: a systematic review of *in vivo* studies. Cannabis Cannabinoid Res. 6, 177–195. https://doi.org/10.1089/can.2020.0105.

Hoch, E., Lorenzetti, V., 2020. Mapping and mitigating the health risks of legalizing recreational cannabis use: a call for synergy between research and policy. World Psychiatry 19, 189–191. https://doi.org/10.1002/wps.20738.

Ibarra-Lecue, I., Unzueta-Larrinaga, P., Barrena-Barbadillo, R., Villate, A., Horrillo, I., Mendivil, B., Landabaso, M.A., Meana, J.J., Etxebarria, N., Callado, L.F., Urigüen, L., 2022. Cannabis use selectively modulates circulating biomarkers in the blood of schizophrenia patients. Addict. Biol. 27, e13233. https://doi.org/10.1111/adb.13233.

Jantsch, J., da Rodrigues, F., Wickert, F., Fraga, G., Dias, V.S., Bitencourt, Y.M., Giovenardi, M., Guedes, R.P., 2025. Cannabidiol attenuates diet-induced metabolic endotoxemia, neuroinflammation, and anxiety-like behaviors in male aged rats. Brain Behav. Immun. 130, 106121. https://doi.org/10.1016/j.bbi.2025.106121.

Karoly, H.C., Bidwell, L.C., Mueller, R.L., Hutchison, K.E., 2018. Investigating the relationships between alcohol consumption, cannabis use, and circulating cytokines: a preliminary analysis. Alcoholism Clin. Exp. Res. 42, 531–539. https://doi.org/10.1111/acer.13592.

Keen, L., Pereira, D., Latimer, W., 2014. Self-reported lifetime marijuana use and interleukin-6 levels in middle-aged African Americans. Drug Alcohol Depend. 140, 156–160. https://doi.org/10.1016/j.drugalcdep.2014.04.011.

Keen, L., Turner, A.D., Callender, C., Campbell, A., 2015. Differential effects of self-reported lifetime marijuana use on interleukin-1 alpha and tumor necrosis factor in african american adults. J. Behav. Med. 38, 527–534. https://doi.org/10.1007/s10865-015-9625-6.

Klein, T.W., 2005. Cannabinoid-based drugs as anti-inflammatory therapeutics. Nat. Rev. Immunol. 5, 400–411. https://doi.org/10.1038/nri1602.

Kreis, I., Fjelnseth Wold, K., Åsbø, G., Bärthel Flaaten, C., Engen, M.J., Lyngstad, S.H., Hustad Widing, L., Sheikh, M.A., Frogner Werner, M.C., Bakken, E., Ueland, T., Steen, N.E., Melle, I., 2025. Recent cannabis use affects the association between baseline immune markers and long-term outcomes in psychosis. Transl. Psychiatry 15, 282. https://doi.org/10.1038/s41398-025-03498-x.

Lake, S., Murray, C.H., Henry, B., Strong, L., White, K., Kilmer, B., Cooper, Z.D., 2025. High-potency cannabis use and health: a systematic review of observational and experimental studies. Am. J. Psychiatry. https://doi.org/10.1176/appi.ajp.20240269.

Lima, M.G., Tardelli, V.S., Brietzke, E., Fidalgo, T.M., 2021. Cannabis and inflammatory mediators. Eur. Addict. Res. 27, 16–24. https://doi.org/10.1159/000508840.

Lisano, J.K., Kisiolek, J.N., Smoak, P., Phillips, K.T., Stewart, L.K., 2020. Chronic cannabis use and circulating biomarkers of neural health, stress, and inflammation in physically active individuals. Appl. Physiol. Nutr. Metab. 45, 258–263. https://doi.org/10.1139/apnm-2019-0300.

Lisano, J.K., Skrzynski, C.J., Giordano, G., Bryan, A.D., Bidwell, L.C., 2025. Inflammatory state moderates response to cannabis on negative affect and sleep quality in individuals with anxiety. Front. Behav. Neurosci. 19. https://doi.org/10.3389/fnbeh.2025.1549311.

Llorca-Bofí, V., Mur, M., Font, M., Palacios-Garrán, R., Sellart, M., del Agua-Martínez, E., Bioque, M., Arteaga-Henríquez, G., 2024. Differences in total and differential white blood cell counts and in inflammatory parameters between psychiatric inpatients with and without recent consumption of cannabinoids, opioids, or cocaine: a retrospective single-center study. Brain Behav. Immun. Health 42, 100898. https://doi.org/10.1016/j.bbih.2024.100898.

Makowski, D., Ben-Shachar, M.S., Chen, S.H.A., Lüdecke, D., 2019. Indices of effect existence and significance in the bayesian framework. Front. Psychol. 10. https://doi.org/10.3389/fpsyg.2019.02767.

