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Risk-thresholds for the association between frequency of cannabis use and the development of psychosis: a systematic review and meta-analysis

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Abstract

Background. Epidemiological studies show a dose–response association between cannabis use and the risk of psychosis. This review aimed to determine whether there are identifiable risk-thresholds between the frequency of cannabis use and psychosis development.

Methods. Systematic search of Embase, MEDLINE, PsycINFO, CINAHL, and Web of Science for relevant studies (1 January 2010–26 April 2021). Case–control or cohort studies that investigated the relationship between cannabis use and the risk of psychosis development that reported effect estimates [odds ratios (OR), hazard ratios (HR), risk ratios (RR)] or the raw data to calculate them, with information on the frequency of cannabis consumption were included. Effect estimates were extracted from individual studies and converted to RR. Two-stage dose–response multivariable meta-analytic models were utilized and sensitivity analyses conducted. The Newcastle Ottawa Scale was used to assess the risk of bias of included studies.

Results. Ten original (three cohorts, seven case–control) studies were included, including 7390 participants with an age range of 12–65 years. Random-effect model meta-analyses showed a significant log-linear dose–response association between cannabis use frequency and psychosis development. A restricted cubic-splines model provided the best fit for the data, with the risk of psychosis significantly increasing for weekly or more frequent cannabis use [RR = 1.01, 95% confidence interval (CI) 0.93–1.11 yearly; RR = 1.10, 95% CI 0.97–1.25 monthly; RR = 1.35, 95% CI 1.19–1.52 weekly; RR = 1.76, 95% CI 1.47–2.12 daily]

Conclusion. Individuals using cannabis frequently are at increased risk of psychosis, with no significant risk associated with less frequent use. Public health prevention messages should convey these risk-thresholds, which should be refined through further work.

Introduction

Cannabis use is common in the general population in many high-income countries. Some cannabis policy regimes have become more liberal, including legalization and regulation of adult use and supply in some instances (Fischer, Daldegan-Bueno, & Boden, 2020; Hall et al., 2019). Non-medical cannabis use has been legalized in Canada, Uruguay, and Mexico, and in fifteen US states, with other jurisdictions considering such a step.

An essential component of public health-oriented approaches to cannabis policy is how to best reduce health harms among – the mostly young – populations of users (Fischer, Rehm, & Hall, 2009; Hoch & Lorenzetti, 2020; Melchior et al., 2019). The main risks for adverse health outcomes of non-medical cannabis use include acute and chronic neurocognitive functioning impairments; mental health problems (psychosis/schizophrenia, depression); cannabis use disorder (CUD), cannabis-impaired driving and motor-vehicle crashes resulting in injuries/death, and pulmonary problems associated with cannabis smoking (Duperrouzel, Granja, Pacheco-Colon, & Gonzales, 2020; Leung, Chan, Hides, & Hall, 2020; National Academies

of Sciences Engineering & Medicine, 2017; Preuss et al., 2021; Sánchez-Gutiérrez et al., 2020; Volkow et al., 2016).

Recent reviews have confirmed a moderately significant association between cannabis use and psychosis (Kiburi, Molebatsi, Ntlantsana, & Lynskey, 2021; Polkosnik, Sorkhou, & George, 2021; van der Steur, Batalla, & Bossong, 2020). The association between cannabis use and mental health problems, most notably psychosis, receives prominent attention in policy debates, even though other adverse outcomes (e.g. cannabis-impaired driving, CUD) are more common and make greater contributions to the cannabis-attributable burden-of-disease (DeVylder, Mittal, & Schiffman, 2021; Hall & Degenhardt, 2008; Imtiaz et al., 2016; Leyton, 2019). Psychotic disorders, such as schizophrenia, are severe clinical and usually chronic events, entailing extensive health and societal costs (de Oliveira, Cheng, Rehm, & Kurdyak, 2016; DeVylder et al., 2021; Hasin & Walsh, 2021). The relationship between cannabis use and psychosis is multidirectional, with psychosis caused by cannabis use being just one possible pathway. The exact mechanisms underlying this relationship continue to be debated (Murray & Hall, 2020; Wright, Cather, Gilman, & Evins, 2020). The proportion of first-episode psychosis (FEP) attributable to cannabis use was estimated to be 12% in five national European sites (Di Forti et al., 2019). Current evidence however, suggests that the legalization of non-medical cannabis use may lead to an increased incidence of psychosis (Hamilton & Monaghan, 2019; Ksir & Hart, 2016; Murray & Hall, 2020). Therefore, evidence-based methods to reduce cannabis-attributable psychosis outcomes are crucially important for individual users and public health protection, especially in liberalized policy environments for cannabis.

