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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. The authors 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. The authors developed ecologically relevant potency (percent THC) exposure-comparison categories (1%–9%, 10%–19%, 20%–30%, kief/resin [~30%–50%], concentrates [≥60%]) and used a landmark scientific report on cannabis and cannabinoids to determine outcome eligibility. Two reviewers independently conducted article screening and 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 the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) framework.

Results: Of 4,545 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, cardiorespiratory, cancer, and pre- and perinatal outcomes. Policies to curb high-potency cannabis use may be warranted while the evidence base improves.

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, and anxiogenic and psychotic-like symptoms—particularly at high doses) and chronic (e.g., dependence syndrome, respiratory disease, and 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’s documented therapeutic effects, including analgesia, appetite stimulation, and antiemesis (3).

The concentration of THC in cannabis (colloquially known as “potency”) has increased steadily over the past 25 years in the United States and elsewhere (5). Before 2000, the average potency of herbal cannabis seized in the United States was <5% THC (6), whereas the average potency of herbal cannabis is now ~20% in most state-regulated nonmedical 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, and wax [10, 11]), reaching up to 95% THC (12). An estimated

50% of cannabis-using U.S. 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 it 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 nonacute mental health outcomes, including anxiety, depression, psychosis, and cannabis use disorder, and found that higher-potency use was associated with increased risks, but the study defined potency in relative (rather than chemically defined) terms (20). In expanding focus toward 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., potency 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 predefined potency levels and a wide range of acute, nonacute, and therapeutic health outcomes.

METHODS

This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (21; see Table S1 in the online supplement) and was registered at Prospero (CRD42021281470).

Search

We searched Ovid MEDLINE, Embase, APA PsycInfo, Web of Science Core Collection, and Cochrane Library from database inception to May 10, 2023, for peer-reviewed studies examining use of high-potency cannabis (see Table S2 in the online supplement for details on the 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 the online supplement, we developed and prespecified ecologically relevant potency categories for exposure-comparison purposes (1%–9% THC, 10%–19% THC, 20%–30% THC, kief/resin [~30%–50% THC], and 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: nonacute adverse health measures; secondary 1: acute adverse health measures related to the extracted primary outcomes; secondary 2: therapeutic measures) for inclusion in the review.

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 the online supplement) were filtered out; the remaining records were imported into Covidence (Veritas Health Innovation). At this stage, all records underwent screening of titles and abstracts by two independent reviewers, with discrepancies resolved through a 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); reassessment 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 that 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 were 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 and 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 Table S3 in the online supplement), opting for vote counting based on direction of effect estimate (referred to here 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, and 0 for a “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 nonuse 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 observational studies rated as having “poor” quality or experimental studies rated as having “high” risk of bias). 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 the online supplement.

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 selected 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 4,545 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 (see Figure S1 in the online supplement). Most studies (N=25) were conducted in the United States, 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, and “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 nonacute adverse health (i.e., primary) outcome spanning the mental health, “problem” cannabis use, other substance use, and psychosocial domains. Apart from one between-subject 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 subanalyses 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 (see Table S4 in the online supplement). 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 time frame to observe an effect, unreliable or imprecise exposure assessment, and lack of sufficient control for confounding.

Potency categories most often compared among primary outcome studies were concentrates (Con) versus herbal cannabis of any potency (Can-Mix; N=11 [10, 12, 37, 42, 43, 47–51, 55]) and mid-potency herbal cannabis (Can-Mid) versus low-potency herbal cannabis (Can-Low; N=6 [34, 35, 39, 41, 45, 56]). Studies also directly compared Con versus Can-Low (34, 35, 56), Resin (Res) versus Can-Mix (52) or Can-Low (35, 56), and high-potency herbal cannabis (Can-High) versus Can-Low (66). In addition, five studies indirectly compared Can-Mid to Can-Low via a nonuse 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 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 nonacute outcomes—specifically, measures reviewed under the mental health and “problem” cannabis use domains (see Tables S7 and S8 in the online supplement). Six studies were experimental: three were rated at “high” risk of bias and used between-subject naturalistic open-label experimental designs (63–65), and three were rated at different risks of bias depending on outcome—“high” (69), “some concerns” (67, 68), and “low” (69)—and used within-subject placebo-controlled randomized controlled designs (see Table S6 in the online supplement). Three cross-sectional studies (33, 34, 50) rated as “poor” quality (see Table S5 in the online supplement) were also considered. Can-Mid versus Can-Low was the most reported potency comparison in acute outcome studies (N=4 [33, 63, 67, 69], and N=1 study employing indirect comparison via placebo [68]). Other comparisons included Con versus 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) and one as “fair” (36) (see Table S4 in the online supplement). Potency comparisons included Con versus Can-Mix (36, 46), Can-High versus Can-Low (46, 61, 62), and Can-Mid versus Can-Low (46, 61, 62).

Adverse Health Outcomes

Mental health. Thirteen studies assessed the relationship between higher-potency cannabis use and at least one nonacute 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 subcategories under the nonacute mental health domain, certainty in the evidence was rated as “very low” (see Table S6 in the online supplement). This outcome domain also included eight studies of acute outcomes, including anxiety and paranoia (see Table S7 in the online supplement), 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 (see 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 ($r=0.18$, $p<0.001$, and $r=0.15$, $p<0.05$, respectively); depression symptoms did not correlate with frequency of use of either product (60).

