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High-Potency Cannabis Use and Health:

A Systematic Review of Observational and Experimental Studies

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ABSTRACT

Objective: Amid continuously rising concentrations of delta-9-tetrahydrocannabinol (THC) in cannabis (i.e., potency), high-potency cannabis is a major topic in contemporary cannabis policy discussions, yet its impact on health is not well understood. We conducted a systematic review of observational and experimental studies examining the relationship between high-potency cannabis use and a range of health outcomes.

Methods: Records were obtained from a systematic search of five biomedical research databases. We developed ecologically relevant potency (%THC) exposure-comparison categories (1-9%, 10-19%, 20-30%, kief/resin [~30-50%], concentrates [≥60%]) and used a landmark scientific report on cannabis/cannabinoids to determine outcome eligibility. Two reviewers independently conducted article screening/selection, extraction, and quality assessment. Findings were synthesized using both quantitative (association direction, binomial test) and narrative approaches. Certainty in the evidence was determined via GRADE.

Results: Of 4545 screened records, 42 were eligible. Most studies addressed outcomes in the mental health, "problem" cannabis use, and other substance use domains. Findings in the "problem" cannabis use domain were suggestive of an association with higher-potency cannabis use. Findings were less consistent in other domains but tended to favor poorer outcomes with higher-potency use. Therapeutic outcomes were limited and mixed. Overall, certainty in the evidence was "very low".

Conclusions: Findings within the "problem" cannabis use domain were suggestive of an association with high-potency use. Research is largely limited to cross-sectional studies spanning few adverse health domains, underscoring the need for prospective studies probing therapeutic, cardio-respiratory, cancer, and pre/perinatal outcomes. Policies to curb high-potency cannabis use may be warranted while the evidence base improves.

Word Count: 249 (max: 250)

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Introduction

Cannabis is one of the world's most used psychoactive substances (1) and is associated with adverse health risks, both acute (e.g., cognitive impairment, motor vehicle crashes and other injury, anxiogenic and psychotic-like symptoms—particularly at high doses) and chronic (e.g., dependence syndrome, respiratory disease, psychosis/schizophrenia—particularly among those who use frequently (2, 3)). These risks are attributed to delta-9-tetrahydrocannabinol (THC), the primary psychoactive component of the cannabis plant. THC's partial agonism of the CB1 receptor acutely increases dopamine release, but is associated with a blunted dopamine effect over longer periods of exposure (4). THC is also responsible for many of cannabis' documented therapeutic effects including analgesia, appetite-stimulation, and anti-emesis (3).

The concentration of THC in cannabis (colloquially known as "potency") has increased steadily over the past 25 years in the United States (US) and elsewhere (5). Before 2000, the average potency of herbal cannabis seized in the US was <5% THC (6), whereas the average potency of herbal cannabis is now ~20% in most state-regulated non-medical retail markets (7-9). The past decade has seen a rise in availability and use of extremely high-potency cannabis products such as solvent-based concentrates (e.g., butane hash oil, dabs, shatter, wax, etc. (10, 11)), reaching up to 95% THC (12). An estimated 50% of cannabis-using US adults report vaping or dabbing concentrated products, and this prevalence is higher in state-regulated markets (13, 14); indeed, higher-potency (>20% THC) herbal cannabis and concentrates now account for the majority of products offered and sold in these markets (7, 9, 15).

The shift toward high-potency cannabis has fueled widespread public health concern (10, 16, 17); yet, relatively little is known about how this relates to a range of acute and chronic health outcomes, sparking calls for more research (18, 19). A recent review covered observational studies on certain non-acute mental health outcomes including anxiety, depression, psychosis, and cannabis use disorder, and concluded

increased risks associated with higher-potency use, but defined potency in relative (rather than chemically-defined) terms (20). In expanding focus towards acute and other long-term health measures, there is also a practical need to compare health outcomes across potency levels defined by absolute THC concentrations to inform policy decisions regarding cannabis potency in regulated markets (e.g., taxes, caps, and other pricing structures). We conducted a systematic review to identify and synthesize evidence from observational and experimental studies examining the association between use of cannabis at various pre-defined potency levels and a wide range of acute, non-acute, and therapeutic health outcomes.

Methods

This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines ((21); see SA1) and was registered in Prospero (CRD42021281470).

Search

We searched Ovid Medline, Embase, APA PsycInfo, Web of Science Core Collection, and Cochrane Library from inception to May 10, 2023 for peer-reviewed studies examining use of high-potency cannabis (see SA2 for detailed search strategy). We supplemented the database search by hand-searching reference lists of notable review papers, commentaries, and articles eventually selected for full-text review.

Eligibility Criteria

We used the Population, Interventions, Comparisons, Outcomes, and Study Design (PICOS) framework (22) to guide selection of studies for inclusion. As summarized in Table 1 and detailed in SA3, we developed and pre-specified ecologically relevant potency categories for exposure-comparison purposes (i.e., 1-9% THC, 10-19% THC, 20-30% THC, kief/resin [~30-50% THC], concentrates [≥60% THC]) and used the National Academies of Sciences, Engineering, and Medicine's report on the health effects of cannabis and

cannabinoids (3) to guide selection of outcomes (primary: non-acute adverse health measures; secondary 1: acute adverse health measures related to the extracted primary outcomes; secondary 2: therapeutic measures) for inclusion in the review.

[Table 1 around here]

Screening

All records were imported into EndNote (Version X9, Clarivate Analytics) and duplicates were removed. Records with exclusionary title keywords (e.g., "mouse", "in vitro"; see SA4) were filtered out; remaining records were imported into Covidence (Veritas Health Innovation). At this stage, all records underwent a title/abstract screening by two independent reviewers, with discrepancies resolved through an independent third reviewer. All records that received two "yes" or "maybe" votes were screened in-full by two independent reviewers, with discrepancies resolved through discussion, sometimes involving a senior author. Reasons for exclusion were recorded at this stage. We adopted a sensitive preliminary inclusion strategy in which acute (secondary) outcome studies moved to the extraction phase if eligibility was met for all other criteria (i.e., population, intervention/exposure, comparator, and study design); re-assessment for final inclusion was made after extraction of all primary outcomes (see below).

Data extraction and quality assessment

Two reviewers independently extracted data into a standardized form which captured information on study period, study design, sample characteristics, potency of cannabis exposure and comparator(s), outcome measurement and definition, and measures of association. Primary outcome studies were extracted first. Acute outcome studies were reviewed against the included primary outcomes and secondary outcomes that lacked relevance to a reviewed primary outcome were excluded at this stage. Reviewer discrepancies in extracted data and secondary outcome eligibility was resolved through discussion involving a senior author.

The National Heart, Lung and Blood Institute study quality assessment tools were used to assess internal validity and risk of bias for cross-sectional, cohort, and case-control studies (23). The Cochrane Risk of Bias 2 (RoB2) tool was used to assess risk of bias in experimental studies (24). Quality assessment was conducted independently by two reviewers for each exposure-outcome relationship evaluated in a study; discrepancies were resolved through discussion.

Data Synthesis

Quantitative synthesis

A meta-analysis was not feasible given substantial variation in exposure-comparator combinations, study designs, outcome measurements/scales, and analytic methods across studies. In line with Cochrane recommendations, we used an alternative quantitative method to synthesize the primary findings (25), adhering to the Synthesis without Meta-analysis (SWiM) reporting guidelines ((26); See SA5), opting for vote counting based on direction of effect estimate (herein, referred to as "association direction") as our synthesis method (25-27) due to substantial heterogeneity in types of effect estimates reported. Studies that compared mutually exclusive cannabis potency groups on a primary outcome of interest were eligible for the quantitative synthesis. We grouped studies by primary outcome and recorded the direction of association from the point estimate as the standardized metric for each study (1 if the estimate sided with a "detrimental" direction; 0 for "beneficial" direction). The number corresponding to the direction of association was assigned regardless of statistical significance (27). For studies that indirectly compared a higher- and lower-potency group via a non-use group, we derived crude point estimates as appropriate (e.g., ratio of odds ratios) and recorded the direction of association. We used an effect direction plot to visually summarize this data and a binomial (sign) test to examine evidence of an association with each outcome (27). Studies with conflicting findings (i.e., <70% consistency when multiple results are reported) were included in the plot but did not contribute to the sign test (27). Wherever possible, we tested the robustness of findings by further restricting the quantitative synthesis to higher quality studies (i.e., excluding "Poor" quality observational or "High" risk of bias experimental studies). To account for low number of studies for some

outcomes, we also repeated the quantitative synthesis for broad domain-specific outcome categories (e.g., mental health). These sensitivity analyses are reported in SA6 and SA7, respectively.

Qualitative synthesis

All primary outcome studies were grouped together by outcome domain and summarized in descriptive tables. We used the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) framework (28), modified for reviews lacking a single meta-analysis effect estimate (29), to assess the certainty in the body of evidence for each primary outcome domain subgroup. We contextualized trends or outliers from quantitative synthesis with examples from select studies, prioritizing higher-quality ratings. Studies excluded from quantitative synthesis were narratively summarized. Wherever possible, we supplemented primary outcome findings with observations from acute outcome studies, prioritizing higher-quality ratings. Acute adverse outcome studies were also summarized in descriptive tables. We conducted a tabular and narrative summary of secondary findings related to therapeutic effects.

Results

Overview of included studies

Of 4545 unique records screened, 42 studies (n=35 observational (10, 12, 30-62), n=7 experimental (63-69)) met the inclusion criteria and were included in the review (SF1). Most studies (n=25) were conducted in the US, followed by the United Kingdom (n=7). With very few exceptions (33, 46, 61, 62), observational studies relied on self-reported product use (e.g., concentrates, kief, “skunk”/sinsemilla) and inferred an estimated potency level for each of these products via documented region- and time-specific trends. The exposure index period in observational studies ranged from lifetime to past 21 days and most studies examined the exposure dichotomously (e.g., yes vs. no) rather than on a gradient (e.g., frequency of use). Experimental studies derived potency estimates through laboratory testing of cannabis product (controlled

laboratory-based studies) or inspection of labels from commercially purchased products (open-label naturalistic experiments).

Primary outcome studies

In total, 31 studies (10, 12, 30-32, 34, 35, 37-45, 47-60, 66) reported on the association between high-potency cannabis and at least one non-acute adverse health (i.e., primary) outcome spanning the mental health, "problem" cannabis use, other substance use, and psychosocial domains. Apart from one between-subjects naturalistic experimental study (66), primary outcome studies used observational designs including cross-sectional (10, 12, 34, 35, 37, 42, 44, 45, 47-52, 54-56, 59, 60), prospective cohort (30-32, 43, 57, 58), case-control (38-40), and sub-analyses of case/control data (41, 53). Quality ratings were generally low, with most studies (n=18 (10, 12, 34, 35, 37, 42, 43, 45, 47-56)) receiving a "Poor" quality rating for at least one reported association (SA8). Nine (30-32, 35, 41, 44, 45, 59, 60) and five studies (38-40, 57, 58) received at least one "Fair" or "Good" quality rating, respectively. Common reasons for downgrading study quality included low or lack of information on study power, exposure not being measured prior to the outcome, insufficient timeframe to observe an effect, unreliable/imprecise exposure assessment, and lack of sufficient control for confounding.

Potency categories most often compared among primary outcome studies were concentrates (Con) vs. herbal cannabis of any potency (Can-Mix; n=11 (10, 12, 37, 42, 43, 47-51, 55)) and mid-potency herbal cannabis (Can-Mid) vs. low-potency herbal cannabis (Can-Low; n=6 (34, 35, 39, 41, 45, 56)). Studies also directly compared Con vs. Can-Low (34, 35, 56), Resin (Res) vs. Can-Mix (52) or Can-Low (35, 56), and high-potency herbal cannabis (Can-High) vs. Can-Low (66). In addition, five studies indirectly compared Can-Mid to Can-Low via a non-use group (38, 40, 53, 57, 58) and seven indirectly compared exposure to a higher- and lower-potency product via separate instruments employing an equal scale of measurement; most were focused on Con and Can-Mix (30-32, 54, 59, 60) and one on Can-Mid and Can-Low (44)).

Secondary outcome studies

The primary findings were supplemented by secondary findings obtained from nine studies (33, 34, 50, 63-65, 67-69) examining acute measures in the psychosocial-cognitive domain (see Table 1) or acute indicators of the above-reviewed non-acute outcomes—specifically, measures reviewed under the mental health (see ST1) and "problem" cannabis use domains (see ST2). Six studies were experimental: three, rated at "High" risk of bias, used between-subjects naturalistic open-label experimental designs (63-65) and three, rated at different risks of bias depending on outcome—"High" (69), "Some concerns" (67, 68), and "Low" (69)—used within-subjects, placebo-controlled randomized controlled designs (SA10). Three cross-sectional studies (33, 34, 50) rated as "Poor" quality (SA9) were also considered. Can-Mid vs. Can-Low was the most reported potency comparison in acute outcome studies (n=4 (33, 63, 67, 69) + n=1 indirect comparison via placebo (68)). Other comparisons included Con vs. Can-Mix (50, 63), Can-High (64), Can-Mid (34), or Can-Low (65).

Four studies (36, 46, 61, 62) assessed symptom change among people taking cannabis for a specific medical indication. All employed a naturalistic observational study design using real-time patient-recorded data tracked through a phone application; three were rated as "Poor" quality (46, 61, 62), one as "Fair" (36) (SA8). Potency comparisons included Con vs. Can-Mix (36, 46), Can-High vs. Can-Low (46, 61, 62), and Can-Mid vs. Can-Low (46, 61, 62).

Adverse health outcomes

Mental health

Thirteen studies assessed the relationship between higher-potency cannabis use and at least one non-acute mental health outcome including psychosis (n=11), anxiety (n=4), depression (n=4), posttraumatic stress disorder (PTSD; n=2), and bipolar disorder (n=1; Table 2). For all outcome sub-categories under the non-acute mental health domain, certainty in the evidence was rated as "Very low" (SA10). This outcome

domain also included 8 studies of acute outcomes including anxiety and paranoia (ST1), summarized under their respective subdomains below.

Anxiety and Depression

Four studies examined both anxiety and depression (12, 45, 54, 60); two were included in the quantitative analysis (12, 45) and reported a "detrimental" association direction for anxiety and depression (p=0.500; Figure 1). The other two studies provided results that were generally consistent with no or weak association with higher-potency cannabis (Table 2). For example, in a cross-sectional survey of adults who use cannabis, anxiety symptoms positively correlated with frequency of both Con and Can-Mix use, but at a similar magnitude (r=0.18, p<0.001; r=0.15, p<0.05, respectively); depression symptoms did not correlate with frequency of either product (60).

We identified seven studies assessing acute anxiety (five experimental (63-65, 68, 69), two cross-sectional ((33, 34); ST1). These studies generally reported no association (33, 64, 65) or a modest positive association (33, 34, 68, 69) between higher-potency cannabis and acute anxiety. For example, a within-subjects study administering controlled doses of Can-Mid and Can-Low found significantly higher "anxious/nervous" scores after Can-Mid (23.0) relative to Can-Low (5.7; p<0.016 (69)). The exception was one between-subjects naturalistic experiment in which significantly lower tension scores were recorded after *ad libitum* Con relative to Can-Mix use (0.38 vs. 0.60, p<0.01 (63)). Two studies (one between-subjects naturalistic experiment (64), one cross-sectional (50)) assessed cannabis potency in relation to acute mood changes. The cross-sectional study found slightly lower (Cohen's d=-0.17) retrospectively-reported negative affect for Con relative to Can-Mix (p=0.003; (50)), while the naturalistic experiment did not observe group differences (Con vs. Can-High) in mood ratings after use (p=0.37; (64); ST1).

Psychosis

Ten studies examined psychosis (including psychotic disorder (38-41, 54, 57, 58), psychotic symptoms/experiences (45, 53), cannabis-associated psychosis (47, 56)) in relation to high-potency cannabis use—either in direct comparison to a lower potency group, or indirectly to a lower potency group via a shared no use group—and were considered for quantitative synthesis. Due to substantial overlap in study samples, designs, and outcome measures, some studies were grouped together ((41)+(38), (40)+case analysis from (53), (57)+(58)), yielding eight studies for quantitative synthesis. Five ((39, 45), (41)+(38), (40)+case analysis from (53), (57)+(58)) recorded a "detrimental" direction of association (p=0.727; Figure 1). For example, a large multi-site case-control study found that use of Can-Mid, but not Can-Low, significantly increased the odds of psychosis relative to no use (AOR=1.6, 95% CI=1.2-2.2 (40)).

We reviewed five studies (three experimental (65, 68, 69), two cross-sectional (34, 50)) that reported on an acute (secondary) outcome related to psychosis/psychotic symptoms (e.g., paranoia; ST1). Most found evidence of greater symptomology after higher-potency use. For example, a within-subjects, placebo-controlled study compared the effects of Can-Mid and Can-Low and recorded significantly higher peak paranoia scores following exposure to Can-Mid (17.4 on a 100 mm visual analog scale) relative to Can-Low (6.8, p<0.016 (69)).

Other mental health: PTSD and Bipolar Disorder

Two cross-sectional studies included a measure of PTSD (12, 54), one of which also assessed for bipolar disorder (54). Neither outcome was included in the quantitative synthesis since only one study (12) allowed for a direct potency comparison (see instead Table 2). One study found higher PTSD prevalence among cannabis-using adults who use Con (33%) relative to Can-Mix only (19%), but this did not reach statistical significance (p=0.11 (12)). The second recorded significantly elevated odds of Con and Res, but not Can-Mix, use among cannabis-using adults who self-reported a PTSD or bipolar diagnosis (54).

[Table 2 around here]

High-frequency and "problem" cannabis use

Seventeen studies assessed the relationship between higher-potency cannabis use and at least one non-acute measure of high-frequency cannabis use (n=10) or cannabis use disorder (CUD) and contributing symptoms (n=12). These studies are summarized in Table 3. For both sub-categories in this domain, certainty in the evidence was rated as "Very low" (SA10). This outcome domain also included 4 studies of acute outcomes including drug craving and drug liking (ST2), summarized under their respective subdomains below.

High-frequency cannabis use

All 10 studies of high-frequency cannabis use (12, 30, 34, 35, 37, 45, 48, 50-52, 55) were included in the quantitative syntheses and reported a "detrimental" direction of association (p=0.020). For example, a cohort study found that high school students who used Con or Can-Mix progressed to significantly more cannabis use days at 6-12 month follow-up (ARR=9.42, 95% CI=2.02-35.5 and ARR=2.81, 95% CI=1.78-4.42, respectively), but the estimate for Con was statistically significantly higher than Can-Mix ($p(\Delta\chi 2)$=0.02 (30)).

Cannabis Use Disorder

Eight studies that assessed CUD were included in the quantitative synthesis (10, 12, 35, 45, 47, 48, 51, 55); six (10, 12, 35, 45, 47, 51) recorded a "detrimental" direction of association (p=0.289; Figure 1). The sole "Fair" quality study grouped a cross-sectional sample into latent classes based on self-reported use of different cannabis products (detailed class descriptions in Table 3 footnotes). Relative to the Can-Low class, severity of cannabis dependence scores were significantly higher in classes characterized by Can-Mid use (b=0.155-0.429) and Res use (b=0.262; p<0.05) but not in either class characterized by Con use (35). Findings from the indirect comparison studies excluded from quantitative synthesis (n=4 (31, 44, 59, 60)) were inconsistent in noting a probable relationship between high-potency cannabis and CUD. For example, in a cohort of young adults, there was a significant positive association between higher-frequency Con use

and cannabis consequences (b=0.200, p<0.05; Table 3), but not between Con frequency and hazardous cannabis use or Con-Vape frequency and either outcome (60).

We included four studies (three experimental (65, 68, 69), one cross-sectional (34)) that reported on acute (secondary) outcomes of subjective measures often used as cues to indicate the reinforcing effects of a drug (i.e., "abuse-liability"), such as 'drug liking', 'pleasant/pleasurable effect', and 'cannabis craving' (ST2). Only one study recorded significantly higher ratings of an acute subjective effect ('drug liking') with higher-potency cannabis (Con vs. Can-Low (65)).

[Table 3 around here]

Use of other substances

We identified eight studies assessing the relationship between higher-potency cannabis use and at least one non-acute measure of other substance use including alcohol (n=4), tobacco (n=3), non-medical use of prescription drugs (n=3), and illicit/unregulated drugs (n=7). These studies are summarized in Table 4. For all sub-categories, certainty in the evidence was rated as "Very low" (SA10). We did not identify any studies assessing an acute indicator of other substance use.

Alcohol and Tobacco

All four alcohol studies (12, 45, 48, 66) were eligible for inclusion in the quantitative synthesis, and one (48) recorded a "detrimental" direction of association (p=0.625; Figure 1). This study found a higher frequency of binge drinking among undergraduate students who use Con relative to Can-Mix (OR=1.8, 95% CI=1.4-2.3; (48)). All three tobacco studies (12, 45, 48) were included in the quantitative synthesis and reported a "detrimental" direction of association (p=0.250; Figure 1); however only one unadjusted estimate was statistically significant and relatively small in magnitude (48).

Prescription and Illicit Drug Use

Due to overlapping study sample and outcomes measured, two studies that assessed both non-medical prescription drug use and illicit drug use ((42)+(43)) were combined into one study for quantitative synthesis. The resulting quantitative analyses included two studies for non-medical prescription drug use ((12), (42)+(43)) and five for illicit drug use ((12, 34, 45, 48), (42)+(43)), all of which recorded a "detrimental" association direction (prescription drug use: p=0.500; illicit drug use: p=0.063). The cohort study excluded from quantitative analysis found significantly elevated odds of prospective (one-year) illicit drug use initiation for high school students and who reported baseline Con (AOR=5.74, 95% CI=3.16-10.43), Con-Vape (AOR=3.11, 95% CI=2.41-4.01), or Can-Mix (AOR=2.57, 95% CI=1.66-4.02) use (32).

[Table 4 around here]

Psychosocial

Only one study was identified for a non-acute psychosocial outcome (49), finding a significantly higher composite score of "academic failure" for high school students who use Con (2.29) relative to Can-Mix (2.15, p<0.05).