While evidence for cannabis use as a causal contributor to psychosis development exist (Polkosnik et al., 2021; Wright et al., 2020), additional cannabis use-specific characteristics that function as moderating factors for this relationship have been identified. These factors include the age-of-use onset, high potency cannabis use, and the frequency of use (Matheson & Le Foll, 2020; Sideli, Quigley, La Cascia, & Murray, 2020; van der Steur et al., 2020). Frequent cannabis use, specifically, has been shown to function as a strong predictor of psychosis and other adverse outcomes (e.g. cognitive functioning, psychosocial outcomes and CUD) (Fischer et al., 2022; Kroon, Kuhns, Hoch, & Cousijn, 2020; Leung et al., 2020; Lorenzetti, Chye, Silva, Solowij, & Roberts, 2019).

Systematic reviews have consistently found a high risk of psychosis associated with frequent cannabis use. An umbrella review (2020) involving four meta-analyses found a dose–response relationship between cannabis use and the risk of psychosis (Hasan et al., 2020). A meta-analysis focusing on adolescents (Kiburi et al., 2021) showed a 2.5-fold increase in the odds of psychosis onset in frequent *v.* infrequent cannabis users [odds ratio (OR) 2.7, 95% confidence interval (CI) 1.65–3.71]. Another meta-analysis showed a four-fold increase in odds of psychosis (OR 3.90, 95%CI 2.84–5.34) for the most frequent cannabis use and a two-fold increase (OR 1.97, 95% CI 1.68–2.31) for moderate as compared to non-use (Marconi, Di Forti, Lewis, Murray, & Vassos, 2016). Elsewhere, a two-fold increase (AOR = 2.09, 95% CI 1.54–2.84) in the odds of psychosis had been found in a comparison of frequent to no cannabis use (Moore et al., 2007). Other reviews, however, have been limited in their level of detail about the relationship between cannabis use frequency and psychosis risk where, for example, frequent use is commonly compared to only infrequent or non-use (Campeny et al., 2020; Hasan et al., 2020; Kiburi et al., 2021; Marconi et al., 2016; Polkosnik et al., 2021; van der Steur et al., 2020). Binary categorizations between frequent use *v.* no use cannot distinguish possibly different risk-by frequency of use levels (e.g. daily, weekly, monthly)(Hoch & Lorenzetti, 2020; Kraan, Velthorst, Koenders, & Zwaart, 2016), and therefore cannot indicate possible thresholds of cannabis use frequency where the risk of psychosis development may significantly change.

Other illustrations of substance use-related risk-thresholds for health outcomes exist. For example, systematic reviews have quantified exposure levels of alcohol use (e.g. by standard drinks/week) that represent risk-thresholds for stroke, cardio-vascular disease and atrial fibrillation (Samokhvalov, Irving, & Rehm, 2010; Tu et al., 2021; Wood et al., 2018), which have been translated into 'Low Risk Drinking Guidelines' (Holmes, Angus, Meier, Buykx, & Brennan, 2019). Similarly, recent 'Lower-Risk Gambling Guidelines' have quantified risk-thresholds for gambling exposure toward problem incidence (Young et al., 2021). Conversely, recently updated 'Lower-Risk Cannabis Use Guidelines' were largely unable to list risk-thresholds for main adverse outcomes due to a lack of adequately quantified exposure data (Fischer et al., 2022). If risk-thresholds for cannabis use frequency and psychosis can be identified, these may inform prevention/educational messages toward reducing cannabis-related harm among users.

In this context, the aim of this systematic review and meta-analysis was to determine whether significant risk thresholds exist between different levels of frequency of non-medical cannabis use and the development of psychosis.

Methods

This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 framework (online Supplementary eTable 1) (Page et al., 2021). The study protocol was registered pre-initiation with the International Register of Systematic Reviews (PROSPERO)(#CRD42021234708). Study data used in the analyses, and other related details are available upon request.

Search strategy

Searches were conducted in Embase, MEDLINE, PsycINFO, CINAHL, and Web of Science. The search strategy (online Supplementary eMethods 1) was initially developed for Embase and subsequently modified for other databases. Search terms included a mixture of Medical Index Subject Headings (MeSH) and keywords related to the main search topics (e.g. cannabis, use frequency/dose–response relationships, and psychosis). Databases were searched from 1 January 2010, through 26 April 2021. Reference lists of included articles were manually searched for potential additional studies of relevance.

Inclusion and exclusion criteria

Studies were included in this review if they: (1) investigated the relationship between cannabis use and risk of psychosis development, (2) were of case–control or cohort design, (3) included hazard ratios (HRs), odds ratios (ORs), or risk ratios (RRs) with 95% confidence intervals (95% CI) or the data required to calculate them, and (4) included quantified information on the frequency

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of cannabis consumption, and specifically allowed attribution to at least three frequency categories (i.e. 'monthly', 'weekly', 'daily/near-daily') because at least three categories were required to complete the dose–response analysis.