We identified seven studies assessing acute anxiety (five experimental [63–65, 68, 69], two cross-sectional [33, 34]; see Table S7 in the online supplement). 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-subject study administering controlled doses of Can-Mid and Can-Low (69) found significantly higher “anxious/nervous” scores after Can-Mid (mean=23.0) relative to Can-Low (mean=5.7; $p<0.016$). The exception was one between-subject naturalistic experiment (63) in which significantly lower tension scores were recorded after ad libitum Con relative to Can-Mix use (mean=0.38 vs. mean=0.60; $p<0.01$). Two studies (one between-subject naturalistic experiment [64], one cross-sectional [50]) assessed cannabis potency in relation to acute mood changes. The cross-sectional study (50) found slightly lower retrospectively reported negative affect for Con relative to Can-Mix (Cohen’s $d=-0.17$; $p=0.003$), and the naturalistic experiment (64) did not show group differences (Con vs. Can-High) in mood ratings after use ($p=0.37$; see Table S7 in the online supplement).

Psychosis. Ten studies examined psychosis (including psychotic disorder [38–41, 54, 57, 58], psychotic symptoms and/or experiences [45, 53], and 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 ($p=0.727$) (see Figure 1). For example, a large multisite case-control study (40) found that use of Can-Mid, but not Can-Low, significantly increased the odds of psychosis relative to no use (adjusted odds ratio=1.6, 95% CI=1.2–2.2).

We reviewed five studies (three experimental [65, 68, 69], two cross-sectional [34, 50]) that reported on an acute (secondary) outcome related to psychosis or psychotic symptoms (e.g., paranoia; see Table S7 in the online supplement). Most found evidence of greater symptomology after higher-potency use. For example, a within-subject placebo-controlled study (69) compared the effects of Can-Mid and Can-Low and recorded significantly higher peak paranoia scores following exposure to Can-Mid relative to Can-Low (mean=17.4 vs. mean=6.8 on a 100-mm visual analog scale; $p<0.016$).

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 Table 2). That study found higher PTSD prevalence among cannabis-using adults who use Con (33%) relative to Can-Mix only (19%), but the difference did not reach statistical significance ($p=0.11$). The other study (54) recorded significantly elevated odds of Con and Res, but not Can-Mix, use among cannabis-using adults who self-reported a PTSD or bipolar disorder diagnosis (54).

High-frequency and “problem” cannabis use. Seventeen studies assessed the relationship between higher-potency cannabis use and at least one nonacute measure of high-frequency cannabis use ($N=10$) or cannabis use disorder and contributing symptoms ($N=12$). These studies are summarized in Table 3. For both subcategories in this domain, certainty in the evidence was rated as “very low” (see Table S6 in the online supplement). This outcome domain also included four studies of acute outcomes, including drug craving and drug liking (see Table S8 in the online supplement), 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 (30) found that high school students who used Con or Can-Mix progressed to significantly more cannabis use days at 6- to 12-month follow-up (adjusted rate ratio=9.42, 95% CI=2.02–35.5, and adjusted rate ratio=2.81, 95% CI=1.78–4.42, respectively), but the estimate for Con was statistically significantly higher than for Can-Mix ($p[\Delta\chi^2]=0.02$).

Cannabis use disorder. Eight studies that assessed cannabis use disorder were included in the quantitative synthesis (10, 12, 35, 45, 47, 48, 51, 55); six of them (10, 12, 35, 45, 47, 51) recorded a “detrimental” direction of association ($p=0.289$) (see Figure 1). The sole “fair” quality study grouped a cross-sectional sample into latent classes based on self-reported use of different cannabis products (see detailed class descriptions in the footnotes to Table 3). Relative to the Can-Low class, cannabis dependence scores were significantly higher in classes characterized by Can-Mid use (b values, 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 cannabis use disorder. For example, in a cohort of young adults, there was a significant positive

association between higher-frequency Con use and cannabis consequences ($b=0.200$, $p<0.05$) (see 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” (see Table S8 in the online supplement). Only one study (65) recorded significantly higher ratings of an acute subjective effect (“drug liking”) with higher-potency cannabis (Con vs. Can-Low).

Use of other substances. We identified eight studies assessing the relationship between higher-potency cannabis use and at least one nonacute measure of other substance use, including alcohol ($N=4$), tobacco ($N=3$), nonmedical use of prescription drugs ($N=3$), and illicit/unregulated drugs ($N=7$). These studies are summarized in Table 4. For all subcategories, certainty in the evidence was rated as “very low” (see Table S6 in the online supplement). We did not identify any studies assessing an acute indicator of other substance use.

Alcohol and tobacco use. 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 ($p=0.625$) (see Figure 1). This study found a higher frequency of binge drinking among undergraduate students who use Con relative to Can-Mix (odds ratio=1.8, 95% CI=1.4–2.3). All three tobacco studies (12, 45, 48) were included in the quantitative synthesis and reported a “detrimental” direction of association ($p=0.250$) (see Figure 1).

Prescription and illicit drug use. Due to overlapping study sample and outcomes measured, two studies that assessed both nonmedical prescription drug use and illicit drug use were combined into one study ([42]+[43]) for quantitative synthesis. The resulting quantitative analyses included two studies for nonmedical 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 that was excluded from quantitative analysis (32) found significantly elevated odds of prospective (1-year) illicit drug use initiation for high school students who reported baseline Con (adjusted odds ratio=5.74, 95% CI=3.16–10.43), Con-Vape (adjusted odds ratio=3.11, 95% CI=2.41–4.01), or Can-Mix (adjusted odds ratio=2.57, 95% CI=1.66–4.02) use.

