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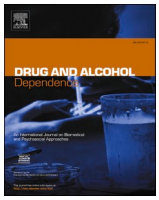

Review

Identifying risk-thresholds for the association between frequency of cannabis use and development of cannabis use disorder: A systematic review and meta-analysis

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ABSTRACT

Background: Cannabis use disorder (CUD) affects one-in-five cannabis users, presenting a major contributor to cannabis-associated disease burden. Epidemiological data identify the frequency of cannabis use as a risk factor for CUD. This review aimed to determine quantifiable risk-thresholds of the frequency of cannabis use for developing CUD.

Methods: Systematic search of Medline, EMBASE, PsycInfo, CINAHL, and Web of Science for cohort/case-control studies that assessed the association between frequency of cannabis use and CUD from 2000 to 2022. Effect estimates were converted to risk ratios (RR). A random-effects multi-level multivariate meta-analytic approach was utilized, and sensitivity analyses conducted. Quality of included studies was assessed with the Newcastle Ottawa Scale.

Results: Six prospective cohort studies were included in this review, drawn from two main source studies. Random-effect modeling showed a significant log-linear dose-response association between the frequency of cannabis use and CUD risk ($p < 0.0001$). The risk of CUD increased from RR:2.03 (95% CI:1.85–2.22) for 'yearly' use, to RR:4.12 (95% CI:3.44–4.95) for 'monthly" use, RR:8.37 (95% CI:6.37–11.00) for 'weekly' use, and RR:16.99 (95% CI:11.80–24.46) for 'daily' use. Multi-level modeling showed an absolute risk increase (ARI) from 3.5% (95% CI:2.6–4.7) for 'yearly' use, to 8.0% (95% CI:5.3–12.1) for 'monthly' use, to 16.8% (95% CI:8.8–32.0) for 'weekly' use, and 36% (95% CI:27.047.9) for 'daily' use.

Conclusion: A limited risk of CUD as a potential outcome of cannabis use exists even at infrequent levels of use, but significantly increases as frequency of use increases. Corresponding information should be conveyed to cannabis users as part of targeted prevention messaging to promote safer cannabis use.

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1. Introduction

Cannabis use has increased markedly into the 21st century, with an estimated 2.8–5.1% of (or approximately 200 million) adults worldwide using cannabis annually (Compton et al., 2019; Degenhardt et al., 2017; United Nations Office on Drugs and Crime, 2020, 2021). In the past decade, cannabis control policy has been liberalized in many jurisdictions, with the legalization of non-medical use and supply in Uruguay (2013), Canada (2018), Mexico (2021), and about half of US States (United Nations Office on Drugs and Crime, 2021), and additional jurisdictions considering similar reforms.

Cannabis use is associated with a variety of – acute and chronic – adverse health outcomes, which ought to be the focus of preventive interventions in an era of increasing use and policy liberalization (Hoch and Lorenzetti, 2020; Melchior et al., 2019). The main adverse health outcomes associated with cannabis use include acute impairments in cognition (e.g., memory, psychomotor, and executive functioning) that can impair motor-vehicle driving ability, leading to collisions with injury and/or deaths (Campeny et al., 2020; Preuss et al., 2021; Sevigny, 2021), as well as cannabis use disorder (CUD) and other mental health harms such as psychosis, anxiety, and depression, in addition to respiratory problems, cardiovascular diseases, and pregnancy/neo-natal problems (Campeny et al., 2020; Hasan et al., 2020; Jouanjus et al., 2017; Leung et al., 2020). Importantly, the associations for most of these adverse outcomes are low or moderate (e.g., risk ratios 1.2 – 2 for main mental health problems or motor vehicle collision involvement following cannabis use) and the majority of individuals who use cannabis do not experience severe adverse health outcomes associated with use (Boden et al., 2020; Budney et al., 2019; Hasin, 2018). Furthermore, most of the abovementioned adverse health outcomes arise in association with intensive (e.g., frequent) use, the use of high-potency cannabis products, and initiation of use at a young age (Arterberry et al., 2019; Callaghan et al., 2020; Connor et al., 2021, Fischer et al. 2022).

The concept of CUD was defined for diagnostic purposes in 2013 to encompass the previous categories of cannabis dependence and abuse based on standardized definition criteria (American Psychiatric Association, 2013; Patel, 2021). CUD is defined by cannabis use despite significant impairment in one's functioning, manifestations of loss of control over cannabis use, and tolerance and withdrawal symptoms when the substance use is ceased or significantly decreased (Budney et al., 2019; Courtney et al., 2017; Patel, 2021; Thomas and Shalvov, 2021). The psychosocial consequences associated with CUD include financial and social difficulties, lower occupational or educational attainment, reduced life satisfaction, and impaired driving ability (Cerdá et al., 2016; Courtney et al., 2017; Meier, 2021). While older estimates were slightly lower (e.g., <10%), recent review results suggested that about 13% of cannabis users develop cannabis dependence; yet, also given its wider diagnostic definition, about one-in-five (20%) users have been estimated to develop CUD (Anthony, 2006; Hasin, 2018; Leung et al., 2020). Notably, recent US-based studies have identified select decreases in the prevalence of CUD among cannabis users in recent decades, to which multiple different factors may have contributed (Compton et al., 2019; Davenport, 2018; Hasin et al., 2016; Santaella-Tenorio et al., 2019; Williams et al., 2017). Overall, CUD is a principal contributor to cannabis-related burden of disease and, hence, a priority target for prevention within a public health-oriented approach to cannabis use (Budney et al., 2019; Connor et al., 2021; Degenhardt et al., 2013; Fischer et al., 2016; Imtiaz et al., 2016).