Studies were excluded if: (1) they included participants with a pre-existing psychotic condition prior to the initiation of cannabis use, diagnosed according to Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association, 2013) or International Classification of Diseases 11th Edition (ICD-11) (World Health Organization, 2018)criteria, (2) investigated cannabis use primarily for medicinal purposes, and (3) included synthetic cannabinoids in their scope.

Only studies published in 2010 onward were considered for inclusion. This cut-off was chosen in part because cannabis potency as a known predictor of use-related psychosis outcomes and has steadily increased in recent years (Sideli et al., 2020). For example, the potency of cannabis in Europe has been reported to have doubled from 8.9% tetrahydrocannabinol (THC) in 2008 to over 17% THC in 2017, while cannabidiol (CBD) levels remained stable (Chandra et al., 2019). No restrictions were placed on participants age or publication language. Grey literature, such as conference abstracts and dissertations were not excluded from database searches (e.g. Web of Science Core Collection). Additional sources of grey literature, such as government websites and clinical trial repositories, were not considered for this review due to the fact that randomized trials and organizational reports would not contain the type of data required for this analysis. Case–control studies with less than ten matched-pairs were excluded due to the increased risk of bias (RoB) encountered in studies with sample sizes below this threshold (Dekkers et al., 2019).

Study selection

All citations identified from the searches were uploaded into Covidence systematic review software (Veritas Health Innovation, 2021) and duplicates removed. Citations were screened initially by title and abstract in duplicate by two independent reviewers, with full-text screening completed in the same manner. Translations were obtained for articles published in non-English languages. Disagreements related to both title/abstract and full text screening were resolved through consensus, and inter-rater reliability (IRR) was calculated. A PRISMA flow diagram presents the results of the study screening and inclusion process (Page et al., 2021).

Data extraction

Study data were extracted by two independent reviewers, using consensus discussions for disagreements, and final data verifications conducted by the study statistician. Basic study characteristics were extracted, including study type and location, sample size, sex and age details. The primary outcome of interest was the risk of psychosis development according to DSM-IV or ICD-11 criteria or validated questionnaires. The exposure measure was the frequency of cannabis use, which was categorically pre-defined based on the frequency of use categories commonly used in the cannabis literature (Callaghan, Sanches, & Kish, 2020; Goodman, Leos-Toro, & Hammond, 2019; Steeger et al., 2021). The categories utilized were as follows: (1) never/no use, (2) 1–11 days a year ('yearly'), (3) 1–3 days a month ('monthly'), (4) 1–4 days a week ('weekly'), and (5) 5–7 days a week ('daily/near-daily'), with study data standardized into these categories for analysis. For studies that presented use frequency information for more than one-time point, the most current frequency of use data were recorded. Effect estimates were obtained from individual studies.

Data analysis

Relative risk (RR) was used as the measure of association between cannabis use frequency and psychosis development (Hogue, Gaylor, & Schulz, 1983). Where reported, ORs were converted to RRs [formula: $RR = OR/[(1-P_o) + (P_o \times OR)$, where P_o is the outcome incidence] (Zhang & Yu, 1998). RRs were calculated from raw data for studies without effect estimates. Two-stage dose–response multi-variate meta-analytic models were conducted to estimate the relationship between the cannabis use frequency and psychosis development using the RR data (Crippa & Orsini, 2016). First, the dose–response associations between log-relative-risk and levels of cannabis use according to frequency categories were analyzed within each study (Greenland & Longnecker, 1992). Second, study-specific estimates were combined across studies using multi-variate random effect modeling [REM] (Jackson et al., 2016). Sensitivity analyses were performed using both quadratic and flexible non-linear models with restricted cubic splines with three knots (10th, 50th, and 90th percentiles) of the distribution (Liu, Cook, Bergström, & Hsieh, 2009; Orsini, Bellocco, & Greenland, 2006). Goodness-of-fit statistics (Akaike information criteria 'AIC', deviance test 'D', and the coefficient of determination 'R^2') were assessed to select the best-fitting model (Discacciati, Crippa, & Orsini, 2017). A hierarchical multi-level multivariate meta-analytical approach for data plotting was used to account for statistical dependence in effect sizes from multiple within-study comparison arms (cannabis use frequencies) to a common control group (non-use) (Assink & Wibbelink, 2016; Gleser & Olkin, 2009; Pastor & Lazowski, 2017). Study-level variables in the analyses included the categories of cannabis use frequency, number of psychosis cases in each exposure group, and the natural logarithm and the standard error for the relative risk logarithms (Liu et al., 2009). All data-analyses were completed using STATA v.16 (IPDFC module) (StataCorp, 2019) and R (dosresmeta and Metafor packages) (R Core Team, 2020; Wei & Royston, 2020).