Psychosocial. Only one study was identified for a nonacute psychosocial outcome (49), and it found a significantly higher composite score of “academic failure” for high school students who used Con relative to Can-Mix (2.29 vs. 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 acute psychosocial-cognitive measures, including memory and attention, decision making, psychomotor function, and self-reported cognitive impairment (see Table S9 in the online supplement). In general,

higher-potency cannabis use tended to be associated 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 (69) recorded a significantly higher peak memory impairment mean score after Can-Mid relative to Can-Low (mean=26.7 vs. mean=3.1; $p<0.016$); 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 (see Table S9 in the online supplement). Psychomotor function was assessed in three within-subject experimental studies (67–69). With the exception of a significantly longer “stop” reaction time in the Stop Signal Task recorded after Can-Mid relative to Can-Low in a within-subject 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 (see Table S10 in the online supplement). In a study tracking acute symptom changes during medical cannabis sessions for headache or migraine (36), there were small but significantly greater symptom reductions after Con use relative to Can-Mix ($b=-0.09$, $p<0.001$) for headache but no difference in symptom reductions for migraine ($b=0.04$, $p>0.05$). 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. One of them (62) did not find differences in anxiety symptom reduction relative to Can-Low after Can-High or Can-Mid use (both p values >0.05); the other (61) yielded more observations over a longer eligibility period (~1,000 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 values <0.001).

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 nonacute 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, and shatter) may reveal

additional findings based on differences in amount consumed per occasion with equally potent products (e.g., vape pull: ~4 mg THC vs. dab: ~20 mg 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 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 the online supplement). 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 analysis to higher-quality studies (see the online supplement). Trends observed for nonacute 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, and pre- and perinatal) and 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 individuals who are self-medicating with cannabis and/or are on a trajectory toward cannabis use disorder, 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 two of five (68, 69), three of three (65, 68, 69), and one of three (65) experimental studies, respectively. The evidence base also suffered from imprecise imputation of true potency levels from self-reported product use and high interstudy 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 use 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 found elevated odds of psychosis among individuals who used daily Can-Mid (adjusted odds ratio=4.8) or Can-Low (adjusted odds ratio=2.2) relative to nonusers, 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 and 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 nonacute) and therapeutic outcomes explored through observational and experimental studies. This strength is accompanied by certain limitations. First, while the review was designed to increase public health relevance, its wide scope 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 because 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 and those published in other languages. 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 relationships cannot be deciphered.

While the findings of this review were consistent in only some domains and garnered very-low-certainty evidence overall, until the evidence base matures, cautious policy 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), highlighting the need for improved quality control oversight. On a larger scale, regulatory measures that sway consumers toward lower-THC products may effectively address this issue from both a public health and an 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, or at 30%, as implemented in Connecticut) or dose (e.g., 10 mg per edible package, as implemented in Canada); or taxing cannabis based on THC potency (as implemented in Canada, Illinois, and Connecticut) (81). Ultimately, decisions about regulating or banning high-potency cannabis products will depend on the values and perspectives of the policy 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.

In summary, 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 policy makers may consider implementing behavioral or structural interventions aimed at minimizing use of higher-potency products while the evidence base matures.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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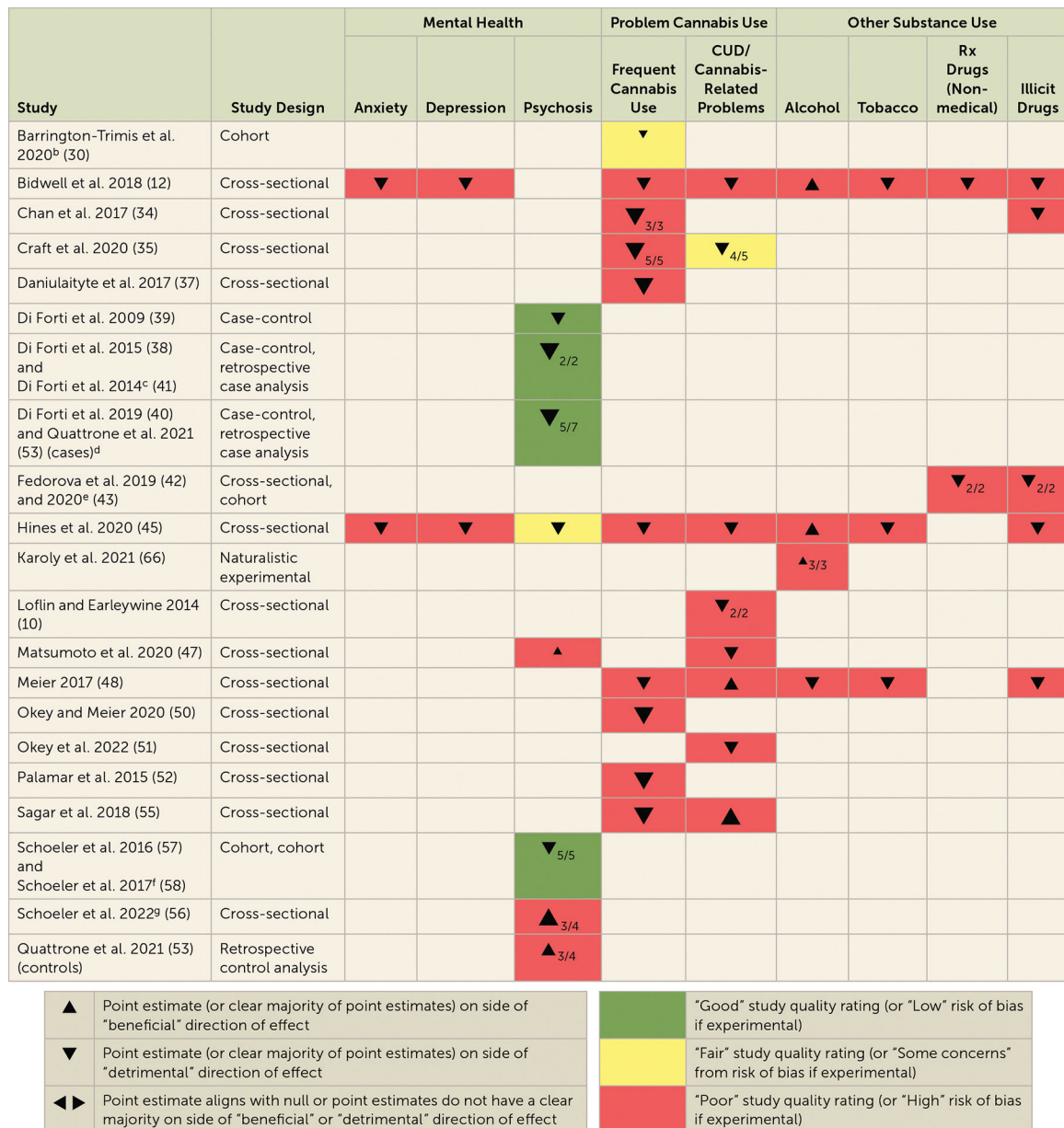


