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

Authors

Kat Petrilli MRes[1], Shelan Ofori MRes[2], Lindsey Hines PhD[3], Gemma Taylor PhD[1], Sally Adams PhD[4], Tom P Freeman PhD[1]

Affiliations

1 Addiction and Mental Health Group (AIM), Department of Psychology, University of Bath, Bath, UK

2 Clinical Psychopharmacology Unit, Clinical Educational and Health Psychology Department, University College London, London, UK

3 Population Health Science, Bristol Medical School, University of Bristol, Bristol, United Kingdom

4 School of Psychology, University of Birmingham, Birmingham, UK

Correspondence to: Kat Petrilli, Department of Psychology, 10 West, University of Bath, Claverton Down, Bath, BA2 7AY, United Kingdom. kp787@bath.ac.uk

Summary

Cannabis potency, defined as concentration of Δ9-Tetrahydrocannabinol (THC), has increased internationally, which may increase the risk of adverse health outcomes. We conducted the first systematic review on the association of cannabis potency with mental health and addiction (PROSPERO: CRD42021226447). We searched Embase, PsycINFO, and MEDLINE (inception to 14/01/21). Inclusion criteria were observational studies of human participants comparing the association of higher potency cannabis (products with higher concentration of THC) and lower potency cannabis (products with lower concentration of THC), as defined by the studies included, with depression, anxiety, psychosis, or cannabis use disorder (CUD). Of 4,171 articles screened, 20 met eligibility criteria: psychosis (n=8), anxiety (n=8), depression (n=7), CUD (n=6). Overall, use of higher potency cannabis, relative to lower potency cannabis, was associated with increased risk of psychosis and CUD. Evidence was mixed for depression

and anxiety. The association of cannabis potency with CUD and psychosis highlights its relevance in healthcare settings, public health guidelines, and policies on cannabis sales. Standardisation of exposure measures and longitudinal designs are needed to strengthen the evidence.

Introduction

Cannabis is the 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 THC causes intoxication, cognitive impairment, anxiety, and transient psychosis-like experiences.[3] These effects are dose-dependent,[4,5] which means that use of higher potency cannabis products (products with higher THC concentrations) may increase risk of harm.

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

Cannabis use has consistently been associated with mental health disorders. Heavy cannabis use has been associated with a fourfold 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 criteria for cannabis use disorder (CUD).[12] Due to the dose-response effects of THC on acute mental health symptoms, the potency of cannabis products may be a key factor determining the health effects of cannabis use. The association of cannabis potency with mental health and addiction has been investigated by an accumulating body of evidence.[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. The need to understand this association is especially pressing given international increases in cannabis potency, which have been particularly evident in new legal markets. We therefore performed the first systematic review on the association of cannabis potency with mental health and addiction.

Methods

Search strategy and selection criteria

This systematic review was conducted according to PRISMA guidelines,[16] using MEDLINE (from Jan 1, 1966 to Jan 14, 2021), Embase (from Jan 1, 1974 to Jan 14, 2021), PsycINFO (from Jan 1, 1597 to Jan 14, 2021). The search included terms describing (i) cannabis AND (ii) potency, AND (iii) mental health or addiction: depression, anxiety, psychosis, or cannabis use disorder (CUD) (appendix p 2). No date or language restrictions were applied but the search was conducted using English terms only. Additional relevant articles were searched for in the references lists of identified articles.

Studies were included if they met the following inclusion criteria: (a) Observational study. (b) Provides data on human participants. (c) Provides quantitative data on the potency of the cannabis used as a direct or indirect comparison between high potency cannabis products and low potency cannabis products. As this exposure was defined according to study-specific criteria rather than absolute values for "high" or "low" potency, it can be interpreted in relative terms (i.e."higher" versus "lower" potency). (d) Provides 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 abuse. (e) Studies the association between cannabis potency and the mental health or addiction outcomes mentioned above. Conference extracts or abstracts, editorials, or correspondence articles were excluded. Studies were grouped for syntheses based on mental health outcomes for depression, anxiety, psychosis, or CUD. We did not include experimental studies due to the need of a real-world exposure to the potency and amount of cannabis used in ecological settings.