Statistical heterogeneity was assessed using the I^2 statistic, with thresholds assessed according to standard recommendations (Deeks, Higgins, & Altman, 2019). Publication bias was assessed by funnel plots, whereby regression/mixed-effects models and variance/standard errors assessed funnel plot asymmetry (Sterne & Egger, 2005).

Methodological quality and certainty-in-findings assessments

The RoB of included studies was assessed using the Newcastle Ottawa Scale versions for both cohort and case–control studies (Wells *et al.*, 2013). Bias for case selection, comparability of cases and controls, and exposure were examined. RoB assessments were completed in duplicate by two independent reviewers and disagreements resolved through consensus discussions. All studies assessed were included in this review, regardless of their methodological quality. Certainty-in-findings for the primary review outcome was assessed using the Grading of Recommendations Assessment, Development and Evaluations (GRADE) approach

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(Schunemann, Brozek, Guyatt, & Oxam, 2013) and reported through the online GRADEPro tool (https://gradepro.org/).

Results

Study selection (see Fig. 1)

The database searches returned 5253 results. After duplicate removal, 2847 records underwent title and abstract screening; 2706 records were excluded, and 141 retrieved for full-text review (online Supplementary eMethods 2). A total of ten original studies (three cohort and seven case–control studies) were included in this review (Arranz et al., 2018; Buchy et al., 2015; Bugra et al., 2013; Castañeda et al., 2020; Di Forti et al., 2015, 2019; Núñez et al., 2016; Rössler, Hengartner, Angst, & Ajdacic-Gross, 2012; Sideli et al., 2018; Valmaggia et al., 2014). Inter-rater reliability was 96% agreement ($\kappa = 0.60$) for title and abstract screening and 92% agreement ($\kappa = 0.62$) for full-text screening, respectively, indicating substantial agreement.

Study characteristics (see Table 1)

Studies included a total of 7390 participants ranging in age from 12 to 65 years. The primary outcome was FEP in 9/10 studies. In one cohort study, there were two primary outcomes, schizotypal signs and schizophrenia nuclear symptoms, which were included as two separate samples (Rössler, 2012-A and Rössler, 2012-B) in the meta-analysis (Rössler et al., 2012). Diagnoses of psychosis in the included studies were based on DSM-IV/ICD-10 criteria (5/10) or commonly utilized questionnaires/tools (5/10). The quality of included studies was assessed as moderate (3/10) or high (7/10; see online Supplementary material eTable 2 for RoB assessments).

Random effect model

The REM showed a significant log-linear dose–response association between the frequency of cannabis use category and risk of psychosis development ($p < 0.0001$). The risk of psychosis development increased with greater cannabis use frequency (Table 2), from RR:1.25 (95% CI 1.10–1.20) for yearly use, to RR:1.32 (95% CI 1.21–1.44) for monthly use, RR:1.51 (95% CI 1.32–1.72) for weekly use, and RR:1.71 (95% CI 1.45–2.06) for daily/near-daily use. Each category increase in cannabis consumption was associated with a 1.15-times (14.7%; 95% CI 9.8%-19.8%) increase in the risk of psychosis development.

Sensitivity analysis

Sensitivity analyses tested for potential non-linearity of associations. The log-linear assumption between cannabis use and risk of psychosis development was relaxed using a quadratic-trend and flexible non-linear model with restricted cubic-splines. In the quadratic-trend model, the risk of psychosis development varied according to cannabis use frequency; it increased from RR:1.01 (95% CI 0.95–1.07) for 'yearly' and RR:1.11 (95% CI 1.03–1.20) for monthly use, to RR:1.35 (95% CI 1.22–1.48) for 'weekly', and RR:1.76 (95%CI 1.29–2.13) for 'daily/near-daily' use (Table 2). The deviation from log-linearity was significant (Wald test $p < 0.05$, $\chi^2 = 42.48$).

The restricted cubic-splines-model demonstrated that the most conservative model had the best data-fit, with similar RRs to the quadratic-trend model. In this model, the risk of psychosis increased from RR:1.01 (95% CI 0.93–1.11) for 'yearly' and RR:1.10 (95% CI 0.97–1.25) for 'monthly' use, to RR:1.35 (95% CI 1.19–1.52) for 'weekly' and RR:1.76 (95% CI 1.47–2.12) for 'daily/near-daily' use. The deviation from log-linearity was statistically significant ($p < 0.05$, $\chi^2 = 37.79$).