Mastrofini, G.F., McFadden, B.A., Chandler, A.J., Lints, B.S., Cintineo, H.P., Rhoades, N. D., Vincenty, C.S., Stray-Gundersen, S.O., Lane, A.D., Arent, S.M., 2024. The effects of a brand-specific, hemp-derived cannabidiol product on physiological, biochemical, and psychometric outcomes in healthy adults: a double-blind, randomized clinical trial. J. Int. Soc. Sports Nutr. 21, 2370430. https://doi.org/10.1080/15502783.2024.2370430.

Meier, M.H., Caspi, A., Cerdá, M., Hancox, R.J., Harrington, H., Houts, R., Poulton, R., Ramrakha, S., Thomson, W.M., Moffitt, T.E., 2016. Associations between cannabis use and physical health problems in early midlife: a longitudinal comparison of persistent cannabis vs tobacco users. JAMA Psychiatry 73, 731–740. https://doi.org/10.1001/jamapsychiatry.2016.0637.

Meier, M.H., Pardini, D., Beardslee, J., Matthews, K.A., 2019. Associations between cannabis use and cardiometabolic risk factors: a longitudinal study of men. Psychosom. Med. 81, 281–288. https://doi.org/10.1097/PSY.0000000000000665.

Menzel, A., Samouda, H., Dohet, F., Loap, S., Ellulu, M.S., Bohn, T., 2021. Common and novel markers for measuring inflammation and oxidative stress ex vivo in research and clinical practice—which to use regarding disease outcomes? Antioxidants 10, 414. https://doi.org/10.3390/antiox10030414.

Mésidor, M., Xu, M., Diop, A., Fantodji, C., Parent, M.-É., Keil, A., 2025. Use of causal inference methods in case-control studies: a methodology review. kwaf182 Am. J. Epidemiol.. https://doi.org/10.1093/aje/kwaf182.

Miller, A.H., 2020. Beyond depression: the expanding role of inflammation in psychiatric disorders. World Psychiatry 19, 108–109. https://doi.org/10.1002/wps.20723.

Miller, B.J., Buckley, P.F., McEvoy, J.P., 2018. Inflammation, substance use, psychopathology, and cognition in phase 1 of the clinical antipsychotic trials of intervention effectiveness study. Schizophr. Res. 195, 275–282. https://doi.org/10.1016/j.schres.2017.08.027.

Mitchell, C.M., El Jordi, O., Yamamoto, B.K., 2019. Inflammatory mechanisms of abused drugs, in: Advances in Neurotoxicology. Elsevier, pp. 133–168. https://doi.org/10.1016/bs.ant.2018.10.006.

Mongan, D., Raj Susai, S., Föcking, M., Byrne, J.F., Zammit, S., Cannon, M., Cotter, D.R., 2023. Associations between plasma inflammatory markers and psychotic disorder, depressive disorder and generalised anxiety disorder in early adulthood: a nested case-control study. Brain Behav. Immun. 111, 90–100. https://doi.org/10.1016/j.bbi.2023.03.025.

Moriarity, D.P., Mengelkoch, S., Slavich, G.M., 2023. Incorporating causal inference perspectives into psychoneuroimmunology: a simulation study highlighting concerns about controlling for adiposity in immunopsychiatry. Brain Behav. Immunity 113, 259–266. https://doi.org/10.1016/j.bbi.2023.06.022.

Morissette, F., Mongeau-Pérusse, V., Rizkallah, E., Thébault, P., Lepage, S., Brissette, S., Bruneau, J., Dubreucq, S., Stip, E., Cailhier, J.-F., Jutras-Aswad, D., 2021. Exploring cannabidiol effects on inflammatory markers in individuals with cocaine use disorder: a randomized controlled trial. Neuropsychopharmacol. 46, 2101–2111. https://doi.org/10.1038/s41386-021-01098-z.

Moshfeghinia, R., Najibi, A., Moradi, M., Assadian, K., Ahmadi, J., 2024. The association between hematological markers of inflammation and chronic cannabis use: a systematic review and meta-analysis of observational studies. Front. Psychiatry 15, 1438002. https://doi.org/10.3389/fpsyt.2024.1438002.

Muniyappa, R., Sable, S., Ouwerkerk, R., Mari, A., Gharib, A.M., Walter, M., Courville, A., Hall, G., Chen, K.Y., Volkow, N.D., Kunos, G., Huestis, M.A., Skarulis, M.C., 2013. Metabolic effects of chronic cannabis smoking. Diabetes Care 36, 2415–2422. https://doi.org/10.2337/dc12-2303.

Ngueta, G., Bélanger, R.E., Laouan-Sidi, E.A., Lucas, M., 2015. Cannabis use in relation to obesity and insulin resistance in the inuit population: cannabis use, obesity, and insulin resistance. Obesity 23, 290–295. https://doi.org/10.1002/oby.20973.