FIGURE 1. Association direction plot for all primary outcomes eligible for quantitative synthesis^a

^a 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 direction of the arrow (numerator). Arrow size denotes the sample size of the high-potency group(s); a large arrow indicates a sample >300, a medium arrow, 50–300, and a small arrow <50. The footnotes below contain study-specific information.

^b Barrington-Trimis et al. 2020 (30): The effect measure contributing to the plot was derived from the authors' post hoc comparison of strength of estimate for concentrates and combustibles.

^c Di Forti et al. 2014 (41): This is a subanalysis of cases from Di Forti et al. 2015 (38); 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.

^d Quattrone et al. 2021 (53) (cases): This study includes a subanalysis of cases from Di Forti et al. 2019 (40); as Di Forti et al. measured psychosis and Quattrone et al. 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.

^e Fedorova et al. 2019 and 2020 (42, 43): These findings were considered together as they contain overlapping samples from the same seed study and provide measures for the same primary outcome subdomains.

^f Schoeler et al. 2017 (58): The findings with respect to psychosis were combined with Schoeler et al. 2016 (57), as Schoeler et al. 2017 included an additional measure related to psychosis (medication adherence) in the same sample as in Schoeler et al. 2016.

^g Schoeler et al. 2022 (56): The arrow size corresponds with the sample size of the intervention group ($N > 300$) for three high-/low-potency comparison estimates for the study's primary outcome (cannabis-associated psychotic symptoms requiring emergency department visit); the reviewed findings also include a subanalysis outcome (cannabis-associated psychotic symptoms requiring hospitalization) for which the size of intervention group was < 50 .

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 follows: concentrate (Con: ≥60% THC [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 two or more 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, as 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: Nonacute adverse health-related measures, defined as conditions or symptoms occurring or persisting beyond the drug’s acute effects. Eligible nonacute adverse outcomes were those that could be classified according to the NASEM ^a 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 experimental studies assessing acute effects of higher-potency cannabis or from observational studies comparing retrospective recall of acute subjective drug effects. To supplement the primary findings, we included only 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. ^b
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, case reports, and case series were excluded.

^aThe NASEM review refers to the National Academies of Sciences, Engineering, and Medicine report on the health effects of cannabis (3). As per the NASEM review, nonacute adverse outcomes were categorized as follows: cancer; cardiometabolic risk; respiratory disease; immunity; injury and death; prenatal, perinatal, and neonatal outcomes; psychosocial; mental health; problem cannabis use (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 (we broadened this subdomain to include measures related to any other non-cannabis substance use and removed “problematic” from its descriptor).

^bTherapeutic outcomes were categorized as chronic pain; cancer; chemotherapy-induced nausea and vomiting; anorexia and weight loss; irritable bowel syndrome; epilepsy; spasticity associated with multiple sclerosis or spinal cord injury; Tourette’s syndrome; amyotrophic lateral sclerosis; Huntington’s disease; Parkinson’s disease; dystonia; dementia; glaucoma; traumatic brain injury/intracranial hemorrhage; addiction; anxiety; depression; sleep disorders; post-traumatic stress disorder; and schizophrenia and other psychosis.

TABLE 2.

Summary of findings for nonacute adverse outcomes: mental health^a

Authors, Year, Reference	Study Design, Location, Period	Sample Characteristics	Exposure		Outcome	QA/R oB	
			Measure, Method of Assessment	Relevant Potencies Compared			
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), $p=0.05^b$, Cohen's $d=0.34$	Poor
Hines et al. 2020 (45)	Cross-sectional, UK, 2015–2017	Young adults who use cannabis: N=1,087; 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, 95% CI=1.11–3.32, $p=0.02$)	Poor
Rup et al. 2021 (54)	Cross-sectional, Canada and USA, 2018	Subset who use cannabis (N=6,413) from a sample of adolescents and adults: full N=25,747; 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, 95% CI=1.31–1.75; Con-Vape, 1.45, 95% CI=1.26–1.67; Res, 1.23, 95% CI=1.08–1.42; Can-Mix, 1.20, 95% CI=1.05–1.38; all p values <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 ^c 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=1,087; 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, 95% CI=0.68–2.32, $p=0.44$)	Poor
Rup et al. 2021 (54)	Cross-sectional, Canada and USA, 2018	Subset who use cannabis (N=6,413) from a sample of adolescents and adults: full N=25,747; 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 dysythymia), past year, self-reported	Depression significantly associated with use of all products (AORs in descending point estimate: Con, 1.69, 95% CI=1.46–1.95; Can-Mix, 1.42, 95% CI=1.23–1.64; Res, 1.37, 95% CI=1.20–1.47; Con-Vape, 1.25, 95% CI=1.11–1.42; all p values <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,	Con ^c and Can-Mix, per	Depression, past week, self-reported via BDI	Depression symptoms did not correlate significantly with frequency of Con use	Fair