We also identified seven studies (five experimental (63, 64, 67-69), two cross-sectional (34, 50)) that assessed high-potency cannabis use in relation to an acute psychosocial-cognitive measures including memory and attention, decision-making, psychomotor function and self-reported cognitive impairment (ST3). In general, higher-potency cannabis use tended to associate with worse subjective memory scores (34, 68, 69) but was not consistently associated with worse performance across attention and memory tasks (63, 64, 67-69). For example, a within-person, placebo-controlled study recorded significantly higher peak memory impairment score after Can-Mid (26.7) relative to Can-Low (3.1, p<0.016; (69); however, no significant differences were recorded in attention or working memory. Neither of the studies that evaluated a decision-making task—one comparing Can-Mid to Can-Low (67), the other comparing Con vs. Can-High

(64)—found a significant difference in scores between potencies (ST3). Psychomotor function was assessed in three within-subjects experimental studies (67-69). With the exception of a significantly longer "Stop" reaction time (Stop Signal Task) recorded after Can-Mid relative to Can-Low in a within-subjects study (67), significant differences in task performance were not observed during the higher- relative to lower-potency sessions.

Therapeutic outcomes

Therapeutic outcomes examined in relation to higher-potency cannabis use included headache or migraine (36), general pain (46), and anxiety (61, 62). Inconsistent findings emerged with respect to both pain (headache or general) and anxiety (ST4). In a study tracking acute symptom changes during medical cannabis sessions for headache or migraine, there were small yet significantly greater symptom reductions after Con use relative to Can-Mix (b=-0.09, p<0.001) for headache but no symptom differences for migraine (b=0.04, p>0.05; (36)). In a similarly designed study examining general pain (46), Con use did not precede significantly greater pain reductions relative to Can-Mix; however, greater symptom reduction was observed after Can-High (b=-0.232, p<0.05), but not Can-Mid, relative to Can-Low. The two anxiety studies (61, 62) were conducted on overlapping samples. The first did not find differences in anxiety symptom reduction relative to Can-Low after Can-High or Can-Mid use (both p>0.05 (62)); the second yielded more observations over a longer eligibility period (~1000 sessions among 441 patients) and noted significant reductions for both higher potency groups relative to Can-Low, but with a lack of dose-dependence (Can-High: b=-0.599; Can-Mid b=-0.618; both p<0.001 (61)).

Discussion

We sought to identify and synthesize evidence from studies examining the association between high-potency cannabis use and a range of health outcomes. We focused primarily on non-acute adverse health

outcomes and supplemented these findings with data on acute adverse and therapeutic health outcomes. Most studies addressed primary outcomes in the mental health, "problem" cannabis use, and other substance use domains. Observational research most often compared people who use cannabis concentrates (generally >60% THC) to those who use herbal cannabis (i.e., generally <30% THC) or those who primarily use 10-19% THC herbal cannabis to those who primarily use 1-9% THC. Importantly, many studies categorized concentrated products for explicit or probable consumption via vape pens into the concentrate group (12, 42, 43, 47, 49, 51, 56, 60). Distinguishing prepared vape products from other concentrates (e.g., dabs, wax, shatter) may reveal additional findings based on differences in amount consumed per occasion with equally potent products (e.g., vape pull: ~4mg THC vs. dab: ~20mg THC, at 80% THC each) (70). Laboratory-based experimental studies most often compared 10-19% THC against 1-9% THC herbal cannabis; however, some studies circumvented federal restrictions on experimental potency levels (71) by randomizing assignment to an intervention for self-administration by participants outside of the lab (e.g., in their home (64-66)).

In the context of very low certainty evidence across all outcomes, the reviewed findings are suggestive of a positive association between higher-potency cannabis use and high-frequency cannabis use, cannabis-related problems, or symptoms of cannabis use disorder. This is reflected in a "detrimental" direction of association observed for higher-potency cannabis under the "problem" cannabis use domain, accompanied by a significant pooled binomial test result (see SA7). Findings related to mental health and other substance use were less consistent but tended to favor poorer symptoms with higher-potency use. This was particularly apparent with psychosis, where evidence of an association with higher-potency use was strengthened after restricting to higher-quality studies (see SA6). Trends observed for non-acute anxiety and psychosis outcomes were generally supported with data on relevant acute measures where they could be obtained; data pertaining to acute indicators of "problem" cannabis use were less consistent.

In undertaking this review, we noted several research gaps and limitations of the existing research. While the evidence base is limited overall, it is mostly focused on potential mental health harms. Benefits and adverse effects associated with high-potency cannabis use for therapeutic purposes is an increasingly critical area of research as rising potency levels have also affected the medical market (8). Further, research specific to potency effects is currently completely lacking in many adverse outcome areas (e.g., cancer, cardiovascular and respiratory, prenatal/perinatal) while somewhat sparse and inconsistent in others (e.g., mental health), yielding very low certainty in the evidence overall.

There are numerous limitations identified in the findings, which may offer potential explanations for the inconsistencies observed across studies. Most of the included observational studies were cross-sectional and suffered from the well-documented limitations of such study designs—most notably, the inability to delineate temporality in exposure-outcome relationships. Concerns related to reverse causality are particularly high in studies under the mental health and "problem" cannabis use domains, where those self-medicating with cannabis and/or on a trajectory towards CUD, respectively, may transition to higher-potency use to address increased tolerance. Experimental research conducted on groups with similar cannabis use profiles provided important acute data to further inform this question, with acute increases in anxiety, paranoia, and indicators of cannabis "abuse liability" following higher-potency administration observed in 2/5 (68, 69), 3/3 (65, 68, 69), and 1/3 (65) experimental studies, respectively. The evidence base also suffered from imprecise imputation of true potency levels from self-reported product use and high inter-study variability in cannabis measurement/definition (e.g., any use vs. frequency of use; lifetime use vs. "current" use—the definition of which may vary across studies). Only a minority of studies that directly compared potency groups incorporated usage frequency into the exposure (38, 40, 41, 57). The importance of accounting for intensity of exposure to high-potency cannabis is well-illustrated by a study that saw elevated odds of psychosis for those who use daily Can-Mid (AOR=4.8) or Can-Low (AOR=2.2) relative to non-users, but noted a crude positive association only for any Can-Mid use before factoring in frequency (40). Average amount consumed per use-day (e.g., amount in dry weight or milligrams of THC) is also a

critical—but currently lacking—detail to incorporate into potency exposure assessments, as recent experimental research demonstrates that consumers may engage in behaviors to adjust down cannabis dosage with higher-potency intake (also known as "titration" (72)). Titration could also explain variability across experimental studies, as some involved *ad libitum* self-administration (63-66) while others involved controlled administration of THC doses that increased proportionally with potency (67-69). However, the extent to which titration behaviors successfully translate to lower THC exposure remains contested (72). While the focus of this review was on THC, cannabis contains hundreds of other chemical constituents including cannabidiol (CBD), minor cannabinoids, and terpenes (73) that are hypothesized to influence THC's effects on mood and other subjective effects, cognition, and psychosis/psychotic-like symptoms (74-77). Observational studies lacked data on non-THC cannabis constituents and some of the reviewed experimental studies administered high- and low-potency cannabis that differed in CBD concentrations (64-66).

Our review covers a wide breadth of research on high-potency cannabis and health, spanning adverse (both acute and non-acute) and therapeutic outcomes explored through observational and experimental studies. This strength is accompanied by certain limitations. First, while designed to increase public health relevance, the wide scope of review prevented the exploration of a more specific research question potentially more appropriate for meta-analysis. In line with current Cochrane guidance for reviews lacking a meta-analysis, we opted for an alternative quantitative synthesis and data visualization method that does not rely on vote counting based on statistical significance (26). The association direction method was selected as it suited the variability between studies in the type of estimate reported; however, the binomial test suffers from low power when only a few direction values are considered (27). To counteract this limitation, we also pooled subdomain results to increase power across domains. Nevertheless, the binomial test should not be the sole factor used to interpret findings; thus, our inclusion of a qualitative synthesis supports a more nuanced interpretation of the findings. As is the case in all systematic reviews, our search strategy may have missed potentially important material including studies yet to be peer-reviewed or those

published in another language. There are also several limitations within the included studies themselves, as discussed above—most notably, a high representation of findings from low-quality studies in which a temporal interpretation of exposure-outcome relationship cannot be deciphered.

While the findings of this review were only consistent in some domains and garnered very low certainty evidence overall, until the evidence base matures, cautious decision-makers may be looking to behavioral and structural interventions to limit high-potency cannabis use. Given that basic literacy around THC potency, including what it means and how to identify it on a product, is lacking for many consumers (78, 79), educational efforts to support consumers in making informed decisions about the potency of their products are warranted. However, product potency labels can be unreliable (9, 80), strengthening the need for improved quality control oversight. On a larger scale, regulatory measures that sway consumers towards lower-THC products may effectively address this issue from both a public health and economic perspective. Such measures include bans on certain products (e.g., non-flower cannabis products, as implemented in Uruguay); capping THC products at a certain potency (e.g., flower capped at 15%, as implemented in Uruguay; 30%, as implemented in Connecticut) or dose (e.g., 10 mg per edible package, implemented in Canada); or taxing cannabis based on THC potency (as implemented in Canada, Illinois, Connecticut (81)). Ultimately, decisions about regulating or banning high potency cannabis products will depend on the values and perspectives of the decision-makers. Those who prioritize public health may opt for potency limits or product bans before there is a consensus about the evidence. Those who prioritize business interests may argue that tightly regulating or banning these products will push consumers to the unregulated market which could be more harmful from a health perspective. A potency-based tax structure may best bridge the gap between these interests as it is less extreme than a product ban, avoids incentivizing production of higher THC potency per unit weight (in the case of weight-based tax), and offers the additional economic benefit of not fluctuating with market price (in the case of price-based tax (81)). Our goal is not to settle the debate about whether regulating or banning high potency cannabis products will be a net win or loss from a public health perspective; rather, we hope to educate readers about the state-of-the evidence on the health

consequences of using high potency cannabis products and how it can be improved. Research into the public health benefit of potency caps, potency tax structures, and other regulatory interventions should be prioritized and followed closely by jurisdictions seeking to responsibly regulate cannabis.

Conclusion

We identified 42 observational and experimental studies addressing the relationship between high-potency cannabis and health. Studies on this topic were limited to mental health, "problem" cannabis use, other substance use, and acute psychosocial-cognitive health domains. Higher-potency cannabis use was relatively consistently associated with indicators of "problem" cannabis use. In other domains, findings were less consistent but tended to favor worse symptoms with higher-potency use. Overall, due to inconsistent, indirect, and generally low-quality evidence, certainty in the evidence remains very low. Cautious decision-makers may consider implementing behavioral of structural interventions aimed at minimizing use of higher-potency products while the evidence base matures.

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Disclosures

Outside of this work, ZDC reports receiving study drug from Canopy Growth Corp and True Terpenes and study-related materials from Storz & Bickel.

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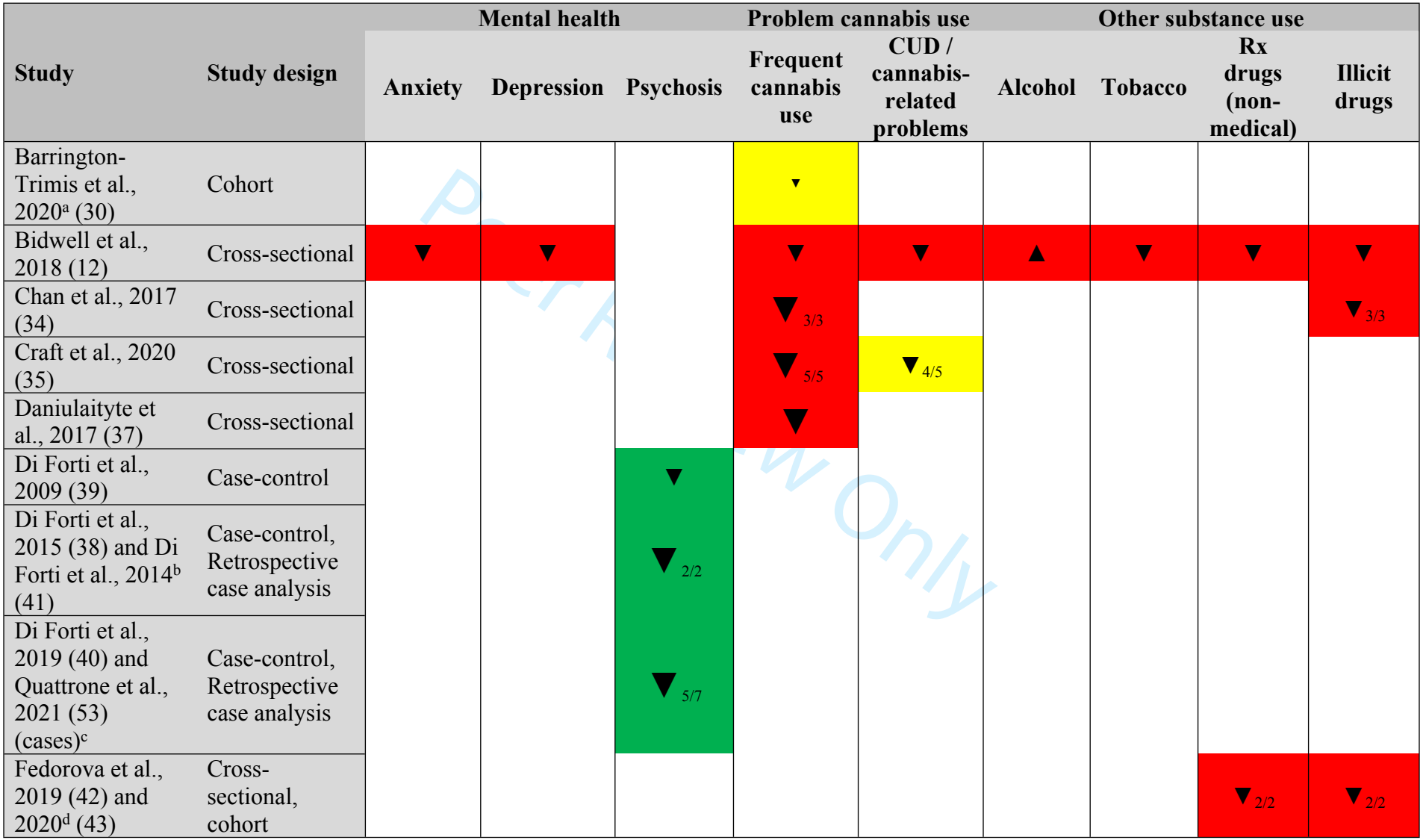
Table 1. Population, Intervention (Exposure), Comparison, Outcome, Study Design (PICOS) criteria for inclusion

Criterion	Description
Population	Adults, adolescents, emerging adults.
Intervention (Exposure)	High potency inhaled cannabis, categorized as: Concentrate ("Con": ≥60% THC [note: if a study explicitly considered vaped concentrates as its own group, we denoted this with the designation "Con-Vape"]), Resin (or kief, hash; "Res": ~30-50% THC), High potency herbal ("Can-High": 20-30% THC), Mid potency herbal ("Can-Mid": 10-19% THC).
Comparison	Lower potency of inhaled cannabis relative to a category above, including additional categories for Low-potency herbal ("Can-Low": <10% THC) and mixed potency herbal (unknown %THC but comparatively lower than "Con" or "Res"; "Can-Mix"). Also accepted: indirect comparison of ≥2 potency categories via a shared no/placebo cannabis comparison group (e.g., Can-Mid and Can-Low vs. No use) or via a no/lower frequency comparison group specific to each potency category, so long as the same scale of measurement was used across potency categories (e.g., days of Can-Mid use and days of Can-Low use).
Outcome	Primary: Non-acute adverse health-related measures, defined as conditions or symptoms occurring or persisting beyond the drug's acute effects. Eligible non-acute adverse outcomes were those that could be classified according to NASEM[1] review on effects of cannabis. Secondary 1: Acute adverse health-related measures, defined as conditions or symptoms occurring acutely after cannabis consumption. These could be from (1) experimental studies assessing acute effects of higher potency cannabis; or (2) observational studies comparing retrospective recall of acute subjective drug effects. To supplement primary findings, we only included acute measures that were covered by the NASEM review (i.e., psychosocial-cognitive) or could serve as possible acute indicators of the extracted primary outcomes. Secondary 2: Symptom-related measures in studies restricted to people taking cannabis for a shared medical/therapeutic purpose. Eligible therapeutic outcomes were those that could be classified according to NASEM's therapeutic section.[2]
Study Design	Observational (cohort, cross-sectional, case-control studies, naturalistic designs) and experimental studies that used quantitative data to test for a statistical relationship between a higher potency cannabis category (vs. a comparatively lower potency category). Abstracts, reviews, commentaries, letters, and case reports/series were excluded.

[1]NASEM refers to the National Academies of Sciences, Engineering, and Medicine report on the health effects of cannabis (3). As per the NASEM review, non-acute adverse outcomes were categorized as: Cancer; cardiometabolic risk; respiratory disease; immunity; injury and death; prenatal, perinatal, and neonatal outcomes; psychosocial; mental health; problem cannabis use [note: we included measures of high-frequency cannabis use in this subdomain along with symptoms/assessments of cannabis use disorder or cannabis-related consequences]; and problem use of other substances [note: we broadened this subdomain to include measures related to any other non-cannabis substance use and removed "problematic" from its descriptor]. [2]Therapeutic outcomes were categorized

as: Chronic pain; cancer; chemotherapy-induced nausea and vomiting; anorexia and weight loss; irritable bowel syndrome; epilepsy; spasticity associated with MS or SCI; Tourette syndrome; amyotrophic lateral sclerosis; Huntington's disease; Parkinson's disease; dystonia; dementia; glaucoma; TBI / intracranial hemorrhage; addiction; anxiety; depression; sleep disorders; PTSD; schizophrenia and other psychosis.

Figure 1. Association direction plot for all primary outcomes eligible for quantitative synthesis



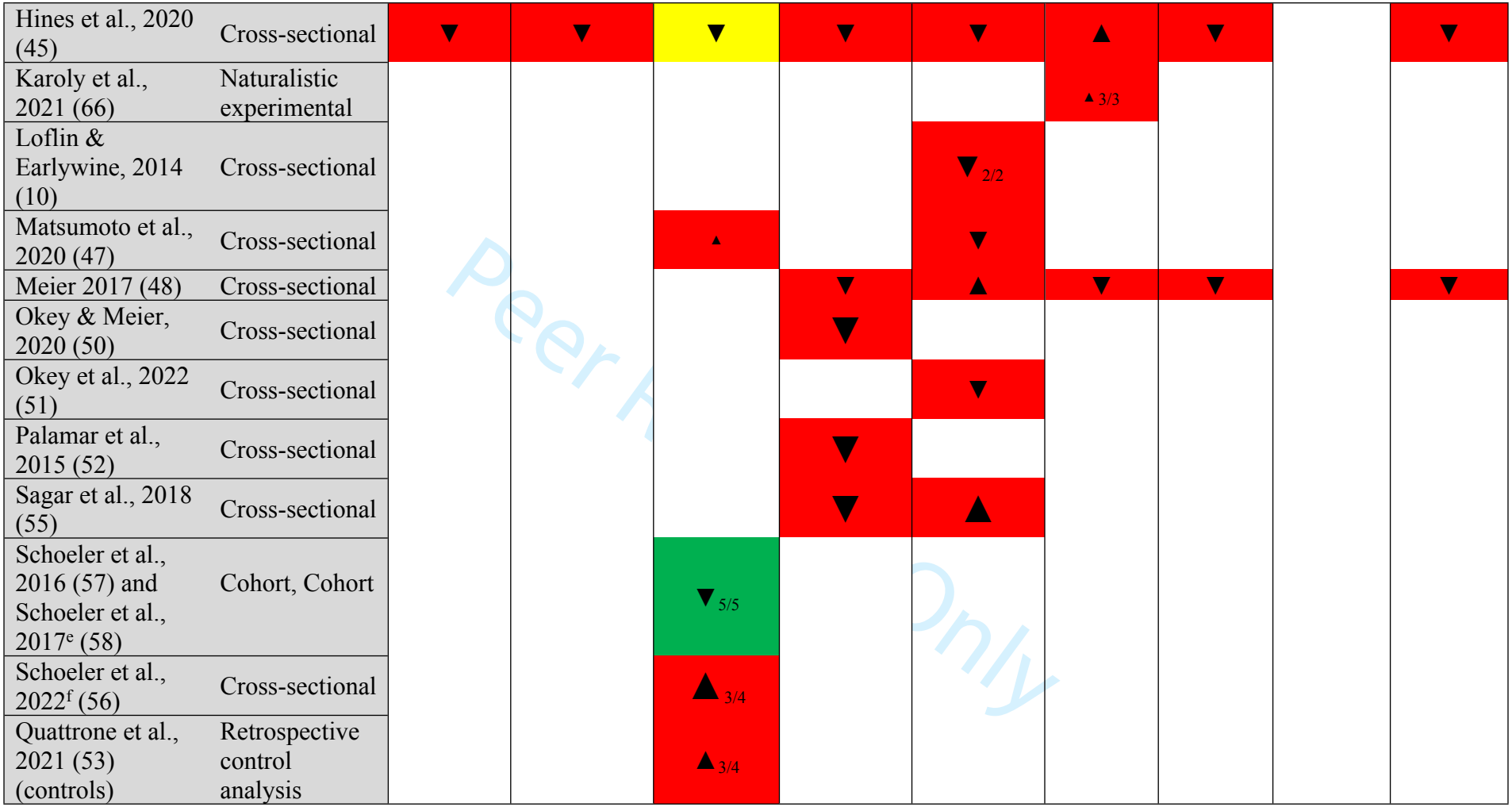


Figure 1 legend:

▲	Point estimate (or clear majority of point estimates) on side of "beneficial" direction of effect
▼	Point estimate (or clear majority of point estimates) on side of "detrimental" direction of effect
◀ ▶	Point estimate aligns with null or point estimates do not have a clear majority on side of "beneficial" or "detrimental" direction of effect
	"Good" study quality rating (or "Low" risk of bias if experimental)
	"Fair" study quality rating (or "Some concerns" from risk of bias if experimental)
	"Poor" study quality rating (or "High" risk of bias if experimental)

Figure 1 caption:

Figure notes: For studies reporting >1 relevant effect estimate for the outcome (e.g., >1 outcome measure; >1 relevant potency comparison with outcome), subscript numbers denote the total number of effect estimates considered (denominator) and the number of effect estimates aligning with the sign of the arrow (numerator). Size of arrow denotes sample size of the high-potency group(s): Large arrow = >300, Medium arrow = 50-300, Small arrow = <50.