Okafor, C.N., Li, M., Paltzer, J., 2020. Self-reported cannabis use and biomarkers of inflammation among adults in the United States. Brain Behav. Immun. Health 7, 100109. https://doi.org/10.1016/j.bbih.2020.100109.

Olivieri, F., Marchegiani, F., Matacchione, G., Giuliani, A., Ramini, D., Fazioli, F., Sabbatinelli, J., Bonafè, M., 2023. Sex/gender-related differences in inflammaging. Mech. Ageing Develop. 211, 111792. https://doi.org/10.1016/j.mad.2023.111792.

Orum, M.H., Kara, M.Z., 2020. Monocyte-to-lymphocyte ratio and platelet-tolymphocyte ratio in opioid use disorder and marijuana use disorder. | Dusunen Adam. J. Psychiatry Neurol. Sci. | EBSCOhost [WWW Document]. https://doi.org/10.14744/DAJPNS.2020.00073.

Ouzzani, M., Hammady, H., Fedorowicz, Z., Elmagarmid, A., 2016. Rayyan—a web and mobile app for systematic reviews. Syst. Rev. 5, 210. https://doi.org/10.1186/s13643-016-0384-4.

Pacifici, R., Zuccaro, P., Pichini, S., Roset, P.N., Poudevida, S., Farré, M., Segura, J., De la Torre, R., 2003. Modulation of the immune system in cannabis users. JAMA 289, 1929–1931. https://doi.org/10.1001/jama.289.15.1929-b.

Pacifici, R., Zuccaro, P., Farré, M., Poudevida, S., Abanades, S., Pichini, S., Langohr, K., Segura, J., De La Torre, R., 2007. Combined immunomodulating properties of 3,4-methylenedioxymethamphetamine (MDMA) and cannabis in humans. Addiction 102, 931–936. https://doi.org/10.1111/j.1360-0443.2007.01805.x.

Page, M.J., McKenzie, J.E., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D., Shamseer, L., Tetzlaff, J.M., Akl, E.A., Brennan, S.E., Chou, R., Glanville, J., Grimshaw, J.M., Hróbjartsson, A., Lalu, M.M., Li, T., Loder, E.W., Mayo-Wilson, E., McDonald, S., McGuinness, L.A., Stewart, L.A., Thomas, J., Tricco, A.C., Welch, V.A., Whiting, P., Moher, D., 2021. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 372, n71. https://doi.org/10.1136/bmj.n71.

Rajasekera, T.A., Joseph, A., Pan, H., Dreyfuss, J.M., Fida, D., Wilson, J., Behee, M., Fichorova, R.N., Cinar, R., Spagnolo, P.A., 2025. Sex Differences in Endocannabinoid and Inflammatory Markers Associated with Posttraumatic Stress Disorder. medRxiv 2025.01.13.25320467. https://doi.org/10.1101/2025.01.13.25320467.

Rajavashisth, T.B., Shaheen, M., Norris, K.C., Pan, D., Sinha, S.K., Ortega, J., Friedman, T.C., 2012. Decreased prevalence of diabetes in marijuana users: cross-sectional data from the National Health and Nutrition Examination Survey (NHANES) III. BMJ Open 2, e000494. https://doi.org/10.1136/bmjopen-2011-000494.

Rakotoarivelo, V., Mayer, T.Z., Simard, M., Flamand, N., Di Marzo, V., 2024. The impact of the CB2 cannabinoid receptor in inflammatory diseases: an update. Molecules 29, 3381. https://doi.org/10.3390/molecules29143381.

Ribeiro, C.B., Castro, F. de O.F. de, Dorneles, G.P., de Sousa Barros, J.B., Silva, J.M., Tavares, C., Carvalho, H.R., Carlos da Cunha, L., Nagib, P., Hoffmann, C., Peres, A., Torres Romäo, P.R., Pfrimer, I.A.H., Fonseca, S.G. da, 2021. The concomitant use of cannabis and cocaine coexists with increased LPS levels and systemic inflammation in male drug users. Cytokine 141, 155472. https://doi.org/10.1016/j.cyto.2021.155472.

Romeo, B., Lestra, V., Martelli, C., Benyamina, A., Hamdani, N., 2022. Cannabis cessation, inflammatory markers and schizophrenia. J. Dual Diagn. 18, 33–41. https://doi.org/10.1080/15504263.2021.2013697.

Romeo, B., Lestra, V., Martelli, C., Amirouche, A., Benyamina, A., Hamdani, N., 2024. Increased markers of inflammation after cannabis cessation and their association with psychotic symptoms. Acta Neuropsychiatr. 36, 118–127. https://doi.org/10.1017/neu.2023.24.

