Association of cannabis potency with mental ill health and addiction: a systematic review

Kat Petrilli, Shelan Ofori, Lindsey Hines, Gemma Taylor, Sally Adams, Tom P Freeman

Cannabis potency, defined as the concentration of Δ⁹-tetrahydrocannabinol (THC), has increased internationally, which could increase the risk of adverse health outcomes for cannabis users. We present, to our knowledge, the first systematic review of the association of cannabis potency with mental health and addiction (PROSPERO, CRD42021226447). We searched Embase, PsycINFO, and MEDLINE (from database inception to Jan 14, 2021). Included studies were observational studies of human participants comparing the association of high-potency cannabis (products with a higher concentration of THC) and low-potency cannabis (products with a lower concentration of THC), as defined by the studies included, with depression, anxiety, psychosis, or cannabis use disorder (CUD). Of 4171 articles screened, 20 met the eligibility criteria: eight studies focused on psychosis, eight on anxiety, seven on depression, and six on CUD. Overall, use of higher potency cannabis, relative to lower potency cannabis, was associated with an increased risk of psychosis and CUD. Evidence varied for depression and anxiety. The association of cannabis potency with CUD and psychosis highlights its relevance in health-care settings, and for public health guidelines and policies on cannabis sales. Standardisation of exposure measures and longitudinal designs are needed to strengthen the evidence of this association.

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Addiction and Mental Health Group, Department of Psychology, University of Bath, Bath, UK (K Petrilli MRes, G Taylor PhD, T P Freeman PhD); **Clinical Psychopharmacology Unit, Clinical Educational and Health Psychology Department, University College London, London, UK** (S Ofori MRes); **Population Health Science, Bristol Medical School, University of Bristol, Bristol, UK** (L Hines PhD); **School of Psychology, University of Birmingham, Birmingham, UK** (S Adams PhD)

Correspondence to:
Mx Kat Petrilli, Department of Psychology, University of Bath, Bath BA2 7AY, UK
kp787@bath.ac.uk

Introduction

Cannabis is the third most commonly used drug globally, after alcohol and nicotine.[1] The cannabis plant produces at least 144 cannabinoids,[2] with the main psychoactive cannabinoid being Δ⁹-tetrahydrocannabinol (THC). Experimental studies show that THC causes intoxication, cognitive impairment, anxiety, and transient psychosis-like experiences.[3] The effects of THC are dose dependent,[4,5] which means that higher potency cannabis products (products with high THC concentrations) could increase the risk of harm to cannabis users.

Understanding the health effects of higher potency cannabis products is timely because THC concentrations in cannabis have increased globally in recent decades.[6] In the USA and Europe, the concentration of THC has more than doubled over the past 10 years, and new legal markets have facilitated the rapid development of cannabis products with higher potencies than earlier products, such as concentrated extracts.[7] For example, in Washington's legal market, both higher potency flower products, with more than 20% THC concentration, and concentrated extracts, with more than 60% THC concentration, have become increasingly prevalent over time. Conversely, market shares for lower potency flower products, with THC concentrations of less than than 15%, have declined significantly.[8]

Cannabis use has consistently been associated with mental health disorders. Heavy cannabis use has been associated with a four-times increased risk of psychosis, and this relationship is dose dependent.[9] Cannabis use has also been associated with increased odds of developing depressive,[10] as well as anxiety[11] disorders. In addition, 22% of people who use cannabis are estimated to meet the criteria for cannabis use disorder (CUD).[12] Because of the dose-response effects of THC on symptoms of acute mental health disorders, the potency of cannabis products could be a key factor determining the health effects of cannabis use. The association of cannabis potency with mental health and addiction has been previously investigated, and substantial evidence exists to support the association.[13–15] However, to date, this evidence has never been systematically reviewed. Understanding the association of cannabis potency with health outcomes is crucial for effectively managing cannabis use in clinical settings, generating evidence-based guidelines for safer use, and informing international cannabis policy to minimise the risk of harm to people who use cannabis. The need to understand the association of cannabis potency with mental health outcomes is especially pressing because of international increases in cannabis potency and the availability of higher potency cannabis products, which have been particularly evident in new legal markets. Therefore, we did, to our knowledge, the first systematic review on the association of cannabis potency with mental ill health and addiction.

Methods

Search strategy and selection criteria

We did this systematic review according to PRISMA guidelines,[16] using MEDLINE (from Jan 1, 1966, to Jan 14, 2021), Embase (Jan 1, 1974, to Jan 14, 2021), and PsycINFO (from Jan 1, 1597, to Jan 14, 2021). Start dates were from database inception in all cases. Our search included terms describing (1) cannabis AND (2) potency, AND (3) mental health or addiction: depression, anxiety, psychosis, or cannabis use disorder (CUD; appendix p 2). Although we did not apply date or language restrictions to our search, we used only English terms. We searched for additional relevant articles in the references lists of identified articles.

We included studies if they met the following inclusion criteria: (a) observational study; (b) provided data on human participants; (c) provided quantitative data on the

See Online for appendix

potency of the cannabis used as a direct or indirect comparison between higher potency cannabis products and lower potency cannabis products (because cannabis exposure was defined according to study-specific criteria rather than absolute values for high-potency or low-potency, it can be interpreted in relative terms—ie, higher *vs* lower potency); (d) provided quantitative data on symptoms, measured by clinical interviews or self-report, diagnosis, or relapse for one or more of the following: depression, anxiety, psychosis, CUD or cannabis dependence, or misuse; and (e) included an association between cannabis potency and the mental health or addiction outcomes mentioned in criterion (d). Conference extracts or abstracts, editorials, or correspondence articles were excluded. We grouped studies for syntheses on the basis of mental health outcomes for depression, anxiety, psychosis, or CUD. We did not include experimental studies because of the need for a real-world exposure to the potency and amount of cannabis used in naturalistic settings.

We retrieved studies using the titles-first strategy[17] with the systematic review management platform Covidence. KP and SO independently identified the articles that met the inclusion criteria outlined (inter-rater agreement 96·2%). Any discrepancies in the studies selected resulted in a title and abstract search by both reviewers (inter-rater agreement 89·9%). KP and SO retrieved and independently assessed the full text of the studies to establish final eligibility (inter-rater agreement 89·9%). Specific exclusion for any studies was reported (appendix p 5). KP, SO, and TPF resolved any disagreements over the eligibility of studies. The protocol was prospectively registered on PROSPERO, CRD42021226447.

Data analysis

A standard Microsoft Excel database was used by KP and SO, independently, for data extraction. Data extraction was cross-checked by KP to ensure accuracy. The key extracted data were: first author, publication year, study context, study population (sex or gender, and age), analysis methods, details of categorisation of cannabis potency in the study, details of mental health and addiction outcomes, details of cannabis use (such as frequency, amount used, age of onset), estimate of the effect and measure of precision of estimate for the association of cannabis potency with mental health or addiction outcomes in fully adjusted models, and information on the covariates adjusted for. For studies with multiple publications, we extracted data from each publication separately and then collated using guidance in the Cochrane handbook.[18] KP and SO independently assessed the risk of bias for each outcome using a modified version of the Newcastle-Ottawa Scale, and discussed any discrepancies with KP, SO, and TPF. We categorised studies as good, fair, or poor quality, according to the scores obtained for each of the domains assessed (appendix p 6).