Study-specific figure notes: [a]Barrington-Trimis et al., 2020: Effect measure contributing to plot was derived from authors' post hoc comparison of strength of estimate for concentrates and combustibles. [b]Di Forti et al., 2014: This is a sub-analysis of cases from Di Forti et al., 2015; as Di Forti et al., 2015 measured psychosis and Di Forti et al., 2014 measured an aspect of that outcome (timing of psychosis onset), the findings with respect to psychosis were considered together. Study quality color corresponds with Di Forti et al., 2015. [c]Quattrone et al., 2021 (cases): This study includes a sub-analysis of cases from Di Forti et al., 2019; as Di Forti et al., 2019 measured psychosis and Quattrone et al., 2021 measured aspects of the psychosis outcome (psychosis symptom dimensions), the findings with respect to psychosis were considered together. Study quality color corresponds with Di Forti et al., 2019. [d]Federova et al., 2019 and 2020: These findings were considered together as they contain overlapping samples from the same seed study and provide measures for the same primary outcome sub-domains; [e]Schoeler et al., 2017: The findings with respect to psychosis were combined with Schoeler et al., 2016 as Schoeler et al., 2017 included an additional measure related to psychosis (medication adherence) on the same sample from Schoeler et al., 2016. [f]Schoeler et al., 2022: Size of arrow corresponds with sample size of intervention group (n>300) for three high-low potency comparison estimates for study's primary outcome (CAPS requiring emergency department visit); the reviewed findings also include a sub-analysis outcome (CAPS requiring hospitalization) for which the size of intervention group was <50.

Table 2. Summary of findings for non-acute adverse outcomes: mental health

Author(s), year	Study design, location, period	Sample characteristics	Exposure		Outcome	Summary of findings	QA / RoB
			Measure, method of assessment	Relevant potencies compared	Measure, method of assessment		
Anxiety							
Bidwell et al., 2018 (12)	Cross-sectional, USA, 2017	Adults who use cannabis: n = 131; non-male = 49%; mean age = 42	Frequency and type of cannabis used, current (period not defined), self-reported	Con (including Con-Vape; ≥4 times/week) vs. Can-Mix (any)	Anxiety, past-week, self-reported via Likert scale (range 0-4)	Higher mean anxiety score for Con (1.1, SD=1.3) vs. Can-Mix (0.7, SD=0.9), p=0.05[a], Cohen's d=0.34	Poor
Hines et al., 2020 (45)	Cross-sectional, UK, 2015-2017	Young adults who use cannabis: n = 1087; non-male = 57%; mean age = 24	Type of cannabis used, past year, self-reported	Can-Mid vs. Can-Low	Generalized anxiety disorder, current, self-assessed via CIS-R	Can-Mid associated with significantly higher odds of anxiety (AOR=1.92 [1.11-3.32], p=0.02)	Poor
Rup et al., 2021 (54)	Cross-sectional, Canada and USA, 2018	Subset who use cannabis (n = 6413) from a sample of adolescents and adults: full n = 25747; female = 51%; age = distributed evenly across age groups	Type of cannabis product(s) used, past year, self-reported	Con, Con-Vape, Res, Can-Mix (all yes vs. no)	Anxiety (including phobia, OCD, or panic disorder), past year, self-reported	Anxiety significantly associated with use of all products (AORs in descending point estimate: Con=1.51 [1.31-1.75]; Con-Vape=1.45 [1.26-1.67]); Res=1.23 [1.08-1.42]); Can-Mix=1.20 [1.05-1.38]; all p<0.05)	Poor
Steeger et al., 2021 (60)	Cross-sectional, USA, 2017-2020	Adults who use cannabis: n = 300; non-male = 42%; mean age = 35	Frequency and type of cannabis used, past month, self-reported	Con[b] and Can-Mix, per increasing frequency on continuous scale	Anxiety, past-week, self-reported via BAI	Anxiety symptoms were significantly positively correlated with frequency of Con use (r=0.18, p<0.01) and Can-Mix use (r=0.15, p<0.05)	Fair
Depression							
Bidwell et al., 2018 (12)	Cross-sectional, USA, 2017	Adults who use cannabis: n = 131; non-male = 57%; mean age = 42	Frequency and type of cannabis used, current (period not defined), self-reported	Con (including Con-Vape; ≥4 times/week) vs. Can-Mix (any)	Depression, past-week, self-reported via Likert scale (range 0-4)	No difference in mean depression score for Con (0.72, SD=1.0) vs. Can-Mix (0.62, SD=0.9), p=0.57	Poor

Hines et al., 2020 (45)	Cross-sectional, UK, 2015-2017	Young adults who use cannabis: n = 1087 non-male = 57%; mean age = 24	Type of cannabis used, past year, self-reported	Can-Mid vs. Can-Low	Moderate-severe depression, current, self-reported via CIS-R	Can-Mid not significantly associated with major depression (AOR=1.28 [0.68-2.32], p=0.44)	Poor
Rup et al., 2021 (54)	Cross-sectional, Canada and USA, 2018	Subset who use cannabis (n = 6413) from a sample of adolescents and adults: full n = 25747; female = 51%; age = distributed evenly across age groups	Type of cannabis product(s) used, past year, self-reported	Con, Con-Vape, Res, Can-Mix (all yes vs. no)	Depression (including dysthymia), past-year, self-reported	Depression significantly associated with use of all products (AORs in descending point estimate: Con=1.69 [1.46-1.95]; Can-Mix=1.42 [1.23-1.64]; Res=1.37 [1.20-1.47]; Con-Vape=1.25 [1.11-1.42]; all p<0.05)	Poor
Steeger et al., 2021 (60)	Cross-sectional, USA, 2017-2020	Adults who use cannabis: n = 300; non-male = 42%; mean age = 35	Frequency and type of cannabis used, past month, self-reported	Con[b] and Can-Mix, per increasing frequency on continuous scale	Depression, past-week, self-reported via BDI	Depression symptoms did not correlate significantly with frequency of Con use (r=0.09, p>0.05) or Can-Mix use (r=0.10, p>0.05)	Fair
Psychosis							
Di Forti et al., 2009[c] (39)	Case-control, UK, 2005-2008	Subset with cannabis use experience (n = 268) from a sample of adults with psychosis (n = 280) and healthy controls (n = 174): full n = 454; female = 31%; mean age = 26	Type of cannabis preferentially (most often) used, lifetime, self-reported	Can-Mid vs. Can-Low	First episode of psychosis (ICD-10 coded), validated with SCAN	Can-Mid associated with significantly higher odds of psychosis relative to Can-Low (AOR=6.8 [2.6-25.4], p<0.05)	Good
Di Forti et al., 2014[c] (41)	Retrospective analysis of cases from a case-control study, UK, 2005-2010	Adults with psychosis: n = 410; female = 44%; mean age = 29	Type and frequency of cannabis preferentially used, lifetime, self-reported	Can-Mid vs. Can-Low; Can-Mid (daily), Can-Mid (<weekly), Can-Low (daily), Can-Low (<weekly) vs. None	Time to onset of first episode of psychosis (ICD-10 coded), validated with SCAN	Can-Mid significantly associated with earlier psychosis onset relative to Can-Low (AHR=1.68 [1.08-2.63], p=0.002); Relative to no use, Daily Can-Mid and <Weekly Can-Mid significantly associated with earlier psychosis onset. (AHR=1.99 [1.50-2.65], p<0.001; AHR=1.48 [1.17-2.04], p=0.015, respectively); No significant association between Daily or <Weekly Can-Low use and psychosis onset	Fair

Di Forti et al., 2015[c] (38)	Case-control study, UK, 2005-2011	Adults with psychosis (n = 410) and healthy controls (n = 310): full n = 780; female = 39%; mean age = 29	Type and frequency of cannabis preferentially used, lifetime, self-reported	Can-Mid, Can-Low vs. None	First episode of psychosis (ICD-10 coded), validated with SCAN	Relative to no use, significantly elevated odds of psychosis for Can-Mid (AOR=2.91 [1.52-3.60], *p*=0.001) but not Can-Low (AOR=0.83 [0.52-1.77], *p*=0.903); Daily Can-Mid conferred the highest odds of psychosis (AOR=5.40, [2.80-11.30], *p*=0.001), followed by Weekly Can-Mid (AOR=2.70, *p*=0.008) and Monthly Can-Mid (AOR=1.90, *p*=0.020); Can-Low not significantly associated with psychosis at any frequency	Good
Di Forti et al., 2019[d] (40)	Case-control, multinational, 2010-2015	Adults with psychosis (n = 901) and healthy controls (n = 1237); full n = 2138; female = 47%; mean age = 34	Type and most consistent frequency of cannabis most used, lifetime, self-reported	Can-Mid, Can-Low vs. None	First episode of psychosis (ICD-10 coded), validated with OPCRIT system	Relative to no use, significantly elevated odds of psychosis for Can-Mid (AOR=1.6 [1.2-2.2], *p*=0.003), but not Can-Low (AOR=1.1 [0.9-1.5] *p*=0.380); Daily Can-Mid conferred the highest odds of psychosis (AOR=4.8 [2.5-6.3]), followed by Daily Can-Low (AOR=2.2, [1.4-3.6]); Weekly and ≤Monthly Can-Mid and Can-Low were not significantly associated with psychosis	Good
Hines et al., 2020 (45)	Cross-sectional, UK, 2015-2017	Young adults who use cannabis: n=1087; non-male = 57%; mean age=24	Type of cannabis used, past year, self-reported	Can-Mid vs. Can-Low	Psychotic experiences, past-year, self-reported via semi-structured interview	Can-Mid not significantly associated with psychotic experiences (AOR=1.29 [0.67-2.50], *p*=0.45)	Fair
Matsumoto et al., 2020 (47)	Cross-sectional, Japan, 2019	Adults in treatment for cannabinoid-related mental or behavioral disorder: n = 71; female = 17%; mean age = 35	Type of cannabis products used, lifetime, self-reported	Con/Con-Vape/Res vs. Can-Mix	Diagnosis of "Residual and late-onset psychotic disorder due to use of cannabinoids", current, clinician-reported	Con group (Con, Con-Vape, and/or Res) had significantly lower odds of psychotic disorder due to cannabis relative to Can-Mix (AOR=0.11 [0.02-0.56], *p*=0.007)	Poor
Rup et al., 2021 (54)	Cross-sectional, Canada and USA, 2018	Subset who use cannabis (n = 6413) from a sample of adolescents and adults: full n =	Type of cannabis product(s) used, past year, self-reported	Con, Con-Vape, Res (kief), Can-Mix (all yes vs. no)	Psychotic disorder (including schizophrenia), past-year, self-reported	Psychotic disorder significantly associated with Con (AOR=1.71 [1.18-2.47]) and Res (AOR=1.62 [1.34-2.32]; both *p*<0.05), but not Con-Vape	Poor

		25747; female = 51%; age = distributed evenly across age groups				(AOR=1.31 [0.93-1.84]) or Can-Mix (AOR=0.89 [0.59-1.33])	
Schoeler et al., 2016[e] (57)	Prospective cohort, UK, 2002-2013	Patients with first episode psychosis: n = 256; female = 40%; mean age = 28	Type and continuity of cannabis used in the first 2 years after psychosis onset, self-reported	Can-Mid (daily), Can-Mid (monthly), Can-Low (daily or monthly) vs. Former Can-Mix (no current use)	Psychosis relapse requiring hospital admission, within 2 years of psychosis onset, assessed via clinical records	Can-Mid (daily) group had significantly higher odds of relapse relative to former cannabis use group (AOR=3.28 [1.22-9.18], p=0.02); No significant association for any other cannabis use group (p>0.05; See Table 3 in Schoeler et al., 2016 for all estimates)	Good
					Number of psychosis relapses, assessed as above	No significant association with any cannabis use group (p>0.05), including Can-Mid (daily) use (AIRR=1.77 [0.96-3.25], p=0.07; See Table 3 in Schoeler et al., 2016 for all estimates)	
					Length of relapse (cumulative time spent in hospital), assessed as above	No significant association with any cannabis use group (p>0.05), including Can-Mid (daily) use (b=0.61, [-0.31-1.55], p=0.17; See Table 3 in Schoeler et al., 2016 for all estimates)	
					Time to first psychosis relapse, assessed as above	Can-Mid (daily) use group had significantly shorter time to first relapse relative to former cannabis use group (b=-0.22 [-0.40, -0.05], p=0.02); No significant association for any other cannabis use group (p>0.05; See Table 3 in Schoeler et al., 2016 for all estimates)	
Schoeler et al., 2017[e] (58)	Prospective cohort, UK, 2002-2013	Patients with first episode psychosis: n = 233; female = 40%; mean age = 28	Type and continuity of cannabis used in the first 2 years after psychosis onset, self-reported	Can-Mid (continued), Can-Low (continued) vs. no use	Antipsychotic medication adherence, within 2 years of psychosis onset, assessed via clinical records	Relative to no use, continued Can-Mid was positively associated with treatment non-adherence (AOR=5.26 [1.91-15.68], p=0.002); No significant association for continued Can-Low (AOR=1.50 [0.28-9.22], p=0.64)	Good
Schoeler et al., 2022 (56)	Cross-sectional study,	Subset with data on cannabis-associated psychotic symptoms (CAPS; n = 148109)	Type of cannabis most often used, past	Con[b], Res, Can-Mid vs. Can-Low	CAPS requiring emergency medical treatment, past-year, self-reported	Relative to Can-Low, Res was significantly associated with CAPS (RR=2.11 [1.53-2.90], adj. p<0.001); No significant associations for Con	Poor

	multinational, 2014-2019	from a sample of adults who use cannabis: full n = 233475; non-male = 28%; age = majority (58%) ≤ 25 years	year, self-reported			(RR=0.39 [0.10-1.59]) or Can-Mid (RR = 0.96 [0.73-1.26]; both adj. *p*=1.00)	
		Subset who experienced CAPS (n = 277) from above subsample		Can-Mid vs. Can-Low	Hospitalized due to CAPS, past-year, self-reported	No difference in percent hospitalized between those who used Can-Mid (36.6%) versus Can-Low (38.1%) before CAPS (p=0.82)	
Quattrone et al., 2021[d] (53)	Separate analysis of cases and controls from case-control study, multinational, 2010-2015	Adults with psychosis: n = 901; non-male = 38%; mean age = 31	Type of cannabis used, lifetime, self-reported	Can-Mid and Can-Low vs. None	Psychotic symptoms in first 4 weeks after psychosis onset, assessed by trained investigator via OPCRIT system	Relative to no use, no significant association with overall psychosis factor for Can-Mid (*b*=0.02 [-0.12-0.17], *p*>0.05) or Can-Low (*b*=0.06 [0.07-0.19], *p*>0.05). Dimension-specific findings: both Can-Mid (*b*=0.27) and Can-Low (*b*=0.23) positively associated with manic symptom dimension (*p*<0.01); both Can-Mid (*b*=-0.24) and Can-Low (*b*=-0.20) negatively associated with negative symptom dimension (*p*<0.05); Can-Mid positively associated with positive symptom dimension (*b*=0.22, *p*<0.01); Neither potency associated with disorganization or depressive symptom dimensions (*p*>0.05; See Table S6.1 in Quattrone et al., 2021 for all estimates)	Poor
		Healthy community controls: n = 1325; non-male = 53%; mean age = 36			Psychotic-like experiences, current, self-reported via CAPE	No significant associations between Can-Mid or Can-Low (vs. no use) in general psychotic experience factor or any of the assessed symptom dimensions (positive, negative, depressive; *p*>0.05; See Table S6.2 in Quattrone et al., 2021 for all estimates)	
Other mental health							
Bidwell et al., 2018 (12)	Cross-sectional, USA, 2017	Adults who use cannabis: n = 131; non-male = 49%; mean age = 42	Frequency and type of cannabis used, current (period not	Con (including Con-Vape; ≥4 times/week) vs. Can-Mix (any)	Clinical diagnosis of PTSD, current, self-reported	PTSD reported more by Con group (32.8%) vs. Can-Mix (19.0%), but not statistically significant (*p*=0.11)	Poor

			defined), self-reported				
Rup et al., 2021 (54)	Cross-sectional, Canada and USA, 2018	Subset who use cannabis (n = 6413) from a sample of adolescents and adults: full n = 25747; female = 51%; age = distributed evenly across age groups	Type of cannabis product(s) used, past year, self-reported	Con, Con-Vape, Res (kief), Can-Mix (all yes vs. no)	PTSD, past-year, self-reported	PTSD significantly associated with Con (AOR=1.43 [1.15-1.78]), Res (AOR=1.45 [1.18-1.78]), and Con-Vape (AOR=1.37 [1.14-1.66], all $p<0.05$), but not Can-Mix (AOR=1.16 [0.92-1.48])	Poor
					Bipolar disorder or mania, past-year, self-reported	Bipolar disorder or mania significantly associated with Con (AOR=1.63 [1.26-2.10]) and Res (AOR=1.69 [1.25-2.28], both $p<0.05$), but not Con-Vape (AOR=1.06 [0.84-1.34]) or Can-Mix (AOR=1.17 [0.86-1.59])	

Study-specific notes: [a]Bidwell et al. did not consider this comparison statistically significant with alpha set to 0.01 for 52 pairwise comparisons; [b]This group likely included Con-Vape via "hash oil" or "oil" use; [c]Di Forti et al., 2009, 2014, and 2015 contain overlapping samples from the Genetics and Psychosis (GAP) study, including 100% case overlap between Di Forti et al., 2014 and 2015; [d]Di Forti et al., 2019 and Quattrone et al., 2021 contain overlapping samples from the EUropean network of national schizophrenia network studying Gene-Environment Interactions (EU-GEI) study, including 100% case overlap; [e]Schoeler et al., 2016 and 2017 contain samples with close to 100% overlap. **Abbreviations:** (A)HR = (Adjusted) Hazard Ratio; (A)IRR = (Adjusted) Incidence Rate Ratio; (A)OR = (Adjusted) Odds Ratio; BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; CAPE = Community Assessment of Psychic Experiences; CIS-R = Clinical Interview Schedule-Revised; ICD-10 = International Classification of Diseases (10th Edition); OCD = Obsessive Compulsive Disorder; OPCRIT = OPerational CRITeria; QA = Quality Assessment; RoB = Risk of Bias; PTSD = Post-Traumatic Stress Disorder; SD = Standard Deviation. **Cannabis potency category definitions:** Can-Low = ≤10% THC flower; Can-Mid = 10-19% THC flower; Can-High = ≥20% THC flower; Res = hashish, resin, kief, assumed to have 20-50% THC; Con = Concentrated cannabis product, assumed to have 60-99% THC; Can-Mix = Cannabis of unspecified or multiple potency categories, but estimated to be lower than the higher potency exposure from that study.

Table 3. Summary of findings for non-acute adverse outcomes: high-frequency and "problem" cannabis use

Author(s), year	Study design, location, period	Sample characteristics	Exposure		Outcome	Summary of findings	QA / RoB
			Measure, method of assessment	Relevant potencies compared	Measure, method of assessment		
High-frequency cannabis use							
Barrington-Trimis et al., 2020 (30)	Prospective cohort, USA, 2016-2017	High school students with no history of heavy cannabis use: n = 2685; female = 55%; mean age = 17	Type of cannabis product used, past 30 days, self-reported	Con, Con-Vape, and Can-Mix (combustibles) (all yes vs. no)	Progression of cannabis product use, defined as days of specific product use in past 30-days, averaged over FU, self-reported	Con and Can-Mix significantly associated with progression of use (ARRs: Con=9.42 [2.02-35.50]; Can-Mix=2.81 [1.78-4.42]; ARR for Con > ARR for Can-Mix ($p(\Delta\chi2)=0.02$)	Fair
Bidwell et al., 2018 (12)	Cross-sectional, USA, 2017	Adults who use cannabis: n = 131; non-male = 49%; mean age = 42	Frequency and type of cannabis used, current (period not defined), self-reported	Con (including Con-Vape; ≥4 times/week) vs. Can-Mix (any)	Frequency of cannabis use, current, self-reported	Con group used cannabis on significantly more days (6.0, SD=2.1) relative to Can-Mix group (4.2, SD=3.1), $p<0.001$, Cohen's $d=0.71$	Poor
Chan et al., 2017 (34)	Cross-sectional, multinational, 2015-2016	Young adults and adults (≥16 years) who use cannabis: n = 83867; female = 29%; mean age = 26	Type of cannabis used, past year, self-reported	Con, Can-Mid vs. Can-Low; Con vs. Can-Mid	Daily or almost daily use of cannabis, past year, self-reported	Significant between-group differences in % reporting daily use, with Con (20.0%) > Can-Mid (10.8%) > Can-Low (5.2%), $\chi2=1387$, $p<0.001$	Poor
Craft et al., 2020 (35)	Cross-sectional study, multinational, 2017-2018	Young adults and adults (≥16 years) who use cannabis: n = 55242; female = 28%; mean age = 25	Latent class membership[a] defined by type(s) of cannabis products used, past year, self-reported	Con[b] class 1, Con[b] class 2, Res (hash) class, Can-Mid class 1, Can-Mid class 2 vs. Can-Low class (see Table notes)	Frequency of cannabis use, past year, self-reported	Frequency of use differed significantly across latent classes ($\chi2=12909.25$, $p<0.001$), with ≥daily use highest in Con class 1 (69.0%), Can-Mid class 1 (45.1%), and Con class 2 (35.9%); lowest in Can-Low class (9.3%; See Table 1 in Craft et al., for all estimates)	Poor
Daniulaityte et al., 2017 (37)	Cross-sectional, USA, 2016	Adults who use cannabis: n = 673; female = 22%; mean age = 30	Type of cannabis used, lifetime, self-reported	Con vs. Can-Mix	Daily use of cannabis, past-year, self-reported	Daily cannabis use significantly associated with Con (AOR=4.28 [2.69-6.80], $p<0.001$)	Poor