Studies were retrieved using the titles first strategy[17] using Covidence. Two reviewers (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 title and abstract search by both reviewers (inter-rater agreement 89.9%). The two reviewers retrieved and independently assessed the full text of the studies to determine final eligibility (inter-rater agreement 89.9%). Specific exclusion for any studies was reported (appendix p 5). A third reviewer (TPF) resolved any disagreements over the eligibility of studies. The protocol was prospectively registered on PROSPERO: CRD42021226447.

Data collection process and data items

A standardised Microsoft Excel database was used by two reviewers independently (KP and SO) for data extraction. Data extraction was cross-checked 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, information on covariates adjusted for. For studies with multiple publications, data were extracted from each publication separately and then collated, following guidance in the Cochrane handbook.[18]

Study risk of bias assessment

Risk of bias for each outcome was assessed independently by two reviewers (KP and SO), using a modified version of the Newcastle-Ottawa Scale and discrepancies were discussed with a third reviewer (TPF). Studies were categorised as 'good', 'fair', or 'poor' quality, according to the scores obtained for each of the domains assessed (appendix p 6).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report

Results

Of 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 appendix p 11). Eight studies focused on psychosis, eight on anxiety, seven on depression, and six on CUD.

INSERT FIGURE 1 HERE

Association of cannabis potency and psychosis

We found six studies of psychosis, including two case-control studies (Genetics and Psychosis (GAP) study[13,19–21] and the EU-GEI study[22,23]), one prospective cohort study,[24] and three cross-sectional studies.[15,25,26] Three out of the six studies were rated as 'fair quality'[13,19–24] and the other three as 'poor quality'[15,25,26] in the risk of bias assessment. These scores represent limitations in the measure of exposure across studies as well as in the outcome measure,[15] confounders adjustment[25,26] and sample selection[15,25] in the 'poor quality' studies. We also found two cross-sectional studies of psychosis-like symptoms. One study was rated as 'fair quality'[27] due to limitations in the exposure measure and one as 'poor quality'[28] due to additional limitations in measures of outcome, sample selection and confounders adjustment.

Risk of psychosis diagnosis was assessed by 4 studies. Overall, studies reported increased risk of psychosis with use of higher potency cannabis compared to lower potency cannabis. The GAP study 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) first-episode psychosis patients were more likely to use higher potency cannabis compared with control groups (AOR = 6·8, 95% CI 2·6-25·4).[19] These findings were further investigated in a second article including analysis of the full sample (n=780).[13] Users of higher potency cannabis were three times more likely to have first-episode psychosis compared to those who never used cannabis (AOR= 2·91, 95% CI 1·52-3·60). In contrast, use of lower potency cannabis was not associated with risk of psychosis compared to never use (AOR = 0·83, 95% CI 0·52-1·77).[13] When taking into consideration cannabis potency and frequency of use as a composite variable, daily higher potency cannabis

users were five times as likely to be diagnosed with a psychotic disorder compared with those who never used cannabis (AOR = 5·40, 95% CI 2·80-11·30). Conversely, daily use of lower potency cannabis was not associated with risk of psychotic disorder compared with individuals 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.

These national results from the UK were replicated by the multinational EU-GEI case-control study in Europe and Brazil (n= 2,138).[22] This 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 modestly increase in the risk of psychotic disorder compared to no use (AOR= 1·6, 95% CI 1·2-2·2); while lower potency cannabis use was not associated with risk of psychosis (AOR= 1·1, 95% CI 0·9-1·5).[22] Similarly, daily use of higher potency cannabis had a five times higher odds of psychosis compared to never users (AOR= 4·8, 95% CI 2·5-6·3); while those using lower potency cannabis had two times higher odds of psychosis (AOR = 2·2, 95% CI 1·4-3·6).[22]