Most individuals with CUD who require professional treatment or care may benefit from psychosocial treatment approaches, including cognitive behavioral therapy (CBT), motivation enhancement therapy (MET), social support counseling, psycho-education, and mindfulness-based meditation (Connor et al., 2021; Jutras-Aswad et al., 2019; Sabioni and Le Foll, 2018). There are no approved pharmacotherapeutic options currently available at this time. Trials that have studied anti-depressant and anti-anxiety medications, and cannabinoids have largely failed to find evidence of effectiveness (Connor et al., 2021; Jutras-Aswad et al., 2019; Kondo et al., 2020; Patel, 2021; Williams and Hill, 2019) with some exceptions of positive findings yet to be replicated in larger trials (D'Souza et al., 2019; Freeman et al., 2020).

The etiology of CUD is multifactorial and risk factors identified include a younger age at first use and the intensity of cannabis use as reflected in the amount, potency, and frequency of cannabis use (Arterberry et al., 2019; Hasin, 2018; Leung et al., 2020; Taylor et al., 2019; Volkow et al., 2016). Several studies have identified an association between the frequency of cannabis use and the risk of a CUD and its severity (Compton et al., 2019; Hasin et al., 2016; Santaella-Tenorio et al., 2019; van der Pol et al., 2013). The risk of CUD has been assessed to be higher in those who use cannabis daily (up to one-in-three users) than less frequent users (one-in-ten) (Connor et al., 2021; Leung et al., 2020). Weekly use is also associated with a greater number of CUD symptoms than lesser use, regardless of whether use is initiated in adolescence or adulthood (Guttmannova et al., 2017). However, specific risk thresholds have not been systematically identified for cannabis use frequency and CUD (Leung et al., 2020).

In the case of alcohol use and gambling, risk thresholds for levels of exposure have been calculated for negative outcomes to guide targeted prevention measures (Holmes et al., 2019; Samokhvalov et al., 2010; Wood et al., 2018). Recently, a systematic review and meta-analysis identified risk-thresholds for frequency of cannabis use and the risk of psychosis outcomes (Robinson et al., 2022). The aim of this systematic review and meta-analysis was to determine whether there are quantifiable risk-thresholds of the frequency of cannabis use for developing CUD.

2. Methods

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 framework (PRISMA checklist eTable 1) (Page et al., 2021). The protocol for this study was registered pre-initiation with the International Register of Systematic Reviews (PROSPERO)(CRD#42021287703).

2.1. Search strategy

Searches were conducted in the Embase, PsycINFO, MEDLINE, CINAHL, and Web of Science databases. The search strategy was developed for Embase and modified for use in subsequent databases (eMethods 1). Search terms utilized included both Medical Index Subject Headings and keywords related to the primary search topics of cannabis use, use disorder, and use frequency/dose-response relationships. Databases were searched from January 1, 2000, through December 15, 2021. The reference lists of included studies were also searched for additional studies of relevance.

2.2. Inclusion and exclusion criteria

Studies were included in this review if they examined the relationship between frequency of cannabis use and the development of CUD or cannabis abuse or dependence in individuals who use cannabis primarily for non-medical (recreational) purposes. Further, studies were included in this review if they: (1) were of case-control or cohort (prospective or retrospective) design, (2) included effect estimates such as hazard ratios (HRs), risk ratios (RRs), or odds ratios (ORs) with 95% confidence intervals (95% CI) or provided the data that could be used to calculate them (Kaplan Meier curve), (3) included information on the frequency of cannabis use stratified into at least three frequency categories (required for dose-response analysis) and (4) diagnosed CUD or cannabis abuse/dependence according to DSM-IV, DSM-5 or ICD-10 criteria (American Psychiatric Association, 1994, 2013; World Health

Table 1
Characteristics of studies included in meta-analysis.