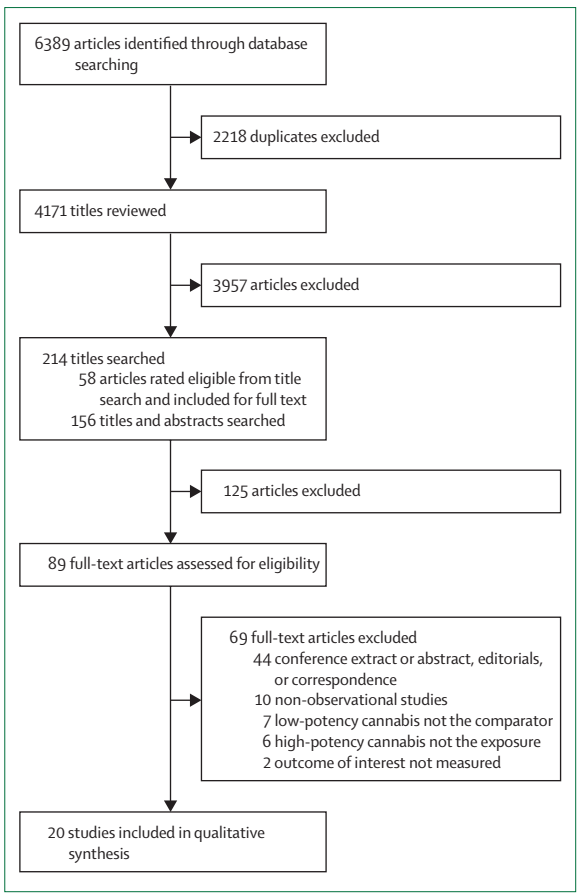

Figure: **PRISMA flowchart outlining the study selection process**

Results

Of the 4171 articles screened, 20 studies with 119 581 participants were selected for inclusion (figure 1). Summary details and risk of bias assessments are summarised in tables 1–4 (further details provided in the appendix p 11). Eight studies investigated psychosis or psychosis-like symptoms, eight investigated anxiety, seven investigated depression, and six investigated CUD.

We found six studies of psychosis, including two case-control studies (Genetics and Psychosis [GAP] study[13,19–21] and the European Network of National Schizophrenia Networks Studying Gene-Environment Interactions [EU-GEI] study[22,23]) published over six articles, one prospective cohort study,[24] and three cross-sectional studies.[15,25,26] Three of the six studies were rated as fair quality[13,19–24] and the other three were rated as poor quality[15,25,26] in the risk of bias assessment (table 1). These ratings represent limitations in the measure of exposure across studies, the outcome measure,[15] the adjustment for confounders,[25,26] and the sample selection[15,25] in the poor quality studies. We also found two cross-sectional studies of psychosis-like symptoms: we rated one study as fair quality[27] because of limitations in the exposure

	Study type	Location and years of study	Participants	Exposure and comparator	Method for collecting exposure	Temporal relationship exposure–outcome	Outcomes	Confounding variables adjusted for	Main findings	Risk of bias rating
Di Forti et al, (2009)[19]; Di Forti et al (2014)[20]; Di Forti et al (2015)[13]; Sideli et al (2018)[21]	Case-control	UK, 2005–10	410 patients with first-episode psychosis (mean age 27·1 years; 34% women, 66% men) and 370 healthy controls (mean age 30·0 years; 44% women, 56% men)	Skunk-type cannabis *vs* hash-type cannabis	Self-reported	Exposure: lifetime; outcome: recent first-episode psychosis	First-episode psychosis: Schedules for Clinical Assessment in Neuropsychiatry and Psychosis Screening Questionnaire	Age, gender, ethnicity, level of education, employment status, number of cigarettes, alcohol units, other drugs used	Three times more likely to have a diagnosis of psychosis (OR 2·91, 95% CI 1·52–3·60), which was not the case for hash-type users (0·83, 0·52–1·77); five times more likely to have a diagnosis of psychosis with daily use (5·40, 2·80–11·30); association with childhood trauma is partially independent of childhood abuse in higher potency cannabis users (2·16, 1·15–4·06); and earlier onset of psychosis of about 4 years (HR 1·68, 95% CI 1·08–2·63)	Fair quality (8)
Di Forti et al (2019)[22]; Quattrone et al (2020)[23]	Case-control	England, France, Netherlands, Italy, Spain, and Brazil; 2010–15	901 patients with first-episode psychosis (mean age 31·2 years; 38·1% women, 61·9% men) and 1237 controls (mean age 36·0 years; 53% women, 47% men)	Cannabis types with THC ≥10% *vs* cannabis types with THC <10%	Self-reported	Exposure: lifetime use; outcome: recent first-episode psychosis	First-episode Psychosis: ICD-10	Age, gender, ethnicity, level of education, employment status, use of tobacco, alcohol, other drugs	Slight increase in risk of psychosis for higher potency cannabis use (OR 1·6, 95% CI 1·2 to 2·2), but not for lower potency cannabis use (1·1, 0·9 to 1·5); daily use, almost five-times increased risk for people who use higher potency cannabis (4·8, 2·5 to 6·3) and two-times increased risk for people who use lower potency cannabis (2·2, 1·4 to 3·6); and more likely to experience positive symptoms when using higher potency cannabis compared with no cannabis use (b 0·22, 95% CI 0·02 to 0·29); not present in participants using lower potency cannabis compared with no cannabis use (0·09, –0·12 to 0·28)	Fair quality (8)

(Table 1 continues on next page)