Hines et al., 2020 (45)	Cross-sectional, UK, 2015-2017	Young adults who use cannabis: n = 1087; non-male = 57%; mean age = 24	Type of cannabis used, past year, self-reported	Can-Mid vs. Can-Low	Regular (≥weekly) cannabis use, past-year, self-reported	Significantly higher odds of regular cannabis use for Can-Mid relative to Can-Low (AOR=4.38 [2.89-6.63], p<0.001)	Poor
Meier 2017 (48)	Cross-sectional, USA, study period not reported	Undergraduate students who use cannabis: n = 273; female = 65%; mean age = 23	Type of cannabis used, past year, self-reported	Con vs. Can-Mix	Frequency of cannabis use, past year, self-reported	Odds of Con use increased significantly with frequency of cannabis use (OR=4.1 [2.9-5.7], p<0.001)	Poor
Okey and Meier, 2020 (50)	Cross-sectional, USA, study period not reported	Adults who use cannabis: n = 849; non-male = 48%; mean age = 33	Type of cannabis used, lifetime, self-reported	Con vs. Can-Mix	Frequency of cannabis use, past year, self-reported via ordinal categories from 0 (none) to 12 (≥daily)	Con users reported significantly higher frequency of use (10.1, SD=2.7) compared to Can-Mix (8.4, SD=3.5; t=7.83, adjusted p=0.003)	Poor
Okey et al., 2022 (51)	Cross-sectional, USA, study period not reported	College students who use cannabis: n = 387; female = 59%; mean age = 19	Type of cannabis typically used, current (period not defined), self-reported	Con[b]/Res vs. Can-Mix	Frequency of cannabis use, current, self-reported	Significantly higher frequency of cannabis use among Con/Res group relative to Can-Mix (t=-3.09, p=0.002, Cohen's d=-0.34)	Poor
Palamar et al., 2015 (52)	Cross-sectional, USA, 2007-2011	High school seniors who use cannabis: N = 2650; female = 47%; age = majority (55%) ≥18 years	Type of cannabis used, past year, self-reported	Res[b] vs. Can-Mix	Frequency of cannabis use, past year, self-reported	Relative to the lowest frequency group (3-5 times/year), the odds of Res use increased significantly with frequency of cannabis use (AORs ranged from 2.28 [1.30-3.98; 6-9 times/year] to 9.26 [5.84-14.69; >40 times/year]; all p<0.05; See Table 4 in Palamar et al., 2015 for all estimates)	Poor
Sagar et al., 2018 (55)	Cross-sectional, USA, 2016-2017	Subset of people who use cannabis and dabs (n = 1037) from a sample of adults who use cannabis: full n = 4077; female = 39%; mean age = 44	Type of cannabis used, current (period not defined), self-reported	Con vs. Former Con (i.e., Current Can-Mix)	Frequency of cannabis flower use, current, self-reported	Significantly higher proportion of current Con users endorsed weekly and daily cannabis use (χ2=7.675, p=0.022)	Poor
Cannabis use disorder (including indicators or consequences)							

Bedillion et al., 2022 (31)	Prospective cohort, USA, study period not reported	Young adults who use cannabis for non-medical purposes: n = 155; female = 59%; mean age = 21	Frequency of cannabis product use, past 21 days, self-reported at BL with EMA	Con, Con-Vape, Can-Mix (joint), Can-Mix (bowl), Can-Mix (bong), per increasing frequency on continuous scale	Hazardous cannabis use at 6-month FU, self-reported via CUDIT-R	No significant associations between frequency of use of any product and hazardous cannabis use at FU (all $p>0.05$)	Fair
					Cannabis-related consequences at 6-month FU, self-reported via B-MACQ	Frequency of Con significantly positively associated with B-MACQ score at FU ($b=0.200$, $p=0.006$); No significant associations between frequency of Con-vape, Can-Mix (bong), Can-Mix (bowl) or Can-Mix (joint) and B-MACQ score at FU ($p>0.05$)	
Bidwell et al., 2018 (12)	Cross-sectional, USA, 2017	Adults who use cannabis: n=131; non-male = 49%; mean age = 42	Frequency and type of cannabis used, current (period not defined), self-reported	Con (including Con-Vape; ≥4 times/week) vs. Can-Mix (any)	CUD symptoms, current, self-reported via MINI	Con group had more CUD symptoms (2.1, SD=2.5) relative to Can-Mix (1.1, SD=2.0); $p=0.02$[c], Cohen's $d=0.43$	Poor
Craft et al., 2020 (35)	Cross-sectional study, multinational, 2017-2018	Young adults and adults (≥16 years) who use cannabis: n = 55242; female = 28%; mean age = 25	Latent class membership[b] defined by type(s) of cannabis products used, past year, self-reported	Con[b] class 1, Con[b] class 2, Res (hash) class, Can-Mid class 1, Can-Mid class 2 vs. Can-Low class (see Table notes)	Severity of cannabis dependence, current, self-reported via SDS	Relative to Can-Low class, severity of dependence was significantly elevated for Res class ($b=0.262$ [0.188-0.337], $p<0.001$), Can-Mid classes (class 1: $b=0.429$ [0.350-0.505], $p<0.001$; class 2: $b=0.155$ [0.100-0.209], $p<0.001$); No significant association for Con classes ($p>0.05$; See Table 3 in Craft et al., 2020 for all estimates)	Fair
Freeman and Winstock, 2015 (44)	Cross-sectional, UK, 2009	Subset of people with past-month use of "skunk", "herbal/grass", and "resin" (n = 403) from a sample of adults who use cannabis: full n = 929; non-male = 30%; mean age = 24	Frequency and type of cannabis used, past month, self-reported	Can-Mid, Can-Low (herbal), and Can-Low (resin), per increasing frequency on continuous scale	Severity of cannabis dependence, current, self-reported via SDS	Days of Can-Mid use significantly positively associated with SDS score ($b=0.096$ [0.051-0.143], $p<0.001$); Days of Can-Low use not significantly associated with SDS score (herbal: $b=0.018$ [-0.030-0.069], $p=0.477$; resin: $b=0.025$ [-0.018-0.067], $p=0.245$)	Fair
Hines et al., 2020 (45)	Cross-sectional,	Young adults who use cannabis: n =	Type of cannabis used,	Can-Mid vs. Can-Low	Cannabis use problems, past-year,	Relative to Can-Low, Can-Mid use significantly associated with cannabis	Poor

	UK, 2015-2017	1087; non-male = 57%; mean age = 24	past year, self-reported		self-reported via CAST	use problems (AOR=4.08 [1.41-11.81], p=0.009)	
Loflin and Earlywine, 2014 (10)	Cross-sectional, USA, study period not reported	Adolescents and adults who use cannabis and concentrates: n = 357; female = 41%; mean age = 29	Type of cannabis used, lifetime, self-reported	Con vs. Can-Mix (within-person comparison of perceived effects)	Cannabis tolerance after use, self-reported via 4-point Likert scale	Con significantly and positively associated with tolerance (t=12.22, p<0.001, Cohen's d=0.82)	Poor
					Cannabis withdrawal after use, self-reported via 4-point Likert scale	Con significantly and positively associated with withdrawal (t=6.18, p<0.001, Cohen's d=0.42)	
Matsumoto et al., 2020 (47)	Cross-sectional, Japan, 2019	Adults in treatment for cannabinoid-related mental or behavioral disorder: n = 71; female = 17%; mean age = 35	Type of cannabis products used, lifetime, self-reported	Con/Con-Vape/Res vs. Can-Mix	Diagnosis of "Dependence Syndrome due to use of Cannabinoids", current, clinician-reported	Significantly higher odds of cannabinoid dependence syndrome for Con group relative to Can-Mix (AOR=6.85 [1.98-25.15], p=0.004)	Poor
Meier 2017 (48)	Cross-sectional, USA, study period not reported	Propensity score-matched subset (n = 128) from a sample of undergraduate students who use cannabis: full n = 273; female = 65%; mean age = 23	Type of cannabis used, past year, self-reported	Con vs. Can-Mix	Cannabis-related consequences, current, self-reported via MACQ	MACQ score for physical dependence domain was significantly higher in Con group (χ2=4.6, p=0.032); no significant group differences for domains of impaired control, academic/occupational, social-interpersonal, self-care, self-perception, risk behavior, or blackout (p>0.05; See Table 4 in Meier 2017 for all estimates)	Poor
Okey et al., 2022 (51)	Cross-sectional, USA, study period not reported	College students who use cannabis: n = 387; female = 59%; mean age = 19	Type of cannabis typically used, current (period not defined), self-reported	Con[b]/Res vs. Can-Mix	Negative cannabis-related consequences, past 30 days, self-reported via MACQ	Overall MACQ score was significantly higher for Con/Res relative to Can-Mix (total consequences: t=2.24, p=0.03, Cohen's d=0.23), with significant domain-specific differences for self-perception (t=3.23, p=0.001, Cohen's d=0.34) and impaired control (t=2.12, p=0.03, Cohen's d=0.26), but not social-interpersonal, self-care, risky behavior, academic/occupational, physical dependence, or black out (p>0.05; See Table 1 in Okey et al., 2022 for all estimates)	Poor

Sagar et al., 2018 (55)	Cross-sectional, USA, 2016-2017	Subset of people who use cannabis and dabs (n = 1037) from a sample of adults who use cannabis: full n = 4077; female = 39%; mean age = 44	Type of cannabis used, current (period not defined), self-reported	Con vs. Former Con (i.e., Current Can-Mix)	Cannabis dependence, current, self-reported via SDS	Significantly higher proportion of current Con users endorsed domain 1: worried about cannabis use ($\chi2$=8.149, p=0.044); no significant differences between current and former Con users for other 4 domains or overall SDS score (p>0.05)	Poor
Simpson et al., 2021 (59)	Cross-sectional, USA, 2018-2019	Young adults who use cannabis: n = 1007; female = 37%; mean age = 19	Type of cannabis product used, past 30 days, self-reported	Con, Con-Vape, and Can-Mix (combustibles), per increasing frequency on a categorical scale	Latent class membership defined by indicators of problematic cannabis use (non-symptomatic, non-recreational, moderate, severe), past 12 months, self-reported via CAST	Relative to non-current use, semi-frequent and frequent users of Con-Vape and Can-Mix, and infrequent users of Con had significantly higher odds of classification as non-symptomatic, moderate, and severe classes relative to the non-symptomatic class (p<0.05; See Table 3 in Simpson et al., 2021 for all estimates)	Fair
Steeger et al., 2021 (60)	Cross-sectional, USA, 2017-2020	Adults who use cannabis: n = 300; non-male = 42%; mean age = 35	Frequency and type of cannabis used, past month, self-reported	Con[b] and Can-Mix, per increasing frequency on continuous scale	Cannabis dependence, current, self-reported via MDS	Dependence score was not correlated with frequency of concentrate use (r=0.06, p>0.05), but was significantly positively correlated with frequency of flower use (r=0.16, p<0.01)	Fair
					Cannabis withdrawal after last time used cannabis, self-reported via MWC	Withdrawal score was significantly positively correlated with frequency of concentrate use (r=0.21, p<0.01) and flower use (r=0.26, p<0.01)	
					Cannabis craving, current, self-reported via MCQ	Craving score was significantly positively correlated with frequency of concentrate use (r=0.22, p<0.01) and flower use (r=0.23, p<0.01)	

Study-specific notes: [a]Latent class descriptions from Craft et al., 2020, based on ≥50% endorsement probabilities for past-year product use: Con class 1: 100% Con, 100% Can-Mid, 90% Res (kief), 70% Res (hash), 70% Can-Low; Con class 2: 100% Con, 80% Can-Mid, 60% Can-Low; Res class: 100% Res (hash), 70% Can-Low, 50% Can-Mid; Can-Mid class 1: 100% Can-Mid, 80% Res (hash), 80% Can-Low; Can-Mid class 2: 100% Can-Mid, 60% Can-Low; Can-Low class: 100% Can-Low; [b]This group likely included Con-Vape via "hash oil" or "oil" products; [c]Bidwell et al. did not consider this comparison statistically significant with alpha set to 0.01 for 52 pairwise comparisons. **Abbreviations:** (A)OR = (Adjusted) Odds Ratio; (A)RR = (Adjusted) Rate Ratio; BL = Baseline; (B-)MACQ = (Brief) Marijuana Consequences Questionnaire; CAST = Cannabis Abuse Screening Test; CUD = Cannabis Use Disorder; CUDIT-R = Cannabis Use Disorder Identification Test-Revised; EMA = Ecological Momentary Assessment; FU = Follow-Up; MDS = Marijuana Dependence Scale; MINI = Mini International Neuropsychiatric Interview; MCQ = Marijuana Craving Questionnaire; MWC = Marijuana Withdrawal Checklist; QA = Quality Assessment; RoB = Risk of Bias. **Cannabis potency category definitions:** Can-Low = ≤10% THC flower; Can-Mid = 10-19% THC

flower; Can-High = ≥20% THC flower; Res = hashish, resin, kief, assumed to have 20-50% THC; Con = Concentrated cannabis product, assumed to have 60-99% THC; Can-Mix = Cannabis of unspecified or multiple potency categories, but estimated to be lower than the higher potency exposure from that study.

Table 4. Summary of findings for non-acute adverse outcomes: Use of other substances

Author(s), year	Study design, location, period	Sample characteristics	Exposure		Outcome	Summary of findings	QA / RoB
			Measure, method of assessment	Relevant potencies compared	Measure, method of assessment		
Alcohol							
Bidwell et al., 2018 (12)	Cross-sectional, USA, 2017	Adults who use cannabis: n = 131; non-male = 49%; mean age = 42	Frequency and type of cannabis used, current (period not defined), self-reported	Con (including Con-Vape; ≥4 times/week) vs. Can-Mix (any)	Alcohol use, current, self-reported	Prevalence of alcohol use did not differ significantly between Con group (50.7%) relative to Can-Mix (56.3%), p=0.64	Poor
Hines et al., 2020 (45)	Cross-sectional, UK, 2015-2017	Young adults who use cannabis: n = 1087; non-male = 57%; mean age = 24	Type of cannabis used, past year, self-reported	Can-Mid vs. Can-Low	Moderate-severe alcohol use disorder, current, self-reported via DSM-5 criteria	Relative to Can-Low, Can-Mid not significantly associated with moderate-severe AUD (AOR=0.90 [0.49-1.64], p=0.73)	Poor
Karoly et al., 2021 (66)	Between-subjects naturalistic experiment (open-label, random assignment), USA, study period not reported	Adults who use cannabis: n = 120 (n = 84 assigned review-relevant potencies); female = 39%; mean age = 33	Type of cannabis used, experimentally assigned	Can-High vs. Can-Low	Number of drinks per drinking day and percent drinking days, past 5 days, self-reported via TLFB	Compared to Can-Low, Can-High group did not have significantly more drinks/drinking day (b=-0.250, p=0.277) or a higher percent of drinking days (b=-0.013, p=0.600)	High (RoB)
					Percent alcohol-cannabis co-use days, past 5 days, self-reported via TLFB	Compared to Can-Low, Can-High group did not have a higher percent of alcohol-cannabis co-use days (b=-0.037, p=0.128).	
Meier 2017 (48)	Cross-sectional, USA, study period not reported	Undergraduate students who use cannabis: n = 273; female = 65%; mean age = 23	Type of cannabis used, past year, self-reported	Con vs. Can-Mix	Frequency of binge alcohol use, past year, self-reported	Frequency of binge drinking significantly associated with Con use (OR=1.8 [1.4-2.3], p<0.001)	Poor
Tobacco							
Bidwell et al., 2018 (12)	Cross-sectional, USA, 2017	Adults who use cannabis: n = 131; non-male = 49%; mean age = 42	Frequency and type of cannabis used, current	Con (including Con-Vape; ≥4	Cigarette use, current, self-reported	Prevalence of cigarette use did not differ significantly between Con group (19.4%) relative to Can-Mix (17.2%), p=0.92	Poor

			(period not defined), self-reported	times/week) vs. Can-Mix (any)			
Hines et al., 2020 (45)	Cross-sectional, UK, 2015-2017	Young adults who use cannabis: n = 1087; non-male = 57%; mean age = 24	Type of cannabis used, past year, self-reported	Can-Mid vs. Can-Low	Tobacco dependence, current, self-reported via FTND	Relative to Can-Low, Can-Mid not significantly associated with tobacco dependence (AOR=1.42 [0.89-2.27], *p*=0.14)	Poor
Meier 2017 (48)	Cross-sectional, USA, study period not reported	Undergraduate students who use cannabis: n = 273; female = 65%; mean age = 23	Type of cannabis used, past year, self-reported	Con vs. Can-Mix	Frequency of tobacco use, past year, self-reported	Frequency of tobacco use significantly associated with Con use (OR=1.5 [1.2-2.0], *p*=0.001)	Poor
Prescription drugs (non-medical use)							
Bidwell et al., 2018 (12)	Cross-sectional, USA, 2017	Adults who use cannabis: n=131; non-male = 49%; mean age = 42	Frequency and type of cannabis used, current (period not defined), self-reported	Con (including Con-Vape; ≥4 times/week) vs. Can-Mix (any)	Prescription opioid use (non-medical, not-as-prescribed), current, self-reported	Prevalence of prescription opioid use did not differ significantly between Con group (14.9%) relative to Can-Mix (6.3%), *p*=0.19	Poor
Fedorova et al., 2019[a] (42)	Cross-sectional, USA, 2014-2015	Young adults who use cannabis: n = 366; female = 34%; mean age = 21	Type of cannabis used, past 90 days, self-reported	Con[b] vs. Can-Mix	Use of prescription drugs for purposes other than as prescribed, past 90 days, self-reported	Relative to Can-Mix, Con use not significantly associated with prescription drug use (AOR=1.2 [0.7-2.2], *p*>0.05)	Poor
Fedorova et al., 2020[a] (43)	Prospective cohort, USA, 2014-2018	Young adults who use cannabis: n = 301; non-male = 35%; mean age = 21	Type of cannabis used, past 90 days, self-reported at 4 FUs	Con[b] vs. Can-Mix	Trajectory of prescription drug use (high or low), identified via discrete mixture models based on use of prescription drugs for purposes other than prescribed, past 90 days, self-reported at 4 FUs	Higher odds of Con use among high prescription drug use trajectory group (AOR=2.16 [1.49-3.15], *p*<0.001)	Poor
Illicit drugs							

Braymiller et al., 2023 (32)	Prospective cohort, USA, 2016-2017	High school students: n = 2163; female = 54%; mean age = 17	Type of cannabis product used, lifetime, self-reported	Con, Con-Vape, Can-Mix (combustibles) (all yes vs. no)	Initiation of illicit (non-cannabis) drug use at 1 year FU, self-reported	Use of each product significantly increased odds of illicit drug use initiation (AORs in descending point estimate order: Con=5.74 [3.16-10.43]; Con-Vape=3.11 [2.41-4.01]; Can-Mix=2.57 [1.64-4.02]; all $p<0.05$)	Fair
Bidwell et al., 2018 (12)	Cross-sectional, USA, 2017	Adults who use cannabis: n = 131; non-male = 49%; mean age = 42	Frequency and type of cannabis used, current (period not defined), self-reported	Con (including Con-Vape; ≥4 times/week) vs. Can-Mix (any)	Illicit drug use, current, self-reported	Prevalence of illicit drug use did not differ significantly between Con group (16.4%) relative to Can-Mix (9.4%), $p=0.35$	Poor
Chan et al., 2017 (34)	Cross-sectional, multinational, 2015-2016	Young adults and adults (≥16 years) who use cannabis: n = 83867; female = 29%; mean age = 26	Type of cannabis used, past year, self-reported	Con, Can-Mid vs. Can-Low; Con vs. Can-Mid	Number of other substances used (MDMA, cocaine, amphetamines, heroin, LSD), past-year, self-reported	Number of other drugs used was significantly associated with Con use (AOR vs. Can-Mid=1.29 [1.25-1.31]; AOR vs. Can-Low=1.66 [1.63-1.70]) and Can-Mid (AOR vs. Can-Low=1.30 [1.28-1.32]; all $p<0.05$)	Poor
Fedorova et al., 2019[a] (42)	Cross-sectional, USA, 2014-2015	Young adults who use cannabis: n = 366; female = 34%; mean age = 21	Type of cannabis used, past 90 days, self-reported	Con[b] vs. Can-Mix	Use of illicit drugs, past 90 days, self-reported	Relative to Can-Mix, Con use significantly associated with illicit drug use (AOR=2.8 [1.6-4.9], $p<0.001$)	Poor
Fedorova et al., 2020[a] (43)	Prospective cohort, USA, 2014-2018	Young adults who use cannabis: n = 301; non-male = 35%; mean age = 21	Type of cannabis used, past 90 days, self-reported at 4 FUs	Con[b] vs. Can-Mix	Trajectory of illicit drug use (high or low), identified via discrete mixture models based on use of illicit drugs, past 90 days, self-reported at 4 FUs	Significantly higher odds of Con use among high illicit drug use trajectory group (AOR=2.40 [1.67-3.44], $p<0.001$)	Poor
Hines et al., 2020 (45)	Cross-sectional, UK, 2015-2017	Young adults who use cannabis: n = 1087; non-male = 57%; mean age = 24	Type of cannabis used, past year, self-reported	Can-Mid vs. Can-Low	Use of illicit drugs, past-year, self-reported	Relative to Can-Low, Can-Mid not significantly associated with illicit drug use (AOR=1.29 [0.77-2.17], $p=0.34$)	Poor
Meier 2017 (48)	Cross-sectional, USA, study period not reported	Undergraduate students who use cannabis: n = 273; female = 65%; mean age = 23	Type of cannabis used, past year, self-reported	Con vs. Can-Mix	Frequency of other illicit drug use, past year, self-reported	Frequency of illicit drug use significantly associated with Con use (OR=2.1 [1.5-3.0], $p<0.001$)	Poor

Study-specific notes: [a]Fedorova et al., 2019 and Fedorova et al., 2020 contain overlapping samples obtained from the Cannabis, Health & Young Adults (CHAYA) project. [b]This group likely included Con-Vape via "hash oil" or "oil" use. **Abbreviations:** (A)OR = (Adjusted) Odds Ratio; AUD = Alcohol Use Disorder; BL = Baseline; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; FTND = Fagerström Test for Nicotine Dependence; FU = Follow-Up; QA = Quality Assessment; RoB = Risk of Bias; TLFB = Timeline Follow-Back. **Cannabis potency category definitions:** Can-Low = ≤10% THC flower; Can-Mid = 10-19% THC flower; Can-High = ≥20% THC flower; Res = hashish, resin, kief, assumed to have 20-50% THC; Con = Concentrated cannabis product, assumed to have 60-99% THC; Can-Mix = Cannabis of unspecified or multiple potency categories, but estimated to be lower than the higher potency exposure from that study.