Cross-sectionally, in an online survey of drug users conducted over 20 countries (typically high-income countries) (n=181,870), users of higher potency herbal cannabis showed increased risk of lifetime diagnosis of psychosis compared to users of lower potency cannabis (OR = 1·28, 95% CI 1·07-1·53). However, this association was not found when comparing users of butane hash oil (BHO), a higher potency product, to lower potency cannabis users.[15] This study presents limitations in the outcome measure, which relies on self-report lifetime diagnosis, as well as 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 those who used higher potency cannabis were less likely to report residual and late onset psychotic disorder compared those who used lower potency cannabis (OR = 0·212, 95% CI 0·061 – 0·735).[26]

Two studies examined symptoms of psychosis. In a sample of patients with first episode psychosis (n=901), use of higher potency cannabis was associated with a 0·22 increase in

positive symptoms compared to those who did not use cannabis (b= 0·22, 95% CI 0·02 to 0·29) while this relationship was not present when comparing lower potency cannabis use with no cannabis use (b= 0·09, 95% CI = -0·12 to 0·28).[23] In a cross-sectional study of herbal and concentrate cannabis use in healthy participants (n=156), symptoms of psychosis were not associated with use of higher potency concentrates (r= .11, 95% CI -0·20 – 0·40) while use of higher potency herbal cannabis was associated with less symptoms of psychosis (r = -0·27, 95% CI -0·45 – -0·06).[25]

Additionally, higher potency cannabis use has also been associated with an earlier onset of psychotic disorder in an article using data from the GAP case-control study.[20] After adjusting for gender and frequency of use, users of higher potency cannabis had a significantly earlier onset of psychosis, of approximately 4 years, (HR= 1·68, 95% CI 1·08-2·63) compared to lower potency cannabis users.[20]

In a prospective cohort study (n=256), daily use of higher potency cannabis was associated with risk of relapse in the first two years after onset of psychosis.[24] Daily use of higher potency cannabis had three times higher odds of relapse compared with former cannabis users (AOR = 3·28, 95% CI 1·22-9·18). The risk of relapse for use of lower potency cannabis or infrequent higher potency cannabis use was not increased when compared with former users (OR = 1·82, 95% CI 0·36 – 8·75).[24]

In contrast to the literature on psychotic disorders, the evidence from two studies so far does not suggest an association between higher potency cannabis use and psychosis-like symptoms.[27,28] A within-person comparison of the effects of herbal cannabis and concentrates (n= 574) showed participants rated herbal cannabis use as producing more psychosis-like experiences (M=1·2) compared with concentrate use (M=1·1). However, the effects were small (Cohen's d= 0·12) and the sample was formed mainly by herbal cannabis users with only infrequently concentrate users present in the study.[28] Another cross-sectional study investigating psychotic-like experiences (n=1087) did not find evidence to support higher potency cannabis use was associated with psychosis-like experiences, when compared to lower potency cannabis use (AOR = 1·29, 95% CI 0·67 – 2·50), after adjusting for frequency of cannabis use.[27]

INSERT TABLE 1 HERE

Association of cannabis potency and CUD

We found six cross-sectional studies of CUD.[14,25–27,29,30] One out of six studies was rated as 'fair quality'[27], and five as 'poor quality'[14,25,26,29,30] in the risk of bias assessment. These scores represent limitations in the measure of exposure in all studies, as well as outcome measures,[25,29] sample selection,[14,25,26,29,30] and confounder adjustment[25,26,29] in the 'poor quality' studies.