	Study type	Location and years of study	Participants	Exposure and comparator	Method for collecting exposure	Temporal relationship exposure–outcome	Outcomes	Confounding variables adjusted for	Main findings	Risk of bias rating
(Continued from previous page)										
Schoeler et al (2016)[24]	Prospective cohort	UK, 2002–15	256 patients with psychosis (age NS; 39% women, 61% men)	Skunk-like cannabis *vs* hash-like cannabis	Self-reported	Exposure: two years after onset of psychosis; outcome: within 2 years of onset of psychosis	Psychosis relapse: admission to psychiatric inpatient ward	Alcohol use, other illicit drug use, cigarette use, care intensity at onset, and medication adherence	Daily use, three-times increased risk of relapse in people who continued to use higher potency cannabis (OR 3·28, 95% CI 1·22–9·18) compared with people who continued to use lower potency cannabis (1·82, 0·36–8·75)	Fair quality (8)
Chan et al (2017)[15]	Cross-sectional	20 countries; 2015–16	181 870 participants of annual drug survey (mean age of people who use butane hash oil 25·68 years; 19·49% women, 79·85% men, 0·66% transgender; HI-POT mean age 25·80 years; 24·91% women, 74·63% men, 0·46% transgender; CANN mean age 27·61 years; 39·69% women, 59·84% men, 0·47% transgender)	Butane hash oil *vs* HI-POT; butane hash oil *vs* CANN; and HI-POT *vs* CANN	Self-reported with pictorial aids	Exposure: past 12 months; outcome: lifetime diagnosis	Psychosis: self-report lifetime diagnosis	Age, gender, sexual orientation, education level, other substance use	Increased risk of diagnosis of psychosis in HI-POT compared with CANN (OR 1·28, 95% CI 1·07–1·53); and no difference in risk between HI-POT and butane hash oil (0·89, 0·69–1·09) or butane hash oil and CANN (1·11, 0·85–1·46)	Poor quality (3)
Prince et al (2019)[25]	Cross-sectional	USA; years NS	156 people who use cannabis (mean age 30·4 years; 52·1% female; 47·9% male)	Cannabis concentrate *vs* herbal cannabis	Self-reported and optional photo upload (legal status)	Exposure: current use; outcome: past 2 weeks	Psychosis symptoms: DSM-5 Cross-Cutting Symptom Measure—adult	NA	No association with higher potency concentrate use (r 0·11, 95% CI –0·20 to 0·40); and fewer symptoms of psychosis with higher potency herbal cannabis (–0·27, –0·45 to –0·06)	Poor quality (3)

(Table 1 continues on next page)

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measure, and the other study as poor quality[28] because of additional limitations in measures of outcome, sample selection, and adjustment for confounders.

Risk of psychosis diagnosis was assessed in four studies. Overall, the studies reported increased risk of psychosis with use of higher potency cannabis compared with lower potency cannabis. The GAP study[13,19–21] included participants with first-episode psychosis and a control group from the same geographical area who did not meet the criteria for current or previous psychotic disorder. In a preliminary analysis (n=454), patients with first-episode psychosis were more likely to use higher potency cannabis than the control groups (adjusted odds ratio [aOR] 6·8, 95% CI 2·6–25·4).[19] These findings on the incidence of first-episode psychosis were further investigated in a second article that included analysis of the full sample (n=780).[13] People who used higher potency cannabis were three times more likely to have first-episode psychosis compared with people who had never used cannabis (aOR 2·91, 1·52–3·60). In contrast, use of lower potency cannabis was not associated with increased risk of psychosis compared with never-use (0·83, 0·52–1·77).[13] When taking into consideration cannabis potency and the frequency of use as a composite variable, people who used higher potency cannabis daily were five times more likely to be diagnosed with a psychotic disorder compared with those who never used cannabis (5·40, 2·80–11·30). Conversely, daily use of lower potency cannabis was not associated with risk of psychotic disorder compared with people who never used cannabis.[13] This study also found that the association between higher potency cannabis and psychosis is partially independent of the occurrence of childhood trauma,[21] which is a common risk factor for the development of psychosis.

The national results from the UK GAP study[13,19,21] were replicated by the multinational EU-GEI case-control study in Europe and Brazil (n=2138).[22] The study included patients with first-episode psychosis within 17 catchment areas and a sample of control participants representative of the catchment area's population at risk with regards to age, gender, and ethnicity. After adjusting for daily use of cannabis, use of higher potency cannabis was associated with a modest increase in the risk of psychotic disorder compared with never-use (aOR 1·6, 95% CI 1·2–2·2), whereas lower potency cannabis use was not associated with a risk of psychosis (1·1, 0·9–1·5).[22] Similarly, daily use of higher potency cannabis had a five-times increased odds of psychosis compared with never use (4·8, 2·5–6·3), whereas people using lower potency cannabis had two-times higher odds of psychosis (2·2, 1·4–3·6) compared with never-users.[22]

Cross-sectionally, in an online survey of people who use drugs in 20 countries (typically high-income countries; n=181 870), people who use higher potency herbal cannabis showed an increased risk of lifetime diagnosis of psychosis compared with people who use lower potency cannabis (odds ratio [OR] 1·28, 95% CI

	Study type	Location and years of study	Participants	Exposure and comparator	Method for collecting exposure	Temporal relationship exposure–outcome	Outcomes	Confounding variables adjusted for	Main findings	Risk of bias rating
(Continued from previous page)										
Matsumoto et al (2020)[26]	Cross-sectional	Japan; years NS	71 adults with mental health and behavioural disorders due to use of cannabinoids (mean age 35·1 years; 16·9% female, 83·1% male)	Liquid or resin cannabis vs dry or herbal cannabis	Self-reported	Exposure: NS; outcome: current diagnosis	Chronic psychosis: clinical interview ICD-10	..	No association with chronic psychosis (OR 0·212, 95% CI 0·061 to 0·735)	Poor quality (3)
Hines et al (2020)[27]	Cross-sectional	UK, 2015–17	1087 people who used cannabis in the past year (mean age 24 years; 42·5% female; 57·5% male)	Higher potency cannabis (typically ≥10% THC; skunk or other stronger types of herbal cannabis) vs lower potency cannabis (typically <10% THC; herbal cannabis or marijuana, hashish or resin or solid, or other)	Self-reported	Exposure: past 12 months; outcome: past 12 months	Psychosis-like symptoms: psychosis-like symptoms semi-structured interview	Sex and childhood socioeconomic position, psychotic experiences at age 12 years, cannabis use frequency	No association with psychosis-like experiences (OR 1·29, 95% CI 0·67–2·50)	Fair quality (6)
Okey et al (2020)[28]	Cross-sectional	USA, years NS	574 people who used cannabis in the past year (mean age 32·2 years; 44·6% female, 55·4% male)	Cannabis concentrate vs herbal cannabis	Self-reported with pictorial aids	Exposure: lifetime use; outcome: NS	Psychosis-like symptoms: self-report measure (scale)	..	Fewer psychosis-like experiences, but difference was small (herbal mean 1·2; cannabis concentrates mean 1·1; Cohen's d 0·12, 95% CI NS)	Poor quality (1)

b=unstandardised regression coefficient. CANN=lower potency herbal cannabis use with no butane hash oil use. HI-POT=higher potency herbal cannabis use with no butane hash oil use.