Heterogeneity, publication bias, and certainty-in-findings

Multi-level-modeling was used to plot the data (Fig. 2), displaying significant heterogeneity ($I^2 = 87.2\%$; $p < 0.001$). A large proportion of the variance was explained by within-study-differences (86.67%), with between-study variance contributing to 0.56% of heterogeneity (online Supplementary eFig. 1). There was some funnel plot asymmetry when assessing publication bias, but the majority of estimates were clustered around the summary-effect-estimate. The counter-enhanced funnel plot did not reveal studies to be missing in areas of low statistical significance (online Supplementary eFig. 2) (Peters, Sutton, Jones, Abrams, & Rushton, 2008). Certainty-in-findings was rated as moderate according (GRADE), largely due to the observational nature of study designs and heterogeneity (online Supplementary eTable 3).

Discussion

This systematic review and meta-analysis found a dose–response relationship between the frequency of cannabis use and the development of psychosis, as shown by previous reviews (Hasan et al., 2020; Kiburi et al., 2021; Marconi et al., 2016; Moore et al., 2007; Polkosnik et al., 2021; van der Steur et al., 2020). Prior meta-analyses specifically documented a higher risk among daily users, mostly as compared to no or lower frequency use, with ORs ranging from 2.09 to 3.90 (Kiburi et al., 2021; Marconi et al., 2016; Moore et al., 2007). One systematic review and meta-analysis (2016) failed to find a statistically significant relationship between cannabis use and the odds of developing psychosis (Kraan et al., 2016) but only considered lifetime cannabis use, likely entailing associations too weak for detection.

Importantly, this review identified discernable risk-thresholds by cannabis use at a higher frequency for psychosis development. Specifically, weekly cannabis use was associated with a 35% (RR 1.35) increase in risk, and daily/near-daily use was associated with a 76% (RR 1.76%) increase in the risk of psychosis development compared to no use, according to the model of best-fit (restricted cubic-splines). Conversely, there were no significant increases in risk associated with monthly and yearly use in this model, suggesting an absence of increased risk for lower frequency use.

The role of cannabis use in the incidence of psychotic outcomes as a causal contributor is complex, because their causes are known to be multifactorial, being influenced by the environment, genes and their interactions (Ben Amar & Potvin, 2007; Hall & Degenhardt, 2008; Hamilton, 2017; Wright et al., 2020). Recent research has confirmed the importance of genetic influences, specifically polymorphisms on specific genes (e.g. COMT, AKT1) that make affected individuals more vulnerable to the psychogenetic effects of cannabis (Misiak et al., 2018; Polkosnik et al., 2021; van der Steur et al., 2020). The present review further compounds the evidence that specific (frequent) cannabis exposure patterns appear to significantly contribute to the multifactorial interplay toward psychosis outcomes.