	Location	Design	Study Name	Main Outcome	Measure	Participants (n)	Male (%)	Age Range or Mean (SD)	Follow-Up (years)	Standardized Frequency of Use Categories
Chen (2021)	United States	Cohort	NESARC	DSM-IV Cannabis abuse or dependence at wave 2	DSM-IV Manual	31 646	12 742 (40.3)	18–99	3	None 1–3 days a month (monthly) 1–4 days a week (weekly)
Coffey (2003)	Australia	Cohort	VAHS	DSM-IV Cannabis dependence	CIDI	1601	865 (54)	14.9–20.7	6	None 1–3 days a month (monthly) 1–4 days a week (weekly) 5–7 days a week (daily/near daily)
Coffey (2016)	Australia	Cohort	VAHS	DSM-IV Cannabis dependence in adulthood	DSM-IV Manual	1520	696 (45.8)	14.9–24.1	10	None 1–3 days a month (monthly) 1–4 days a week (weekly) 5–7 days a week (daily/near daily)
Silins (2014)	Australia/ New Zealand	Cohort	Australian Temperament Project Christchurch Health and Development Study VAHS	DSM-5/ICD-10 Cannabis use disorder Cannabis dependence in the past 12 months	CIDI	3177	Not listed	17–30	17	None 1–11 days a year (yearly) 1–3 days a month (monthly) 1–4 days a week (weekly) 5–7 days a week (daily/near daily)
Swift (2008)	Australia	Cohort	VAHS	DSM-IV cannabis dependence	CIDI	1520	696 (45.8)	14.9–24.1	10	None 1–3 days a month (monthly) 1–4 days a week (weekly) 5–7 days a week (daily/near daily)
Swift (2009)	Australia	Cohort	VAHS	DSM-IV cannabis dependence	CIDI	1520	696 (45.8)	14.9–24.1	10	None 1–3 days a month (monthly) 1–4 days a week (weekly)

CIDI – Composite International Diagnostic Interview
DSM-IV – Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
DSM-5 – Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ICD-10 – International Classification of Diseases, Tenth revision
NESARC – National Epidemiologic Survey on Alcohol and Related Conditions
VAHS – Victorian Adolescent Health Study

Organization, 2018).

The frequency-of-use categories utilized in individual studies were converted for the meta-analysis into standardized categories pre-defined from the literature (described in Section 2.5). Only human subject studies published in peer-reviewed journals were considered for inclusion. No restrictions were placed on the age of participants or language in studies. Also given the changing nature of cannabis use characteristics (e.g., re: potency, use modes), only studies conducted/published since 2000 were considered for inclusion in order to rely on relatively recent study data.

Studies were excluded from this review if they included samples with primarily medical cannabis use (e.g., chronic pain patients or use for nausea due to cancer treatments). Studies were also excluded if: (1) they included participants with pre-existing substance use disorders (including CUD), (2) employed a study design other than case-control or cohort, (3) include only special populations (e.g., prisoners), and (4) included the use of synthetic cannabinoids (e.g., K2 or spice).

2.3. Study selection

Once identified through the systematic database searches, all citations were uploaded into Covidence web-based systematic review software (Veritas Health Innovation, 2021) and duplicates removed. Citations were screened for inclusion by title and abstract by two independent reviewers. Disagreements in screening were resolved through consensus discussions. Screening of full-text articles was completed in the same manner.

2.4. Assessment of methodological quality and certainty in the evidence

The quality of included studies was assessed using the Newcastle-Ottawa Scale (NOS) versions tailored for cohort and case-control studies (Wells et al., 2013). The NOS was designed for quality assessment of non-randomized studies included in meta-analyses and its use is supported by the Cochrane Scientific Committee. The methodological quality assessments of included studies were completed in duplicate by two independent reviewers and disagreements resolved through consensus discussions. All relevant studies identified were included in

the meta-analysis, regardless of their methodological quality.

The certainty in the findings for the primary review outcome of risk of CUD according to frequency of cannabis use category was assessed using Grading of Recommendations Assessment, Development and Evaluations (GRADE) approach (Schunemann et al., 2013) and reported through the online GRADEPro tool (https://gradepro.org/).

2.5. Data extraction

Data from included studies were extracted in duplicate by two independent reviewers into a standardized Microsoft Excel file created specifically for this review. Disagreements in data extraction were resolved through consensus discussions. A statistician completed final verification of all outcome data extracted.

Data extracted from each study included general information, such as the year of publication, study funding sources, geographical setting, study design (case-control, or cohort (retrospective or prospective)), number of participants, sex, and age range of participants. Outcome-specific information extracted included the number of participants diagnosed with CUD per frequency of cannabis use category and the associated effect estimate (HR, OR, or RR). The method of CUD assessment was also recorded (e.g., standardized questionnaire, clinical interview). The exposure measure was frequency of cannabis use, which was categorically predefined based on existing literature (Callaghan et al., 2020; Goodman et al., 2019; Steeger et al., 2021) as: (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'). The frequency of use data from individual studies were classified into these categories for data analysis. For studies that presented frequency of use information for more than one time point (e.g., past and current use), we recorded data for the most current time point.