Table 1: **Summary of study characteristics and findings, psychosis**

	Study type	Location and years of study	Participants	Exposure and comparator	Method for collecting exposure	Temporal relationship exposure–outcome	Outcomes	Confounding variables adjusted for	Main findings	Risk of bias rating
Freeman et al (2015)[14]	Cross-sectional	UK, 2009–10	2514 participants of an annual drug survey (mean age 24·25 years; 29·8% women, 70·2% men)	Skunk cannabis *vs* grass and resin cannabis	Self-reported	Exposure: past 12 months; outcome: last month	Severity of Dependence Scale	Gender and age	Frequent use of higher potency cannabis predicted a greater severity of dependence (b 0·254, 95% CI 0·161 to 0·357); use of lower potency cannabis was not associated with dependence (grass 0·020, −0·029 to 0·070; resin 0·025, −0·019 to 0·067)	Poor quality (4)
Prince et al (2019)[25]	Cross-sectional	USA; years NS	156 people who use cannabis (mean age 30·4 years; 52·1% female; 47·9% male)	Cannabis concentrates *vs* herbal cannabis	Self-reported and optional photo upload (legal status)	Exposure: current use; outcome: past month	Self-report questionnaire	..	No association with use of higher potency herbal use (*r* 0·09, 95% CI −0·12 to 0·30); fewer symptoms of cannabis use disorder with higher potency concentrate use (−0·05, −0·35 to −0·26)	Poor quality (2)
Matsumoto et al (2020)[26]	Cross-sectional	Japan; years NS	71 adults with mental health and behavioural disorders due to use of cannabinoids (mean age 35·1 years; 16·9% female, 83·1% male)	Liquid or resin cannabis *vs* dry or herbal cannabis	Self-reported	Exposure: NS; outcome: current diagnosis	Clinical interview ICD-10	..	Seven-times increased risk of dependence syndrome (OR 6·850, 95% CI 1·866–25·145)	Poor quality (3)
Hines et al (2020)[27]	Cross-sectional	UK; 2015–17	1087 people who used cannabis in the past year (mean age 24 years; 42·5% female, 57·5% male)	Higher potency cannabis (typically ≥10% THC; skunk or other stronger types of herbal cannabis) *vs* lower potency cannabis (typically <10% THC; herbal cannabis or marijuana, hashish or resin or solid, or other)	Self-reported	Exposure: past 12 months; outcome: past 12 months	Cannabis Abuse Screening Test	Sex, childhood socioeconomic position, age at onset of cannabis use, cannabis use frequency	Four times more likely to report recent cannabis use problems (OR 4·08, 95% CI 1·41–11·81)	Fair quality (6)
Bidwell et al (2018)[29]	Cross-sectional	USA; 2017	191 people who use cannabis. People who frequently use cannabis concentrates (mean age 37·5 years; 40·3% female, 59·7% male); people who frequently use herbal cannabis (mean age 46·9 years; 51·7% female, 48·3% male)	People who frequently use cannabis concentrate *vs* people who frequently use herbal cannabis	Self-reported	Exposure: NS; outcome: current diagnosis	MINI cannabis screening test	..	People who frequently use cannabis concentrate (mean 2·1) did not endorse significantly more symptoms of cannabis use disorder compared with people who frequently use herbal cannabis (mean 1·3), 95% CI NS	Poor quality (1)

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	Study type	Location and years of study	Participants	Exposure and comparator	Method for collecting exposure	Temporal relationship exposure–outcome	Outcomes	Confounding variables adjusted for	Main findings	Risk of bias rating
(Continued from previous page)										
Craft 2020[20]	Cross-sectional	175 countries; 2017–18	55 240 participants of an annual drug survey (mean age 25·03 years; 27·7% women, 71·2% men, 1·1% other)	Sinsemilla and herbal; hashish and herbal cannabis vs herbal cannabis	Self-reported with pictorial aids	Exposure: past 12 months; outcome: last month	Severity of Dependence Scale	Age, gender, amount of cannabis use, frequency of cannabis use and whether participants added tobacco when preparing their cannabis	Greater severity of dependence in the higher potency cannabis classes (sinsemilla and herbal b 0·155, 95% CI 0·100 to 0·209; hashish and herbal 0·262, 0·188–0·337)	Poor quality (4)

b=unstandardised regression coefficient.

Table 2: **Summary of study characteristics and findings, cannabis use disorder**

1·07–1·53). However, the association with psychosis was not found when comparing people who use butane hash oil, a higher potency product than herbal cannabis, to people who use lower potency cannabis.[15] This study has limitations in the outcome measure, which relies on self-reported lifetime diagnosis, and low rates of psychosis in the sample. Another study, which had limitations of heterogeneity in measures of cannabis-related psychosis and a small sample size (n=71), found that people who used higher potency cannabis were less likely to report residual and late onset psychotic disorder compared with people who used lower potency cannabis (OR 0·212, 95% CI 0·061–0·735).[26]

Two studies examined the symptoms of psychosis. In a sample of patients with first-episode psychosis (n=901), use of higher potency cannabis was associated with an increase in positive symptoms compared with people who did not use cannabis (standardised regression coefficient [β] 0·22, 95% CI 0·02 to 0·29) whereas this relationship was not found when comparing lower potency cannabis use with no cannabis use (0·09, –0·12 to 0·28).[23] In a cross-sectional study of herbal cannabis and cannabis concentrate use in healthy participants (n=156), symptoms of psychosis were not associated with use of higher potency concentrates (correlation coefficient *[r]* 0·11, 95% CI –0·20 to 0·40), whereas the use of higher potency herbal cannabis was associated with fewer symptoms of psychosis (–0·27, –0·45 to –0·06).[25]

The use of higher potency cannabis was also associated with an earlier onset of psychotic disorder than the use of lower potency cannabis in an article that included data from the GAP case-control study.[20] After adjusting for gender and the frequency of use, people who used higher potency cannabis had a significantly earlier onset of psychosis, by approximately 4 years (hazard ratio [HR] 1·68, 95% CI 1·08–2·63) compared with people who used lower potency cannabis.[20]

In a prospective cohort study (n=256), daily use of higher potency cannabis was associated with risk of relapse in the first 2 years after the onset of psychosis.[24] 58% of participants who used higher potency cannabis daily relapsed compared with 24% of people who used to use cannabis (aOR 3·28, 95% CI 1·22–9·18). The risk of relapse for the use of lower potency cannabis or infrequent higher potency cannabis use was not increased when compared with people who formerly used cannabis (aOR 1·82, 95% CI 0·36–8·75).[24]

Two studies examined psychosis-like symptoms.[27,28] Negative effects included negative affect, cognitive impairment, psychosis-like experiences, physiological effects, and reduced consciousness.[28] A within-person comparison of the effects of herbal cannabis and cannabis concentrates (n=574) showed that participants reported more psychosis-like experiences when using herbal cannabis (mean=1·2) than when using cannabis concentrates (mean=1·1). Participants answered questions from a scale of 0 (not at all) to 10 (extremely) about the