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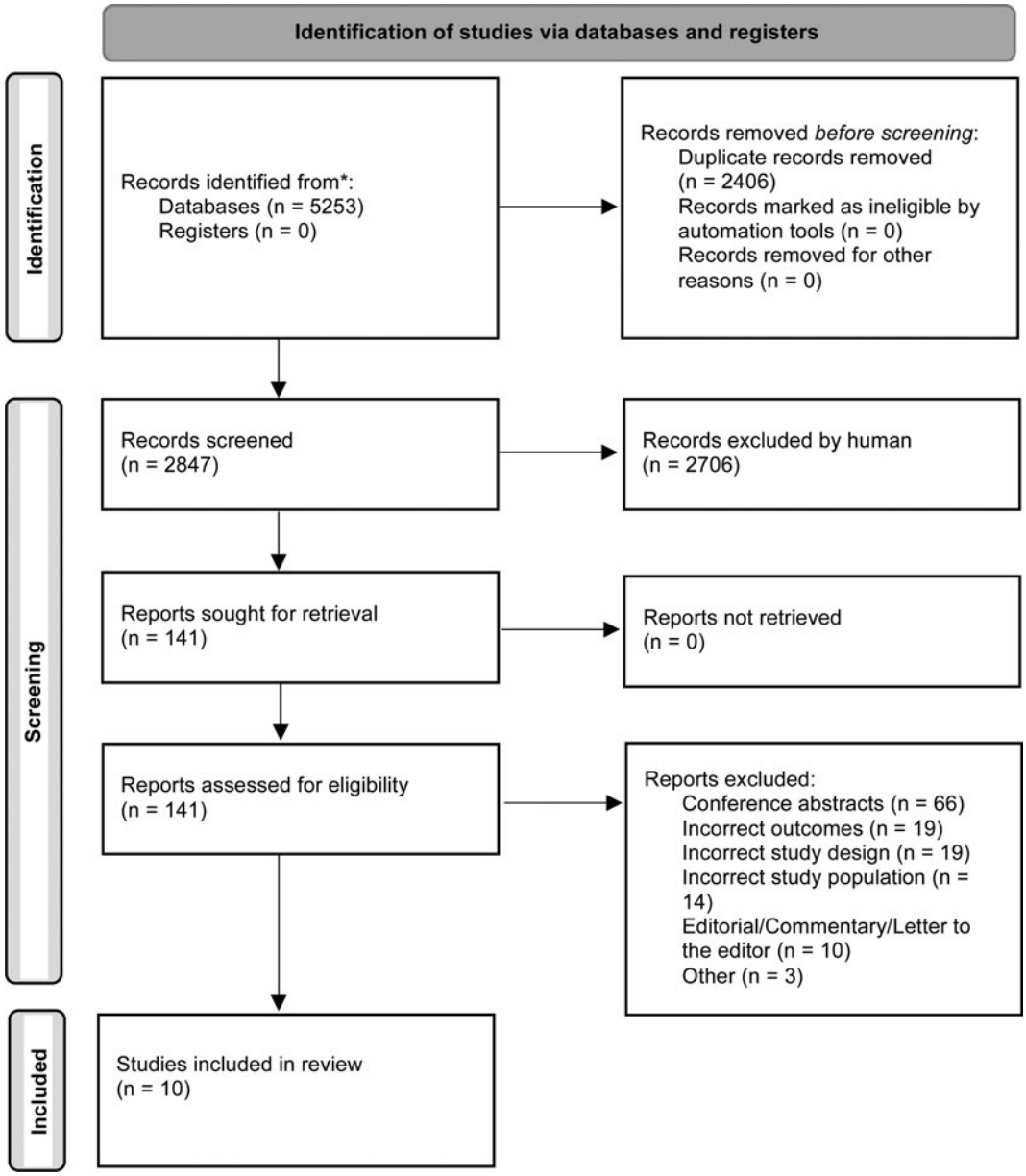

Fig. 1. PRISMA flow diagram for study selection process.

Beyond the role of use frequency, epidemiological data have identified the use of high potency cannabis, early age-of-use onset (e.g. pre-25), childhood trauma, and concurrent other substance use as contributing factors to psychosis development (Di Forti et al., 2015; Hall & Lynskey, 2020; Kiburi et al., 2021; van der Steur et al., 2020). Multiple risk-factors may interact to increase the risk for cannabis use-related psychosis more than the contributions of individual factors alone (Ben Amar & Potvin, 2007; Hosseini & Oremus, 2019). For example, an early age-of-use in adolescence combined with frequent use was found to increase the risk significantly as compared to either risk-factor alone, with genetic pre-dispositions as likely additional contributors (Kiburi et al., 2021). Similarly, the combination of daily use with high potency cannabis confers almost double the odds of developing psychosis (Di Forti et al., 2015).

The present review's findings have implications for evidence-based, public health-oriented targeted prevention messaging for cannabis use. While existing prevention content commonly convey categorical warnings regarding the link between cannabis use and risk for psychosis, our findings suggest that such a risk is significantly clearest for more frequent – i.e., 'weekly' or higher – patterns of cannabis use (Ghonaim, 2018; Ladegard, Thurstone, & Rylander, 2020; Murray, David, & Ajnakina, 2021). Correspondingly, the data suggest a low risk for less frequent or occasional-only (e.g. less-than-weekly) cannabis use. These results translate into the consequential refinement of prevention/education messages, for example as offered by the LRCUG (Fischer et al., 2022) or other pertinent recommendation sources.

While more frequent cannabis use to be appears associated with an elevated risk of psychosis, this risk is likely further influenced by other risk-factors (e.g. genetics, family history, cannabis potency) that require additional consideration for and incorporation into prevention messaging beyond mere frequency-of-use factors (Di Forti et al., 2015; Hamilton & Sumnall, 2021; Kiburi

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Table 1. Characteristics of cohort and case–control studies included in a meta-analysis