2.6. Data synthesis

Relative risk was used as the measure of association between the frequency of cannabis use and the development of CUD across studies. Where HRs were reported, they were treated as relative risk. Where ORs were reported, they were transformed to RRs using the formula $RR = OR/[(1\text{-}P_o)+ (P_o x OR)$, where P_o is the incidence of the outcome of interest (Zhang and Yu, 1998).

RRs were calculated from raw data for studies without effect estimates. Multi-variate dose-response meta-analytic models were used to estimate the relationship between cannabis use frequency and CUD development using the RR data. The dose-response associations between log relative risk and levels of cannabis use according to frequency categories were analyzed within each study cohort and then study specific estimates were combined across studies using multi-variate random effects models (Crippa and Orsini, 2016; Greenland and Longnecker, 1992; van Houwelingen et al., 2002). The absolute risk increases associated with 'yearly, 'monthly', 'weekly', and 'daily/near daily' cannabis use were also calculated based on a multi-level model.

We used a random-effects multi-level multivariate meta-analytic approach to account for dependency between effect sizes (i.e., the correlation between effect sizes due to multiple measures such as cannabis use frequencies or more than one follow-up points from the same study cohort). In such cases, various outcome measures and comparisons from the same study cohort were nested within-study first, and variance in observed effect sizes was decomposed into sampling, within-study cohort, and between-study cohort variance to account for intra-cluster correlation in the true effects (Berkey et al., 1998; Gleser and Olkin, 2009; van Houwelingen et al., 2002).

The statistical heterogeneity (I^2) statistic was also estimated using a multi-level meta-analytical approach, i.e., within-cluster heterogeneity (multiple arms from same study cohort) and between-cluster heterogeneity (effect sizes across studies) (Cheung et al., 2009; Chung et al., 2013). Overall I^2 for each summary effect size was estimated to represent the heterogeneity not attributable to sample error. It is the sum of within-cluster and between-cluster heterogeneity. Sensitivity analyses were performed using ORs as an outcome measure and using both quadratic and flexible non-linear models with restricted cubic splines with three knots at the 10th%, 50th%, and 90th% percentiles of the distribution (Liu et al., 2009; Orsini et al., 2006).

We examined the goodness-of-fit statistics (Akaike information criteria 'AIC', deviance test 'D', and the coefficient of determination 'R^{2}') to select the best-fitting model (Discacciati et al., 2017). To test statistical stability and robustness of the results, we further carried out subgroup and meta-regression analysis based on consumption use frequency, study length of follow-up and study cohort (van Houwelingen et al., 2002). Study-level variables in the analyses included the categories of cannabis use frequency, number of CUD cases in each exposure level, length of follow-up, and the natural logarithm and the standard error for the logarithm of the RRs or ORs. Publication bias could not be assessed because there were too few studies (<10). All data-analyses were completed using STATA v.16 (IPDFC module) and R (dosresmeta and Metafor packages) (R Core Team, 2020; StataCorp, 2019; Wei and Royston, 2020).

3. Results

3.1. Study selection

The database searches returned 11,546 records. After the removal of duplicates (n = 6949), 4597 records underwent screening by title/abstract. This led to the exclusion of 4520 records, with 76 moving forward to full text screening. A total of six prospective cohort studies were included in this review (Chen et al., 2021; Coffey et al., 2003; Coffey and Patton, 2016; Silins et al., 2014; Swift et al., 2009, 2008). A list of articles excluded during full text review is provided in the supplementary material along with the reasons for exclusion (eMethods 2). The PRISMA flow diagram depicting the study selection process is presented in Fig. 1.

3.2. Study characteristics

The studies included in the review comprised a total of 40,984 participants (mix of male and female) ranging in age from 14.9 to 30 years. The length of follow-up ranged from 3 to 17 years. Five of the studies (Coffey et al., 2003; Coffey and Patton, 2016; Silins et al., 2014; Swift et al., 2009, 2008) utilized data from the Victorian Adolescent Health Study (VAHS). One study included data from the Christchurch Health and Development cohort study and the Australian Temperament Project in addition to VAHS data (Silins et al., 2014). For the studies that utilized VAHS data, we used data from publications with unique follow-up points and reporting in the main analysis. Studies with subgroup analysis of the same cohort and same follow-up point were not considered for analysis. Five of the studies (Chen et al., 2021; Coffey et al., 2003; Coffey and Patton, 2016; Swift et al., 2009, 2008) utilized the DSM-IV definition of cannabis dependence or abuse as the primary outcome measure and one study (Silins et al., 2014) utilized the DSM-5 definition for CUD. All six studies used the Composite International Diagnostic Interview (CIDI) (Robins et al., 1988) to assess the primary outcome measure of CUD. Study characteristics are detailed in Table 1.

The quality of included studies was judged as high (3/6) (Chen et al., 2021; Coffey et al., 2003; Swift et al., 2009) or moderate (3/6) (Coffey and Patton, 2016; Silins et al., 2014; Swift et al., 2008). Full ROB assessments can be found in the supplementary material (eTable 2).