Authors, Year, Reference	Study Design, Location, Period	Sample Characteristics	Exposure		Outcome		QA/R oB
			Measure, Method of Assessment	Relevant Potencies Compared	Measure, Method of Assessment	Summary of Findings	
			past month, self-reported	increasing frequency on continuous scale		(r=0.09, p>0.05) or Can-Mix use (r=0.10, p>0.05)	
Psychosis							
Di Forti et al. 2009 ^d (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, 95% CI=2.6–25.4, p<0.05)	Good
Di Forti et al. 2014 ^d (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 (<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, 95% CI=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, 95% CI=1.50–2.65, p<0.001; AHR=1.48, 95% CI=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 ^d (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, 95% CI=1.52–3.60, p=0.001 but not p=0.9); daily Can-Mid conferred the highest odds of psychosis (AOR=5.40, 95% CI=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 ^e (40)	Case-control, multinational, 2010–2015	Adults with psychosis (N=901) and healthy controls (N=1,237); full N=2,138; 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, 95% CI=1.2–2.2, p=0.003) but not Can-Low (AOR=1.1, 95% CI=0.9–1.5, p=0.380); daily Can-Mid conferred the highest odds of psychosis (AOR=4.8, 95% CI=2.5–6.3), followed by daily Can-Low (AOR=2.2, 95% CI=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=1,087; non-cannabis: N=1,087; 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	Can-Mid not significantly associated with psychotic experiences (AOR=1.29, 95% CI=0.67–2.50, p=0.45)	Fair

Authors, Year, Reference	Study Design, Location, Period	Sample Characteristics	Exposure		Outcome		QA/R oB
			Measure, Method of Assessment	Relevant Potencies Compared	Measure, Method of Assessment	Summary of Findings	
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	via semistructured interview 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, 95% CI=0.02–0.56, p=0.007)	Poor
Rup et al. 2021 (54)	Cross-sectional, Canada and USA, 2018	Subset who use cannabis (N=6,413) from a sample of adolescents and adults: full N=25,747; 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)	Psychotic disorder (including schizophrenia), past year, self-reported	Psychotic disorder significantly associated with Con (AOR=1.71, 95% CI=1.18–2.47) and Res (AOR=1.62, 95% CI=1.34–2.32; both p values <0.05) but not Con-Vape (AOR=1.31, 95% CI=0.93–1.84) or Can-Mix (AOR=0.89, 95% CI=0.59–1.33)	Poor
Schoeler et al. 2016 ^f (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 use (no current use)	Psychosis relapse requiring hospital admission, within 2 years of psychosis onset, assessed via clinical records Number of psychosis relapses, assessed as above Length of relapse (cumulative time spent in hospital), assessed as above Time to first psychosis relapse, assessed as above	Can-Mid (daily) group had significantly higher odds of relapse relative to former cannabis use group (AOR=3.28, 95% CI=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. [57] for all estimates) No significant association with any cannabis use group (p>0.05), including Can-Mid (daily) use (AIRR=1.77, 95% CI=0.96–3.25, p=0.07; see Table 3 in Schoeler et al. [57] for all estimates) No significant association with any cannabis use group (p>0.05), including Can-Mid (daily) use (b=0.61, 95% CI=-0.31–1.55, p=0.17; see Table 3 in Schoeler et al. [57] for all estimates) Can-Mid (daily) use group had significantly shorter time to first relapse relative to former cannabis use group (b=-0.22, 95% CI=-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. [57] for all estimates)	Good
Schoeler et al. 2017 ^f (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 nonadherence (AOR=5.26, 95% CI=1.91–15.68, p=0.002); no significant association for continued Can-Low (AOR=1.50, 95% CI=0.28–9.22, p=0.64)	Good
Schoeler et al. 2022 (56)	Cross-sectional, multinational, 2014–2019	Subset with data on cannabis-associated psychotic symptoms	Type of cannabis most often used,	Con ^c , Res, Can-Mid vs. Can-Low	CAPS requiring emergency medical treatment, past year,	Relative to Can-Low, Res was significantly associated with CAPS (RR=2.11, 95% CI=1.53–2.90, adj. p<0.001); no significant	Poor

Authors, Year, Reference	Study Design, Location, Period	Exposure			Outcome	QA/R oB
		Sample Characteristics	Measure, Method of Assessment	Relevant Potencies Compared		
Quattrone et al. 2021 ^e (53)	Separate analysis of cases and controls from case-control study, multinational, 2010–2015	(CAPS) (N=148,109) from a sample of adults who use cannabis: full N=233,475; non-male, 28%; age, majority (58%) ≤25 years Subset who experienced CAPS (N=277) from above subsample	past year, self-reported	Can-Mid vs. Can-Low	self-reported Hospitalized due to CAPS, past year, self-reported	associations for Con (RR=0.39, 95% CI=0.10–1.59) or Can-Mid (RR = 0.96, 95% CI=0.73–1.26; both adj. p values, 1.00) No difference in percent hospitalized between those who used Can-Mid (36.6%) versus Can-Low (38.1%) before CAPS (p=0.82)
		Adults with psychosis: N=901; non-male, 38%; mean age, 31 Healthy community controls: N=1,325; non-male, 53%; mean age, 36	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 Psychotic-like experiences, current, self-reported via CAPE	Relative to no use, no significant association with overall psychosis factor for Can-Mid (b=0.02, 95% CI=-0.12–0.17, p>0.05) or Can-Low (b=0.06, 95% CI=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. [53] for all estimates) 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. [53] 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 defined), self-reported	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)
Rup et al. 2021 (54)	Cross-sectional, Canada and USA, 2018	Subset who use cannabis (N=6,413) from a sample of adolescents and adults: full N=25,747; 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 Bipolar disorder or mania, past year, self-reported	PTSD significantly associated with Con (AOR=1.43, 95% CI=1.15–1.78), Res (AOR=1.45, 95% CI=1.18–1.78), and Con-Vape (AOR=1.37, 95% CI=1.14–1.66, all p values <0.05) but not Can-Mix (AOR=1.16, 95% CI=0.92–1.48) Bipolar disorder or mania significantly associated with Con (AOR=1.63, 95% CI=1.26–2.10) and Res (AOR=1.69, 95% CI=1.25–2.28) (both p values <0.05) but not