	Location	Cannabis legalization status	Funding	Design	Population	Main outcome	Measure	Participants	Sex (% Male)	Age range or mean (s.d.)
Arranz et al. (2018)	Spain	Decriminalized	Y	Case–control	Cases: FEP patients Controls: Community sample	FEP	DSM-IV	207	61	18–35
Buchy et al. (2015)	Canada & United States	Mixed	Y	Case–control	Cases: Clinically high-risk youth Controls: no information	FEP (transition to psychosis)	SIPS	1013	56	Cases: 18.5 (±4.2) Controls: 19.6 (±4.7)
Bugra et al. (2013)	Switzerland	Decriminalized	N	Cohort	Individuals with at risk mental state	FEP	BPRS	136	63	Cases: 20 (±3) Controls: 23(±4)
Castañeda et al. (2020)	Chile	Illegal	Y	Case–control	Cases: FEP patients Controls: community sample	FEP	MINI	134	71	18–25
Di Forti et al. (2015)	United Kingdom	Illegal	Y	Case–control	Cases: FEP patients Controls: community sample	FEP	ICD-10	780	62	18–65
Di Forti et al. (2019)	United Kingdom	Illegal	Y	Case–control	Cases: FEP patients Controls: community sample	FEP	ICD-10	2112	53	18–64
Núñez et al. (2016)	Spain	Decriminalized	Y	Case–control	Cases: FEP patients Controls: community sample	FEP	DSM-IV	158	56	13–47
Rössler et al. (2012)	Switzerland	Decriminalized	Y	Cohort	General population-based sample	Schizotypal signs Schizophrenia nuclear symptoms	SCL-90-R	2223	47	19–50
Sideli et al. (2018)	United Kingdom	Illegal	Y	Case–control	Cases: FEP patients Controls: community sample	FEP	ICD-10	445	59	18–65
Valmaggia et al. (2014)	United Kingdom	Illegal	N	Cohort	Individuals at ultra-high risk pf psychosis	FEP (transition to psychosis)	Not detailed (clinical follow-up)	182	57	22.9 (± 4.5)

BPRS, Brief Psychiatric Rating Scale; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders; FEP, First episode psychosis; ICD-10, International Classification of Disease; MINI, Mini International Neuropsychiatric Interview; SCL-90-R, Symptom Checklist 90 Revised; SIPS, Structured interview for Prodromal Symptoms

Table 2. Results of linear dose–response model for the association between a category of cannabis use frequency and sensitivity analyses for potential non-linearity of associations using alternate models

	Model		
	Linear-dose–response	Quadratic trend	Restricted cubic splines
Frequency of cannabis use	RR (95% CI)	RR (95% CI)	RR (95% CI)
Never	1.0 (reference)	1.0 (reference)	1.0 (reference)
1–11 days a year (Yearly)	1.15 (1.10–1.20)	1.01 (0.95–1.07)	1.01 (0.93–1.11)
1–3 days a month (Monthly)	1.32 (1.21–1.44)	1.11 (1.03–1.20)	1.10 (0.97–1.25)
1–4 days a week (Weekly)	1.51 (1.32–1. 72)	1.35 (1.22–1. 48)	1.35 (1.19–1. 52)
5–7 days a week (Daily)	1.73 (1.45–2.06)	1.76 (1.49–2.13)	1.76 (1.47–2.1)