3.3. Meta-analyses

3.3.1. Random-effect model

The results of the log-linear dose-response model showed a statistically significant association between frequency of cannabis use category and risk of CUD ($p < 0.0001$). Each increase in the cannabis

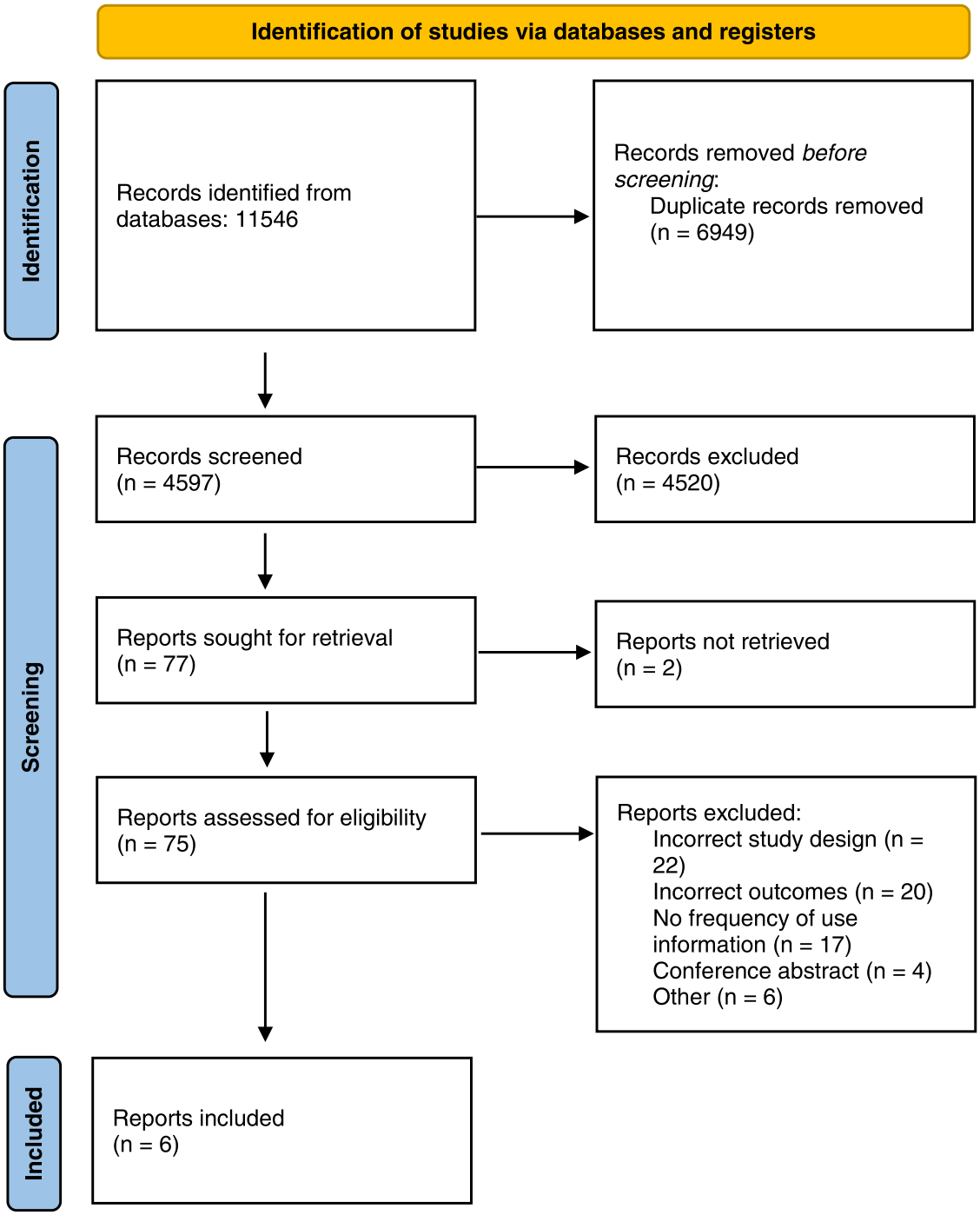

Fig. 1. PRISMA flow diagram of the study selection process.

consumption category (e.g., from yearly to monthly use or monthly to weekly use) was associated with 2.03 times (95% CI: 1.85 – 2.22 times) increased the risk of CUD. The risk increased from RR:2.03 (95% CI:1.85–2.22) for 'yearly' use, to RR:4.12 (95% CI:3.44–4.95) for 'monthly" use, RR:8.37 (95% CI:6.37–11.00) for 'weekly' use, and RR:16.99 (95% CI:11.80–24.46) for 'daily' use (Table 2).