	Study type	Location and years of study	Participants	Exposure and comparator	Method for collecting exposure	Temporal relationship exposure-outcome	Outcomes	Confounding variables adjusted for	Main findings	Risk of bias rating
Chan et al (2017)[15]	Cross-sectional	20 countries 2015–16	181 870 participants of annual drug survey; butane hash oil mean age 25·68 years; 19·49% women, 79·85% men, 0·66% transgender; HI-POT mean age 25·80 years; 24·91% women, 74·63% men, 0·46% transgender; CANN mean age 27·61 years; 39·69% women, 59·84% men, 0·47% transgender	Butane hash oil *vs* HI-POT; butane hash oil *vs* CANN; and HI-POT *vs* CANN	Self-report with pictorial aids	Exposure: past 12 months; outcome: lifetime diagnosis	Self-report lifetime diagnosis	Age, gender, sexual orientation, education level, other substance use	People who use butane hash oil were about twice as likely to report an anxiety diagnosis compared with CANN users (OR 1·80, 95% CI 1·60–2·01) and HI-POT (1·72, 1·55–1·91); the odds of anxiety diagnosis in HI-POT was not higher than for CANN (1·05, 0·98–1·12)	Poor quality (3)
Prince et al (2019)[25]	Cross-sectional	USA; years NS	156 people who use cannabis (mean age 30·4 years; 52·1% female, 47·9% male)	Cannabis concentrates *vs* herbal cannabis	Self-reported and optional photo upload (legal status)	Exposure: current use; outcome: past 2 weeks	DSM-5 Cross-Cutting Symptom Measure–adult	..	No association with higher potency herbal cannabis use (r 0·03, 95% CI –0·18 to 0·24) or higher potency cannabis concentrate use (0·21, –0·10 to 0·49)	Poor quality (3)
Hines et al (2020)[27]	Cross-sectional	UK; 2015–17	1087 people who used cannabis in the past year (mean age 24 years; 42·5% female; 57·5% male)	Higher potency cannabis (typically ≥10% THC; skunk or other stronger types of herbal cannabis) *vs* lower potency (typically <10% THC; herbal cannabis or marijuana, hashish or resin or solid, or other)	Self-reported	Exposure: past 12 months; outcome: current diagnosis	Clinical Interview Schedule–revised	Sex, childhood socioeconomic position, depression symptom score at 13 years of age, cannabis use frequency	Participants were about twice as likely to report generalised anxiety disorder (OR 1·92, 95% CI 1·11–3·32) as participants who used lower potency cannabis	Fair quality (6)
Bidwell et al (2018)[29]	Cross-sectional	USA; 2017	191 people who use cannabis; people who frequently use cannabis concentrates (mean age 37·5 years; 40·3% female, 59·7% male); people who frequently use herbal cannabis (mean age 46·9 years; 51·7% female, 48·3% male)	People who frequently use cannabis concentrate *vs* people who frequently use herbal cannabis	Self-reported only	Exposure: NS; outcome: current diagnosis	Mental health self-report scale	..	No difference in severity of anxiety between people who frequently use cannabis concentrates (mean 1·1, SD 1·3) and people who frequently use herbal cannabis (mean 0·66, SD 1·0; 95% CI NS)	Poor quality (0)
Brunt et al (2014)[31]*	Cross-sectional	Netherlands; 2011–12	102 people who use medical cannabis for chronic pain, multiple sclerosis, cancer, and nausea (mean age 52·8 years; 51% female, 49% male)	THC high (19% THC); THC medium (12% THC) *vs* THC low (6% THC)	Self-reported (legal status)	Exposure: current use; outcome: current symptoms	Self-report visual analogue scale	Age, sex, medical indication, dose, and method of administration	Feelings of anxiety were higher with use of THC high (mean 3·42) and THC medium (mean 2·80), compared with THC low (mean 1·62), 95% CI NS	Fair quality (5)

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extent to which they had experienced symptoms as a result of their cannabis use, such as visions and out-of-body experiences.[28] However, the standardised effect size was small (Cohen's d=0·12) and the sample mostly comprised people who used herbal cannabis and cannabis concentrates infrequently.[28] Another cross-sectional study investigating psychosis-like experiences (n=1087) did not find evidence to support an association between higher potency cannabis use and psychosis-like experiences, when compared with lower potency cannabis use (aOR 1·29, 95% CI 0·67–2·50), after adjusting for frequency of cannabis use.[27]

We found six cross-sectional studies of CUD.[14,25–27,29,30] We rated one of the six studies as fair quality,[27] and five studies as poor quality[14,25,26,29,30] in the risk of bias assessment (table 2). These ratings represent limitations in the measure of exposure in all studies and outcome measures,[25,29] sample selection,[14,25,26,29,30] and adjustment of confounder[25,26,29] in the poor quality studies.

Increased risk of dependence was reported in a sample of Japanese patients (n=71), with the use of high-potency cannabis associated with a seven-times increased risk of dependence syndrome compared with people who use lower potency cannabis (OR 6·9, 95% CI 1·19–25·15).[26] In a UK sample (n=1087), people who used higher potency cannabis were four times more likely to report having recently experienced problems because of their cannabis use than people who used lower potency cannabis (aOR 4·08, 95% CI 1·41–11·81).[27] In another UK sample (n=2514), a one-day increase in the frequency of higher potency cannabis use per month was associated with a 0·254 increased severity of dependence scale score (β 0·821, unstandardised regression coefficient [b] 0·254, 95% CI 0·161–0·3578; range 0–15, cutoff for cannabis dependence ≥3), whereas there was no association for use of lower potency cannabis.[14] Similar results were found in a separate study with data from 175 different countries (most responses were from a few high-income countries; n=55 240).[30] Use of higher potency cannabis types was associated with increased scores of severity of dependence (use of sinsemilla and herbal β 0·023, b 0·155, 95% CI 0·100–0·209; use of hashish and herbal β 0·028, b 0·262, 95% CI 0·188–0·337; range 0–15, cutoff for cannabis dependence ≥3) compared with lower potency cannabis use.[30] Although hashish has previously been classified as a lower potency cannabis product, these results follow the evidence that its potency has increased internationally.[6]

Varied findings were reported by one study when comparing higher potency herbal cannabis and cannabis concentrate use. In a sample of 156 participants, use of higher potency herbal cannabis was not associated with more symptoms of CUD (*r* 0·09, 95% CI –0·12 to 0·30). Conversely, use of higher potency cannabis concentrate was associated with fewer symptoms of CUD (–0·05, –0·35 to –0·26).[25]

Another study comparing cannabis concentrates and herbal cannabis (n=191) did not find a significant