Supplementary Files for Lake et al. High-Potency Cannabis Review

Supplemental Files

Supplementary Files for Lake et al. High-Potency Cannabis Review

Supplemental Methods

SA1. PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title page
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Introduction
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Introduction (paragraph 3)
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Table 1 and Methods (“Data Synthesis”)
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Methods (“Search”), SA2
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	SA2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Methods (“Screening”)
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Methods (“Data extraction and quality assessment”)
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Table 1, SA3
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Methods (“Data extraction and quality assessment”)
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Methods (“Data extraction and quality assessment”)
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	SA3, Methods (“Quantitative synthesis”)
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	SA3, Methods (“Quantitative synthesis”)
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Methods (“Quantitative synthesis”)

Section and Topic	Item #	Checklist item	Location where item is reported
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Methods ("Quantitative synthesis")
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Methods ("Quantitative synthesis")
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Methods ("Quantitative synthesis")
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Methods ("Quantitative synthesis")
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Methods ("Qualitative synthesis" – conducted as part of GRADE)
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Methods ("Qualitative synthesis")
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Results ("Overview of included studies")
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	SF1
Study characteristics	17	Cite each included study and present its characteristics.	Results ("Overview of included studies"), Tables 2-4
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Tables 2-4 and SA9, SA10
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Tables 2-4
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Figure 1
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Results (first paragraph of each domain section)
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	SA6, SA7
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	SA6, SA7
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	SA10
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	SA10
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Discussion (paragraphs 1 and 2)
	23b	Discuss any limitations of the evidence included in the review.	Discussion (paragraphs 3 and 4)

Section and Topic	Item #	Checklist item	Location where item is reported
	23c	Discuss any limitations of the review processes used.	Discussion (paragraph 6)
	23d	Discuss implications of the results for practice, policy, and future research.	Discussion (paragraph 5)
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Methods (paragraph 1)
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Methods (paragraph 1)
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Acknowledgments
Competing interests	26	Declare any competing interests of review authors.	Acknowledgments
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	NA

SA2. Search strategy

Database	Search terms
Ovid Medline	1. exp Cannabis/ 2. tetrahydrocannabinol.mp. 3. marijuana.mp. 4. exp Medical Marijuana/ 5. cannabis.mp. 6. exp Marijuana Smoking/ or exp Cannabinoids/ or delta-9-tetrahydocannabinol.mp. 7. THC.mp. 8. cannabinoid*.mp. 9. (strong* adj2 potency).ti,ab. 10. ((strong adj2 dos*) or (high* adj2 percent*) or (high* adj2 conentrat*)).ti,ab. 11. (cannabi* adj2 concentrate$).ti,ab. 12. (cannabi* adj2 extract$).ti,ab. 13. (marijuana adj2 concentrate$).ti,ab. 14. marijuana adj2 extract$).ti,ab. 15. (high* adj2 potency).ti,ab. 16. (high* adj2 potent).ti,ab. 17. (high* adj2 dos*).ti,ab. 18. (high* adj3 strength).ti,ab. 19. (THC adj2 concentrate$).ti,ab. 20. (THC adj2 extract$).ti,ab. 21. (delta-9-thc or "delta 9 thc").ti,ab. 22. (dab* or wax or butter or budder or shatter or resin or rosin or distillate or hash* or crystalline).ti,ab. 23. (high* adj2 thc).ti,ab. 24. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 21 25. 9 or 10 or 15 or 16 or 17 or 18 or 22 26. 11 or 12 or 13 or 14 or 19 or 20 or 23 27. 24 and 25 28. 26 or 27 29. limit 28 to (english language and humans)
EMBASE	1. 'cannabis'/exp OR 'cannabis' 2. 'tetrahydrocannabinol' 3. 'marijuana'/exp 4. 'cannabinoids'/exp OR cannabinoid? 5. thc 6. 'delta 9 tetrahydrocannabinol' 7. 'delta 9 thc' 8. ((strong NEAR/2 potency):ab,ti) OR ((strong NEAR/2 dos*):ab,ti) OR ((high NEAR/2 potency):ab,ti) OR ((high* NEAR/2 potent):ab,ti) OR ((high* NEAR/2 dos*):ab,ti OR ((high* NEAR/2 percent*):ab,ti) OR ((high* NEAR/2 concentrat*):ab,ti)) 9. (high* NEAR/2 strength):ab,ti 10. ((cannabi* NEAR/2 concentrate?):ab,ti) OR ((cannabi* NEAR/2 extract?):ab,ti) OR ((marijuana NEAR/2 concentrate*):ab,ti) OR ((marijuana NEAR/2 extract?):ab,ti OR ((high* NEAR/2 thc):ab,ti) 11. ((thc NEAR/2 concentrate?):ab,ti) OR ((tetrahydrocannabinol NEAR/2 concentrate?):ab,ti) OR (thc NEAR/2 extract?):ab,ti OR (tetrahydrocannabinol NEAR/2 extract?):ab,ti 12. dab*:ab,ti OR wax:ab,ti OR shatter:ab,ti OR rosin:ab,ti OR resin:ab,ti OR butter:ab,ti OR budder:ab,ti OR distillate:ab,ti OR crystalline:ab,ti OR hash*:ab,ti 13. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 14. 8 OR 9 OR 12 15. 13 and 14 16. 10 or 11 17. 15 or 16 18. limit 17 to [humans]/lim AND [english]/lim

Supplementary Files for Lake et al. High-Potency Cannabis Review

APA PsycInfo	1. (Cannabis OR tetrahydrocannabinol OR marijuana OR cannabinoid* OR thc OR (delta 9 thc) OR (delta 9 tetrahydrocannabinol)) 2. (AB,TI(strong* NEAR/2 potency) OR AB,TI(strong* NEAR/2 dos*) OR AB,TI(high* NEAR/2 potent) OR AB,TI(high* NEAR/2 dos*) OR AB,TI(high* NEAR/2 strength) OR AB,TI(high* NEAR/2 potency) OR AB,TI(high* NEAR/2 percent*) OR AB,TI(high* NEAR/2 concentrat*)) OR (TI,AB(dab*) OR TI,AB(wax) OR TI,AB(shatter) OR TI,AB(rosin) OR TI,AB(resin) OR TI,AB(butter) OR TI,AB(budder) OR TI,AB(distillate) OR TI,AB(crystalline) OR TI,AB(hash*)) 3. 1 AND 2 4. (TI,AB(cannabi* NEAR/2 concentrate?) OR TI,AB(cannabi* NEAR/2 extract?) OR TI,AB(marijuana NEAR/2 concentrate*) OR TI,AB(marijuana NEAR/2 extract?) OR TI,AB(high* NEAR/2 thc)) OR (AB,TI(thc NEAR/2 concentrate?) OR AB,TI(tetrahydrocannabinol NEAR/2 concentrate?) OR AB,TI(thc NEAR/2 extract?) OR AB,TI(tetrahydrocannabinol NEAR/2 extract?)) 5. 3 or 4 6. Limit 5 to peer-reviewed, language = English, 7. Include: Subject = male; humans; female; adult; adolescent; young adult Exclude: Subject = animals; rats; mice; rats, sprague-dawley; rats, wistar; mice, inbred c57bl; animal models
Web of Science Core Collection	1. (Cannabis OR tetrahydrocannabinol OR marijuana OR cannabinoid* OR thc OR (delta 9 thc) OR (delta 9 tetrahydrocannabinol)) 2. TI=((strong* NEAR/2 potency) OR (strong* NEAR/2 dos*) OR (high* NEAR/2 potent) OR (high* NEAR/2 dos*) OR (high* NEAR/2 strength) OR (high* NEAR/2 potency) OR (high* NEAR/2 percent*) OR (high* NEAR/2 concentrat*) OR dab* OR wax OR shatter OR rosin OR resin OR butter OR budder OR distillate OR crystalline OR hash*) 3. AB=((strong* NEAR/2 potency) OR (strong* NEAR/2 dos*) OR (high* NEAR/2 potent) OR (high* NEAR/2 dos*) OR (high* NEAR/2 strength) OR (high* NEAR/2 potency) OR (high* NEAR/2 percent*) OR (high* NEAR/2 concentrat*) OR dab* OR wax OR shatter OR rosin OR resin OR butter OR budder OR distillate OR crystalline OR hash*) 4. 2 OR 3 5. TI=((cannabi* NEAR/2 concentrate?) OR (cannabi* NEAR/2 extract?) OR (marijuana NEAR/2 concentrate*) OR (marijuana NEAR/2 extract?) OR (high* NEAR/2 thc) OR (thc NEAR/2 concentrate?) OR (tetrahydrocannabinol NEAR/2 concentrate?) OR (thc NEAR/2 extract?) OR (tetrahydrocannabinol NEAR/2 extract?)) 6. AB=((cannabi* NEAR/2 concentrate?) OR (cannabi* NEAR/2 extract?) OR (marijuana NEAR/2 concentrate*) OR (marijuana NEAR/2 extract?) OR (high* NEAR/2 thc) OR (thc NEAR/2 concentrate?) OR (tetrahydrocannabinol NEAR/2 concentrate?) OR (thc NEAR/2 extract?) OR (tetrahydrocannabinol NEAR/2 extract?)) 7. 5 OR 6 8. 1 AND 3 9. 8 OR 7 10. TS=((animal) or (rat$) or (mouse) or (mice) or (rodent$)) 11. 9 NOT 10 12. Limit to English
Cochrane Library	1. TI, AB, KEY: (Cannabis OR tetrahydrocannabinol OR marijuana OR cannabinoid* OR thc OR (delta 9 thc) OR (delta 9 tetrahydrocannabinol)) 2. TI, AB, KEY: ((strong* NEAR/2 potency) OR (strong* NEAR/2 dos*) OR (high* NEAR/2 potent) OR (high* NEAR/2 dos*) OR (high* NEAR/2 strength) OR (high* NEAR/2 potency) OR (high* NEAR/2 percent*) OR (high* NEAR/2 concentrat*) OR dab* OR wax OR shatter OR rosin OR resin OR butter OR budder OR distillate OR crystalline OR hash*) 3. TI, AB, KEY: ((cannabi* NEAR/2 concentrate?) OR (cannabi* NEAR/2 extract?) OR (marijuana NEAR/2 concentrate*) OR (marijuana NEAR/2 extract?) OR (high* NEAR/2 thc) OR (thc NEAR/2 concentrate?) OR (tetrahydrocannabinol NEAR/2 concentrate?) OR (thc NEAR/2 extract?) OR (tetrahydrocannabinol NEAR/2 extract?)) 4. [MeSH]: Cannabis (explode) 5. 1 OR 4 6. 2 AND 5 7. 3 OR 6

SA3. Detailed Population, Intervention (Exposure), Comparison, Outcomes, Study designs (PICOS) eligibility criteria

Population

The population of interest was adults and/or adolescents/emerging adults. Studies assessing therapeutic outcomes were further restricted to people experiencing a shared symptom or condition. Studies may or may not be restricted to cannabis-using samples.

Intervention (exposure)

The exposure of interest was potency (% THC) of cannabis or cannabis-based products. As we were interested in comparing higher potency cannabis against lower potency cannabis, we established several categories to distinguish between potency levels and facilitate comparisons. Herbal cannabis was categorized as: (1) High potency herbal ("Can-High": ≥20% THC); (2) Mid potency herbal ("Can-Mid": 10-19% THC); and (3) Low potency herbal ("Can-Low": 1-9% THC). These potency categories were based on a preliminary literature search of studies reporting THC concentration in samples of cannabis obtained from regulated and unregulated markets in regions around the world (1-10). Accordingly, the categories approximately correspond with above-, equal to-, and below-average herbal THC potency observed in most North American and European markets in recent years and are consistent with current analyses of potency categories used in current medical cannabis research (11, 12). THC concentrates (e.g., solvent-based extracts such as butane hash oil, wax, shatter), which can contain 50-95% THC (13), were categorized into a separate potency category for concentrates ("Con"), considered the highest potency group. Given a well-documented "potency valley" between flower and concentrates (9), we did not require the THC potency of concentrates to be reported for categorization into this group. If the concentrate product was a vape oil/liquid rather than a combustible product, we further specified this with the designation "Con-Vape". Resin, hashish, and kief varying from 10-50% (14, 15), were categorized into a resin category ("Res"), generally considered to have a higher potency than flower but a lower potency than concentrates. If a study

reported potency estimates for Con or Res within the range of one of the herbal cannabis categories, we re-categorized it accordingly.

We excluded observational studies that did not measure, report, or infer (from peer-reviewed or government data) an approximate concentration of THC in herbal cannabis. In experimental studies, if potency was not explicitly stated, we calculated it from the dose of THC and total weight of cannabis administered. Studies assessing THC potency as a continuous measure (e.g., per 1% increase in THC) were excluded, as were studies focusing on the use of edibles or other ingestible preparations as these products are generally sold as standardized serving sizes defined by milligrams of THC.

Comparison

Studies were included if they compared of the above-listed cannabis potency categories to a comparatively lower potency category (e.g., Can-High vs. Can-Mid). Comparators could also represent a mix of categories, denoted as "Can-Mix" (e.g., any herbal cannabis), so long as the exposure was of a comparatively higher potency (e.g., Con). Studies that compared ≥2 potency groups separately against a no/placebo cannabis use group rather than directly against each other (e.g., Can-Mid and Can-Low vs. None) were retained for indirect comparison of the active cannabis potency groups via the shared no/placebo group. Studies that assessed exposure to ≥2 potency categories via non-mutually exclusive assessments using the same scale of measurement (e.g., Con use [yes vs. no] and Can-Mix use [yes vs. no], or frequency of Con use and frequency of Can-Mix use) were also retained to indirectly inform the research question (qualitative synthesis only).

Outcome

Primary: Non-acute adverse health-related measures

Our primary focus was non-acute adverse health-related measures, which we defined as conditions or symptoms occurring or persisting beyond the drug's acute effects. We used the National Academies of

Sciences, Engineering, and Medicine's (NASEM) comprehensive cannabis and health review to guide non-acute "outcomes" in this review (16). Eligible non-acute adverse health outcomes were classified into the following categories: cancer; cardiometabolic risk; respiratory disease; immunity; injury and death; prenatal, perinatal, and neonatal outcomes; psychosocial; mental health; problem cannabis use; and problem use of other substances, excluding "outcomes" with an index/recall period that exceeded one year (e.g., lifetime depression) or preceded that of the "exposure" (e.g., past-year depression; past-month cannabis potency).

Secondary: Acute adverse health-related measures

Acute adverse outcomes were included as secondary outcomes to supplement the primary findings related to non-acute adverse outcomes. Here, we considered: (1) experimental studies assessing acute effects of higher potency cannabis; or (2) observational studies that compared retrospective recall of acute subjective drug effects. To narrow the scope of secondary findings relevant to this review, we only included measures that were covered by the NASEM review or could serve as possible acute indicators of the extracted primary outcomes. For example, if cannabis use disorder was extracted as a primary outcome, acute measures of reinforcement or "abuse liability" would be eligible for inclusion as secondary outcomes. The exception to this was acute cognitive measures (e.g., learning, memory, attention): we included these measures regardless of whether a cognitive non-acute measure was extracted, as they were covered by the NASEM review (under the "Psychosocial" domain).

Secondary: Therapeutic measures

We considered both acute (e.g., pain relief) and non-acute "therapeutic" outcomes (e.g., change in pain intensity over time). These were symptom-related measures obtained from studies in which all participants shared a common condition or symptom for which cannabis was being used (e.g., anxiety, pain). Identification and classification of eligible therapeutic outcomes was guided by Part 2 of the NASEM review, which included: chronic pain; cancer; chemotherapy-induced nausea and vomiting; anorexia and

weight loss; irritable bowel syndrome; epilepsy; spasticity associated with MS or SCI; Tourette syndrome; amyotrophic lateral sclerosis; Huntington's disease; Parkinson's disease; dystonia; dementia; glaucoma; TBI / intracranial hemorrhage; addiction; anxiety; depression; sleep disorders; PTSD; schizophrenia and other psychosis.

Study design

We included peer-reviewed observational (cohort, case-control, cross-sectional, other naturalistic design) and experimental studies that statistically tested for a relationship between higher potency cannabis use (vs. a lower potency category) and an eligible outcome. Abstracts, reviews, commentaries, letters, and case reports/series were ineligible.

Supplementary Files for Lake et al. High-Potency Cannabis Review

SA4. List of title keywords used to eliminate records from consideration ahead of two-author screening

1) Review
2) Case study
3) FAAH
4) Fatty acid amide hydrolase
5) Endocannabinoid
6) Synthetic
7) Spice
8) K2
9) Letter
10) Protocol
11) Mouse
12) Rat
13) In vivo
14) In vitro
15) Hemp

SA5. Synthesis Without Meta-analysis (SWiM) Checklist

SWiM is intended to complement and be used as an extension to PRISMA			
SWiM reporting item	**Item description**	**Page in manuscript where item is reported**	**Other***
Methods			
1 Grouping studies for synthesis	1a) Provide a description of, and rationale for, the groups used in the synthesis (e.g., groupings of populations, interventions, outcomes, study design)	Table 1 and SA3	
	1b) Detail and provide rationale for any changes made subsequent to the protocol in the groups used in the synthesis	NA	
2 Describe the standardised metric and transformation methods used	Describe the standardised metric for each outcome. Explain why the metric(s) was chosen, and describe any methods used to transform the intervention effects, as reported in the study, to the standardised metric, citing any methodological guidance consulted	Methods, p4	
3 Describe the synthesis methods	Describe and justify the methods used to synthesise the effects for each outcome when it was not possible to undertake a meta-analysis of effect estimates	Methods, p4	
4 Criteria used to prioritise results for summary and synthesis	Where applicable, provide the criteria used, with supporting justification, to select the particular studies, or a particular study, for the main synthesis or to draw conclusions from the synthesis (e.g., based on study design, risk of bias assessments, directness in relation to the review question)	Methods, p4	
5 Investigation of heterogeneity in reported effects	State the method(s) used to examine heterogeneity in reported effects when it was not possible to undertake a meta-analysis of effect estimates and its extensions to investigate heterogeneity	Methods, p4-5	
6 Certainty of evidence	Describe the methods used to assess certainty of the synthesis findings	Methods, p5 (GRADE applied to outcomes across quantitative and qualitative synthesis)	

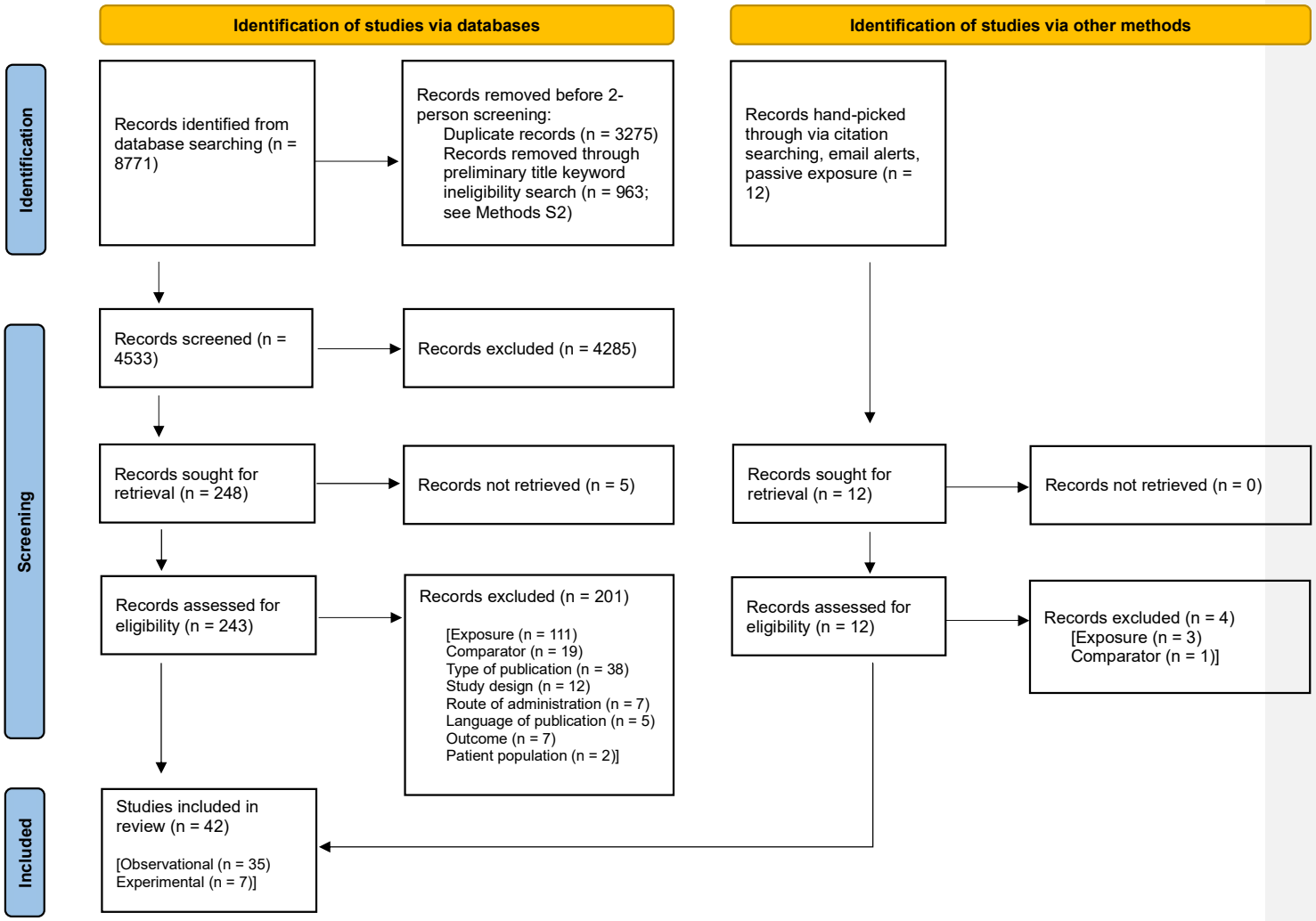
7 Data presentation methods	Describe the graphical and tabular methods used to present the effects (e.g., tables, forest plots, harvest plots). Specify key study characteristics (e.g., study design, risk of bias) used to order the studies, in the text and any tables or graphs, clearly referencing the studies included	Methods, p4	
Results			
8 Reporting results	For each comparison and outcome, provide a description of the synthesised findings, and the certainty of the findings. Describe the result in language that is consistent with the question the synthesis addresses, and indicate which studies contribute to the synthesis	Results, p 7-11 (first paragraph of each subdomain results section)	
Discussion			
9 Limitations of the synthesis	Report the limitations of the synthesis methods used and/or the groupings used in the synthesis, and how these affect the conclusions that can be drawn in relation to the original review question	Discussion, p16-17	

Supplementary Files for Lake et al. High-Potency Cannabis Review

Supplemental Results

Supplementary Files for Lake et al. High-Potency Cannabis Review

SF1. Prisma flowchart



Supplementary Files for Lake et al. High-Potency Cannabis Review

SA6. Quantitative synthesis restricted to higher quality* studies

**Note: "Higher" quality refers to observational studies graded as "Fair"/"Good" quality and experimental studies graded as "Low"/"Some Concerns" risk of bias*

Mental health

Psychosis

All five studies that recorded a "detrimental" effect direction had a quality rating of "Fair" (17) or "Good" ((18), (19)+(20), (21)+case analysis from (22), (23)+(24)) and were included in a sensitivity analysis, yielding p=0.0625. All were conducted on UK-based or multinational samples and compared "skunk" cannabis (categorized as Can-Mid) against lower-potency traditional herbal cannabis (categorized as Can-Low).