Increased risk of dependence was reported in a sample of Japanese patients (n= 71), with higher potency cannabis use being associated with seven times increased in the risk of dependence syndrome compared to lower potency cannabis users (OR = 6·9, 95% CI 1·1866 – 25·145).[26] In a UK sample (n=1,087), higher potency cannabis users were four times more likely to report recent cannabis use problems compared to lower potency cannabis users (AOR= 4·08, 95% CI 1·41-11·81).[27] In another UK sample (n=2,514), a one day increase in frequency of higher potency cannabis use per month was associated with a 0.254 increase severity of dependence scale score (standardised coefficient: β= 0·821, unstandardized coefficient: b= 0·254, 95% CI 0·161 – 0·3578; range 0-15, cut-off for cannabis dependence ≥3), while there was no association for use of lower potency cannabis.[14] Similar results were found in a separate study using data from 175 different countries (most responses from few high-income countries) (n=55,240).[30] Use of higher potency cannabis types were associated with increased scores of severity of dependence (use of sinsemilla and herbal standardised coefficient: β= 0·023, unstandardized coefficient: b=0·155, 95% CI = 0·100 – 0·209; use of hashish and herbal standardised coefficient: β=0·028, unstandardized coefficient: b= 0·262, 95% CI = 0·188 – 0·337; range 0-15, cut-off for cannabis dependence ≥3) compared to lower potency cannabis use.[30] While hashish has previously been classified as a lower potency cannabis product, these results follow the evidence that its potency has increased internationally.[6]

Mixed findings were reported when comparing higher potency herbal and concentrate cannabis use by one study. 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 -0·12-0·30). Conversely, use of higher potency concentrate was associated with fewer symptoms of CUD (r -0·05, CI -0·35- -0·26).[25]

Another study comparing concentrate and herbal cannabis (n=191) did not find a significant difference between symptoms of CUD in frequent concentrate users (mean 2·1) compared to frequent herbal cannabis users (mean 1·3).[29] Importantly, the sample of participants included in this study endorsed few CUD symptoms overall.

INSERT TABLE 2 HERE

Association of cannabis potency and anxiety

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

One study found an association between use of higher potency cannabis and anxiety.[27] Use of higher potency cannabis was associated with a 2 times increased in risk of generalised anxiety disorder, compared to lower potency cannabis, in a sample of 1087 past year cannabis users (OR = 1·92, CI 1·11-3·32).[27] In another study (n=181,870), risk of anxiety diagnosis was not higher for users of higher potency herbal cannabis compared to users of lower potency herbal cannabis (OR = 1·05, 95% CI 0·98 – 1·12).[15] However, in the same study, when comparing self-report lifetime anxiety diagnosis in users of BHO, higher potency herbal cannabis users and lower potency herbal cannabis users, users of BHO were twice as likely to report an anxiety diagnosis compared to users of lower potency herbal cannabis (OR = 1·80, 95% CI 1·60- 2·01) and higher potency herbal cannabis (OR = 1·72, 95% CI 1·55 – 1·91).[15] Converserly, in a study comparing use of concentrate cannabis and herbal cannabis (n= 156), use of higher potency concentrate (r 0·21, 95% CI -0·10 - 0·49) as well as use of higher potency herbal cannabis (r 0·03. 95% CI -0·18 -0·24) was not associated with more symptoms of

anxiety.[25] A study of 191 cannabis users also found no difference in severity of anxiety between frequent concentrate users and frequent higher potency herbal cannabis users.[29]

Association of cannabis potency and anxiety in users of medical cannabis

A subset of four studies examined the association between cannabis potency and anxiety in users of 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] One of these studies was rated as 'fair quality' in the risk of bias assessment due to issues in the outcome measure.[31] The other study was rated as 'poor quality' due to issues in the sample selection, adjustment of confounders, and outcome measure.[32]

A cross-sectional study conducted in the Netherlands (n=102) compared the effects of three types of cannabis with higher, medium, and lower THC concentration, and it found on average that levels of anxiety were higher with use of higher THC cannabis (mean = 3·42), followed by medium THC cannabis (mean = 2·80), and lastly lower THC cannabis (mean = 1·62). [31] Another repeated measure study conducted in Canada (n=837) reported greater reduction in anxiety symptoms in cannabis with 21-24% THC (27·3% improvement) compared to cannabis with 15-18% THC (22% improvement). However, this difference was not analysed statistically.[32]

We also found two repeated-measure studies comparing a variety of strains of cannabis in users of medical cannabis for anxiety symptoms.[33,34] Both studies were rated as 'poor quality' in the risk of bias assessment due to issues in the outcome measure and cofounder adjustment.