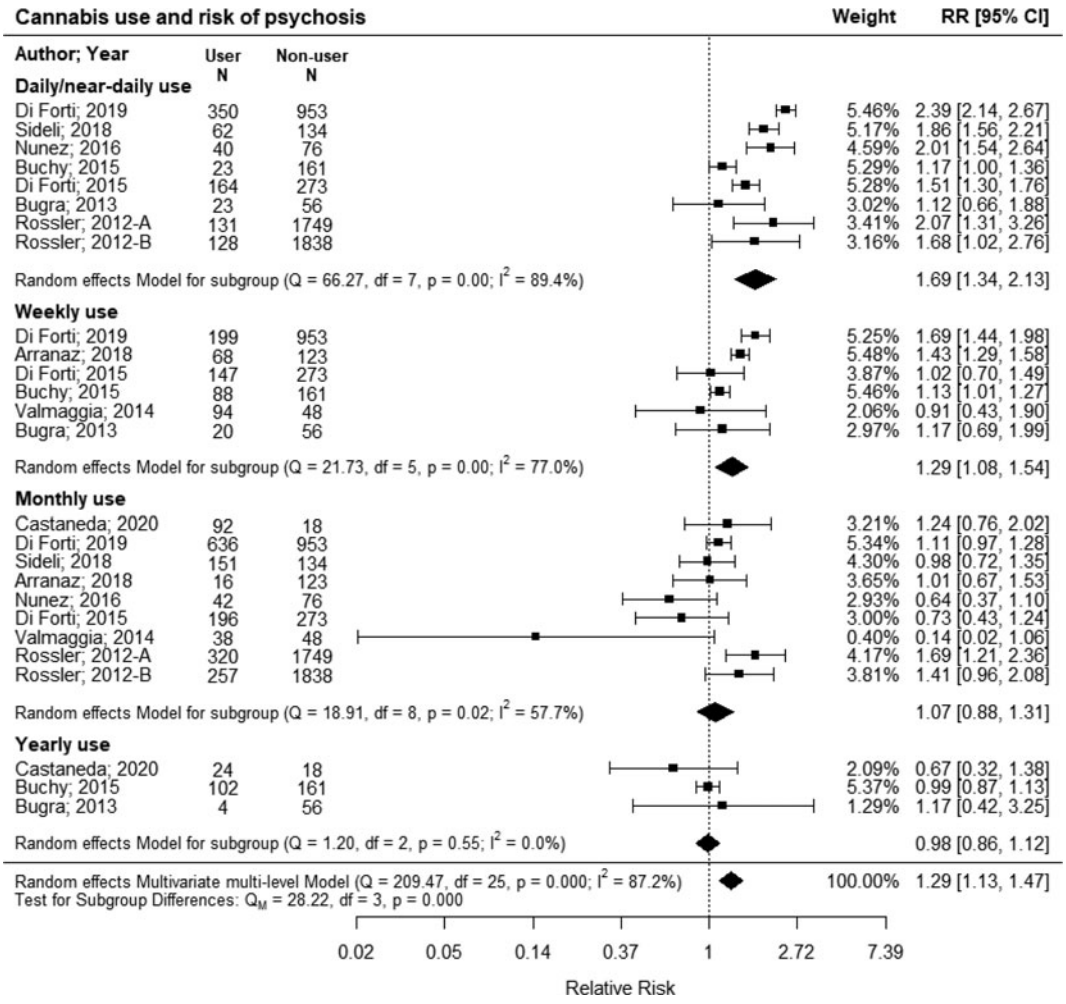

Fig. 2. Risk of developing psychosis associated with frequency of cannabis use. Data are shown for three cohorts and seven case–control studies, according to categories of cannabis use frequency.

et al., 2021; van der Steur et al., 2020). For example, persons who have a first-degree relative (parent or sibling) with a psychosis condition have a 10-fold higher risk of psychosis development; if the risk of daily cannabis use is multiplicative, their risk would increase 20-fold.

Cannabis users, however, should be explicitly advised by evidence-based prevention messaging to keep their cannabis use infrequent in order for their risks for cannabis-attributable psychosis development to be meaningfully lowered. Such exposure-stepped, evidence-based prevention messaging about risk-thresholds for cannabis use and psychosis may be controversial in some realms. However, it is analogous to evidence-based alcohol-related health guidelines where the risk for specific adverse (e.g. cardio-vascular) outcomes is low/absent below certain consumption levels and 'moderate' use is recommended (Furtwaengler & de Visser, 2013; Holmes et al., 2019; Wood

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et al., 2018). Beyond, evidence-based, ideally quantified, risk-thresholds for cannabis use exposure (e.g. frequency, a potency of use) toward other key adverse outcomes (e.g. CUD) should be assessed toward informing public health-oriented prevention efforts (Fischer et al., 2022).

Limitations

This review includes some limitations. First, most of the included studies did not report data on potential contributor factors for outcomes, which therefore could not be controlled for. For example, the use of high-potency cannabis also increases the risk of a psychotic disorder (van der Steur et al., 2020), yet many studies do not report information on the potency of cannabis used by participants, which can differ greatly across products (e.g. skunk, concentrates) and by geographical location. Additionally, half of the included studies either did not control for the possible co-use of alcohol, tobacco, or other recreational substances in their analysis or it was unclear whether these factors were controlled for. All included studies utilized self-report measures of cannabis use frequency, which may be prone to recall bias. While including only studies with multiple use frequency categories, classification of risk into categories may lead to information loss by treating every within-category participant as equal for risk (Wynants et al., 2019). The identification of risk-thresholds was limited to the a-priori defined frequency categories. Differences in design and number of (e.g. numbers of use frequency categories) of included studies also limited our ability to conduct sub-group analyses, such as by year of study or study design. While included studies were rated as having a low RoB according to the Newcastle Ottawa Scale, it is important to note that all included studies are observational designs and therefore overall study quality is lower and the potential RoB higher than if randomized trials were utilized.

Conclusions/future directions

Psychosis as a possible adverse outcome of cannabis use remains a major public health concern. This review found that the risk of psychosis is significantly elevated with frequent, i.e., at least weekly, cannabis use while not significantly elevated with infrequent consumption. These evidence-based insights require effective translation into public health-oriented cannabis prevention efforts. As cannabis use prevalence continues to grow, including in policy reform settings, and use patterns are evolving, the evidence-base on this issue should be regularly updated. Specifically, future reviews should seek to integrate the role of possible contributing factors (e.g. cannabis potency, genetics, age of exposure) to better define risk-thresholds for psychosis development and extend these to other adverse outcomes toward improved public health-oriented interventions for cannabis use.

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Tessa Robinson and Muhammad Usman Ali had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

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