	Study type	Location and years of study	Participants	Exposure and comparator	Method for collecting exposure	Temporal relationship exposure-outcome	Outcomes	Confounding variables adjusted for	Main findings	Risk of bias rating
Continued from previous page)										
Wan et al (2017)[32]*	Repeated measures	Canada; 2015–17	837 people who use medical cannabis for pain relief (mean age 44·9 years; 30·9% women, 68·8% men)	THC 25–28%; THC 20–23% *vs* THC 0·1–0·8%	Self-reported (legal status)	Exposure: NS; outcome: NS	Self-report symptom severity	..	Greatest improvement in symptom severity with higher concentrations of THC (21–24% THC 27·3% improvement; 25–28% THC 25·2% improvement; 15–18% THC 22·0% improvement)	Poor quality (1)
Cuttler et al (2018)[33]*	Naturalistic	Canada; years NS	770 people who use medical cannabis (mean age 33 years, 53% women, 47% men)	High THC *vs* low THC	Self-reported (legal status)	Exposure: current use; outcome: current symptoms	Self-report scale	..	THC content was not predictive of change in anxiety ratings; effect measures NS	Poor quality (2)
Stith et al (2020)[34]*	Naturalistic	USA; 2016–19	670 people who use medical cannabis (age and gender or sex NS)	THC 10–19%; THC 20–30% *vs* THC <9%	Self-reported (legal status)	Exposure: current use; outcome: current symptoms	Self-report symptom severity	Baseline symptom intensity and session length	THC levels above 10% were associated with greater symptom relief (THC 10–19% b –0·618, SE 0·170; THC 20–30% –0·599, 0·165; 95% CI NS)	Poor quality (3)

b=unstandardised regression coefficient. CANN=lower potency herbal cannabis use with no butane hash oil use. HI-POT=higher potency herbal cannabis use with no butane hash oil use. HR=hazard ratio. NS=not specified. OR=odds ratio. THC=Δ^9-tetrahydrocannabinol.

Table 3: **Summary of study characteristics and findings, anxiety**

	Study type	Location and years of study	Participants	Exposure and comparator	Method for collecting exposure	Temporal relationship exposure-outcome	Outcomes	Confounding variables adjusted for	Main findings	Risk of bias rating
Chan et al (2017)[15]	Cross-sectional	20 countries; 2015–16	181 870 participants of annual drug survey; butane hash oil mean age 25·68 years; 19·49% women, 79·85% men, 0·66% transgender; HI-POT mean age 25·80 years; 24·91% women, 74·63% men, 0·46% transgender; CANN mean age 27·61 years; 39·69% women, 59·84% men, 0·47% transgender	People who use butane hash oil *vs* HI-POT; people who use butane hash oil *vs* CANN; and HI-POT *vs* CANN	Self-reported with pictorial aids	Exposure: past 12 months; outcome: lifetime diagnosis	Self-report lifetime diagnosis	Age, gender, sexual orientation, education level, other substance use	Slightly increased odds of diagnosis for HI-POT *vs* CANN (OR 1·18, 95% CI 1·11–1·25), people who use butane hash oil *vs* CANN (1·34, 1·21–1·48) and people who use butane hash oil *vs* HI-POT (1·15, 1·03–1·25)	Poor quality (3)
Prince et al (2019)[25]	Cross-sectional	USA; years NS	156 people who use cannabis (mean age 30·4 years; 52·1% female; 47·9% male)	Cannabis concentrates *vs* herbal cannabis	Self-reported and optional photo upload (legal status)	Exposure: current use; outcome: past 2 weeks	DSM-5 Cross-Cutting Symptom Measure–adult	..	No association with higher potency cannabis concentrate use (*r* 0·17, 95% CI −0·15 to 0·45) or higher potency herbal cannabis use (0·02, −0·19 to 0·23)	Poor quality (3)
Hines et al (2020)[27]	Cross-sectional	UK; 2015–17	1087 people who used cannabis in the past year (mean age 24 years; 42·5% female; 57·5% male)	Higher potency cannabis (typically ≥10% THC; skunk or other stronger types of herbal cannabis) *vs* lower potency (typically <10% THC; herbal cannabis or marijuana, hashish or resin or solid, or other)	Self-reported	Exposure: past 12 months; outcome; current diagnosis	Clinical Interview Schedule—revised	Sex, childhood socioeconomic position, depression symptom score at 13 years of age, cannabis use frequency	Little evidence of an association of higher potency cannabis use and major depression (OR 1·28, 95% CI 0·68–2·32)	Fair quality (6)
Bidwell et al, (2018)[29]	Cross-sectional	USA; 2017	191 people who use cannabis; people who frequently use cannabis concentrate (mean age 37·5 years; 40·3% female, 59·7% male); people who frequently use herbal cannabis (mean age 46·9; 51·7% female, 48·3% male)	People who frequently use cannabis concentrate *vs* people who frequently use herbal cannabis	Self-reported	Exposure: NS; outcome: current diagnosis	Mental health self-report scale	..	No difference in severity of depression between people who frequently use cannabis concentrate (mean 0·72, SD 1·0) and people who frequently use herbal cannabis (mean 0·76, SD 1·1), 95% CI NS	Poor quality (0)

(Table 4 continues on next page)

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difference between symptoms of CUD in frequent concentrate users (mean 2·1) compared with frequent herbal cannabis users (mean 1·3).[29] Importantly, the sample of participants included in this study endorsed few CUD symptoms overall.

We found four cross-sectional studies of anxiety.[15,25,27,29] We rated one study as fair quality[27] and three studies as poor quality[15,25,29] in the risk of bias assessment (table 3). These ratings represent limitations in the exposure measure in all studies, and issues in the sample selection,[15,25,29] outcome measure,[15,29] and adjustment for confounders[25,29] in the poor quality studies.

One study found an association between the use of higher potency cannabis and anxiety.[27] Use of higher potency cannabis was associated with a two-times increased risk of generalised anxiety disorder, compared with lower potency cannabis, in a sample of 1087 people who had used cannabis in the past year (OR 1·92, 95% CI 1·11 to 3·32).[27] In another study (n=181 870), the risk of anxiety diagnosis was not higher for people who used higher potency herbal cannabis compared with people who used lower potency herbal cannabis (1·05, 0·98 to 1·12).[15] However, in the same study, when comparing self-report lifetime anxiety diagnosis, the people who used butane hash oil were twice as likely to report an anxiety diagnosis compared with people who used lower potency herbal cannabis (1·80, 1·60 to 2·01) and higher potency herbal cannabis (1·72, 1·55 to 1·91).[15] Conversely, in a study comparing use of cannabis concentrate and herbal cannabis (n=156), use of higher potency concentrate (r 0·21, 95% CI –0·10 to 0·49) and use of higher potency herbal cannabis (0·03, –0·18 to –0·24) were not associated with more symptoms of anxiety.[25] A study of 191 cannabis users also found no difference in severity of anxiety between people who frequently used cannabis concentrate and people who frequently used higher potency herbal cannabis.[29]

A subset of four studies examined the association between cannabis potency and anxiety in people who used medical cannabis. Two of these studies included patients who used cannabis for the treatment of other conditions, such as chronic pain and multiple sclerosis.[31,32] We rated one of the studies as fair quality in the risk of bias assessment (table 4) because of issues in the outcome measure.[31] We rated the other study as poor quality because of issues in the sample selection, adjustment of confounders, and outcome measure.[32]