Anxiety and depression

Not conducted: no studies graded at higher quality for either outcome.

PTSD and bipolar disorder

Not conducted: no studies graded at higher quality for PTSD; not enough bipolar studies for initial quantitative analysis (n=1).

High-frequency and "problem" cannabis use

High-frequency use

Not conducted: only one study rated above "Poor" quality ((25), rated as "Fair" quality).

Supplementary Files for Lake et al. High-Potency Cannabis Review

"Problem" cannabis use

Not conducted: only one study rated above "Poor" quality ((26), rated as "Fair" quality).

Use of other substances

Alcohol and Tobacco

Not conducted: no studies graded at higher quality for either outcome.

Non-medical prescription and illicit drug use

Not conducted: no studies graded at higher quality for either outcome.

SA7. Quantitative synthesis for broad domain-specific primary outcome categories

Mental health

Pooling all mental health condition-specific findings (including PTSD) into a broader "mental health" outcome led to the inclusion of nine studies, six of which recorded a "detrimental" direction of effect (p=0.508).

High-frequency and "problem" cannabis use

Pooling all high-frequency and "problem" cannabis use primary outcomes into a broader "high-risk cannabis use" outcome led to the inclusion of 11 studies, all of which recorded a "detrimental" direction of effect (p<0.001).

Use of other substances

Pooling all substance class-specific outcomes into a broader "other substance use" outcome led to the inclusion of five studies, four of which recorded a "detrimental" direction of effect (p=0.375).

SA8. Study quality ratings: Observational (assessed with NIH NHLBI quality assessment tools)

Quality assessment: Cross-sectional studies

Article	Outcome(s)	Criteria															Overall rating
		1	2a	2b	3	4	5	6	7	8	9	10	11	12	13	14	
Bidwell et al., 2018	Anxiety	Y	Y	NA	N	Y	N	N	N	N	N	NA	N	NR	NA	N	Poor
	Depression																
	PTSD																
	Frequency of cannabis use																
	CUD symptoms																
	Alcohol use																
	Cigarette use																
	Illicit drug use																
	Prescription opioid use (non-medical)																
Brunt et al., 2014	Anxiety (acute)	Y	Y	NA	Y	Y	N	N	N	Y	Y	NA	N	N	NA	N	Poor
Chan et al., 2017	Daily/almost daily cannabis use	Y	Y	NA	N	Y	N	N	N	Y	N	NA	N	N	NA	Y	Poor
	Use of other substances																
	Acute subjective effects (craving, memory, anxiety, paranoia)									N						NA	
Craft et al., 2020	Severity of cannabis dependence	Y	N	NA	N	Y	N	N	N	N	N	NA	Y	N	NA	Y	Fair
	Frequency of cannabis use												N				Poor
Daniulaityte et al., 2017	Daily cannabis use	Y	Y	NA	N	Y	N	N	N	N	N	NA	N	N	NA	Y	Poor
Federova et al., 2019	Use of prescription drugs (non-medical)	Y	Y	NA	N	Y	N	N	N	N	N	NA	N	N	NA	Y	Poor
	Illicit drug use																
Freeman et al., 2015	Severity of cannabis dependence	Y	Y	NA	N	Y	N	N	N	Y	N	NA	Y	N	NA	Y	Fair
Hines et al., 2020	Regular cannabis use	Y	Y	NA	N	Y	N	N	N	N	N	NA	N	N	NA	Y	Poor
	Cannabis use problems												Y	N			
	Other substance use												N				
	Tobacco dependence												Y				
	Alcohol use disorder																
	Depression																
	Anxiety																
	Psychosis													Y			Fair
Loflin & Earlywine, 2014	Cannabis tolerance	Y	Y	NA	N	Y	Y	N	N	N	N	NA	N	N	NA	N	Poor
	Cannabis withdrawal																
Matsumoto et al., 2021	Diagnosis of cannabis dependence syndrome	Y	Y	NA	N	Y	N	N	N	N	N	NA	Y	N	NA	Y	Poor
	Diagnosis of psychotic disorder due to cannabis																
Meier 2017	Frequency of cannabis use	Y	Y	NA	NR	Y	N	N	N	N	N	NA	N	N	NA	N	Poor
	Cannabis-related consequences												Y			Y	
	Binge drinking frequency												N			N	
	Tobacco use frequency																
	Illicit drug use frequency																
Meier et al., 2019	"Academic failure"	Y	Y	NA	NR	Y	N	N	N	N	N	NA	N	N	NA	N	Poor

Okey & Meier, 2020	Frequency of cannabis use Acute subjective effects (negative affect, psychotic-like experiences, cognitive impairment)	Y	Y	NA	N	Y	N	N	N	N	N	NA	N	N	NA	N NA	Poor
Okey et al., 2022	Frequency of cannabis use Negative cannabis-related consequences	Y	Y	NA	NR	Y	N	N	N	N	N	NA	N Y	N	NA	N	Poor
Palamar et al., 2015	Frequency of cannabis use	Y	Y	NA	Y	Y	N	N	N	N	N	NA	N	N	NA	Y	Poor
Rup et al., 2021	Anxiety Depression PTSD Bipolar disorder Psychotic disorder	Y	Y	NA	CD	Y	N	N	N	Y	N	NA	N	N	NA	Y	Poor
Sagar et al., 2018	Cannabis use frequency Cannabis dependence	Y	Y	NA	N	Y	N	N	N	N	N	NA	N Y	N	NA	N	Poor
Schoeler et al., 2022	CAPS presenting to ER CAPS requiring hospitalization	Y	Y	NA	N	Y	N	N	N	Y N	N	NA	N	N	NA	N	Poor
Simpson et al., 2021	Problematic cannabis use	Y	Y	NA	N	Y	N	N	N	Y	N	NA	Y	N	NA	Y	Fair
Steeger et al., 2021	Cannabis dependence Cannabis withdrawal Cannabis craving Anxiety Depression	Y	Y	NA	N	Y	N	N	N	Y	N	NA	Y	N	NA	Y	Fair

Note: Y = Yes, N = No, NA = Not applicable; NR = Not reporting; CD = Cannot determine.

Criteria: (1) Was the research question or objective clearly stated? **(2a)** Was the study population clearly specified and defined?; **(2b)** Was the cohort free of the outcomes of interest at the time they were recruited? (*Note: 2a and 2b were presented as 1 criteria in the form; we modified into 2 criteria where 2b was graded as NA for all cross-sectional studies*); **(3)** Was the participation rate of eligible persons at least 50%?; **(4)** Were all subjects selected or recruited from the same or similar populations (including same time period)?; **(5)** Was a sample size justification, power description, or variance and effect estimates provided?; **(6)** Was the exposure of interest measured prior to the outcome being measured? (*Note: as per explicit NHLBI guidance, this was graded as N for all cross-sectional studies*); **(7)** Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed? (*Note: as per explicit NHLBI guidance, this was graded as N for all cross-sectional studies*); **(8)** Did the study examine different levels of the exposure as related to the outcome? **(9)** Were the exposure measures clearly defined, valid, reliable, and implemented consistently across study all participants? **(10)** Was the exposure assessed more than one over time? (*Note: we graded as NA for all cross-sectional studies based on interpretation of NHLBI guidance document*); **(11)** Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?; **(12)** Were the outcome assessors blinded to the exposure status of participants?; **(13)** Was loss to follow-up after baseline 20% or less? (*Note: we graded as NA for all cross-sectional studies based on interpretation of NHLBI guidance document*); **(14)** Were key confounding variables measured and adjusted statistically for their impact on the relationship between exposure and outcome?

SA8 (continued). Study quality ratings: Observational (assessed with NIH NHLBI quality assessment tools)

Quality assessment: Cohort studies

Article	Outcome(s)	Criteria														Overall rating
		1	2a	2b	3	4	5	6	7	8	9	10	11	12	13	14	
Barrington-Trimis et al., 2020	Progression of use (concentrates, combustibles, etc.)	Y	Y	NA	N	Y	N	Y	Y	N	N	Y	N	N	N	Y	Fair
Braymiller et al., 2023	Illicit drug use initiation	Y	Y	Y	N	Y	N	Y	Y	Y	N	N	N	N	Y	Y	Fair
Bedillion et al., 2022	Hazardous cannabis use	Y	Y	Y	N	Y	N	Y	Y	Y	N	Y	Y	N	N	Y	Fair
	Cannabis-related consequences																
Cuttler et al., 2020	Headache relief (therapeutic)	Y	Y	Y	Y	Y	N	Y	Y	N	N	NA	N	N	Y	Y	Fair
	Migraine relief (therapeutic)																
Federova et al., 2020	Trajectory of illicit drug use	Y	Y	Y	N	Y	N	N	Y	N	N	Y	N	N	CD	N	Poor
	Trajectory of prescription drug use (non-medical)																
Li et al., 2019	Pain relief (therapeutic)	Y	Y	Y	Y	Y	N	Y	Y	Y	N	NA	N	N	N	N	Poor
Scheoeler et al., 2016	Psychosis relapse	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y	CD	Y	Y	Good
	Number of psychosis relapses																
	Length of relapse																
	Time to first psychosis relapse																
Schoeler et al., 2017	Antipsychotic medication adherence	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y	CD	Y	Y	Good
Stith et al., 2019	Anxiety relief (therapeutic)	Y	Y	Y	Y	Y	N	Y	Y	Y	N	NA	N	N	N	N	Poor
	Depression relief (therapeutic)																
	Back pain relief (therapeutic)																
Stith et al., 2020	Anxiety relief (therapeutic)	Y	Y	Y	Y	Y	N	Y	Y	Y	N	NA	N	N	N	N	Poor

Note: Y = Yes, N = No, NA = Not applicable; NR = Not reporting; CD = Cannot determine.

Criteria: (1) Was the research question or objective clearly stated? **(2a)** Was the study population clearly specified and defined and is cohort free of outcome of interest at time of recruitment?; **(2b)** Was the cohort free of the outcomes of interest at the time they were recruited?; **(3)** Was the participation rate of eligible persons at least 50%?; **(4)** Were all subjects selected or recruited from the same or similar populations (including same time period)?; **(5)** Was a sample size justification, power description, or variance and effect estimates provided?; **(6)** Was the exposure of interest measured prior to the outcome being measured?; **(7)** Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?; **(8)** Did the study examine different levels of the exposure as related to the outcome? **(9)** Were the exposure measures clearly defined, valid, reliable, and implemented consistently across study all participants? **(10)** Was the exposure assessed more than one over time?; **(11)** Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?; **(12)** Were the outcome assessors blinded to the exposure status of participants?; **(13)** Was loss to follow-up after baseline 20% or less?; **(14)** Were key confounding variables measured and adjusted statistically for their impact on the relationship between exposure and outcome?

SA8 (continued). Study quality ratings: Observational (assessed with NIH NHLBI quality assessment tools)

Quality assessment: Case-control studies

Article	Outcome(s)	Criteria													Overall rating
		1	2	3	4	5	6	7	8a	8b	9	10	11	12	13	
Di Forti 2009	Psychosis	Y	Y	NR	N	Y	Y	Y	Y	N	Y	Y	N	NR	Y	Good
Di Forti 2015	Psychosis	Y	Y	NR	N	Y	Y	Y	Y	N	Y	Y	N	NR	Y	Good
Di Forti 2019	Psychosis	Y	Y	NR	N	Y	Y	Y	Y	N	NR	Y	N	NR	Y	Good

Note: Y = Yes, N = No, NA = Not applicable; NR = Not reporting; CD = Cannot determine.
Criteria: (1) Was the research question or objective clearly stated? **(2)** Was the study population clearly specified and defined?; **(3)** Was an appropriate target population clearly defined and did the cases adequately represent the cases that arose in the population?;**(4)** Did the authors include a sample size justification?; **(5)** Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same time frame)? **(6)** Were the definitions, inclusion, and exclusion criteria, algorithms, or processes used to identify or select cases and controls valid, reliable, and implemented consistently across study participants?; **(7)** Were the cases clearly defined and differentiated from controls?; **(8a)** If less than 100 percent of eligible cases were selected for the study, were the cases randomly selected from those eligible? **(8b)** If less than 100 percent of eligible controls were selected for the study, were the controls randomly selected from those eligible? (*Note: 8a and 8b were split into two sub-questions to differentiate process of selecting cases and controls*); **(9)** Was there use of concurrent controls?; **(10)** Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?; **(11)** Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?; **(12)** Were the assessors of exposure/risk blinded to the case or control status of participants?; **(13)** Were key potential confounding variable measured and adjusted statistically in the analysis? If matching was used, did the investigators account for matching during study analysis?

SA8 (continued). Study quality ratings: Observational (assessed with NIH NHLBI quality assessment tools)

Quality assessment: Analysis of cases or controls derived from a case-control study

Article	Outcome(s)	Criteria														Overall rating
		1	2a	2b	3	4	5	6	7	8	9	10	11	12	13	14	
Di Forti et al., 2014	Time to psychosis onset	Y	Y	NA	Y	Y	N	Y	CD	Y	N	N	Y	CD	NA	N	Fair
Quattrone et al., 2021	Psychotic symptoms in cases	Y	Y	NA	NR	Y	N	CD	CD	Y	N	N	Y	NR	NA	Y	Poor
	Psychotic symptoms in controls							N									

Note: Both cohort/cross-sectional and case-control forms were piloted for assessment of these studies, and the cohort/cross-sectional form (with some slight modifications, as noted below) was determined to be more applicable to this style of analysis. Y = Yes, N = No, NA = Not applicable; NR = Not reporting; CD = Cannot determine.
Criteria: (1) Was the research question or objective clearly stated? **(2a)** Was the study population clearly specified and defined?; **(2b)** Was the cohort free of the outcomes of interest at the time they were recruited?; **(3)** Was the participation rate of eligible persons at least 50%?; **(4)** Were all subjects selected or recruited from the same or similar populations (including same time period)?; **(5)** Was a sample size justification, power description, or variance and effect estimates provided?; **(6)** Did the index period of exposure of interest precede the index period of the outcome being measured? (*Note: modified slightly for a retrospective exposure assessment of cases or controls based on criteria 6 in cohort/cross-sectional form*); **(7)** Was the timeframe between exposure index period and outcome assessment period sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed? (*Note: modified slightly from criteria 7 in cohort/cross-sectional form*); **(8)** Did the study examine different levels of the exposure as related to the outcome? **(9)** Were the exposure measures clearly defined, valid, reliable, and implemented consistently across study all participants? **(10)** Was the exposure retrospectively assessed for more than one index period? (*Note: modified slightly from criteria 10 in cohort/cross-sectional form*); **(11)** Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?; **(12)** Were the outcome assessors blinded to the exposure status of participants?; **(13)** Was loss to follow-up after baseline 20% or less? (*Note: we graded as NA for retrospective analysis of cases or controls from a case-control study based on interpretation of NHLBI guidance document*); **(14)** Were key confounding variables measured and adjusted statistically for their impact on the relationship between exposure and outcome?

SA9. Study risk of bias ratings (assessed Cochrane RoB2 Tool)

Risk of bias assessment: Parallel design studies

Article	Outcome(s)	Criteria																						Overall rating
		1.1	1.2	1.3	2.1	2.2	2.3	2.4	2.5	2.6	2.7	3.1	3.2	3.3	3.4	4.1	4.2	4.3	4.4	4.5	5.1	5.2	5.3	
Bidwell et al., 2020	Tension	Y	Y	N	Y	PN	PN	NA	NA	Y	NA	PY	NA	NA	NA	N	N	Y	Y	PY	NI	PN	PN	High
	Verbal recall																	PN	NA	NA				
	Episodic and working memory																							
	Attention and inhibitory control																							
Cuttler et al., 2021	Subjective effects (mood, anxiety)	Y	Y	N	Y	PY	N	NA	NA	Y	NA	Y	NA	NA	NA	N	N	Y	Y	PY	NI	PN	PN	High
	Prospective memory																	PN	NA	NA				
	Source memory																							
	False memory																							
	Temporal order																							
	Decision making																							
Drennan et al., 2021	Drug liking	Y	Y	N	Y	PN	PN	NA	NA	Y	NA	N	PY	NA	NA	N	N	Y	Y	PY	NI	N	PN	High
	Tension																							
	Anxiety																							
	Paranoia																							
Karoly et al., 2021	Frequency of alcohol use	Y	Y	N	Y	PN	Y	Y	PN	Y	NA	N	PY	NA	NA	N	N	Y	Y	PN	NI	PN	PN	High
	Frequency of alcohol-cannabis co-use																							

Y/PY = 'Yes' or 'Probably yes'; **N/PN** = 'No' or 'Probably no'; **NI** = 'No information'; **NA** = 'Not applicable'. **Criteria: (1.1)** Was the allocation sequence random? **(1.2)** Was the allocation sequence concealed until participants were enrolled and assigned to interventions? **(1.3)** Did baseline differences between intervention groups suggest a problem with the randomization process? **(2.1)** Were participants aware of their assigned intervention during the trial? **(2.2)** Were carers and people delivering the interventions aware of participants' assigned intervention during the trial? **(2.3)** Were there deviations from the intended intervention that arose because of the trial context? **(2.4)** Were these deviations likely to have affected the outcome? **(2.5)** Were these deviations from intended interventions balanced between groups? **(2.6)** Was an appropriate analysis used to estimate the effect of assignment to intervention? **(2.7)** Was there potential for a substantial impact (on the result) of the failure to analyze participants in the group to which they were randomized? **(3.1)** Were data for this outcome available for all, or nearly all, participants randomized? **(3.2)** Is there evidence that the result was not biased by missing outcome data? **(3.3)** Could missingness in the outcome depend on its true value? **(3.4)** Is it likely that missingness in the outcome depended on its true value? **(4.1)** Was the method of measuring the outcome inappropriate? **(4.2)** Could measurement or ascertainment of the outcome have differed between intervention groups? **(4.3)** Were outcome assessors aware of the intervention received by study participants? **(4.4)** Could assessment of the outcome have been influenced by knowledge of intervention received? **(4.5)** Is it likely that assessment of the outcome was influenced by knowledge of intervention received? **(5.1)** Were the data that produced this result analyzed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis? **(5.2)** Is the numerical result being assessed likely to have been selected, on the basis of the results from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain? **(5.3)** Is the numerical result being assessed likely to have been selected, on the basis of the results from multiple eligible analyses of the data?

SA9 (continued). Study risk of bias ratings (assessed Cochrane RoB2 Tool)

Risk of bias assessment: Crossover design studies

Article	Outcome(s)	Criteria																										Overall rating
		1.1	1.2	1.3	S.1	S.2	S.3	2.1	2.2	2.3	2.4	2.5	2.6	2.7	3.1	3.2	3.3	3.4	4.1	4.2	4.3	4.4	4.5	5.1	5.2	5.3	5.4	
Ramaekers et al., 2006	Tower of London: correct decisions and planning time	Y	Y	PN	Y	NA	Y	N	N	NA	NA	NA	Y	NA	N	PY	NA	NA	N	N	N	NA	NA	NI	PN	PN	N	Some concerns
	Stop signal task: stop reaction time, errors of commission and omission																											
	Iowa gambling task: ratio of good/bad																											
Spindle et al., 2018	Subjective effects (like drug effect, pleasant drug effect, paranoia, anxious/nervous, craving)	Y	Y	PN	PY	NA	Y	N	N	NA	NA	NA	Y	NA	N	PY	NA	NA	N	N	Y	Y	PY	NI	PN	PN	N	High
	Memory impairment																											
	Digit symbol substitution																				N	NA	NA					Some concerns
	Divided attention																											
	Paced auditory serial addition																											
Spindle et al., 2021	Subjective effects (like drug effect, pleasant drug effect, paranoia, anxious/nervous, craving, memory impairment)	Y	Y	PN	Y	NA	Y	N	N	NA	NA	NA	Y	NA	N	PY	NA	NA	N	N	Y	Y	PY	Y	PN	PN	N	High
	Digit symbol substitution																				N	NA	NA					Low
	Divided attention																											

	Paced auditory serial addition																									
	DRUID total impairment																									

Y/PY = 'Yes' or 'Probably yes'; **N/PN** = 'No' or 'Probably no'; **NI** = 'No information'; **NA** = 'Not applicable'. **Criteria: (1.1)** Was the allocation sequence random? **(1.2)** Was the allocation sequence concealed until participants were enrolled and assigned to interventions? **(1.3)** Did baseline differences between intervention groups suggest a problem with the randomization process? **(S.1)** Was the number of participants allocated to each of the two sequences equal or nearly equal? **(S.2)** Were period effects accounted for in the analysis? **(S.3)** Was there sufficient time for any carryover effects to have disappeared before outcome assessment in the second period? **(2.1)** Were participants aware of their assigned intervention during the trial? **(2.2)** Were carers and people delivering the interventions aware of participants' assigned intervention during each period of the trial? **(2.3)** Were there deviations from the intended intervention that arose because of the trial context? **(2.4)** Were these deviations likely to have affected the outcome? **(2.5)** Were these deviations from intended interventions balanced between groups? **(2.6)** Was an appropriate analysis used to estimate the effect of assignment to intervention? **(2.7)** Was there potential for a substantial impact (on the result) of the failure to analyze participants in the group to which they were randomized? **(3.1)** Were data for this outcome available for all, or nearly all, participants randomized? **(3.2)** Is there evidence that the result was not biased by missing outcome data? **(3.3)** Could missingness in the outcome depend on its true value? **(3.4)** Is it likely that missingness in the outcome depended on its true value? **(4.1)** Was the method of measuring the outcome inappropriate? **(4.2)** Could measurement or ascertainment of the outcome have differed between intervention groups within each sequence? **(4.3)** Were outcome assessors aware of the intervention received by study participants? **(4.4)** Could assessment of the outcome have been influenced by knowledge of intervention received? **(4.5)** Is it likely that assessment of the outcome was influenced by knowledge of intervention received? **(5.1)** Were the data that produced this result analyzed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis? **(5.2)** Is the numerical result being assessed likely to have been selected, on the basis of the results from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain? **(5.3)** Is the numerical result being assessed likely to have been selected, on the basis of the results from multiple eligible analyses of the data? (5.4) Is a result based on data from both periods sought, but unavailable on the basis of carryover having been identified?