The results of the multi-level model showed a statistically significant association between frequency of cannabis use category and the absolute risk increase (ARI) of CUD ($p < 0.001$). The ARI compared to no use was 3.5% (95% CI:2.6–4.7) for 'yearly' use, 8.0% (95% CI:5.3–12.1) for 'monthly' use, 16.8% (95% CI:8.8–32.0) for 'weekly' use, and 36.0% (95% CI:27.0–47.9%) for 'daily' use (Table 2) (eFig. 1).

3.3.2. *Sensitivity analysis*

Sensitivity analyses were conducted to test for the potential non-linearity of the association using alternate models. The log-linear assumption between cannabis use frequency and risk of CUD was relaxed using a quadratic trend and flexible non-linear model with restricted cubic-splines. In the quadratic-trend model, the risk of CUD varied according to cannabis use frequency, increasing from RR:2.37 (95% CI:1.90–2.97) for 'yearly' use, to RR:5.05 (95% CI:3.52–7.25) for 'monthly' use, RR:9.63 (95% CI:6.28–14.79) for 'weekly', and RR:16.47 (95% CI:10.47–25.90) for 'daily' use. The deviation from log-linearity was significant (Wald test $p < 0.05$, $chi^2 = 162.95$).

The restricted cubic splines model was the more conservative model. It demonstrated results similar to the quadratic-trend model. In the

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

	Model			
Frequency of cannabis use	Linear-dose response RR (95% CI)	Multi-Level ARI (95% CI)	Quadratic trend RR (95% CI)	Restricted cubic splines RR (95% CI)
Never	1.0 (reference)	0 (reference)	1.0 (reference)	1.00 (reference)
1–11 days a year (Yearly)	2.03 (1.85 – 2.22)	3.5% (2.6–4.7%)	2.37 (1.90 – 2.97)	2.30 (1.89 – 2.79)
1–3 days a month (Monthly)	4.12 (3.44 – 4.95)	8.0% (5.3–12.1%)	5.05 (3.52 – 7.25)	5.06 (3.54 – 7.21)
1–4 days a week (Weekly)	8.37 (6.37 – 11.00)	16.8% (8.8–32.0%)	9.63 (6.28 – 14.79)	9.38 (6.25 – 14.06)
5–7 days a week (Daily)	16.99 (11.80 – 24.46)	36.0% (27.0–47.9%)	16.47 (10.47 – 25.90)	16.66 (10.51 – 26.41)

restricted cubic splines model, the risk of CUD varied significantly according to cannabis use frequency category; increasing from RR:2.30 (95% CI:1.89–2.79) for 'yearly' use, to RR:5.06 (95% CI:3.54–7.21) for 'monthly' use, RR:9.38 (95% CI:6.25–14.06) for 'weekly' use, and RR:16.66 (95% CI:10.51–26.41) for 'daily' use. The deviation from log-linearity was significant (Wald test $p < 0.05$, $chi^2 = 150.16$). Results of the sensitivity analyses are depicted in Table 2.

3.3.2.1. Odds ratio as outcome measure. The results of the random effects model show a significant log-linear response association between frequency of cannabis use category and the risk of CUD. Each level of increase in cannabis consumption frequency was associated with 2.25 times (95% CI:1.98–2.58 times) increased odds of CUD. The odds of CUD increased from OR:2.26 (95% CI:1.98–2.58) for 'yearly' use to OR:5.10 (95% CI:3.90–6.66) for 'monthly' use, OR:11.51 (95% CI:7.71–17.19) for 'weekly' use, and OR:26.00 (95% CI:15.24–44.37) for 'daily' use (Table 3).

Sensitivity analyses were conducted to test for potential non-linearity of the association between cannabis use frequency and CUD using a quadratic trend and restricted cubic splines model. The sensitivity analyses provided results similar to that of the random-effect model. In the quadratic trend model, the odds of CUD varied significantly according to frequency of cannabis use category. The odds of CUD increased from OR:2.28 (95% CI:1.85–2.81) for 'yearly' use, to OR:5.16 (95% CI:3.72–7.16) for 'monthly' use, OR:11.58 (95% CI:7.67–17.49) for 'weekly' use, and OR:25.78 (95% CI:14.53–45.73) for 'daily' use. In the restricted cubic splines model, the odds of CUD increased from OR:2.26 (95% CI:1.88–2.72) for 'yearly' use, to OR:5.12 (95% CI:3.68–7.13) for 'monthly' use, OR:11.55 (95% CI:7.69–17.35) for 'weekly' use, and OR:26.05 (95% CI:14.57–46.57) for 'daily' use (Table 3).

Table 3
Results of sensitivity analyses using odds ratios (OR) as the outcome measure. Results are shown for the linear dose-response model for the association between category of cannabis use frequency and sensitivity analyses for potential non-linearity of associations using alternate models using odds ratios as the outcome.