Saroz, Y., Kho, D.T., Glass, M., Graham, E.S., Grimsey, N.L., 2019. Cannabinoid Receptor 2 (CB2) Signals via G-alpha-s and Induces IL-6 and IL-10 Cytokine Secretion in Human Primary Leukocytes. ACS Pharmacol. Transl. Sci. 2, 414–428. https://doi.org/10.1021/acsptsci.9b00049.

Sehlikoğlu, Ş., Yıldız, S., Kazğan Kılıçaslan, A., Kurt, O., Göçüm, E., Han Almiş, B., 2024. Evaluation of complete blood cell count parameters and their role in inflammation in patients with methamphetamine and synthetic cannabis use disorder. Psychiatry Clin. Psychopharmacol. 34, 134–143. https://doi.org/10.5152/pcp.2024.23803.

Shu, C., Zheng, C., Zhang, G., 2024. Exploring the utility of a latent variable as comprehensive inflammatory prognostic index in critically ill patients with cerebral infarction. Front. Neurol. 15, 1287895. https://doi.org/10.3389/fneur.2024.1287895.

Solmi, M., De Toffol, M., Kim, J.Y., Choi, M.J., Stubbs, B., Thompson, T., Firth, J., Miola, A., Croatto, G., Baggio, F., Michelon, S., Ballan, L., Gerdle, B., Monaco, F., Simonato, P., Scocco, P., Ricca, V., Castellini, G., Fornaro, M., Murru, A., Vieta, E., Fusar-Poli, P., Barbui, C., Ioannidis, J.P.A., Carvalho, A.F., Radua, J., Correll, C.U., Cortese, S., Murray, R.M., Castle, D., Shin, J.I., Dragioti, E., 2023. Balancing risks and benefits of cannabis use: umbrella review of meta-analyses of randomised controlled trials and observational studies. BMJ e072348. https://doi.org/10.1136/bmj-2022-072348.

Stewart, J.L., Burrows, K., May, A.C., McNaughton, B.A., Smith, R., Kuplicki, R., Paulus, M.P., Figueroa-Hall, L., 2024. C-reactive protein concentrations diverge as a function of substance use disorder: a pre-registered replication in a clinical sample. Drug Alcohol Depend. 260, 111323. https://doi.org/10.1016/j.drugalcdep.2024.111323.

Suárez-Pinilla, P., López-Gil, J., Crespo-Facorro, B., 2014. Immune system: a possible nexus between cannabinoids and psychosis. Brain Behav. Immun. 40, 269–282. https://doi.org/10.1016/j.bbi.2014.01.018.

Szabo, A., Akkouh, I.A., Ueland, T., Lagerberg, T.V., Dieset, I., Bjella, T., Aukrust, P., Le Hellard, S., Stavrum, A.-K., Melle, I., Andreassen, O.A., Djurovic, S., 2020. Cannabis use is associated with increased levels of soluble gp130 in schizophrenia but not in bipolar disorder. Front. Psychiatry 11, 642. https://doi.org/10.3389/fpsyt.2020.00642.

Thylur, D.S., Goldsmith, D.R., 2022. Brick by brick: building a transdiagnostic understanding of inflammation in psychiatry. Harvard Rev. Psychiatry 30, 40. https://doi.org/10.1097/HRP.0000000000000326.

Volkow, N.D., Swanson, J.M., Evins, A.E., DeLisi, L.E., Meier, M.H., Gonzalez, R., Bloomfield, M.A.P., Curran, H.V., Baler, R., 2016. Effects of cannabis use on human behavior, including cognition, motivation, and psychosis: a review. JAMA Psychiatry 73, 292. https://doi.org/10.1001/jamapsychiatry.2015.3278.

Wang, R., Trigo, J.M., Le Foll, B., 2023a. Effects of sub-chronic nabiximols on biological markers of individuals undergoing a clinical trial for the treatment of cannabis use disorder. Am. J. Transl. Res. 15, 5228–5238.

Wang, X., Lin, C., Jin, S., Wang, Y., Peng, Y., Wang, X., 2023b. Cannabidiol alleviates neuroinflammation and attenuates neuropathic pain via targeting FKBP5. Brain Behav. Immun. 111, 365–375. https://doi.org/10.1016/j.bbi.2023.05.008.

Whiting, P.F., Wolff, R.F., Deshpande, S., Di Nisio, M., Duffy, S., Hernandez, A.V., Keurentjes, J.C., Lang, S., Misso, K., Ryder, S., Schmidlkofer, S., Westwood, M., Kleijnen, J., 2015. Cannabinoids for medical use: a systematic review and meta-analysis. JAMA 313, 2456. https://doi.org/10.1001/jama.2015.6358.