Authors, Year, Reference	Study Design, Location, Period	Exposure			Outcome		QA/RoB
		Sample Characteristics	Measure, Method of Assessment	Relevant Potencies Compared	Measure, Method of Assessment	Summary of Findings	
						Con-Vape (AOR=1.06, 95% CI=0.84–1.34) or Can-Mix (AOR=1.17, 95% CI=0.86–1.59)	

^aWhen a study reported only the percentage of males in their sample, we report the remaining percentage as "non-male" to be inclusive of female, non-binary, and other gender identities. AHR=adjusted hazard ratio; AIRR=adjusted incidence rate ratio; AOR=adjusted odds ratio; BAI=Beck Anxiety Inventory; BDI=Beck Depression Inventory; CAPE=Community Assessment of Psychic Experiences; CAPS=cannabis-associated psychotic symptoms; CIS-R=Clinical Interview Schedule-Revised; HR=hazard ratio; IRR=incidence rate ratio; OCD=obsessive-compulsive disorder; OPCRIT=operational criteria; OR=odds ratio; QA=quality assessment; RoB=risk of bias; RR=risk ratio; PTSD=posttraumatic stress disorder; SCAN=Schedules for Clinical Assessment of Neuropsychiatry. Cannabis potency category definitions: Can-Low= $\leq 10\%$ THC flower; Can-Mid= $10\% - 19\%$ THC flower; Can-High= $\geq 20\%$ 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.

^bBidwell et al. (12) did not consider this comparison statistically significant with alpha set at 0.01 for 52 pairwise comparisons.

^cThis group likely included Con-Vape via "hash oil" or "oil" use.

^dDi Forti et al. 2009, 2014, and 2015 (38, 39, 41) contain overlapping samples from the Genetics and Psychosis (GAP) study, including 100% case overlap between Di Forti et al. 2014 and 2015 (38, 41).

^eDi Forti et al. 2019 (40) and Quattrone et al. 2021 (53) contain overlapping samples from the European Network of National Schizophrenia Network Studying Gene-Environment Interactions (EU-GENI) study, including 100% case overlap.

^fSchoeler et al. 2016 and 2017 (57, 58) contain samples with close to 100% overlap.

TABLE 3.
Summary of findings for nonacute adverse outcomes: high-frequency and “problem” cannabis use^a

Authors, Year, Reference	Study Design, Location, Period	Sample Characteristics	Exposure		Outcome	QA/ RoB
			Measure, Method of Assessment	Relevant Potencies Compared		
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=2,685; 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 follow-up, self-reported	Fair Con and Can-Mix significantly associated with progression of use (ARRs: Con=9.42, 95% CI=2.02–35.50; Can-Mix=2.81, 95% CI=1.78–4.42; ARR for Con > ARR for Can-Mix (p [$\Delta\chi^2$]=0.02)
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	Poor 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
Chan et al. 2017 (34)	Cross-sectional, multinational, 2015–2016	Young adults and adults (≥ 16 years) who use cannabis: N=83,867; female, 29%; mean age, 26	Type of cannabis used, past year, self-reported Latent class membership ^b defined by type(s) of cannabis products 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	Poor Significant between-group differences in % reporting daily use, with Con (20.0%) > Can-Mid (10.8%) > Can-Low (5.2%), $\chi^2=1387$, p<0.001
Craft et al. 2020 (35)	Cross-sectional study, multinational, 2017–2018	Young adults and adults (≥ 16 years) who use cannabis: N=55,242; female, 28%; mean age, 25	Con ^c class 1, Con ^c class 2, Res (hash) class, Can-Mid class 1, Can-Mid class 2 vs. Can-Low class (see table footnotes)	Con ^c class 1, Con ^c class 2, Res (hash) class, Can-Mid class 1, Can-Mid class 2 vs. Can-Low class (see table footnotes)	Frequency of cannabis use, past year, self-reported	Poor Frequency of use differed significantly across latent classes ($\chi^2=12909.25$, p<0.001), with $\geq$ 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. [35], for all estimates)
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	Poor Daily cannabis use significantly associated with Con (AOR=4.28, 95% CI=2.69–6.80, p<0.001)
Hines et al. 2020 (45)	Cross-sectional, UK, 2015–2017	Young adults who use cannabis: N=1,087; non-male, 57%; mean age, 24	Type of cannabis used, past year, self-reported	Can-Mid vs. Can-Low	Regular ($\geq$ weekly) cannabis use, past year, self-reported	Poor Significantly higher odds of regular cannabis use for Can-Mid relative to Can-Low (AOR=4.38, 95% CI=2.89–6.63, p<0.001)
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	Poor Odds of Con use increased significantly with frequency of cannabis use (OR=4.1, 95% CI=2.9–5.7, p<0.001)
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	Poor 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, adj. p=0.003)