SA10. Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) assessments of primary outcomes

GRADE assessment: Mental health

N of studies	Study design	Summary of findings	GRADE domain					Certainty
			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	
Anxiety								
4	Observational (cross-sectional)	Most studies showed small positive significant associations with higher potency product use	Serious[a]	Not serious	Very serious[b]	Not serious	None	⊕◯◯◯ Very low
Bipolar disorder								
1	Observational (cross-sectional)	Positive significant association with bipolar disorder for Con and Res; no association with Con-Vape (vs. no use of that product) or Can-Mix (all assessed as use vs. no use of that product)	Serious[c]	N/A (1 study)	Serious[d]	Not serious	None	⊕◯◯◯ Very low
Depression								
4	Observational (cross-sectional)	Most studies did not find a significant association with depression; one study found significant positive association for both Con and Can-Mix (vs. no use of that product; no direct comparison between the two)	Serious[a]	Not serious	Very serious[b]	Not serious, borderline[e]	None	⊕◯◯◯ Very low
Psychosis								
10	Observational (case-control, cohort, cross-sectional)	Most studies of psychosis incidence/relapse found significant positive associations; studies with measures of psychosis severity/types of symptoms/medication adherence were mixed	Not serious, borderline[f]	Not serious, borderline[g]	Serious[h]	Not serious	None	⊕◯◯◯ Very low
Post-traumatic stress disorder								

2	Observational (cross-sectional)	Positive significant associations with PTSD	Serious[c]	Not serious	Serious[i]	Not serious	None	⊕◯◯◯ Very low

a. Most studies were rated as Poor quality, due in part to shared methodological concerns including risk of selection bias and information bias (assessment of exposure).
b. Two studies didn't directly compare the higher potency product with the lower potency one (they were each compared to no / lower frequency use of that product); another study relied on self-reported use of “skunk” and “herbal” cannabis and assigned potency values on potency data from seized cannabis.
c. Study was rated as Poor quality, due in part to methodological concerns related to information bias (assessment of exposure, outcome).
d. Didn’t directly compare the higher potency product with the lower potency one (they were each compared to no use of that product).
e. Non-significant results in the two smaller studies, possibly due to small number of people enrolled; judged as borderline serious, but not enough information to make a strong determination.
f. Most studies were rated as Fair or Good quality, but with some shared methodological concerns mostly related to risk of information bias (assessment of exposure); three studies were rated as Poor quality with some additional methodological concerns including risk of selection bias, confounding.
g. Several findings come from a subset of studies with high sample overlap, so consistent results are expected given a certain level of data recycling. There are two studies (of Con vs. Can-Mix) showing no/negative association which may be explained by differing outcome definitions. This introduces serious concern for inconsistency in subset of studies looking at concentrate vs. flower but was judged to be only "borderline" serious in the context of the rest of the psychosis studies.
h. Most studies compared mid-potency flower with low-potency flower, relying on self-reported use of different dried flower classifications (e.g., skunk, herbal) with imputed potencies based on indirect data (e.g., seized cannabis); one study compared use of Con and Can-Mix to no use of those products preventing direct comparison due to non-identical control groups.
i. This study didn’t directly compare the higher potency product with the lower potency one (they were each compared to no use of that product).

SA10 (continued). Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) assessments of primary outcomes

GRADE Assessment: "Problem" cannabis use

N of studies	Study design	Summary of findings	GRADE domain					Certainty
			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	
High-frequency cannabis use								
11	Observational (cohort, cross-sectional)	Significant positive association with higher potency cannabis use	Very serious[a]	Not serious	Serious[b]	Not serious, borderline[c]	None	⨁◯◯◯ Very low
CUD, CUD indicators, cannabis-related consequences								
12	Observational (cohort, cross-sectional)	Mixed, with studies finding either no or significant positive association with higher potency cannabis use	Serious[d]	Serious[e]	Very serious[f]	Serious[g]	None	⨁◯◯◯ Very low

a. All but one study rated as Poor quality, due in part to shared methodological concerns including risk of selection bias, information bias (assessment of exposure, outcome), and confounding.
b. Three studies relied on self-reported use of different dried flower classifications (e.g., skunk, herbal) with imputed potencies based on indirect data (e.g., seized cannabis).
c. Only six studies could be assessed for precision (provided 95% CIs around an effect estimate), all lower bound of all within range of meaningful effect. Two studies that couldn't be assessed for precision had very high sample sizes, reducing concerns.
d. Most studies rated as Poor quality, due in part to shared methodological concerns incuding risk of selection bias, information bias (assessment of exposure), and confounding.
e. Findings ranged from null to increased risk associated with higher potency use, but there was no consistent finding from a clear majority of studies.
f. Four studies didn't directly compare the higher potency product with the lower potency one (they were each compared to lower frequency use of that product); one study compared current high potency users to former high potency users; two studies relied on self-reported use of different dried flower classifications (e.g., skunk, herbal) with imputed potencies based on indirect data (e.g., seized cannabis).
g. Most studies assessed the outcome continuously and cumulatively represent n > 400 but imprecision could not be judged in five studies and there are additional concerns about imprecision in several individual studies.

SA10 (continued). Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) assessments of primary outcomes

GRADE Assessment: Use of other substances

N of studies	Study design	Summary of findings	GRADE domain					Certainty
			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	
Illicit drugs								
7	Observational (cohort, cross-sectional)	Most studies found positive significant association with higher potency cannabis use	Serious[a]	Not serious, borderline[b]	Serious[c]	Not serious	None	⊕◯◯◯ Very low
Alcohol								
4	Observational (cross-sectional), experimental	Most studies did not find significant association with high potency cannabis use	Serious[d]	Not serious, borderline[e]	Not serious, borderline[f]	Serious[g]	None	⊕◯◯◯ Very low[h]
Prescription drug use (non-medical)								
3	Observational (cross-sectional, cohort)	Mixed, with studies finding either no or significant positive association with higher potency cannabis use	Serious[i]	Serious[j]	Not serious	Serious[k]	None	⊕◯◯◯ Very low
Tobacco								
3	Observational (cross-sectional)	Mixed, with studies finding either no or significant positive association with higher potency cannabis use	Serious[l]	Serious[m]	Not serious, borderline[n]	Serious[o]	None	⊕◯◯◯ Very low

a. All but one study rated as Poor quality, due in part to shared methodological limitations including risk of selection bias, information bias (exposure, outcome assessment); additional concerns related to confounding in four studies.
b. Findings were not consistent across studies but deemed "borderline" with just over 70% consistent in showing positive association with illicit drug use (or suggestive of one via indirect comparison).
c. One study didn't directly compare the higher potency product with the lower potency one (they were each compared to no use of that product); two studies relied on self-reported use of "skunk" and "herbal" cannabis and assigned potency values based on indirect data (e.g., seized cannabis).
d. All observational studies rated as Poor quality, due in part to shared methodological limitations including risk of selection bias, information bias (exposure assessment); two studies had additional concerns related to outcome assessment and confounding; 1 experimental study rated as "High" risk of bias (mainly due to non-blinding of study intervention).
e. Slight inconsistency in findings (one study finding positive association with higher potency use; the rest finding no significant association) but this may be explained by differences in exposure-outcome comparisons across studies (two Con vs. Can-Mix; one Can-Mid vs. Can-Low; one Can-High vs. Can-Low).

f. One study relied on self-reported use of "skunk" and "herbal" cannabis and assigned potency values based on indirect data (e.g., seized cannabis), but deemed "borderline" overall as other studies distinguished between concentrates and flower (clearer potency separation or verified the flower potency).
g. One study had good precision, but the other three either had evidence of poor precision or precision could not be assessed.
h. Note: Since only one study was experimental design, the certainty of evidence was still downgraded from a starting rating of "Low".
i. All studies rated as Poor quality, due in part to methodological concerns related to risk of selection bias, information bias (exposure and outcome assessment); additional concerns related to confounding in two studies.
j. Inconsistency in findings including inconsistencies across two studies with an overlapping study sample; cautiously rated down as low number of studies means one inconsistent finding represents 33%.
k. Cautiously rated down as one study (of three) did not provide effect estimate or 95% CIs but effect estimate (odds ratio) calculated from reported data shows relatively high point estimate (2.63) with $p > 0.5$, suggesting imprecision is likely.
l. All studies rated as Poor quality, due in part to methodological concerns related to risk of selection bias, information bias (exposure assessment); additional concerns related to outcome assessment and confounding in two studies.
m. Inconsistency in findings; cautiously rated down as low number of studies means one inconsistent finding represents 33%.
n. One study relied on self-reported use of different dried flower classifications (e.g., skunk, herbal) with imputed potencies based on indirect data (e.g., seized cannabis).
o. Imprecision could not be assessed in one study; effect estimates in other studies are similar (OR = 1.52, OR = 1.42) but the 95% CIs around estimate from the study with higher sample size spans non-meaningful value, suggesting low precision.

SA10 (continued). Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) assessments of primary outcomes

GRADE Assessment: Psychosocial

N of studies	Study design	Summary of findings	GRADE domain					Certainty
			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	
Academic performance								
1	Observational (cross-sectional)	Positive significant association between "academic failure" and higher potency use	Very serious[a]	N/A (1 study)	Not serious	Not serious, borderline[b]	None	⨁◯◯◯ Very low

a. Study rated as Poor quality due in part to methodological concerns including risk of selection bias, information bias (exposure and outcome assessment), and confounding.
b. Precision difficult to assess as no 95% CIs provided, but sample size is very large (>40,000), reducing concerns of imprecision

ST1. Summary of secondary findings: Acute indicators of adverse mental health outcomes

Commented [SL1]: Update RoB after re-do

Author(s), year	Study design, location, period	Sample characteristics	Cannabis use		Outcome measure, method of assessment	Summary of findings	Quality / RoB
			Measure, method of assessment	Relevant potencies compared			
Anxiety							
Bidwell et al., 2020	Between-subjects naturalistic experiment (open-label, random assignment), USA, study period not reported	Healthy adults who use cannabis: n = 121; non-male = 45%; mean age = 28	Type of cannabis used, experimentally assigned	Con vs. Can-Mix; Con 1 (90% THC) vs. Con 2 (70% THC); Can-Mid vs. Can-Low (administered via participant's preferred mode)	Tension, self-reported via POMS at BL and 2 acute FU assessments[a]	Significantly lower tension after Con use (FU1=0.38; FU2=0.22) relative to Can-Mix (FU1=0.60; FU2=0.40; $F_{1,230}$=9.90, p<0.01); No significant main effect of THC potency on tension within Con or Can-Mix groups (p>0.05)	High (RoB)
Brunt et al., 2014	Cross-sectional, Netherlands, 2011-2012	People who use cannabis for medical purposes: n = 102; female = 51%; mean age = 53	Type of cannabis prescribed, current, self-reported	Can-Mid 1 (19% THC), Can-Mid 2 (12% THC) vs. Can-Low	Anxiety after use of prescribed cannabis, retrospectively self-reported via VAS	Anxiety scores differed by prescribed cannabis type ($F_{2,93}$=5.44, p=0.006), with significantly higher scores for Can-Mid 1 vs. Can-Low (p=0.004); no significant difference in anxiety scores between Can-Mid 2 and Can-Low (p>0.05)	Poor
Chan et al., 2017	Cross-sectional, multinational, 2015-2016	Subset (n = 5676) who use Con and Can-Mid from a sample of young adults and adults (≥16 years) who use cannabis: full n = 83867; female = 29%; mean age = 26	Type of cannabis used, past year, self-reported	Con vs. Can-Mid (within-subject comparison)	Anxiety, assessed with item "Restless/anxious", self-reported via 10-point scale	Significantly more restless/anxious after Con use (3.73, SD=2.43) relative to Can-Mid (3.22, SD=2.32; t=12.99, p<0.001, Cohen's d=0.22)	Poor
Cuttler et al., 2021	Between-subjects naturalistic experiment (open-label, random assignment),	Healthy adults who use cannabis: n = 80[b]; Non-male = 56%; mean age = 24	Type of cannabis used, experimentally assigned	Con vs. Can-High (administered via participant's preferred mode)	Anxiety, self-reported via 10-point scale at BL and 3 acute FU assessments[c]	Anxiety ratings did not differ significantly between groups overall (F=0.34, p=0.80) or by time (F=1.51, p=0.15)	High (RoB)

	USA, study period not reported						
Drennan et al., 2021	Between-subjects naturalistic experiment (open-label, random assignment), USA, study period not reported	Healthy adults who use cannabis: n = 54; non-male = 48%; mean age = 30	Type of cannabis used, experimentally assigned	Con vs. Can-Low (administered via participant's preferred mode)	Anxiety, self-reported via VAS at BL and 2 acute FU assessments[d]	Anxiety decreased significantly from BL at FU 1 for Can-Low (t=-2.40, p=0.02), and at FU 2 for Con (t=-3.09, p<0.001); however, no significant between-group differences at either FU (both p>0.05)	High (RoB)
					Tension, self-reported via subscale of POMS at BL and 2 acute FU assessments[d]	Tension decreased significantly from BL at FU1 (t=-2.77, p=0.01) and FU2 (t=-3.79, p<0.001) for Can-Low; however, no significant between-group differences at either FU (both p>0.05)	
Spindle et al., 2018[e]	Within-subjects randomized controlled trial, USA, 2016-2017	Healthy adults who use cannabis: n = 17; non-male = 47%; mean age = 27	Type of cannabis used, experimentally assigned	Can-Mid, Can-Low vs. placebo (vaporized); Can-Mid, Can-Low vs. placebo (smoked)	Anxious/Nervous, self-reported via DEQ at BL and 10 acute FU assessments[f]	For both smoked and vaporized conditions, significantly (p<0.025) higher anxious/nervous score after Can-Mid (smoked: 21.4, SD=32.2; vaporized: 25.5, SD=28.0), but not Can-Low (smoked: 3.1, SD=10.5; vaporized: -3.6, SD=7.4), relative to placebo (smoked: -3.3, SD=8.2; vaporized: -9.3, SD=15.2)	High (RoB)
Spindle et al., 2021[g]	Within-subjects randomized controlled trial, USA, 2020-2023	Healthy adults who use cannabis, n = 20; nonn-male = 50%; mean age = 28	Type of cannabis used, experimentally assigned	Can-Mid vs. Can-Low (vaporized)	Anxious/Nervous, self-reported via DEQ at BL and 8 acute FU assessments[h]	Significantly higher peak anxious/nervous score after Can-Mid (23.0, SD=25.9) relative to Can-Low (5.7, SD=22.1, p<0.016)	High (RoB)
Depression							
Cuttler et al., 2021	Between-subjects naturalistic experiment (open-label, random assignment), USA, study period not reported	Healthy adults who use cannabis: n = 80[b]; Non-male = 44%; mean age = 24	Type of cannabis used, experimentally assigned	Con vs. Can-High (administered via participant's preferred mode)	Mood rating (from extremely negative to extremely positive), self-reported via 10-point scale at BL and 3 acute FU assessments[c]	Mood ratings did not differ significantly between groups overall (F=1.05, p=0.37), but there was a significant group by time interaction (F=2.31, p=0.02) where mood increased significantly from BL to FU 1 in Can-High (p<0.05) but not Con (p>0.05)	High (RoB)

Okey and Meier, 2020	Cross-sectional, USA, study period not reported	Subset who use(d) Con and Can-Mix (n = 574) from a sample of adults who use cannabis, n = 849; non-male = 48%; mean age = 33	Type of cannabis used, lifetime, self-reported	Con vs. Can-Mix (within-subject comparison)	Negative affect acutely after using, self-reported via series of Likert scales	Negative affect rated as significantly lower after Con use relative to Can-Mix use (t=-6.13, p=0.003, Cohen's d=-0.17)	Poor
Psychosis							
Chan et al., 2017	Cross-sectional, multinational, 2015-2016	Subset (n = 5676) who use Con and Can-Mid from a sample of young adults and adults (≥16 years) who use cannabis: full n = 83867; female = 29%; mean age = 26	Type of cannabis used, past year, self-reported	Con vs. Can-Mid (within-subject comparison)	Paranoia, self-reported with item "worried about people looking at or talking to you", self-reported via 10-point scale	Significantly more paranoid after Con use (3.26, SD=2.48) relative to Can-Mid (2.95 SD=2.23; t=10.57, p<0.001, Cohen's d=0.18)	Poor
Drennan et al., 2021	Between-subjects naturalistic experiment (open-label, random assignment), USA, study period not reported	Healthy adults who use cannabis: n = 54; non-male = 48%; mean age = 30	Type of cannabis used, experimentally assigned	Con vs. Can-Low (administered via participant's preferred mode)	Paranoid, self-reported via Likert scale at BL and 2 FU assessments[d]	Paranoia increased significantly from BL at FU1 for Con (t=2.83, p<0.001) and non-significantly for Can-Low (p>0.05), leading to significantly higher rating for Con vs. Can-Low at FU1 (p<0.05); paranoia increased non-significantly from BL at FU2 for Con and decreased non-significantly for Can-Low (both p>0.05), leading to significantly higher paranoia rating for Con vs. Can-Low at FU2	High (RoB)
Okey and Meier, 2020	Cross-sectional, USA, study period not reported	Subset who use(d) Con and Can-Mix (n = 574) from a sample of adults who use cannabis, n = 849; non-male = 48%; mean age = 33	Type of cannabis used, lifetime, self-reported	Con vs. Can-Mix (within-subject comparison)	Psychotic-like experiences acutely after using, self-reported via series of Likert scales	Psychotic-like experiences rated as significantly lower after Con use relative to Can-Mix use (t=-1.2, p=0.003, Cohen's d=-0.12)	Poor
Spindle et al., 2018[e]	Within-subjects randomized controlled	Healthy adults who use cannabis: n = 17; non-male = 47%; mean age = 27	Type of cannabis used, experimentally assigned	Can-Mid, Can-Low vs. placebo (vaporized); Can-Mid, Can-	Paranoid, self-reported via DEQ at BL and 10 acute FU assessments[f]	Significantly higher (p<0.025) peak paranoia score after Can-Mid (17.4, SD=30.0), but not Can-Low (7.9, SD=16.9), relative to placebo (0.0,	High (RoB)

	trial, USA, 2016-2017			Low vs. placebo (smoked)		SD=0.0) in the vaporized condition; no significant differences from placebo for Can-Mid or Can-Low in the smoked condition (p>0.025)	
Spindle et al., 2021[g]	Within-subjects randomized controlled trial, USA, 2020-2023	Healthy adults who use cannabis, n = 20; non-male = 50%; mean age = 28	Type of cannabis used, experimentally assigned	Can-Mid vs. Can-Low (vaporized)	Anxious/Nervous, self-reported via DEQ at BL and 8 acute FU assessments[h]	Significantly higher peak paranoid score following Can-Mid (17.4, SD=24.5) relative to Can-Low (6.8, SD=19.1; p<0.016)	High (RoB)
Study-specific notes: [a]Assessment times (post-administration): FU1=immediately (mean 15 mins), FU2=2 hours; [b]For the purpose of this review, we focus on the n=40 participants who were assigned to either the high THC / no CBD or THC concentrate group; some reported statistics are from omnibus tests involving all 80 participants; [c]Assessment times (post-administration): FU1=immediately (1 min), FU2=25 mins, FU3=50 mins; [d]Assessment times (post-administration): FU1=immediately, FU2=1 hour; [e]p<0.025 considered statistically significant in this study; [f]Assessment times (post-administration): FU1=10 mins, FU2=30 mins, FU3=1 hour, FU4=1.5 hours, FU5=2 hours, FU6=3 hours, FU7=4 hours, FU8=5 hours, FU9=6 hours, FU10=8 hours; outcome is taken at FU time in which effects peaked for that outcome; [g]p<0.016considered statistically significant in this study; [h]Assessment times (post-administration): FU1=immediately, FU2=1 hour, FU3=2 hours, FU4=3 hours, FU5=4 hours, FU6=5 hours, FU7=6 hours, FU8=8 hours; however, FU3 used as the cut-off time for calculating peak outcome effect. **Abbreviations:** BL = Baseline; DEQ = Drug Effects Questionnaire; FU = Follow-up; POMS = Profile of Mood States; RoB: Risk of Bias; SD = Standard Deviation; VAS = Visual Analog Scale. **Cannabis potency category definitions:** Can-Low = ≤10% THC flower; Can-Mid = 10-19% THC flower; Can-High = ≥20% THC flower; Res = hashish, resin, kief, assumed to have 20-50% THC; Con = Concentrated cannabis product, assumed to have 60-99% THC; Can-Mix = Cannabis of unspecified or multiple potency categories, but estimated to be lower than the higher potency exposure from that study.							