	Model		
Frequency of cannabis use	Linear dose-response OR (95% CI)	Quadratic trend OR (95% CI)	Restricted cubic splines OR (95% CI)
Never	1.0 (reference)	1.0 (reference)	1.00 (reference)
1–11 days a year (Yearly)	2.26 (1.98 – 2.58)	2.28 (1.85 – 2.81)	2.26 (1.88 – 2.72)
1–3 days a month (Monthly)	5.10 (3.90 – 6.66)	5.16 (3.72 – 7.16)	5.12 (3.68 – 7.13)
1–4 days a week (Weekly)	11.51 (7.71 – 17.19)	11.58 (7.67 – 17.49)	11.55 (7.69 – 17.35)
5–7 days a week (Daily)	26.00 (15.24 – 44.37)	25.78 (14.53 – 45.73)	26.05 (14.57 – 46.57)

3.3.3. Subgroup analysis and meta-regression

The subgroup analysis based on multi-level modeling showed that the length of follow-up (years) was non-significant (eTable 3). Meta-regression analyses were completed on cannabis use category and follow-up time (eTable 4). The meta-regression analysis showed significant differences and trends based on cannabis use category, which is in line with the dose-response relationship identified in the random-effect model. Meta-regression analysis based on length of follow-up either for overall or within each frequency of cannabis use category was non-significant, with overlapping confidence intervals (similar to the subgroup analysis above). It is important to note that the number of response categories differed across studies, which limited this analysis.

3.4. Heterogeneity, publication bias, and quality of evidence

Heterogeneity was assessed using multi-level-modeling and was shown to be significant (I^2 =93.34%) (eFig. 2). The vast majority of this variance was explained by within-study differences (I^2 =73.88%). The sampling error variance and between-study variance were small at 6.66% and 19.45% respectively. Due to the small number of studies included in this review, publication bias was not assessed. Quality of the evidence was rated as low according to the GRADE criteria (eTable 5), largely due to the observational nature of the studies. Although the effect sizes found in this study were large, the choice was made not to move the certainty in the findings up to moderate because of the large confidence intervals associated with the RRs for the weekly and daily frequency of use categories.

4. Discussion

Cannabis use is prevalent in many societies, and subject to increasingly liberal controls (e.g., legalization) in a growing number of jurisdictions. While select decreases in prevalence (e.g., in the US) have recently been observed, CUD is a possible principal adverse and chronic health outcome of concern associated with cannabis use estimated to affect approximately one-in-five users (Hasin, 2018; Leung et al., 2020).

The results of this systematic review and meta-analysis confirm a dose-response relationship between the frequency of cannabis use and the development of CUD. These results are consistent with the – somewhat limited – previous evidence that has assessed the associations between frequency of cannabis use and CUD (Callaghan et al., 2020; Leung et al., 2020). Importantly, and extending the results of previous studies, the present review was able to identify and quantify specific levels of risk for four different categorical levels of the frequency of cannabis use, ranging from 'yearly' to 'daily', for CUD. The results of the meta-analysis showed that every level of cannabis use above no use was associated with a statistically significant risk of CUD, and that higher levels of use frequency were associated with statistically significantly higher risk for CUD than lower ones. Although previous research has shown that CUD risk is increased with weekly or daily use (Guttmannova et al., 2017; Leung et al., 2020), this meta-analysis indicates that there is no level of cannabis use that is not associated with at least some risk of CUD. While the risk of CUD for individuals using cannabis 'yearly' may be considered relatively low (RR:2.03), each level of use increase was associated with 2.08 times increased risk of CUD, cumulating with 8 times the risk associated with 'daily' compared to 'yearly' use. To inform a risk-based population- and public health-focused perspective, ARIs were also calculated for the relationship between the frequency of cannabis use

and the development of CUD. Here, 'yearly' cannabis use was associated with a 3.5% increase in absolute risk of CUD which increased all the way to 36% for 'daily' use, implying that one-in-three – or a substantive proportion – of daily cannabis users may be expected to develop CUD.

The results of the present review entail clear and concrete messages to inform the prevention of CUD among those who choose to use cannabis. Namely, messages including that cannabis use even at lower frequency levels may lead to a CUD. Secondly, and most importantly, the higher frequencies of cannabis use significantly increases a user's chances of developing a CUD, and therefore should be avoided. These findings further inform and corroborate concrete recommendations for 'lower-risk use' of cannabis, specifically the importance of limiting frequency of use to reduce the risk of primary adverse health outcomes, as for example articulated in the recently updated 'Lower-Risk Cannabis Use Guidelines' (LRCUG) (Fischer et al., 2022).

Pathways for the development of CUD are likely multifactorial and include additional factors beyond frequency of use that may or may not be amenable to modification by the user. For example, factors such as a family history of substance use disorder (SUD), being male, and genetic predispositions, have been identified as accounting for 40–60% of the risk of a SUD (Demontis et al., 2019; Lopez-Leon et al., 2021). Further studies suggest a role of potential genetic predispositions for problematic cannabis use, including the identification of contributing polymorphisms on multiple genes (Demontis et al., 2019; Hurd et al., 2019).