In a US study (n=670), use of higher potency strains was associated with reductions in VAS scores of symptoms of anxiety compared to lower potency cannabis types (THC <10%) (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 medical cannabis users.[33]

INSERT TABLE 3 HERE

Association of cannabis potency and depression

We found four cross-sectional studies of depression.[15,25,27,29] One study was rated as 'fair quality'[27] and three as 'poor quality'[15,25,29] in the risk of bias assessment. These scores represent limitations in the exposure measure in all studies as well as 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) conducted over 20 countries (typically high-income countries), use of higher potency concentrate cannabis (OR= 1·34, 95% CI 1·21 – 1·48) as well as higher potency herbal cannabis (OR 1·18, 95% CI 1·11 – 1·25), compared to lower potency herbal cannabis, were associated with a slight increase in odds of depression diagnosis.[15] Conversely, in a UK sample of 1087 past year cannabis users, there was little evidence to suggest increased risk of major depression in higher potency cannabis users compared to lower potency cannabis users (AOR= 1·28, 95% CI 0·68 – 2·32).[27] Another US study of 191 participants found no difference in the severity of depression between frequent concentrate users (M= 0·72; higher potency) and frequent herbal cannabis users (M= 0·76; lower potency).[29] Similarly, a cross-sectional study of 151 cannabis users in the US found no association between symptoms of depression and use of higher potency concentrate cannabis (r 0·17, 95% CI -0·15 - 0·45) or higher potency herbal cannabis (r 0·02, 95% CI -0·19 – 0·23).[25]

Association of cannabis potency and depression in users of medical cannabis

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

In a Canadian study (n=837) of users of medical cannabis for pain relief comparing different strains of cannabis, strains with the greatest THC concentration showed the greatest symptom improvement (32%). However, lower potency cannabis with 0·1-0·8% THC concentration also showed a 25.2% improvement in symptoms of depression and the differences were not analysed statistically.[32]

Mixed results have also been found in studies examining the effects of cannabis potency in users of medical cannabis for symptoms of depression. While in one US study (n=1,819), use of higher potency cannabis was associated with a reduction of 0·549 points in symptoms of depression (b -0·549, SE 0·272; range= -10 to 9) compared to lower potency cannabis,[35] another Canadian study (n=561) found greatest reduction in ratings of depression with use of lower potency cannabis.[33]

INSERT TABLE 4 HERE

Discussion

Overall, the evidence suggests use of higher potency cannabis, compared to lower potency cannabis, is associated with increased risk of psychosis, and this risk is higher in daily cannabis users. Higher potency cannabis use has also been associated with earlier onset of psychosis, more symptoms of psychosis, and increased risk of relapse. These results are in line with experimental studies showing that THC produces dose-dependent psychotic symptoms.[5] Thus, these findings suggest that exposure to greater doses of THC from consumption of higher potency cannabis is associated with poorer mental health outcomes. The evidence so far does not suggest use of higher potency cannabis is associated with psychosis-like symptoms, although fewer studies have been conducted using this outcome and they have used poorer quality study designs than those addressing psychotic disorders.

Use of higher potency cannabis was also consistently associated with increased risk of CUD, recent cannabis use problems, and severity of cannabis dependence. Pre-clinical studies have found THC is reinforcing in a dose-dependent manner.[36,37] Thus, exposure to higher 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 also found THC is anxiety-inducing,[5] supporting the findings that use of higher potency cannabis could result in worse anxiety outcomes compared to use of lower potency cannabis. There is little evidence so far to suggest an

association between higher potency cannabis use and depression, with one study so far suggesting an association.

Studies on users of medical cannabis found mixed 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. While these studies present better measures of cannabis potency exposure, as specified concentrations of THC in medicinal products, the findings are difficult to interpret due to the inclusion of participants with heterogeneous demographics, as well as the measurement of short-term outcomes. These findings should be considered with caution since medical cannabis was used as a treatment for a range of medical conditions. Thus, there are likely confounders involved that cannot be controlled for. For example, improvements in the medical conditions for which participants were primarily using the cannabis for, such as chronic pain. For users of cannabis as a treatment for depression or anxiety without other known underlying conditions, the studies do 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.