Authors, Year, Reference	Study Design, Location, Period	Sample Characteristics	Exposure		Outcome		QA/ RoB
			Measure, Method of Assessment	Relevant Potencies Compared	Measure, Method of Assessment	Summary of Findings	
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 ^C Res vs. Can-Mix	Frequency of cannabis use, current, self-reported categories (from 0 [none] to 12 [$\geq$ daily])	Significantly higher frequency of cannabis use in Con/Res group relative to Can-Mix ($=-3.09$, $p=0.002$, Cohen's $d=-0.34$)	Poor
Palamar et al. 2015 (52)	Cross-sectional, USA, 2007–2011	High school seniors who use cannabis: N=2,650; female, 47%; age, majority (55%) ≥ 18 years	Type of cannabis used, past year, self-reported	Res ^C 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 [95% CI=1.30–3.98] for 6–9 times/year to 9.26 [95% CI=5.84–14.69] for >40 times/year; all p values <0.05 ; see Table 4 in Palamar et al. [52] for all estimates)	Poor
Sagar et al. 2018 (55)	Cross-sectional, USA, 2016–2017	Subset of people who use cannabis and dabs (N=1,037) from a sample of adults who use cannabis: full N=4,077; 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 ($\chi^2=7.675$, $p=0.022$)	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 nonmedical purposes: N=155; female, 59%; mean age, 21	Frequency of cannabis product use, past 21 days, self-reported at baseline 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 follow-up, self-reported via CUDIT-R	No significant associations between frequency of use of any product and hazardous cannabis use at follow-up (all p values >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)	Cannabis-related consequences at 6-month follow-up, self-reported via B-MACQ	Frequency of Con significantly positively associated with B-MACQ score at follow-up ($b=0.200$, $p=0.006$); no significant associations between frequency of Con-vape, Can-Mix (bong), Can-Mix (bowl), or Can-Mix (joint) and B-MACQ score at follow-up ($p>0.05$)	Poor
Craft et al. 2020 (35)	Cross-sectional study, multinational, 2017–2018	Young adults and adults (≥ 16 years) who use cannabis: N=55,242; female, 28%; mean age, 25	Latent class membership ^C defined by type(s) of cannabis products used, past year, self-reported	Con ^C class 1, Con ^C class 2, Res (hash) class, Can-Mid class 1, Can-Mid class 2 vs. Can-Low class (see table footnotes)	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); $p=0.02^d$, Cohen's $d=0.43$	Poor

Authors, Year, Reference	Study Design, Location, Period	Sample Characteristics	Exposure		Outcome		QA/ RoB
			Measure, Method of Assessment	Relevant Potencies Compared	Measure, Method of Assessment	Summary of Findings	
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	Relative to Can-Low class, severity of dependence was significantly elevated for Res class (b=0.262, 95% CI=0.188–0.337, p<0.001), Can-Mid classes (class 1: b=0.429, 95% CI=0.350–0.505, p<0.001; class 2: b=0.155, 95% CI=0.100–0.209, p<0.001); no significant association for Can classes (p>0.05; see Table 3 in Craft et al. [35] for all estimates)	Fair
Hines et al. 2020 (45)	Cross-sectional, UK, 2015–2017	Young adults who use cannabis: N=1,087; non-male, 57%; mean age, 24	Type of cannabis used, past year, self-reported	Can-Mid vs. Can-Low	Severity of cannabis dependence, current, self-reported via SDS	Days of Can-Mid use significantly positively associated with SDS score (b=0.096, 95% CI=0.051–0.143, p<0.001); days of Can-Low use not significantly associated with SDS score (herbal: b=0.018, 95% CI=–0.030–0.069, p=0.477; resin: b=0.025, 95% CI=–0.018–0.067, p=0.245)	Fair
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 Cannabis withdrawal after use, self-reported via 4-point Likert scale	Relative to Can-Low, Can-Mid use significantly associated with cannabis use problems (AOR=4.08, 95% CI=1.41–11.81, p=0.009)	Poor
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	Con significantly and positively associated with tolerance (t=12.22, p<0.001, Cohen's d=0.82) Con significantly and positively associated with withdrawal (t=6.18, p<0.001, Cohen's d=0.42)	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	Significantly higher odds of cannabinoid dependence syndrome for Con group relative to Can-Mix (AOR=6.85, 95% CI=1.98–25.15, p=0.004)	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	Con/Res vs. Can-Mix	Negative cannabis-related consequences, past 30 days, self-reported via MACQ	MACQ score for physical dependence domain significantly higher in Con group ($\chi^2=4.6$, 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 [48] for all estimates)	Poor

Authors, Year, Reference	Study Design, Location, Period	Sample Characteristics	Exposure		Outcome		QA/ RoB
			Measure, Method of Assessment not defined), self-reported	Relevant Potencies Compared	Measure, Method of Assessment	Summary of Findings	
Sagar et al. 2018 (55)	Cross-sectional, USA, 2016–2017	Subset of people who use cannabis and dabs (N=1,037) from a sample of adults who use cannabis: full N=4,077; female, 39%; mean age, 44	Type of cannabis used, current (period not defined), self-reported	Con vs. former Con use (i.e., current Can-Mix use)	Cannabis dependence, current, self-reported via SDS	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 blackout ($p>0.05$; see Table 1 in Okey et al. [51] for all estimates)	Poor
Simpson et al. 2021 (59)	Cross-sectional, USA, 2018–2019	Young adults who use cannabis: N=1,007; 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, nonrecreational, moderate, severe), past 12 months, self-reported via CAST	Relative to noncurrent use, semifrequent 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. [59] for all estimates)	Fair
Stieglor 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 ^C and Can-Mix, per increasing frequency on continuous scale	Cannabis dependence, current, self-reported via MDS Cannabis withdrawal after last time used cannabis, self-reported via MWC Cannabis craving, current, self-reported via MCQ	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 ($r=0.16$, $p<0.01$) Withdrawal score was significantly positively correlated with frequency of concentrate use ($r=0.21$, $p<0.01$) and flower use ($r=0.26$, $p<0.01$) Craving score was significantly positively correlated with frequency of concentrate use ($r=0.22$, $p<0.01$) and flower use ($r=0.23$, $p<0.01$)	Fair