More modifiable risk factors include avoiding an early initiation age (e.g., before 16 years) of cannabis use and minimizing the quantity and potency of cannabis that is used (Arterberry et al., 2019; Budney and Borodovsky, 2017; Callaghan et al., 2020; Connor et al., 2021). Specifically, the use of high THC content cannabis products is associated with a higher risk for CUD (Arterberry et al., 2019; Craft et al., 2020; Pierre, 2017). Few studies have assessed multiple risk factors, which may be in part due to the difficulty in collecting accurate or comparable potency information. This situation will hopefully improve in the future as increasing amounts of cannabis consumed comes from legal markets (particularly in North America), and involves regulated products with specified THC and CBD content (Hammond and Goodman, 2020; Mahamad et al., 2020). Such content information also provides necessary information for allowing adherence to the recommendations of consuming lower potency products.

The prevalence of CUD in a population can be also influenced by ecological factors, such as societal norms, cannabis legislation, price, availability, and supply (Connor et al., 2021). Frequency of use in jurisdictions that have legalized may be increased by pricing competition between legal and illegal sources, increased availability of or access to cannabis products, and increased 'normalization' of cannabis use (Hall and Lynskey, 2020; Smart and Pacula, 2019; Taylor et al., 2019). Evidence-based prevention messaging should be developed to encourage recreational cannabis users to keep their use as infrequent as possible if they wish to decrease their risk of CUD. This messaging will be especially important in jurisdictions where cannabis use has been legalized and more potent cannabis products are more readily available at lower prices. In addition to prevention and education messaging, targeted prevention measures, for example brief interventions for 'at-risk' cannabis users should include a primary focus on reducing the frequency of use as a main predictor of possible CUD development (Fischer et al., 2013; Halladay et al., 2019; Martin and Copeland, 2008).

4.1. Limitations

This systematic review and meta-analysis has some limitations. First, most of the studies reported did not collect information on the quantity of cannabis used or its potency, both of which have been shown to be risk factors for CUD (Arterberry et al., 2019; Callaghan et al., 2020). The frequency of use categories utilized for analysis may lead to data distortion in treating all individuals within a given level as the same; such possible distortions may be amplified by increasing potency (e.g., THC) levels of cannabis products used and the risk conferred by the use frequency levels of cannabis applied (Wynants et al., 2019). Additionally, five of the six studies included in this review came from one main large source study (VAHS), which limits the unique data assessed in the meta-analyses. Although all the studies included in this review were assessed as being of moderate or high quality, they all were observational, with a consequently higher ROB and lower quality than studies with experimental designs. The results of this study therefore cannot be utilized as proof for the causal association between the frequency of cannabis use and CUD, but rather as supporting a risk association. Few studies have used the new DSM-5 CUD criteria, which may have influenced the results since DSM-4 abuse/dependence do not exactly match the DSM-5 diagnostic criteria (Livne et al., 2021).

4.2. Conclusions/future directions

The results of this systematic review and meta-analysis demonstrate that the risk for CUD as a possible adverse outcome of cannabis use is present even at infrequent levels of use. However, the risk significantly increases with each higher level of use category. This essential, evidence-based information should inform public health-oriented prevention and education messaging for cannabis use, and specifically messages for lower-risk use options (Fischer et al., 2022). In addition, also considering the present review's limited number of original source studies, large longitudinal cohort studies are needed to advance the science in this area. These should ideally collect data on key cannabis use characteristics (e.g., use initiation, frequency, quantity, potency, mode-of-use) and other related risk factors (e.g., genetic, mental health, other substance use indicators).

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CRediT authorship contribution statement

Tessa Robinson: Conceptualization, Methodology, Investigation, Writing – original draft, Project administration. **Muhammad Usman Ali**: Methodology, Data curation, Formal analysis, Writing – original draft. **Bethany Easterbrook**: Methodology, Investigation, Writing – review & editing. **Stephanie Coronado-Montoya**: Investigation, Writing – review & editing. **Dimitri Daldegan-Bueno**: Investigation, Writing – review & editing. **Wayne Hall**: Conceptualization, Methodology, Writing – review & editing. **Didier Jutras-Aswad**: Conceptualization, Methodology, Writing – review & editing. **Benedikt Fischer**: Conceptualization, Methodology, Writing – original draft, Supervision, Funding acquisition.

Declaration of Competing Interest

The authors make the following declarations of relevant financial activities outside of the submitted work: BF has held research grants and contracts in the areas of substance use, health and policy from public funding and government (i.e., public-only) organizations in the past three years. DJA has received investigational products (last in 2018) from Insys Therapeutics for a clinical trial funded by the Canadian Institutes of Health Research (CIHR). In the last 36 months he has received grants/contracts funding for substance use-related research from public and governmental agencies and has expert-consulted on related issues with public/government agencies.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.drugalcdep.2022.109582.

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