A cross-sectional study done in the Netherlands (n=102) compared the effects of three types of cannabis with high (19%), medium (12%), and low (6%) THC concentration, and found on average that feelings of anxiety were higher with use of high THC cannabis (mean 3·42), followed by medium THC cannabis (mean 2·80), and finally low THC cannabis (mean 1·62).[31] Another repeated measure study done in Canada (n=837) reported greater reduction in anxiety symptoms in cannabis with 21–24% THC (27·3% improvement) compared with cannabis with

	Study type	Location and years of study	Participants	Exposure and comparator	Method for collecting exposure	Temporal relationship exposure-outcome	Outcomes	Confounding variables adjusted for	Main findings	Risk of bias rating
(Continued from previous page)										
Wan et al (2017)[32]*	Repeated measures	Canada; 2015–17	837 people who use medical cannabis for pain relief (mean age 44·9 years; 30·9% women, 68·8% men)	THC 25–28%; THC 20–23% vs THC 0·1–0·8%	Self-reported (legal status)	Exposure: NS; outcome: NS	Self-report symptom severity	..	Cannabis with 25–28% THC showed the greatest symptom improvement (32%), followed by cannabis with 0·1–0·8% THC (25·2%) and cannabis with 20–23% THC (20%)	Poor quality (1)
Li et al (2020)[35]*	Naturalistic	USA; 2016–19	1819 people who use medical cannabis (mean age NS; sex or gender NS)	THC 20–35% vs THC <10%	Self-reported (legal status)	Exposure: current use; outcome: current symptoms	Self-report symptom intensity	Labelled plant phenotype, combustion method, and starting symptom level	Use of cannabis with higher THC concentration was associated with greater symptom relief (b –0·549, SE 0·272), 95% CI NS	Poor quality (3)
Cuttler et al (2018)[33]*	Naturalistic	Canada; years NS	561 people who use medical cannabis (mean age 33 years; 53% women, 47% men)	High THC vs low THC	Self-reported (legal status)	Exposure: current use; outcome: current symptoms	Self-report scale	..	Use of cannabis with the lowest concentration of THC resulted in the greatest reductions on ratings of depression. Effect measures NS	Poor quality (2)

b=unstandardised regression coefficient. CANN=lower potency herbal cannabis use with no butane hash oil use. HI-POT=higher potency herbal cannabis use with no butane hash oil use. HR=hazard ratio. NS=not specified. OR=odds ratio. THC=Δ⁹-tetrahydrocannabinol. *Studies in users of medical cannabis.

Table 4: **Summary of study characteristics and findings, depression**

15–18% THC (22% improvement). However, this difference was not analysed statistically.[32]

We also found two repeated-measure studies comparing various strains of cannabis in people who used medical cannabis for anxiety symptoms.[33,34] We rated both studies as poor quality in the risk of bias assessment because of issues in the outcome measure and adjustment of confounder.

In a US study (n=670), the use of higher potency cannabis strains (THC 10–19% and THC 20–30%) was associated with reductions in visual analogue scale scores of symptoms of anxiety compared with lower potency cannabis types (THC <9%; THC 10–19%, b 0·618; THC 20–30%, b 0·599; range 0–10).[34] Another Canadian study found no association between cannabis potency and anxiety ratings in people who used medical cannabis.[33]

We found four cross-sectional studies of depression.[15,25,27,29] We rated one study as fair quality[27] and three studies as poor quality[15,25,29] in the risk of bias assessment. These ratings represent limitations in the exposure measure in all studies and issues in the sample selection[15,25,29] outcome measure,[15,29] and adjustment of confounder[25,29] in the poor quality studies.

In a study (n=181 870) done in 20 countries (typically high-income countries), use of higher potency cannabis concentrate (OR 1·34, 95% CI 1·21 to 1·48) and higher potency herbal cannabis (1·18, 1·11 to 1·25), compared with lower potency herbal cannabis, were associated with a slight increase in odds of depression diagnosis.[15] Conversely, in a UK sample of 1087 people who used cannabis in the past year, there was little evidence to suggest an increased risk of major depression in people who used higher potency cannabis compared with people who used lower potency cannabis (aOR 1·28, 95% CI 0·68 to 2·32).[27] Another US study of 191 participants found no difference in the severity of depression between people who frequently used cannabis concentrate (mean=0·72; higher potency) and people who frequently used herbal cannabis (0·76; lower potency).[29] Similarly, a cross-sectional study of 151 people who used cannabis in the US found no association between symptoms of depression and use of higher potency cannabis concentrate (r 0·17, 95% CI –0·15 to 0·45) or higher potency herbal cannabis (0·02, 0·19 to 0·23).[25]

A subset of studies examined the association between cannabis potency and depression in people who used medical cannabis. We found three repeated-measures studies, rated as poor quality[32,33,35] in the risk of bias assessment because of issues in the outcome measure,[32,33,35] adjustment of confounder,[32,33,35] and sample selection.[32]

In a Canadian study (n=837) comparing different strains of cannabis in people who used medical cannabis for pain relief, strains with the greatest THC concentration gave the most symptom improvement (32%). However, lower potency cannabis, with 0·1–0·8% THC concentration, also gave a 25·2% improvement in symptoms of depression, but the differences were not analysed statistically.[32]

Varied results have also been found in studies examining the effects of cannabis potency in people who use medical cannabis for symptoms of depression. Although in one US study (n=1819), the use of higher potency cannabis was associated with a reduction in symptoms of depression (b –0·549, SE 0·272; range –10 to 9) compared with lower potency cannabis,[35] another Canadian study (n=561) found the greatest reduction in ratings of depression with use of lower potency cannabis.[33]

Discussion

To our knowledge, this is the first systematic review on the association of cannabis potency and mental health and addiction. Overall, the evidence suggests that the use of higher potency cannabis, compared with lower potency cannabis, is associated with an increased risk of psychosis, and this risk is higher in people who use cannabis daily. Higher potency cannabis use has also been associated with an earlier onset of psychosis, more symptoms of psychosis, and an increased risk of relapse. These results are in line with experimental studies showing that THC produces dose-dependent psychosis-like symptoms.[5] Thus, the findings from this systematic review suggest that exposure to greater doses of THC from consumption of higher potency cannabis is associated with poorer mental health outcomes. The evidence to date does not suggest that the use of higher potency cannabis is associated with psychosis-like symptoms, although fewer studies have been done using this outcome, and they have used poorer quality study designs than the studies addressing psychotic disorders.

Use of higher potency cannabis was also consistently associated with an increased risk of CUD, recent cannabis use problems, and severity of cannabis dependence. Preclinical studies have found that THC can be an effective reinforcer of drug-taking behaviour in a dose-dependent manner, which indicates a potential for drug misuse.[36,37] Thus, exposure to high doses of THC could increase the risks of developing a CUD.[14] In addition, increases in cannabis potency have been associated with CUD treatment entry,[38] supporting the association between higher potency cannabis use and CUD.