^aWhen a study reported only the percentage of males in their sample, we report the remaining percentage as "non-male" to be inclusive of female, non-binary, and other gender identities. AOR=adjusted odds ratio; ARR=adjusted rate ratio; B-MACQ=Brief Marijuana Consequences Questionnaire; CAST=Cannabis Abuse Screening Test; CUD=Cannabis Use Disorder Identification Test-Revised; EMA=ecological momentary assessment; MACQ=Marijuana Consequences Questionnaire; MDS=Marijuana Dependence Scale; MINI=Mini International Neuropsychiatric Interview; MCQ=Marijuana Craving Questionnaire; MWC=Marijuana Withdrawal Checklist; OR=odds ratio; QA=quality assessment; RoB=risk of bias; SDS=Severity of Dependence Scale. Cannabis potency category definitions: Can-Low= $\leq 10\%$ THC flower; Can-Mid= 10% – 19% THC flower; Can-High= $\geq 20\%$ 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.

^b Latent class descriptions from Craft et al. 2020 (35), 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.

^c This group likely included Con-Vape via "hash oil" or "oil" products.

^d Bidwell et al. (12) did not consider this comparison statistically significant with alpha set to 0.01 for 52 pairwise comparisons.

TABLE 4.

Summary of findings for nonacute adverse outcomes: use of other substances^a

Authors, Year, Reference	Study Design, Location, Period	Sample Characteristics	Exposure		Outcome	QA/RoB	
			Measure, Method of Assessment	Relevant Potencies Compared			
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%) and Can-Mix (56.3%), $p=0.64$	Poor
Hines et al. 2020 (45)	Cross-sectional, UK, 2015–2017	Young adults who use cannabis: N=1,087; 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, 95% CI=0.49–1.64, $p=0.73$)	Poor
Karoly et al. 2021 (66)	Between-subject 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 Percent alcohol-cannabis co-use 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 higher percent drinking days ($b=-0.013$, $p=0.600$) Compared to Can-Low, Can-High group did not have higher percent alcohol-cannabis co-use days ($b=-0.037$, $p=0.128$).	High (RoB)
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, 95% CI=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 (period not defined), self-reported	Con (including Con-Vape; ≥ 4 times/week) vs. Can-Mix (any)	Cigarette use, current, self-reported	Prevalence of cigarette use not significantly different between Con group (19.4%) and Can-Mix (17.2%), $p=0.92$	Poor
Hines et al. 2020 (45)	Cross-sectional, UK, 2015–2017	Young adults who use cannabis: N=1,087; 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, 95% CI=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, 95% CI=1.2–2.0, $p=0.001$)	Poor
Prescription drugs (non-medical use)							

Authors, Year, Reference	Study Design, Location, Period	Sample Characteristics	Exposure		Outcome		QA/Ro B
			Measure, Method of Assessment	Relevant Potencies Compared	Measure, Method of Assessment	Summary of Findings	
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 (nonmedical, not as prescribed), current, self-reported	Prevalence of prescription opioid use not significantly different between Con group (14.9%) and Can-Mix (6.3%), $p=0.19$	Poor
Fedorova et al. 2019 ^b (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 ^c 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, 95% CI=0.7–2.2, $p>0.05$)	Poor
Fedorova et al. 2020 ^b (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 follow-ups	Con ^c 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 follow-ups	Higher odds of Con use in the high prescription drug use trajectory group (AOR=2.16, 95% CI=1.49–3.15, $p<0.001$)	Poor
Illicit drugs							
Braymiller et al. 2023 (32)	Prospective cohort, USA, 2016–2017	High school students: N=2,163; 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 follow-up, self-reported	Use of each product significantly increased odds of illicit drug use initiation (AORs in descending point estimate order: Con, 5.74, 95% CI=3.16–10.43; Con-Vape, 3.11, 95% CI=2.41–4.01; Can-Mix, 2.57, 95% CI=1.64–4.02; all p values <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%) and 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=83,867; 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, 95% CI=1.25–1.31; AOR vs. Can-Low, 1.66, 95% CI=1.63–1.70) and Can-Mid use (AOR vs. Can-Low, 1.30, 95% CI=1.28–1.32; all p values <0.05)	Poor
Fedorova et al. 2019 ^b (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 ^c 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, 95% CI=1.6–4.9, $p<0.001$)	Poor

Authors, Year, Reference	Study Design, Location, Period	Sample Characteristics	Exposure		Outcome		QA/RoB
			Measure, Method of Assessment	Relevant Potencies Compared	Measure, Method of Assessment	Summary of Findings	
Fedorova et al. 2020 ^b (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 follow-ups	Con ^c 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 follow-ups	Significantly higher odds of Con use in the high illicit drug use trajectory group (AOR=2.40, 95% CI=1.67–3.44, p<0.001)	Poor
Hines et al. 2020 (45)	Cross-sectional, UK, 2015–2017	Young adults who use cannabis: N=1,087; 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, 95% CI=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, 95% CI=1.5–3.0, p<0.001)	Poor

^aWhen a study reported only the percentage of males in their sample, we report the remaining percentage as “non-male” to be inclusive of female, non-binary, and other gender identities. AOR=adjusted odds ratio; AUD=alcohol use disorder; FTND=Fagerstrom Test for Nicotine Dependence; OR=odds ratio; QA=quality assessment; RoB=risk of bias; TLFB=timeline followback. Cannabis potency category definitions: Can-Low= $\leq 10\%$ THC flower; Can-Mid= 10% – 19% THC flower; Can-High= $\geq 20\%$ 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.

^bFedorova et al. 2019 and 2020 (42, 43) contain overlapping samples obtained from the Cannabis, Health, and Young Adults (CHAYA) project.

^cThis group likely included Con-Vape via “hash oil” or “oil” use.