Strengths of this systematic review include its PROSPERO registration as well as use of PRISMA reporting guidelines. In addition, two independent reviewers completed searches, data extraction, and risk of bias assessment. To our knowledge, this is the first systematic review on the association of cannabis potency and mental health and addiction.

When considering the quality of the evidence, so far, none of the studies were categorised as 'good quality' from the risk of bias assessment. These 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 participants as higher or lower potency cannabis users. This may introduce bias due to different reasons. Firstly, it relies on the participant accurately recalling the type of cannabis they have used and effectively communicating this to researchers. Secondly, another source of potential bias in some of the studies reviewed is the use of different cannabis products as a proxy of cannabis potency. There is evidence that varying cannabis products differ in laboratory analysed THC concentrations, offering preliminary validation for

this method, and this has been shown both when cannabis type is categorised by people who use cannabis[39,40], as well as 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/lower potency (e.g. based on an arbitrary THC cut-offs) cannot capture the full range of cannabis products and potencies people are exposed to. Another potential source of bias is that studies do not account for levels of THC intake vs THC content in cannabis products which can vary due to 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. While it may offer a useful proxy for THC exposure in research and clinical settings, it carries limitations which should be addressed in future by more precise estimations of THC exposure. The lack 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) and/or quantified metabolites of THC to increase standardisations of exposure measures and facilitate harmonisation of evidence.

The studies presented also are heterogenous in the definition of higher and lower potency cannabis. Some studies categorised higher potency cannabis as higher potency herbal cannabis, while others categorised it as concentrate cannabis use, or quantified levels of THC. Some studies compared the effects of higher potency cannabis and lower potency cannabis as a control. Other studies separately examined the effects of higher potency cannabis and lower potency cannabis against no cannabis use, with the comparison between higher potency and lower potency cannabis use being indirect. Thus, a limitation of the evidence presented in this review is that the exposure (higher versus lower potency cannabis) can only be interpreted in relative terms within each study, rather than in absolute terms across all studies.

Because of these limitations, bias in the measure of exposure due to use self-report measures, lack of standardised precise measures of THC exposure that accounts for titrating effects, and

heterogeneity in categorisations of higher potency and lower potency cannabis, it was not possible to perform meta-analysis.

Another common limitation is the use of cross-sectional study designs which cannot establish direction of association. For example, due to 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 a variety of potential confounds or none. The contribution of other measures of cannabis use, such as frequency of use or amount used were often not taken into consideration, with amount used only adjusted for in one study[30]. In some studies, frequency of use was adjusted for as a confounding variable while others created a composite variable for cannabis potency and frequency of use. Longitudinal studies are needed to understand the direction of the association between cannabis potency and mental health as well as the contribution of other factors such as frequency of use.

Based on the evidence available, we suggest future studies include common confounders such as age, sex, gender, socioeconomic status, use of alcohol, tobacco, and other illicit drugs. We recommend studies report models with and without adjustments for frequency of use and amount of cannabis used as 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 use of higher potency cannabis through the development of tolerance, in which case adjusting for frequency of use as a confounder would be appropriate. Alternatively, if higher potency cannabis leads to more frequent use, frequency of use might be a mediator of the effect of higher potency cannabis on mental health. In addition, we recommend future studies to 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 (CBD). While the concentration of THC in samples of cannabis has increased over the years, concentration of cannabidiol (CBD) have remained

virtually negligible.[6] Variation in concentrations of CBD or other cannabinoids may have contributed to outcomes reported in this study. However, evidence for CBD interacting with the effects of THC have been mixed[44] and THC is the primary cannabinoid responsible for the health effects of cannabis use.

In conclusion, these findings highlight the potential for an increased risk of negative mental health outcomes and addiction with higher potency cannabis use. These findings support recommendations to discourage use of higher potency products for lower-risk use.[45] This recommendation should be incorporated into education tools as well as 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, 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 interest

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

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