There is some evidence to suggest that higher potency cannabis use could be associated with anxiety. Experimental studies have found that THC is induces anxiety,[5] supporting the findings that use of higher potency cannabis could result in worse anxiety outcomes compared with use of lower potency cannabis. There is little evidence to suggest an association between higher potency cannabis use and depression, with one study so far suggesting an association.

Studies of people who use medical cannabis found varied results, both in samples of participants using cannabis to treat depression and anxiety symptoms, and in samples of participants using cannabis to treat other conditions, such as chronic pain. Although these studies

show better measures of cannabis potency exposure than other studies, as specified concentrations of THC in medicinal products, the findings are difficult to interpret because of the inclusion of participants with heterogeneous demographics and the measurement of short-term outcomes. The findings on medical cannabis should be considered with caution, because medical cannabis was used as a treatment for a range of medical conditions. Thus, there are likely to be confounders involved for which we cannot control (eg, improvements in the medical conditions for which participants were primarily using the cannabis, such as chronic pain). For people who use cannabis as a treatment for depression or anxiety without other known underlying conditions, the studies did not account for important confounders to do with underlying reasons to use cannabis. Thus, these findings are likely to be affected by self-selection bias.

When considering the quality of the evidence, none of the studies were categorised as good quality from the risk of bias assessment. The risk of bias scores are reflected by a set of limitations found across the literature. One of these key limitations was the measure of exposure. The majority of studies relied on self-report measures of cannabis products used to categorise the cannabis use of participants as higher potency or lower potency. The use of self-report measures could introduce bias. It relies on the participant accurately recalling the type of cannabis they used and effectively communicating this information to researchers. Another source of potential bias in some of the studies reviewed is the use of different cannabis products as a proxy of cannabis potency. Cannabis products have been shown to differ in laboratory analysed THC concentrations, both when cannabis type is categorised by people who use cannabis[39,40] and when cannabis type is categorised by forensic scientists.[7] However, self-reported measures of cannabis products do not provide a precise indication of THC concentration in cannabis, only an approximation. Also, a dichotomous categorisation of higher or lower potency (eg, based on an arbitrary THC cutoff) cannot capture the full range of cannabis products and potencies to which people are exposed. Finally, another potential source of bias is that studies do not account for levels of THC intake versus THC content in cannabis products, which can vary because of potential titration effects.[41] Evidence suggests that titration effects to cannabis potency are partially effective.[41] Such titration effects would be expected to attenuate associations of cannabis potency with mental health and addiction rather than inflate them. Thus, overall, the measure of exposure across the literature is a highly simplified measure of THC content in cannabis. Although it might offer a useful proxy for THC exposure in research and clinical settings, the measure of exposure carries limitations that should be addressed in future by more precise estimations of THC exposure. The scarcity of standardised tools to measure cannabis consumption, including cannabis potency, also hinders the integration of evidence. Future studies should incorporate tools such as the iCannToolkit[42] and the standard THC unit[43] (a dose of 5 mg of THC), or quantified metabolites of THC, to increase standardisations of exposure measures and facilitate harmonisation of evidence.

The studies presented are heterogenous in the definition of higher potency cannabis and lower potency cannabis. Some studies categorised higher potency cannabis as high-potency herbal cannabis, whereas other studies categorised higher potency cannabis as cannabis concentrate use or a quantified concentration of THC. Some studies compared the effects of higher potency cannabis with lower potency cannabis as a control. Other studies separately examined the effects of higher potency cannabis and lower potency cannabis compared with no cannabis use, with the comparison between the use of higher potency and lower potency cannabis being indirect. Thus, the exposure (higher potency cannabis *vs* lower potency cannabis) can only be interpreted in relative terms within each study, rather than in absolute terms across all studies.

Because of the limitations found during this systematic review (ie, bias in the measure of exposure because of self-report measures, absence of standardised precise measures of THC exposure that accounts for titrating effects, and heterogeneity in categorisations of higher potency cannabis and lower potency cannabis), it was not possible to do a meta-analysis.

Another common limitation is the use of cross-sectional study designs, which cannot establish direction of association. For example, because of reverse causation, participants with poorer mental health outcomes could use higher potency cannabis as a form of self-medication. In addition, the contribution of potential confounds in the relationship between cannabis potency and mental health is not clear. There is currently no agreement on possible confounders modifying this relationship, with different studies accounting for various potential confounds or none. The contribution of other measures of cannabis use, such as the frequency of use or the amount used, were often not taken into consideration, with the amount used only adjusted for in one study.[30] In some studies, the frequency of use was adjusted for as a confounding variable, whereas other studies created a composite variable for cannabis potency and the frequency of use. Longitudinal studies are needed to understand the direction of the association between cannabis potency and mental health and the contribution of other factors, such as the frequency of use.

Based on the evidence available, we suggest that future studies should include common confounders such as age, sex, gender, socioeconomic status, and use of alcohol, tobacco, and other illicit drugs. We recommend that studies should report models with and without adjustments for the frequency of use and the amount of cannabis used because more research is needed to understand whether they act as confounders or as mediators. For example, it is possible

that frequent use of cannabis leads to the use of higher potency cannabis through the development of tolerance, in which case adjusting for the frequency of use as a confounder would be appropriate. Alternatively, if higher potency cannabis leads to more frequent use, the frequency of use might be a mediator of the effect of higher potency cannabis on mental health. In addition, we recommend future studies address temporality issues by ensuring measures of exposure precede measures of outcomes.

We only considered the effects of THC and did not include studies examining the effects of other cannabinoids, such as cannabidiol (also known as CBD). Although the concentration of THC in samples of cannabis has increased over the years, the concentration of cannabidiol has remained virtually negligible.[6] Variation in concentrations of cannabidiol or other cannabinoids might have contributed to outcomes reported in this study. However, evidence for cannabidiol interacting with the effects of THC have been varied,[44] and THC is the primary cannabinoid responsible for the health effects of cannabis use.

In conclusion, the findings from this systematic review highlight the potential for an increased risk of negative mental health outcomes and addiction with higher potency cannabis use. The findings support recommendations to discourage the use of higher potency cannabis products for low risk use.[45] This recommendation should be incorporated into education tools and in the management of cannabis use in clinical settings. Policy makers should carefully consider cannabis potency when regulating cannabis in legal markets, such as through limits or taxes based on THC concentration.

Contributors

KP and TPF formulated the review protocol and search strategy. LH, SA, and GT commented on search strategy and review protocol. KP did the database search. KP and SO independently screened and selected studies. KP, SO, and TPF resolved any disagreements over the eligibility of studies. KP and SO independently did data extraction. KP and SO independently assessed the studies for risk of bias. KP, SO, and TPF resolved any disagreements over the risk of bias assessment. KP wrote the manuscript and prepared figures and tables. SO, LH, SA, GT, and TPF commented on all drafts.

Declaration of interests

GT reports previous funding from Pfizer (GRANT scheme) and owns a scientific consulting company doing work unrelated to this project. KP, SO, LH, SA, and TPF declare no competing interests.

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