ST2. Summary of secondary findings: Acute indicators of high-frequency and "problem" cannabis use

Commented [SL2]: Update RoB after re-do

Author(s), year	Study design, location, period	Sample characteristics	Cannabis use		Outcome measure, method of assessment	Summary of findings	Quality / RoB
			Measure, method of assessment	Relevant potencies compared			
Cannabis use disorder (including indicators or consequences)							
Chan et al., 2017	Cross-sectional, multinational, 2015-2016	Subset (n = 5676) who use Con and Can-Mid from a sample of young adults and adults (≥16 years) who use cannabis: full n = 83867; female = 29%; mean age = 26	Type of cannabis used, past year, self-reported	Con vs. Can-Mid (within-subject comparison)	Pleasant drug effect, assessed with item "Overall pleasurable effect", self-reported via 10-point scale	Significantly lower overall pleasurable effect score for Con (7.79, SD=1.89) relative to Can-Mid (8.44, SD=1.51; t=21.12, p<0.001, Cohen's d=0.32)	Poor
					Craving, assessed with item "Urge to use more when stoned", self-reported via 10-point scale	Significantly lower craving after Con use (3.91, SD=2.40) relative to Can-Mid (4.74, SD=2.53; t=24.72, p<0.001, Cohen's d=0.39)	
Drennan et al., 2021	Between-subjects naturalistic experiment (open-label, random assignment), USA, study period not reported	Healthy adults who use cannabis: n = 54; non-male = 48%; mean age = 30	Type of cannabis used, experimentally assigned	Con vs. Can-Low (administered via participant's preferred mode)	Drug liking, self-reported via DEQ at BL and 2 FU assessments[b]	Significantly higher drug liking score at FU1 for Con vs. Can-Low ($F_{1,51}$=6.28, p=0.01)	High (RoB)
Spindle et al., 2018[c]	Within-subjects randomized controlled trial, USA, 2016-2017	Healthy adults who use cannabis: n = 17; non-male = 47%; mean age = 27	Type of cannabis used, experimentally assigned	Can-Mid, Can-Low vs. placebo (vaporized); Can-Mid, Can-Low vs. placebo (smoked)	Pleasant drug effect, self-reported via DEQ at BL and 10 acute FU assessments[d]	Similar (but not statistically compared) peak pleasant ratings after Can-Mid (smoked: 44.2, SD=31.2; vaporized: 57.4, SD=26.8) and Can-Low (smoked: 42.4, SD=31.6; vaporized: 59.2, SD=29.6)—both significantly higher (p<0.025) than placebo (smoked: 10.2, SD=16.0; vaporized: 1.2, SD=4.9)	High (RoB)

					Cannabis craving, self-reported via DEQ at BL and 10 acute FU assessments[d]	No significant change in peak craving relative to placebo after Can-Mid or Can-Low in either inhalation condition (all $p>0.025$)	
Spindle et al., 2021[e]	Within-subjects randomized controlled trial, USA, 2020-2023	Healthy adults who use cannabis, n = 20; non-male = 50%; mean age = 28	Type of cannabis used, experimentally assigned	Can-Mid vs. Can-Low (vaporized)	Like drug effect, self-reported via DEQ at BL and 3 acute FU assessments[f]	Peak ratings of like drug effect did not differ significantly after Can-Mid (66.3, SD=32.0) relative to Can-Low (58.4, SD=36.1; $p>0.016$)	High (RoB)
					Pleasant drug effect, self-reported via DEQ at BL and 3 acute FU assessments[f]	Peak ratings of pleasant drug effect did not differ significantly after Can-Mid (68.1, SD=32.5) relative to Can-Low (62.1, SD=37.6; $p>0.016$)	
					Cannabis craving, self-reported via DEQ at BL and 3 acute FU assessments[f]	Peak cannabis craving did not differ significantly after Can-Mid (5.9, SD=17.1) relative to Can-Low (1.4, SD=4.9; $p>0.016$)	

Study-specific notes: [a]Assessment time (post-administration): FU1 = immediately (mean 15 mins); [b]Assessment times (post-administration): FU1=immediately, FU2=1 hour; [c]$p<0.025$ considered statistically significant in this study; [d]Assessment times (post-administration): FU1=10 mins, FU2=30 mins, FU3=1 hour, FU4=1.5 hours, FU5=2 hours, FU6=3 hours, FU7=4 hours, FU8=5 hours, FU9=6 hours, FU10=8 hours; outcome is taken at FU time in which effects peaked for that outcome; [e]$p<0.016$considered statistically significant in this study; [f]Assessment times (post-administration): FU1=immediately, FU2=1 hour, FU3=2 hours, FU4=3 hours, FU5=4 hours, FU6=5 hours, FU7=6 hours, FU8=8 hours; however, FU3 used as the cut-off time for calculating peak outcome effect. **Abbreviations:** BL = Baseline; DEQ = Drug Effects Questionnaire; FU = Follow-up; SD = Standard Deviation. **Cannabis potency category definitions:** Can-Low = ≤10% THC flower; Can-Mid = 10-19% THC flower; Can-High = ≥20% THC flower; Res = hashish, resin, kief, assumed to have 20-50% THC; Con = Concentrated cannabis product, assumed to have 60-99% THC; Can-Mix = Cannabis of unspecified or multiple potency categories, but estimated to be lower than the higher potency exposure from that study.

ST3. Summary of findings: Non-acute psychosocial measures (primary) and acute cognitive measures under the psychosocial domain (secondary)

Commented [SL3]: Update RoB after re-do

Author(s), year	Study design, location, period	Sample characteristics	Cannabis use		Outcome measure, method of assessment	Summary of findings	Quality / RoB
			Measure, method of assessment	Relevant potencies compared			
Academic performance (Primary)							
Meier et al., 2019	Cross-sectional, USA, 2018	Subset of respondents who use cannabis (n = 15679) from a sample of high school students: full n = 47142; female = 50%; mean age = 15	Type of cannabis used, lifetime, self-reported	Con (including Con-Vape) vs. Can-Mix	"Academic failure", current, self-reported via composite measure of letter grades and self-assessment relative to peers (range 1-4)	Con group had significantly higher mean academic failure score (2.29, SE=0.01) relative to Can-Mix (2.15, SE=0.01; $p<0.05$)	Poor
Acute cognitive (Secondary)							
Memory and attention							
Chan et al., 2017	Cross-sectional, multinational, 2015-2016	Subset (n = 5676) who use Con and Can-Mid from a sample of young adults and adults (≥16 years) who use cannabis: full n = 83867; female = 29%; mean age = 26	Type of cannabis used, past year, self-reported	Con vs. Can-Mid (within-subject comparison)	Memory, assessed with item "Forgetful when stoned", self-reported via 10-point scale	Significantly more forgetful after Con use (5.28, SD=2.44) relative to Can-Mid (4.86, SD=2.32; $t=14.27$, $p<0.001$, Cohen's $d=0.22$)	Poor
Bidwell et al., 2020	Between-subjects naturalistic experiment (open-label, random assignment), USA, study period not reported	Healthy adults who use cannabis: n = 121; non-male = 45%; mean age = 28	Type of cannabis used, experimentally assigned	Con vs. Can-Mix; Con 1 (90% THC) vs. Con 2 (70% THC); Can-Mid vs. Can-Low (administered via participant's preferred mode)	Verbal recall, assessed via ISLT at BL 2 acute FU assessments[b]	Number of errors at FU1 were marginally lower for Con (1.50, SE=0.28) relative to Can-Mix (2.21, SE=0.31; $F_{1,200}=5.18$, p=0.02[c] from product*quadratic change interaction term); No significant differences by THC potency within Con and Can-Mix groups (all $p>0.05$)	High (RoB)
					Episodic memory, assessed via task	No significant difference after Con use relative to Can-Mix overall ($F_{1,223}=1.03$,	High (RoB)

					from the NIH Toolbox at BL and 2 acute FU assessments[b]	p=0.31) or by time (p>0.05); no significant differences by THC potency within Con or Can-Mix groups (all p>0.05)	
					Working memory, assessed via task from the NIH Toolbox at BL and 2 acute FU assessments[b]	No significant difference after Con use relative to Can-Mix overall ($F_{1,231}$=0.16, p=0.69), but marginally higher (better) scores in Con relative to Can-Mix at FU 1 (product*quadratic change $F_{1,231}$=5.76, p=0.02[c]) and marginally lower (worse) scores over time after Con 1 relative to Con 2 (potency*linear time $F_{1,125}$=5.94, p=0.02[c]); No significant difference by THC potency in the Can-Mix group (p>0.05)	
					Attention and inhibitory control, assessed via task from the NIH Toolbox at BL and 2 acute FU assessments[b]	Significantly lower scores (worse performance) after Con relative to Can-Mix overall ($F_{1,229}$=21.16, p<0.001); No significant difference by THC potency in Con or Can-Mix groups (both p<0.05)	
Cuttler et al., 2021	Between-subjects naturalistic experiment (open-label, random assignment), USA, study period not reported	Healthy adults who use cannabis: n = 80[b]; non-male = 44%; mean age = 24	Type of cannabis used, experimentally assigned	Con vs. Can-High (administered via participant's preferred mode)	Prospective memory, assessed via prospective memory test (2 measures) at study completion	No significant differences between Con and Can-High in the reminder test or difficulty ratings test (both p>0.05; for all group-specific measures, see Table 2 in Cuttler et al., 2021)	High (RoB)
					Source memory, assessed via source memory test (4 measures) between FUs 2 and 3[e]	No significant differences between Con and Can-High for source memory DI for pictures or words, or total free recall of pictures or words (all p>0.05; for all group-specific measures, see Table 2 in Cuttler et al., 2021)	
					False memory, assessed via DRM false memory paradigm (4	Con had slightly higher susceptibility to related false memories (5.85, SE=2.52) relative to Can-High (5.55, SE=1.89; p<0.05); No significant differences between Con and Can-High in total free	

					measures) between FUs 2 and 3[e]	recall, lures, or unrelated false memories (for all group-specific measures, see Table 2 in Cuttler et al., 2021)	
					Temporal order memory, assessed via temporal order memory test (3 measures) at study completion	No significant differences between Con and Can-High in total free recall, temporal order recall, or temporal order recognition (all p>0.05; for all group-specific measures, see Table 2 in Cuttler et al., 2021)	
Ramaekers et al., 2006	Within-subjects randomized controlled trial, Netherlands, study period not reported	Healthy adults who use cannabis: n = 20; non-male = 30%; age = 19-29	Type of cannabis experimentally assigned	Can-Mid vs. Can-Low (smoked)	Attention and motor impulsivity, assessed via Stop Signal Task (4 measures) at 4 acute FU assessments[f]	No significant difference in commission errors, omission errors, or "Go" trial reaction time after Can-Mis relative to Can-Low (all p<0.05); however, significantly longer "Stop" reaction time after Can-Mid relative to Can-Low ($F_{1,10}$=10.8, p=0.008)	Some concerns (RoB)
Spindle et al., 2018[g]	Within-subjects randomized controlled trial, USA, 2016-2017	Healthy adults who use cannabis: n = 17; non-male = 47%; mean age = 27	Type of cannabis used, experimentally assigned	Can-Mid, Can-Low vs. placebo (vaporized); Can-Mid, Can-Low vs. placebo (smoked)	Memory impairment, self-reported via DEQ at BL and 10 acute FU assessments[h]	Significantly higher (p<0.025) memory impairment peak score after smoked Can-Mid (14.2, SD=27.1) and vaporized Can-Mid (16.2, SD=27.4), but not Can-Low (smoked: 6.5, SD=14.2; vaporized: 12.9, SD=18.0), relative to placebo	Some concerns (RoB)
					Attention and working memory assessed via PASAT (2 measures) at BL and 10 acute FU assessments[h]	Significantly fewer correct trials after Can-Mid (-21.8, SD=24.9) relative to placebo (3.3, SD=13.1) in the vaporized condition only (p<0.025); Similar (not statistically compared) correct trial reaction time for Can-Mid and Can-Low under smoked and vaporized conditions—all significantly higher than placebo (p<0.025; see Spindle et al., 2018 for all estimates)	
					Divided attention, assessed via DAT (3 measures) at BL and 10 acute FU assessments[h]	No significant difference from placebo in number of correctly identified peripheral stimuli for smoked or vaporized Can-Mid or Can-Low (all p>0.025); Significantly longer stimulus tracking time for Can-	

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						Mid (smoked: -231, SD=336; vaporized: -398, SD=308) and Can-Low (smoked: -116, SD=192; vaporized: -254, SD=267) relative to placebo (all $p<0.025$); Significantly further mean distance from stimulus for vaporized Can-Mid (35.4, SD=33.8) and Can-Low (17.8. SD=23.0) relative to placebo (both $p<0.025$; see Spindle et al., 2018 for all estimates)	
Spindle et al., 2021[i]	Within-subjects randomized controlled trial, USA, 2020-2023	Healthy adults who use cannabis, n = 20; non-male = 50%; mean age = 28	Type of cannabis used, experimentally assigned	Can-Mid vs. Can-Low (vaporized)	Memory impairment, self-reported via DEQ at BL and 8 acute FU assessments[j]	Significantly higher peak memory impairment score after Can-Mid (26.7, SD=32.8) relative to Can-Low (3.1, SD=10.6; $p<0.016$)	Low (RoB)
					Attention and working memory assessed via PASAT at BL and 8 acute FU assessments[j]	No significant difference in number of correct trials between Can-Mid (-16.4, SD=19.8) and Can-Low (-4.3, SD=8.4; $p>0.016$)	
					Divided attention, assessed via DAT (2 measures) at BL and 8 acute FU assessments[j]	No significant difference between Can-Mid and Can-Low in total number of correctly identified peripheral stimuli (Can-Mid: 4.2, SD=7.1; Can-Low: -2.4, SD=3.2; $p>0.016$) or mean distance from stimulus (Can-Mid: 28.8, SD=62.8; Can-Low: 13.8, SD=32.0; $p>0.016$)	
Decision-making							
Cuttler et al., 2021	Between-subjects naturalistic experiment (open-label, random assignment), USA, study period not reported	Healthy adults who use cannabis: n = 80[b]; non-male = 44%; mean age = 24	Type of cannabis used, experimentally assigned	Con vs. Can-High (administered via participant's preferred mode)	Decision-making, assessed via 4 tests (under / overconfidence, consistency in risk perception, resistance to framing, resistance to sunk cost) between FUs 2 and 3[c]	No significant differences between Con or Can-Mid in any decision-making test (all $p>0.05$; for all group-specific measures, see Table 2 in Cuttler et al., 2021)	High (RoB)

Ramaekers et al., 2006	Within-subjects randomized controlled trial, Netherlands, study period not reported	Healthy adults who use cannabis: n = 20; non-male = 30%; age = 19-29	Type of cannabis experimentally assigned	Can-Mid vs. Can-Low (smoked)	Decision-making, assessed via Tower of London (2 measures) at FUs 2-4[f]	No significant difference in number of correct decisions or planning time after Can-Mid relative to Can-Low (p>0.05)	Some concerns (RoB)
					Decision-making and risk sensitivity, assessed via Iowa Gambling Task at FU2[f]	No significant difference in net score after Can-Mid relative to Can-Low (p>0.05)	
Psychomotor function and self-reported cognitive impairment							
Okey and Meier, 2020	Cross-sectional, USA, study period not reported	Subset who use(d) Con and Can-Mix (n = 574) from a sample of adults who use cannabis, n = 849; non-male = 48%; mean age = 33	Type of cannabis used, lifetime, self-reported	Con vs. Can-Mix (within-subject comparison)	Cognitive impairment, retrospectively self-reported via series of Likert scales	Cognitive impairment rated as significantly lower after Con use relative to Can-Mix use (t=-4.80, p=0.003, Cohen's d=-0.07)	Poor
Ramaekers et al., 2006	Within-subjects randomized controlled trial, Netherlands, study period not reported	Healthy adults who use cannabis: n = 20; non-male = 30%; age = 19-29	Type of cannabis experimentally assigned	Can-Mid vs. Can-Low (smoked)	Attention and motor impulsivity, assessed via Stop Signal Task (4 measures) at 4 acute FU assessments[f]	No significant difference in commission errors, omission errors, or "Go" trial reaction time after Can-Mis relative to Can-Low (all p<0.05); however, significantly longer "Stop" reaction time after Can-Mid relative to Can-Low ($F_{1,10}$=10.8, p=0.008)	Some concerns (RoB)
Spindle et al., 2018[g]	Within-subjects randomized controlled trial, USA, 2016-2017	Healthy adults who use cannabis: n = 17; non-male = 47%; mean age = 27	Type of cannabis used, experimentally assigned	Can-Mid, Can-Low vs. placebo (vaporized); Can-Mid, Can-Low vs. placebo (smoked)	Psychomotor functioning, assessed via DSST (2 measures) at BL and 10 acute FU assessments[h]	Under vaporized condition, significantly lower total attempted after Can-Mid (-10, SD=12.7) and Can-Low (-6.0, SD=10.0) relative to placebo (4,2, SD=6.4; both p<0.025), and significantly lower total correct after Can-Mid (-13.8, SD=14.9) and Can-Low (-8.3, SD=11.3) relative to placebo (4.9, SD=8.9, both p<0.025); No significant difference from placebo in either measure for smoked Can-Mid or Can-Low (p>0.025)	Some conerns (RoB)
Spindle et al., 2021[i]	Within-subjects	Healthy adults who use cannabis, n = 20;	Type of cannabis used,		Psychomotor functioning, assessed	No significant difference between Can-Mid and Can-Low in total attempted (-	Low (RoB)

	randomized controlled trial, USA, 2020-2023	non-male = 50%; mean age = 28	experimentally assigned	Can-Mid vs. Can-Low (vaporized)	via DSST (2 measures) at BL and 8 acute FU assessments[j]	7.2, SD=12.7 and -3.0, SD=11.7, respectively; p>0.016) or total correct (6.5, SD=12.2 and -4.3, SD=8.4, respectively; p>0.016)	
					Psychomotor functioning, assessed via DRUID at BL and 8 acute FU assessments[j]	No significant difference in global impairment scores between Can-Mid (10.5, SD=15.2) and Can-Low (4.7, SD=8.9; p>0.016)	

Study-specific notes: [a]Assessment time (post-administration): FU1 = immediately (mean 15 mins; [b]Assessment times (post-administration): FU1=immediately (mean 15 mins), FU2=2 hours; [c]p<0.01 was considered statistically significant; [d]For the purpose of this review, we focus on the n=40 participants who were assigned to either the high THC / no CBD or THC concentrate group; some reported statistics are from omnibus tests involving all 80 participants; [e]Assessment times (post-administration): FU1=immediately (1 min), FU2=25 mins, FU3=50 mins; [f]Assessment times (post-administration): FU1=15-30 mins, FU2=1-1.5 hours, FU3=3.25-3.5 hours, FU4=5.25-5.5 hours; [g]p<0.025 considered statistically significant in this study; [h]Assessment times (post-administration): FU1=10 mins, FU2=30 mins, FU3=1 hour, FU4=1.5 hours, FU5=2 hours, FU6=3 hours, FU7=4 hours, FU8=5 hours, FU9=6 hours, FU10=8 hours; outcome is taken at FU time in which effects peaked for that outcome; [i]p<0.025 considered statistically significant in this study; [j]Assessment times (post-administration): FU1=immediately, FU2=1 hour, FU3=2 hours, FU4=3 hours, FU5=4 hours, FU6=5 hours, FU7=6 hours, FU8=8 hours; however, FU3 used as the cut-off time for calculating peak outcome effect. **Abbreviations:** BL = Baseline; DAT = Divided Attention Task; DEQ = Drug Effects Questionnaire; DRM = Deese-Roediger-McDermott false memory paradigm; DSST = Digital Symbol Substitution Task; DRUID = DRiving Under the Influence of Drugs; FU = Follow-up; ISLT = International Shopping List Task; NIH = National Institutes of Health; PASAT = PAced Serial Addition Task; SD = Standard Deviation; SE = Standard Error. **Cannabis potency category definitions:** Can-Low = ≤10% THC flower; Can-Mid = 10-19% THC flower; Can-High = ≥20% THC flower; Res = hashish, resin, kief, assumed to have 20-50% THC; Con = Concentrated cannabis product, assumed to have 60-99% THC; Can-Mix = Cannabis of unspecified or multiple potency categories, but estimated to be lower than the higher potency exposure from that study.

ST4. Summary of secondary findings: Therapeutic health outcomes

Author(s), year	Study design, location, period	Sample characteristics	Cannabis use		Outcome measure, method of assessment	Summary of findings	Quality / RoB
			Measure, method of assessment	Relevant potencies compared			
Cannabis use disorder (including indicators or consequences)							
Cuttler et al., 2020	Naturalistic (between-subjects comparison of pre-post exposure, observational), Canada, 2017-2018	People who use cannabis for headaches: n = 1306 (12293 "sessions"); female = 62%; mean age = 34	Type of cannabis inhaled during use session, self-reported	Con vs. Can-Mix	Headache symptom severity self-reported via 10-point scale before and up to 4 hours after cannabis administration	Con use associated with significantly greater reduction in headache symptom severity (b=-0.09, p<0.001)	Fair
		People who use cannabis for migraine: n = 653 (7441 "sessions"); female = 65%; mean age = 33			Change in migraine symptom severity, assessed as above	Con use not associated with significant change in migraine symptom severity (b=0.04, p>0.05)	
Li et al., 2019	Naturalistic (between-subjects comparison of pre-post exposure, observational), USA, 2016-2018	People who use cannabis for pain: n = 760 (4603 "sessions"), gender and age not reported	Type of cannabis product inhaled during use session, self-reported	Con vs. Can-Mix; Can-High, Can-Mid vs. Can-Low	Pain[1] severity, self-reported via VAS before and up to 4 hours after cannabis administration	Con use not significantly associated with change in pain symptom severity (b=0.025, p>0.05); Relative to Can-Low, Can-High (b=-0.232, p<0.05) but not Can-Mid (b=-0.138, p>0.05) significantly associated with greater symptom reduction	Poor
Stith et al., 2019[2]	Naturalistic (between-subjects comparison of pre-post exposure, observational), USA, 2016-2018	People who use cannabis for anxiety: n = 211 (371 sessions); gender and age not reported	Type of cannabis inhaled during use session, self-reported	Can-High, Can-Mid vs. Can-Low	Anxiety symptom severity, assessed via VAS before and up to 90 minutes after cannabis administration, self-reported	Non-significant reductions in anxiety symptoms for Can-High (b=-0.466) and Can-Mid (b=-0.212) relative to Can-Low (both p>0.05)	Poor

Stith et al., 2020[2]	Naturalistic (between-subjects comparison of pre-post exposure, observational), USA, 2016-2019	People who use cannabis for anxiety: n = 441 (998 sessions); gender and age not reported	Type of cannabis inhaled during use session, self-reported	Can-High, Can-Mid vs. Can-Low	Anxiety symptom severity, assessed via VAS before and up to 4 hours after cannabis administration, self-reported	Significant reductions in anxiety symptoms for Can-High (*b*=-0.599) and Can-Mid (*b*=-0.618) relative to Can-Low (both $p<0.001$)	Poor
Study-specific notes: [1]Pain was aggregated across 11 reported pain categories including gastrointestinal, musculoskeletal, headache, nerve, other. [2]Stith et al., 2019 and Stith et al., 2020 contain overlapping samples. **Abbreviations:** VAS = Visual Analog Scale. **Cannabis potency category definitions:** Can-Low = ≤10% THC flower; Can-Mid = 10-19% THC flower; Can-High = ≥20% THC flower; Res = hashish, resin, kief, assumed to have 20-50% THC; Con = Concentrated cannabis product, assumed to have 60-99% THC; Can-Mix = Cannabis of unspecified or multiple potency categories, but estimated to be lower than the higher potency exposure from that study.							

SR1. References

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